

Efficacy and safety of once-weekly PEG-rhGH versus daily GH in children with Noonan syndrome: a 52-week, randomized controlled trial

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2 **Noonan syndrome: a 52-week, randomized controlled trial**

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36 **Abstract**

Purpose: Short stature is a prominent feature of Noonan syndrome (NS) and currently requires daily recombinant human growth hormone (rhGH) injections, which imposes a substantial treatment burden and limits long-term adherence. To evaluate the efficacy, metabolic impacts, and cardiac safety of once-weekly polyethylene glycol-conjugated rhGH (PEG-rhGH) compared with daily GH in prepubertal children with NS.

Methods: In this 52-week, randomized, active-controlled, open-label trial (ChiCTR2200065823), 30 prepubertal children with molecularly confirmed NS were randomized (1:1) to receive either once-weekly PEG-rhGH (0.20 mg/kg/week) or conventional daily GH (0.033 mg/kg/day). Primary endpoints were annualized height velocity (HV) and change in height SDS (Δ Height SDS), evaluated using ANCOVA adjusting for baseline age and height SDS. Secondary outcomes included bone mineral density (BMD), body composition, metabolic profiles, and echocardiographic parameters.

Results: All 30 patients completed the trial. At 52 weeks, PEG-rhGH achieved an ANCOVA-adjusted LS mean HV of 10.38 cm/year vs. 9.14 cm/year for daily GH (Adjusted ETD: 1.24 cm/year; $P = 0.058$). The adjusted Δ Height SDS was 0.96 for PEG-rhGH vs. 0.79 for daily GH (ETD: 0.18; $P = 0.190$). PEG-rhGH significantly mitigated the transient BMD z-score reduction observed with daily GH ($P = 0.010$) and improved lipid profiles by significantly lowering triglycerides ($P = 0.004$). Echocardiography confirmed no pathological myocardial thickening in either group.

Conclusion: Once-weekly PEG-rhGH demonstrates comparable efficacy to conventional daily GH in promoting catch-up growth in NS, while offering unique protective effects on bone density and lipid profiles. It exhibits excellent cardiovascular safety, representing a substantial clinical advancement for reducing injection burden in patients with NS.

What is Known:

- Short stature is a prominent manifestation of Noonan syndrome (NS), typically treated with daily recombinant human growth hormone (rhGH) injections.
- The strict requirement of daily administration imposes a heavy treatment burden, often leading to injection fatigue and suboptimal long-term adherence in pediatric patients.

What is New:

- Once-weekly PEG-rhGH demonstrated a superior annualized height velocity compared to conventional daily GH over 52 weeks in prepubertal children with NS.
- Alongside robust catch-up growth and excellent cardiovascular safety, PEG-rhGH offered unique protective effects by mitigating rapid bone mineral density loss and improving lipid profiles.

Keywords: Noonan syndrome, long-acting growth hormone, PEG-rhGH, short stature, RASopathy.

Abbreviations: ANCOVA: analysis of covariance BA/CA: bone age to chronological age ratio BMD: bone mineral density ETD: estimated treatment difference GH: growth hormone GHD: growth hormone deficiency HCM: hypertrophic cardiomyopathy HV: height velocity IGF-1: insulin-like growth factor-1 IGFBP-3: insulin-like growth factor-binding protein-3 LAGH: long-acting growth hormone LS: least squares NS: Noonan syndrome PEG-rhGH: polyethylene glycol-conjugated recombinant human growth hormone PFM: body fat percentage SDS: standard deviation score

Introduction

Noonan syndrome (NS) is a relatively common genetic disorder with an estimated incidence of 1 in 1000 to 1 in 2500 live births [1]. It is caused by pathogenic variants in genes encoding components of the RAS/mitogen-activated protein kinase (MAPK) signaling pathway [2]. While NS is characterized by a wide spectrum of clinical manifestations, including distinctive facial features and congenital heart defects, short stature is one of the most prominent and consistent features, affecting approximately 50% to 80% of individuals with this condition [1, 3]. Without intervention, the mean adult height of patients with NS is significantly compromised, which may severely impact their physical and psychological well-being [4].

Recombinant human growth hormone (rhGH) therapy has been approved and widely utilized for the treatment of short stature associated with NS [5]. Conventional rhGH replacement requires daily subcutaneous injections over a period of several years. While daily growth hormone (GH) is effective in accelerating height velocity and improving near-adult height in children with NS [6, 7], the strict requirement of daily administration imposes a substantial treatment burden on patients and their caregivers. This burden frequently leads to injection fatigue, missed doses, and suboptimal treatment adherence, which subsequently compromises the long-term clinical efficacy of the therapy [8]. To mitigate the burden of daily injections and improve patient adherence, long-acting growth hormone (LAGH) preparations designed for once-weekly administration have been rapidly developed over the past decade [9].

However, the development of ideal therapeutic strategies for short stature in NS remains complex due to the underlying RAS/MAPK pathway dysregulation. Recent attempts to repurpose targeted pathway modulators have yielded mixed clinical outcomes. A recent phase 3 randomized controlled trial evaluating simvastatin—an HMG-CoA reductase inhibitor intended to attenuate RAS/MAPK hyperactivation—failed to demonstrate any significant improvement in growth velocity or baseline insulin-like growth factor-1 (IGF-1) levels in children with NS [10]. Conversely, direct targeting of downstream growth plate signaling via vosoritide, a C-type natriuretic peptide analog, has shown robust short-term growth acceleration; however, its clinical application has been hampered by reports of severe skeletal adverse events, including slipped capital femoral epiphyses and genu valgum [11]. These recent findings underscore that while targeting

the MAPK pathway is a biologically sound concept, optimizing traditional GH therapy through long-acting formulations currently represents the safest and most realistic therapeutic strategy.

Recently, once-weekly LAGHs, such as somapacitan, have demonstrated promising efficacy and safety profiles in treating children with NS [9]. Polyethylene glycol-conjugated rhGH (PEG-rhGH) is another well-established LAGH that has demonstrated non-inferiority to daily GH in promoting growth in pediatric patients with growth hormone deficiency (GHD) [12]. However, despite its proven benefits in other growth disorders, robust clinical evidence regarding the efficacy and comprehensive safety—of once-weekly PEG-rhGH specifically in children with NS remains scarce. Furthermore, recent studies emphasize the necessity of a personalized approach to GH therapy in NS patients, repeatedly raising concerns regarding the potential of GH to exacerbate cardiac hypertrophy and requiring vigilant monitoring of cardiovascular safety alongside efficacy. Further prospective studies are needed to evaluate cardiovascular risk of this category of patients [13].

Therefore, we conducted a 52-week, randomized, controlled clinical study to address this knowledge gap. The primary objective of this study was to compare the efficacy and safety of once-weekly PEG-rhGH (0.20 mg/kg/week) with conventional daily GH (0.033 mg/kg/day) in prepubertal children with NS, aiming to simultaneously explore the comprehensive impacts of long-acting GH therapy on growth, metabolic homeostasis, and cardiac morphology.

Materials and Methods

Study Design and Participants

This was a 52-week, randomized, active-controlled, open-label clinical trial designed to evaluate the efficacy and safety of once-weekly PEG-rhGH versus once-daily rhGH in Chinese children with NS. This study was registered with the Chinese Clinical Trial Registry (ChiCTR), registration number ChiCTR2200065823 (Registration Date: November 16, 2022). This study was approved by the Institutional Review Board of Shanghai Children's Medical Center (Approval No: SCMCIRB-K2022027-1), School of Medicine, Shanghai Jiao Tong University and all methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki). Written informed consent to participate in this study was obtained from all participants or their legal guardians. The study cohort comprised 30 prepubertal children diagnosed with NS, confirmed by both characteristic clinical manifestations and molecular genetic testing. Due to the relative rarity of NS, the sample size was determined based on the sample sizes of previously published clinical trials evaluating GH therapy in NS population, in conjunction with the annual volume of newly diagnosed eligible patients at our center. Eligible participants were randomly assigned in a 1:1 ratio to receive either once-weekly PEG-rhGH (Jintrolong, GeneScience Pharmaceuticals, China) at a dose of 0.20 mg/kg/week (PEG-rhGH group, n=15) or daily rhGH (Jintropin, GeneScience Pharmaceuticals, China) at a dose of 0.033 mg/kg/day (Daily GH group, n=15). Allocation concealment was strictly maintained using sequentially numbered,

opaque, sealed envelopes, which were opened only after a patient's eligibility was confirmed and informed consent was formally obtained. The primary efficacy endpoint was the annualized height velocity (HV, cm/year) and the change in height SDS (Δ Height SDS) from baseline to Week 52. CONSORT flow diagram of the study is presented in Figure 1.

Inclusion and Exclusion Criteria

Inclusion Criteria: Patients were included if they met all of the following criteria: (1) prepubertal status (Tanner stage I) with an age of 1 to 8 years for girls and 1 to 9 years for boys; (2) clinical diagnosis of NS based on standard diagnostic criteria; (3) Molecular diagnosis of NS: identifying pathogenic or likely pathogenic variant in NS-associated genes according to American College of Medical Genetics and Genomics (ACMG) guidelines; (4) delayed bone age (BA) relative to chronological age (CA), defined as height < 10th percentile for age and sex; (5) normal thyroid and adrenal cortical function; and (6) no previous GH treatment within 180 days prior to enrollment.

Exclusion Criteria: Patients were excluded if they presented with any of the following: (1) IGF-1 levels > +2.5 SDS; (2) short stature attributable to other identified causes; (3) planned orthopedic surgery within the next year or unhealed fractures; (4) severe hepatic impairment (ALT or AST > 3 times the upper limit of normal), active viral hepatitis; (5) severe renal impairment (eGFR < 60 mL/min/1.73 m² or elevated serum creatinine); (6) severe cardiovascular diseases (e.g., heart failure NYHA class III or above, hypertrophic obstructive cardiomyopathy, severe arrhythmias, or uncontrolled

hypertension); (7) severe neurological disorders (e.g., epilepsy or intracranial mass); (8) abnormal glucose metabolism (impaired fasting glucose, impaired glucose tolerance, or diabetes mellitus) or a family history of diabetes; (9) concomitant severe conditions precluding study completion (e.g., severe obesity, uncontrolled obstructive sleep apnea, active psychiatric disorders, or immunodeficiency); (10) use of medications affecting growth or bone metabolism within 3 months prior to screening (e.g., other GH preparations, aromatase inhibitors, GnRH analogs, sex steroids, anabolic agents, somatostatin analogs, or supraphysiological glucocorticoids); (11) contraindications to GH therapy, including severe diabetic retinopathy, history or presence of malignancy, strong family history of cancer, or consecutively elevated tumor markers; (12) known severe allergies to the study drug or excipients; (13) participation in another interventional clinical trial within the past 3 months; or (14) expected poor compliance with the study protocol.

Clinical and Auxological Assessments

Following the baseline evaluation (Week 0), patients underwent regular follow-up visits at Weeks 4 (V1), 13 (V2), 26 (V3), 39 (V4), and 52 (V5). Anthropometric measurements, including standing height and body weight, were obtained at each visit by trained pediatric endocrinologists using standardized equipment. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Height, weight, and BMI were subsequently converted into standard deviation scores (SDS) based on national growth references for Chinese children [14].

Laboratory and Bone Health Evaluations

To monitor the safety and pharmacodynamic response, fasting blood samples were collected to measure IGF-1 and IGF-binding protein-3 (IGFBP-3) levels, results were expressed as SDS adjusted for age and sex. Complete blood count (CBC), liver and renal function indexes were continuously monitored throughout the trial. Metabolic safety was rigorously assessed by monitoring fasting blood glucose (Glu), glycated hemoglobin (HbA1c), thyroid function test (TFT), blood lipids throughout the 52-week study period. Additionally, bone maturation was evaluated using bone age (BA) radiographs of the left hand and wrist, and the bone age-to-chronological age ratio (BA/CA) was calculated. Full-spine radiographs are used to evaluate skeletal safety, and brain and pituitary magnetic resonance imaging is used to assess neurological safety at baseline and Week 52. Echocardiogram, electrocardiogram, bone mineral density (BMD) and body fat percentage (PFM) were evaluated at baseline, Week 26, and Week 52 to assess cardiac safety, bone health and body composition changes during the rapid catch-up growth phase. PFM were measured by Bioelectrical Impedance Analysis (BIA) using an Inbody 770 (Inbody Co. Ltd., Seoul, South Korea). The BMD of the infants was measured and the BMD z-score was determined by dual-energy X-ray absorptiometry (DXA) (DXA-3000, Shanghai Osteosys Co., Ltd.).

Statistical Analysis

All statistical analyses were performed using Python software (version 3.10, utilizing the SciPy, Pandas, and Statsmodels libraries). Continuous variables are presented as mean $\pm$ standard deviation (SD) for the observed raw data, while categorical variables are expressed as frequencies and percentages. Unadjusted between-group comparisons of baseline characteristics and longitudinal endpoints were performed using the independent-samples Student's t-test, or Welch's t-test when the assumption of equal variances was violated (as determined by Levene's test). Within-group changes from baseline to Week 52 were evaluated using paired t-tests. To robustly evaluate the primary efficacy endpoints at Week 52 (height velocity and Δ Height SDS) and account for potential initial imbalances, an analysis of covariance (ANCOVA) was performed. Baseline age and baseline height SDS were included as pre-specified covariates in the ANCOVA models. To rigorously address observed heteroscedasticity between treatment groups, heteroscedasticity-consistent (HC3) robust standard errors were applied. The ANCOVA-adjusted results are expressed as Least Squares Means (LS Means) $\pm$ standard error (SE), alongside the adjusted estimated treatment differences (ETD) and their corresponding 95% confidence intervals (95% CI). Furthermore, multiple linear regression analysis was conducted to evaluate the independent effects of baseline factors on 52-week catch-up growth. All statistical tests were two-sided, and a P-value < 0.05 was considered statistically significant. Data visualization was generated using the Matplotlib library.

Results

Cohort Demographics, Baseline Auxology, and Genetic Profiles

Patients were recruited and followed up between January 2023 and December 2025. A total of 30 prepubertal children (23 males and 7 females) with a confirmed molecular and clinical diagnosis of NS were enrolled and successfully completed the 52-week follow-up (Figure 1). As detailed in Supplemental Table 1, genetic screening confirmed that the majority of the cohort harbored variants in the *PTPN11* gene ($n = 26$, 86.7%), alongside variants in *SHOC2* ($n = 3$, 10.0%) and *SOS1* ($n = 1$, 3.3%). All identified variants were classified as pathogenic or likely pathogenic according to ACMG guidelines.

The mean age at treatment initiation was 5.12 ± 1.73 years, with 93.3% of the cohort being ≥ 3 years of age. At baseline, the study population presented with severe growth retardation, (mean Height SDS: -3.20 ± 0.89), and a relatively lean body composition (mean BMI SDS: -0.07 ± 1.03). Baseline demographic, auxological, and laboratory parameters—including age, IGF-1 SDS (-0.76 ± 0.82), and BA/CA ratio (0.62 ± 0.18)—were highly comparable between the PEG-rhGH ($n = 15$) and Daily GH ($n = 15$) groups. Although random allocation resulted in a lower baseline Height SDS in the Daily GH group (-3.61 ± 0.90 vs. -2.79 ± 0.67 ; $P = 0.008$), and Daily GH group had a slightly higher baseline BMI SDS compared to the PEG-rhGH group (0.30 ± 0.90 vs. -0.45 ± 1.04 ; $P = 0.044$), overall, randomization was successful in balancing primary severity indicators (Table 1). Primary efficacy evaluations focused on longitudinal Δ Height SDS and annualized HV, and baseline Height SDS was further incorporated as a covariate in subsequent adjusted ANCOVA models.

Primary Auxological Outcomes: Catch-up Growth and Height Velocity

Over the 52-week treatment period, both therapeutic regimens induced robust catch-up growth (Table 2). However, the PEG-rhGH cohort demonstrated a statistically significant superiority in the primary endpoint of annualized HV. At Week 52, the observed mean HV was 10.05 ± 0.84 cm/year in the PEG-rhGH group and 8.65 ± 2.16 cm/year in the daily GH group (Figure 2). To robustly evaluate the treatment efficacy while accounting for initial imbalances, an ANCOVA model adjusting for baseline age and baseline height SDS was performed. The ANCOVA-adjusted Least Squares (LS) mean HV was 10.38 ± 0.35 cm/year for PEG-rhGH versus 9.14 ± 0.54 cm/year for daily GH, resulting in an ETD of 1.24 cm/year (95% CI: -0.04 to 2.51; $P=0.058$) (Supplemental Figure 1).

Similarly, for the Δ Height SDS, the observed mean increase from baseline to Week 52 was 0.89 ± 0.17 in the PEG-rhGH group and 0.84 ± 0.47 in the daily GH group (Figure 3). Following ANCOVA adjustment for the same covariates, the LS mean Δ Height SDS was 0.96 ± 0.05 for the PEG-rhGH cohort and 0.79 ± 0.13 for the daily GH cohort. The adjusted ETD was 0.18 (95% CI: -0.09 to 0.44; $P = 0.190$) (Supplemental Figure 1). These robustly adjusted findings confirm that once-weekly PEG-rhGH is highly effective and demonstrates comparable efficacy to conventional daily GH in improving height standard deviation scores over 52 weeks of treatment.

Longitudinal Changes in Skeletal Maturation, Bone Mineral Density, and Body Composition

Importantly, rapid linear growth was not accompanied by undue acceleration of skeletal maturation. The BA/CA ratio remained highly stable over 52 weeks in both cohorts (PEG-rhGH: 0.651 ± 0.154 vs. Daily GH: 0.606 ± 0.178 ; $P = 0.457$ between groups).

DXA and BIA revealed distinct trajectories in bone health and body composition between the two groups. The Daily GH group experienced a statistically significant decline in BMD z-score from baseline to 52 weeks (-1.17 ± 1.41 to -2.09 ± 0.73 , $P = 0.011$). In contrast, the PEG-rhGH group exhibited a markedly attenuated BMD reduction, culminating in a significant bone-protective advantage at 52 weeks (-1.36 ± 0.73 vs. -2.09 ± 0.73 ; $P = 0.010$). Furthermore, body fat percentage (PFM) significantly decreased in the Daily GH group ($24.36 \pm 6.73\%$ to $17.38 \pm 6.23\%$, $P = 0.001$), whereas it experienced a mild compensatory increase in the PEG-rhGH group from a leaner baseline ($17.36 \pm 6.48\%$ to $20.61 \pm 4.41\%$, $P = 0.046$) (Table 2).

Pharmacodynamic Responses of the GH/IGF-1 Axis

Following 52 weeks of administration, mean IGF-1 SDS and IGFBP-3 SDS increased significantly from baseline in both groups ($P < 0.01$ for within-group changes in IGF-1 SDS; $P = 0.005$ for IGFBP-3 SDS in PEG-rhGH), reflecting adequate receptor engagement. Crucially, the mean IGF-1 SDS at Week 52 in both the PEG-rhGH group (0.75 ± 1.72) and the Daily GH group (0.24 ± 1.17) remained strictly within the physiological safety threshold ($< +2.0$ SDS) (Figure 4). There was no statistically significant difference in IGF-1 SDS between the two modalities at the endpoint ($P =$

0.354), indicating that the superior height velocity of PEG-rhGH was achieved without inducing systemic IGF-1 overexposure.

Metabolic Homeostasis and Favorable Lipid Profile Modulation

Metabolic surveillance (Supplemental Table 2 and Supplemental Figure 2) demonstrated excellent glucose homeostasis throughout the trial. Fasting blood glucose and HbA1c levels remained exceptionally stable over the 52 weeks across both groups ($P > 0.05$ for all between-group and within-group comparisons). Intriguingly, longitudinal lipid profiling uncovered a significant lipid-lowering effect specific to the long-acting formulation. The PEG-rhGH group exhibited a progressive and significant reduction in serum triglycerides from baseline to 52 weeks (1.06 ± 0.64 to 0.64 ± 0.22 mmol/L; within-group $P = 0.038$), resulting in significantly lower triglyceride levels compared to the Daily GH cohort at the 52-week endpoint (0.64 vs. 1.20 mmol/L; $P = 0.004$). Total cholesterol remained stable in both groups. Thyroid function parameters (TSH, FT3, FT4) showed minimal physiological fluctuations. While FT3 showed a slight within-group increase in the PEG-rhGH arm ($P = 0.003$), there were no statistically significant between-group differences in any thyroid metrics at 52 weeks.

Echocardiographic Surveillance and Cardiac Morphological Safety

Given the inherent risk of hypertrophic cardiomyopathy associated with NS, echocardiographic parameters were rigorously monitored (Table 3). At baseline, the

maximal left ventricular posterior wall thickness at end-diastole (LVPWd) and interventricular septum thickness at end-diastole (IVSd) were highly comparable between the groups. Crucially, after 52 weeks of continuous GH exposure, neither group demonstrated pathological myocardial thickening. End-point LVPWd remained statistically unchanged from baseline for both PEG-rhGH (0.45 ± 0.11 to 0.48 ± 0.12 cm; $P = 0.372$) and Daily GH (0.48 ± 0.11 to 0.47 ± 0.08 cm; $P = 0.979$). Similarly, IVSd exhibited no significant intra-group hypertrophy over 52 weeks (PEG-rhGH: $P = 0.833$; Daily GH: $P = 0.127$), and no adverse between-group differences were observed ($P > 0.05$).

Clinical Safety Profile and Adverse Event Incidence

The safety profiles of both treatment regimens were highly favorable and consistent with the established safety records of pediatric GH therapy (Table 4). Adverse events (AEs) were reported by 80.0% ($n=12$) of patients in the PEG-rhGH group and 86.7% ($n=13$) in the Daily GH group. All documented AEs were mild to moderate in severity; no severe AEs or AEs leading to treatment discontinuation occurred. The most frequent AEs ($>10\%$ incidence) included pyrexia, upper respiratory tract infections (URTI), and influenza, which were primarily assessed as unlikely to be related to the trial products. Subclinical hypothyroidism requiring observation occurred in two patients (13.3%) in the PEG-rhGH group and three (20.0%) in the Daily GH group. Notably, local injection site reactions (e.g., induration, bruising)

were infrequent, manifesting in only 6.7% of the PEG-rhGH group compared to 13.3% of the Daily GH group.

Predictive Factors for Growth Response and Genotype-Phenotype Stratification

Multiple linear regression analysis (Supplemental Table 3) evaluated baseline variables influencing 52-week catch-up growth. In the PEG-rhGH cohort, the model ($R^2 = 0.286$) indicated a trend where younger baseline age independently predicted a greater magnitude of Δ Height SDS ($\beta = -0.062$, $P = 0.052$), whereas baseline height SDS was not a significant predictor. Similar trends were not statistically significant in the Daily GH cohort.

Furthermore, an exploratory subgroup analysis was conducted to evaluate the impact of the *PTPN11* mutation—the most prevalent genetic etiology in NS, classically associated with post-receptor GH resistance. Within the *PTPN11*-positive subset ($n = 26$), patients treated with PEG-rhGH achieved an exceptional 52-week Δ Height SDS of 0.89 ± 0.18 , thoroughly mimicking the robust growth response of their *PTPN11*-negative counterparts (0.88 ± 0.14).

Discussion

To our knowledge, this is the first prospective, randomized controlled trial to systematically evaluate the comprehensive efficacy, metabolic impacts, and cardiac safety of once-weekly PEG-rhGH versus conventional daily GH in a genetically confirmed pediatric cohort with NS. We systematically evaluated both the unadjusted

observed data, which reflects real-world clinical growth trajectories, and the ANCOVA-adjusted data, which meticulously controls for baseline age and height SDS imbalances to ascertain the pure therapeutic effect. Derived from this robust statistical methodology, our findings compellingly demonstrate that once-weekly PEG-rhGH delivers highly effective catch-up growth and demonstrates comparable efficacy to conventional daily GH. Specifically, after 52 weeks of treatment, PEG-rhGH achieved an ANCOVA-adjusted LS mean HV of 10.38 cm/year compared to 9.14 cm/year for daily GH (Adjusted ETD: 1.24 cm/year, $P = 0.058$), and yielded an adjusted Δ Height SDS of 0.96 versus 0.79 (Adjusted ETD: 0.18, $P = 0.190$). Concurrently, PEG-rhGH exhibited unique advantages in mitigating transient bone mineral density loss and improving lipid profiles, all while maintaining a highly favorable cardiac and overall safety record.

Short stature in NS is a multifactorial clinical phenotype primarily driven by germline RAS/MAPK pathway mutations [2]. This hyperactivation impairs growth plate chondrogenesis and skeletal maturation, and disrupts JAK/STAT signaling, causing partial post-receptor GH/IGF-1 resistance [15, 16]. Additionally, early-childhood feeding difficulties, delayed puberty, and a blunted pubertal growth spurt further restrict linear growth and final adult height [16]. Recent large-scale data emphasize that while short-term height SDS gains are achievable with daily GH, long-term outcomes remain highly variable and reliant on sustained adherence [5-7]. The introduction of LAGH preparations represents a paradigm shift. Our observation of superior height velocity with PEG-rhGH perfectly aligns with the recently published

REAL8 phase 3 trial, which demonstrated the superiority of once-weekly somapacitan over daily GH in children with NS [9]. By reducing the injection burden from 365 to 52 days annually, LAGH directly eliminates "injection fatigue"—a primary catalyst for poor real-world outcomes in chronic pediatric diseases [18-21]. Furthermore, consistent with The National Cooperative Growth Study (NCGS), data highlighting the importance of age at intervention [22], our regression analyses indicated that younger age at PEG-rhGH initiation is a positive predictor of height SDS gain ($\beta = -0.062$, $P = 0.052$).

Some studies suggest that gain-of-function variants in *PTPN11* (encoding SHP2) trigger hyperactivation of the RAS-MAPK pathway, which induces a mild, post-receptor state of GH insensitivity [23-25]. Historically, *PTPN11*-positive children have exhibited muted growth responses to daily GH [15, 26]. Meanwhile, several studies have demonstrated no difference in growth responses to GH between *PTPN11*-positive and mutation-negative children [27-29]; in some cases, *PTPN11*-positive patients even exhibit superior therapeutic effects under GH treatment [30]. Remarkably, our subgroup analysis revealed that PEG-rhGH circumvented this resistance, eliciting an identical robust height SDS gain in *PTPN11*-positive patients as in their mutation-negative counterparts. However, given the inherently small sample size of our mutation-negative subgroup ($n=4$), this observation remains strictly exploratory. Further large-scale prospective studies are required to validate this hypothesis.

Beyond linear growth, our evaluation uncovered two novel secondary benefits. First, rapid catch-up growth is classically associated with a temporary dilution of bone mineral apparent density. In our cohort, Daily GH elicited a statistically significant reduction in BMD z-score (-1.17 to -2.09, $P=0.011$), whereas PEG-rhGH markedly protected against this deterioration. Second, metabolic profiling revealed a significant reduction in triglycerides specific to the long-acting formulation ($P=0.038$ for PEG-rhGH vs $P=0.671$ for Daily GH). The steady-state exposure of LAGH may synergistically optimize hepatic lipid clearance and fat mass redistribution without altering glucose homeostasis.

Cardiac safety remains the most scrutinized and debated aspect of GH therapy in RASopathies. Children with NS inherently possess a significantly elevated risk of developing hypertrophic cardiomyopathy (HCM)—affecting up to 20% to 30% of patients—driven by the germline hyperactivation of the RAS/MAPK signaling cascade [17, 31]. Because the GH/IGF-1 axis also exerts intrinsic anabolic and trophic effects on myocardial tissue, there has been a pervasive clinical apprehension that exogenous GH therapy, particularly long-acting formulations that provide sustained, steady-state IGF-1 exposure, might synergistically trigger or exacerbate pathological ventricular hypertrophy. Consequently, robust cardiovascular monitoring is strictly mandated in this population [17,31]. A major clinical significance of our study lies in addressing this critical knowledge gap. Through rigorous, paired, and zero-attrition echocardiographic surveillance, we demonstrated absolute cardiac morphological stability over 52 weeks of continuous PEG-rhGH or daily rhGH exposure.

Specifically, no pathological thickening was observed in the IVSd and LVPWd.

These findings provide definitive, pioneering evidence that the sustained pharmacokinetics of PEG-rhGH do not induce adverse myocardial remodeling in properly screened children with NS.

Combined with an incidence of mild adverse events (such as pyrexia and URTI) that mirrors daily GH, and a notably lower rate of injection site reactions, PEG-rhGH presents a highly favorable risk-benefit profile that provides crucial reassurance for prescribing pediatric endocrinologists.

In conclusion, this 52-week prospective, randomized controlled trial demonstrates that once-weekly PEG-rhGH is a highly efficacious and safe alternative to daily GH for prepubertal children with NS. PEG-rhGH not only yielded superior annualized height velocity and also conferred unique secondary physiological benefits, including the mitigation of rapid bone mineral density loss and the optimization of lipid profiles. Crucially, comprehensive echocardiographic monitoring confirmed its excellent cardiovascular safety, with no evidence of treatment-induced myocardial hypertrophy. By significantly reducing the injection burden from 365 to 52 administrations annually while maintaining a robust efficacy and metabolic safety profile, once-weekly PEG-rhGH represents a substantial clinical advancement for optimizing long-term therapeutic outcomes and adherence in patients with NS.

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Authors' Contributions

XL, TW, and WW contributed equally to the study design, data collection, and drafting of the manuscript. XZ, JS, JH, BF, YL, JL, YD, XZ, XM, and TY contributed to clinical assessments, genetic screening, and data interpretation. TC, QL, and XW conceptualized the study, secured funding, provided critical revisions, and approved the final manuscript. All authors reviewed and approved the final manuscript.

Data Availability

Data are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

This study was registered with the Chinese Clinical Trial Registry (ChiCTR), registration number ChiCTR2200065823(Registration Date: November 16, 2022).

The study protocol was approved by the Institutional Review Board of Shanghai Children's Medical Center (Approval No: SCMCIRB-K2022027-1), School of Medicine, Shanghai Jiao Tong University. The study was performed in accordance

with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from the parents or legal guardians of all individual participants included in the study.

Competing interests

The authors declared no conflicts of interest.

Tables and Figures

Table 1. Baseline demographic and clinical characteristics of the study population.

	PEG-rhGH 0.20mg/kg/week (N = 15)	Daily GH 0.033 mg/kg/d (N = 15)	Total (N = 30)
Age group, n (%)			
< 3 years	0 (0.0%)	2 (13.3%)	2 (6.7%)
≥ 3 years	15 (100.0%)	13 (86.7%)	28 (93.3%)
Age (years)	5.01 ± 1.52	5.23 ± 1.94	5.12 ± 1.73
Sex, n (%)			
Male	13 (86.7%)	10 (66.7%)	23 (76.7%)
Female	2 (13.3%)	5 (33.3%)	7 (23.3%)
Height (mean±SDS)	-2.79 ± 0.67	-3.61 ± 0.90	-3.20 ± 0.89
Weight (mean±SDS)	-1.90 ± 0.65	-2.05 ± 0.81	-1.97 ± 0.73
BMI (mean±SDS)	-0.45 ± 1.04	0.30 ± 0.90	-0.07 ± 1.03
HV (cm/year) (mean±SDS)	4.52 ± 0.43	4.65 ± 0.91	4.59 ± 0.70
BA/CA Ratio (mean±SDS)	0.61 ± 0.15	0.63 ± 0.21	0.62 ± 0.18
IGF-1 SDS (mean±SDS)	-0.75 ± 0.81	-0.76 ± 0.87	-0.76 ± 0.82
IGFBP-3 SDS (mean±SDS)	0.36 ± 0.93	0.50 ± 1.00	0.43 ± 0.95

Data are expressed as mean ± standard deviation (SD) for continuous variables, and as number (percentage) for categorical variables.

PEG-rhGH, pegylated recombinant human growth hormone; GH, growth hormone; BMI, body mass index; SDS, standard deviation score; HV, height velocity; BA/CA, bone age to chronological age ratio; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3

Table 2. Summary of Auxological, Metabolic, and Bone Parameters Over 52 Weeks of Treatment.

	Daily GH (n = 15)	PEG-rhGH (n = 15)	P value (Between groups)
Height Velocity (cm/year)			
Baseline	4.65 ± 0.91	4.52 ± 0.43	0.635
Week 26	9.74 ± 2.90	10.46 ± 2.22	0.448
Week 52	8.65 ± 2.16	10.05 ± 0.84	0.031* (Welch's t)
P value (within-group: 0 vs 52w)	<0.001***	<0.001***	
	LS Mean±SE:	LS Mean±SE:	
ANCOVA Adjusted Model	9.14 ± 0.54	10.38 ± 0.35	0.058
Adjusted ETD (95% CI)			1.24 (-0.04, 2.51)
Change in Height SDS (ΔSDS)			
Baseline	0.00 ± 0.00	0.00 ± 0.00	
Week 26	0.47 ± 0.26	0.53 ± 0.22	0.499
Week 52	0.84 ± 0.47	0.89 ± 0.17	0.687 (t-test)
P value (within-group: 0 vs 52w)	<0.001***	<0.001***	
	LS Mean±SE:	LS Mean±SE:	
ANCOVA Adjusted Model	0.79±0.13	0.96 ±0.05	0.190
Adjusted ETD (95% CI)			0.18 (-0.09, 0.44)
BMI SDS			
Baseline	0.30 ± 0.90	-0.45 ± 1.04	0.044
Week 26	-0.22 ± 1.02	0.10 ± 0.76	0.334
Week 52	-0.04 ± 0.69	0.06 ± 0.79	0.708
P value (within-group: 0 vs 52w)	0.129	0.052	
IGF-1 SDS			
Baseline	-0.76 ± 0.87	-0.75 ± 0.81	0.974
Week 26	0.17 ± 1.04	0.51 ± 1.20	0.411
Week 52	0.24 ± 1.17	0.75 ± 1.72	0.354
P value (within-group: 0 vs 52w)	0.002**	0.002**	
IGFBP-3 SDS			
Baseline	0.50 ± 1.00	0.36 ± 0.93	0.692
Week 26	1.13 ± 0.76	1.20 ± 0.87	0.818
Week 52	0.98 ± 1.22	1.23 ± 1.08	0.552
P value (within-group: 0 vs 52w)	0.121	0.005**	
BA/CA Ratio			
Baseline	0.627 ± 0.207	0.614 ± 0.153	0.846
Week 26	0.598 ± 0.169	0.621 ± 0.173	0.713
Week 52	0.606 ± 0.178	0.651 ± 0.154	0.457
P value (within-group: 0 vs 52w)	0.681	0.363	
Bone Mineral Density (BMD)			
Baseline	-1.17 ± 1.41	-0.85 ± 1.20	0.505

Week 26	-1.25 ± 1.31	-0.77 ± 1.46	0.344
Week 52	-2.09 ± 0.73	-1.36 ± 0.73	0.010*
<i>P</i> value (within-group: 0 vs 52w)	0.011*	0.081	
Body Fat Percentage (PFM, %)			
Baseline	24.36 ± 6.73	17.36 ± 6.48	0.007
Week 26	17.27 ± 6.20	20.73 ± 4.52	0.093
Week 52	17.38 ± 6.23	20.61 ± 4.41	0.104
<i>P</i> value (within-group: 0 vs 52w)	0.001**	0.046*	

Data are presented as mean ± standard deviation (SD). Between-group differences at each time point were analyzed using independent samples t-tests. Within-group changes from baseline to week 52 were analyzed using paired t-tests. **P* < 0.05, ***P* < 0.01, ****P* < 0.001. Adjusted ETD and *P*-values were derived from ANCOVA controlling for baseline age and baseline height SDS.

PEG-rhGH, polyethylene glycol-conjugated recombinant human growth hormone; GH, growth hormone; HV, height velocity; SDS, standard deviation score; LS, Least Squares; SE, standard error; BMI, body mass index; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein-3; BA/CA, bone age to chronological age ratio; BMD, bone mineral density; PFM, body fat percentage

Table 3. Echocardiographic parameters before and after 52 weeks of GH treatment in children with Noonan syndrome.

	PEG-rhGH (n = 15)	Daily GH (n = 15)	P-value (between-group)
LVPWd (cm)			
Baseline	0.45 ± 0.11	0.48 ± 0.11	0.488
Week 26	0.52 ± 0.12	0.49 ± 0.13	0.501
Week 52	0.48 ± 0.12	0.47 ± 0.08	0.958
P-value (within-group)	0.372	0.979	
IVSd (cm)			
Baseline	0.54 ± 0.14	0.53 ± 0.14	0.827
Week 26	0.48 ± 0.09	0.56 ± 0.15	0.068
Week 52	0.55 ± 0.19	0.58 ± 0.13	0.657
P-value (within-group)	0.833	0.127	

Between-group differences at each time point were analyzed using the independent samples t-test. Within-group changes from baseline to Week 52 were analyzed using the paired t-test.

GH, growth hormone; PEG-rhGH, polyethylene glycol-conjugated recombinant human growth hormone; LVPWd, maximal left ventricular posterior wall thickness at end-diastole; IVSd, interventricular septum thickness at end-diastole

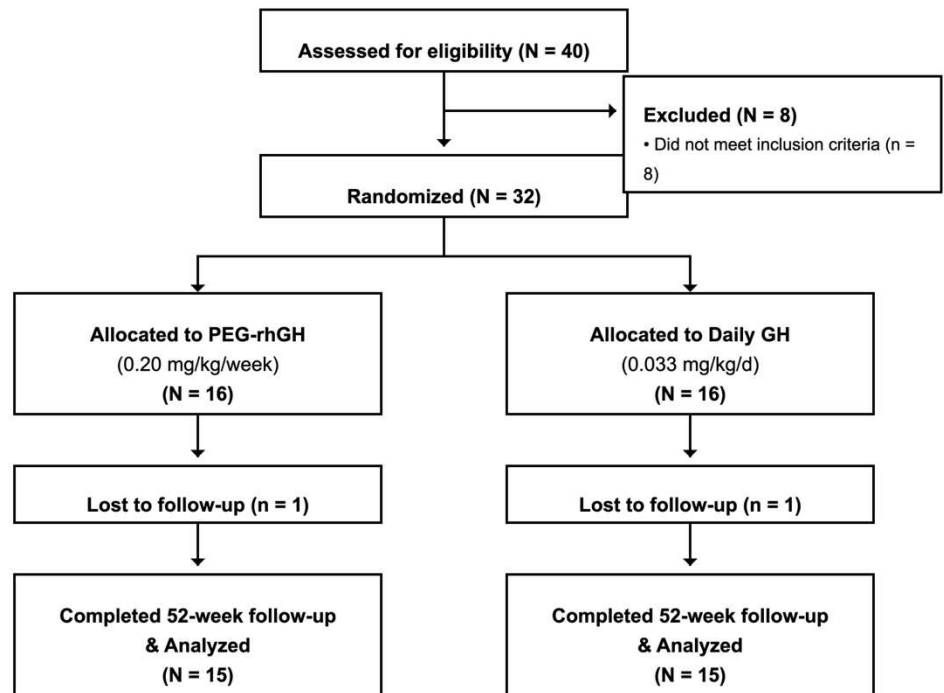
Table 4. Summary of adverse events (AEs) over 52 weeks of growth hormone treatment.

Event Category	PEG-rhGH (N = 15)		Daily GH (N = 15)	
	N (%)	E	N (%)	E
All events	12 (80.0)	40	13 (86.7)	28
Severity				
Severe events	0 (0.0)	0	0 (0.0)	0
Moderate events	7 (46.7)	10	6 (40.0)	11
Mild events	9 (60.0)	28	10 (66.7)	17
Relation to trial product				
Probably related	3 (20.0)	3	5 (33.3)	5
Possibly related	1 (6.7)	1	0 (0.0)	0
Unlikely related	11 (73.3)	35	11 (73.3)	22
Adverse events reported in > 10% of population				
Pyrexia	7 (46.7)	11	3 (20.0)	6
Upper respiratory tract infection	2 (13.3)	3	2 (13.3)	2
Influenza	1 (6.7)	1	3 (20.0)	3
Lower respiratory tract infection	1 (6.7)	1	3 (20.0)	3
Subclinical hypothyroidism	2 (13.3)	2	3 (20.0)	3
Cough	3 (20.0)	3	1 (6.7)	1
Gastroenteritis	2 (13.3)	2	1 (6.7)	1
Rash	2 (13.3)	3	1 (6.7)	1
Injection site reactions	1 (6.7)	1	2 (13.3)	2

Data are based on the safety analysis set, which included all randomized patients who received at least one dose of the assigned trial product. Data are presented as the number of patients experiencing the event (N), the percentage of patients out of the total group population (%), and the total number of events (E). The severity of adverse events (mild, moderate, or severe) and their causal relationship to the trial product (probably, possibly, or unlikely related) were assessed by the local clinical investigators. No severe adverse events or adverse events leading to treatment discontinuation were reported during the 52-week study period in either group. The bottom section presents specific adverse events reported in > 10% (i.e., ≥ 2 patients) of the population in either treatment group; related clinical terms were grouped for clinical relevance (e.g., local induration and bruising were grouped under "Injection site reactions").

GH, growth hormone; PEG-rhGH, polyethylene glycol-conjugated recombinant human
growth hormone; AE, adverse event; N, number of participants experiencing the event;
E, total number of events

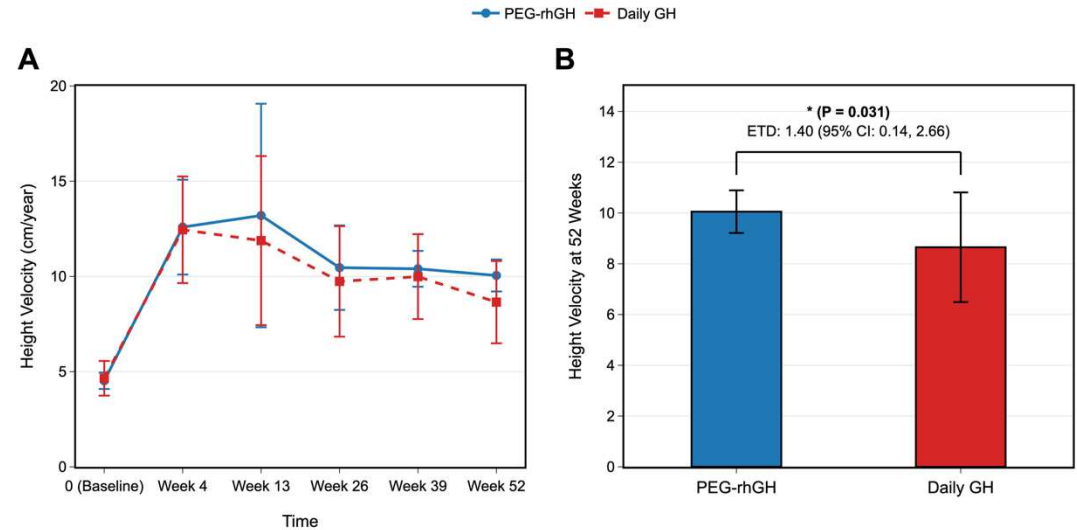
Figure 1. CONSORT flow diagram of the study.



A total of 40 patients were initially assessed for eligibility, of which 8 were excluded for not meeting the inclusion criteria. The remaining 32 prepubertal children with Noonan syndrome were randomly assigned in a 1:1 ratio to receive either once-weekly PEG-rhGH (0.20 mg/kg/week, n = 16) or once-daily GH (0.033 mg/kg/day, n = 16). During the 52-week study period, 2 patients were lost to follow-up (1 in the PEG-rhGH group and 1 in the Daily GH group). Consequently, 30 patients (15 in each group) completed the 52-week follow-up and were included in the final analyses.

PEG-rhGH, polyethylene glycol-conjugated recombinant human growth hormone; GH, growth hormone

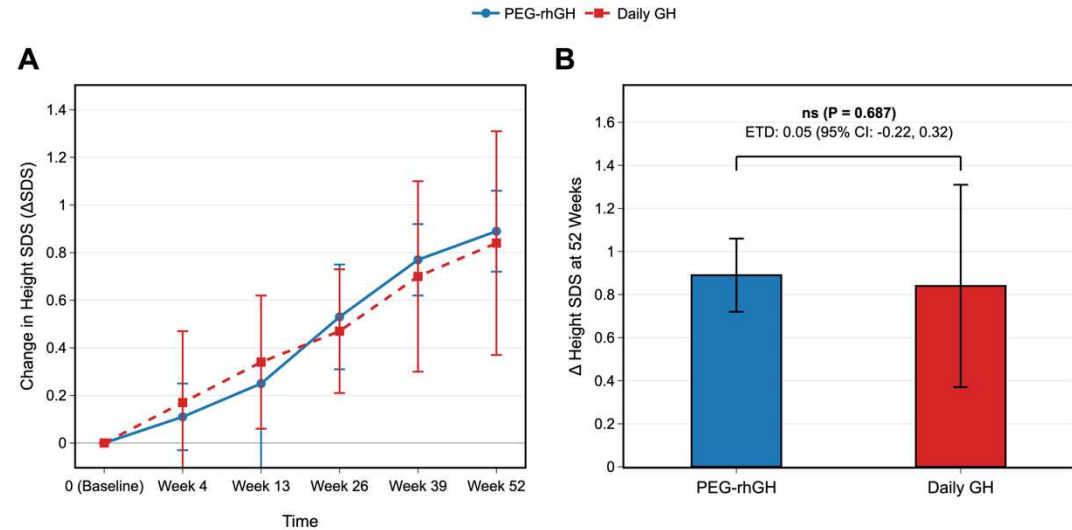
Figure 2. Height velocity in children with Noonan syndrome treated with PEG-rhGH versus Daily GH.



(A) Longitudinal trend of height velocity from baseline to 52 weeks. Data are represented as mean $\pm$ SD. **(B)** Comparison of height velocity at the 52-week endpoint. The PEG-rhGH group demonstrated a statistically significant advantage over the Daily GH group (* P = 0.031 by Welch's independent t-test).

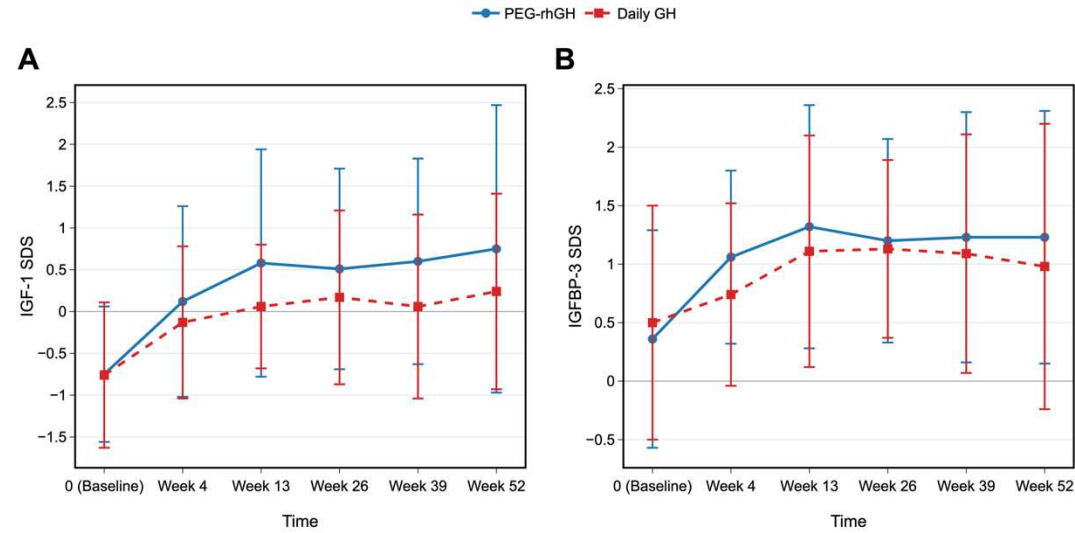
PEG-rhGH, polyethylene glycol-conjugated recombinant human growth hormone; GH, growth hormone; ETD: Estimated treatment difference, CI, confidence interval; Error bars represent standard deviations

Figure 3. Changes in height standard deviation score (SDS) over 52 weeks of growth hormone treatment.



(A) Longitudinal changes in height SDS (Δ Height SDS) from baseline to week 52. Follow-up assessments were conducted at weeks 4, 13, 26, 39, and 52. **(B)** Comparison of the mean Δ Height SDS at the 52-week endpoint between the two treatment groups. PEG-rhGH, polyethylene glycol-conjugated recombinant human growth hormone; GH, growth hormone; ETD, estimated treatment difference; CI, confidence interval; ns, not significant. Error bars represent standard deviations

Figure 4. Longitudinal changes in IGF-1 SDS and IGFBP-3 SDS over 52 weeks of growth hormone treatment.



(A) Mean insulin-like growth factor 1 standard deviation score (IGF-1 SDS) from baseline to week 52. (B) Mean insulin-like growth factor binding protein-3 standard deviation score (IGFBP-3 SDS) from baseline to week 52. The solid blue line with circles represents patients treated with once-weekly PEG-rhGH, and the dashed red line with squares represents patients receiving once-daily GH. Throughout the 52-week study period, mean IGF-1 and IGFBP-3 SDS in both treatment groups increased from baseline but remained well within the physiological safety range (below +2.0 SDS). Data are presented as means, and error bars indicate standard deviations.

PEG-rhGH, polyethylene glycol-conjugated recombinant human growth hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein-3; SDS, standard deviation score

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