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BRIEF REPORT

Persistent growth-promoting effects of vosoritide in children with achondroplasia are accompanied by improvements in physical and social aspects of health-related quality of life

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ABSTRACT

Purpose: : Evaluate the impact of vosoritide on health-related quality of life in children with achondroplasia.

Methods: Participants received vosoritide (15 μg/kg/day) in an extension trial (NCT03424018) after having participated in a placebo-controlled trial (NCT03197766).

Results: The population comprised 119 participants (mean [SD] age 9.7 [2.6] years). Mean treatment duration was 4 (0.78) years. At year 3, the largest mean (SD) changes were observed in the Quality of Life of Short Stature Youth physical score (5.99 [19.41], caregiver reported; 6.32 [20.15], self-reported) and social score (2.85 [8.29] and 6.76 [22.64], respectively). Changes were greatest in participants with ≥1 SD increase in height *z*-score (physical: 11.36 [19.51], caregiver-reported [n = 38]; 8.48 [21.83], self-reported [n = 28]) (social: 5.84 [15.45] and 9.79 [22.80], respectively). To determine how domain scores may change with age in untreated persons, models were produced using observational/untreated-person data. A 1-year increase in age was associated with a change of 0.16 (SE, 0.55) and 0.16 (0.50), for caregiver-reported physical and social domain scores, respectively. Self-reported scores changed by 1.45 (0.71) and 1.92 (0.77), respectively.

Conclusion: These data suggest that after 3 years of treatment, vosoritide demonstrates a positive effect on physical and social functioning among children with achondroplasia, particularly in children with a more pronounced change in height *z*-score.

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Introduction

Achondroplasia, the most prevalent form of disproportionate short-stature skeletal dysplasia, is present in approximately 1 in 25,000 live births.[1,2] It is caused by autosomal dominant gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 gene (*FGFR3*).[2,3] Over-activation of *FGFR3* impairs endochondral ossification, leading to a characteristic pattern of skeletal features,[1,2] including disproportionate short stature and macrocephaly.[1,4] These bone growth and development abnormalities are associated with a high burden of functional impairment and potentially severe medical complications[3,5,6] and reduced quality of life, due in part to disproportionate short stature.[7]

Evidence from phase 2 and 3 clinical trials and extension studies demonstrates that vosoritide, a C-natriuretic peptide analog, increases annualized growth velocity after 1 year of treatment in children with achondroplasia[8,9] and that this improvement is maintained at 3 years.[10] Findings at 2 years indicate trends in improved upper-to-lower body segment proportions, with a least squares mean change from baseline in upper-to-lower body segment ratio of −0.05 (−0.09, −0.001), representing a greater decrease in body ratio.[11] Vosoritide is well tolerated, with a mild adverse event profile in infants and children.[11,12] Vosoritide is approved for the treatment of children with achondroplasia and open epiphyses from birth in the United States, Japan, and Australia and from age ≥4 months in the European Union and ≥6 months in Brazil.

One key issue to address is whether children with achondroplasia derive health-related quality-of-life (HRQoL) benefits through the increased height and improved body proportionality achieved with vosoritide treatment. Such benefits take time to manifest, indicating the need to start treatment early so that children can achieve the maximum functional and HRQoL benefits from their increased stature and improved proportionality. The aim of these preliminary analyses was to investigate the effect of vosoritide on HRQoL in children with achondroplasia in an ongoing open-label extension study.

Materials and Methods

A total of 121 children aged 5 years to <18 years at screening, with a clinical diagnosis of achondroplasia confirmed by genetic testing, were eligible for enrollment in the 111-301 randomized placebo-controlled study (study 111-301; NCT03197766).[8] Of these, 119 were enrolled in the 111-302 open-label extension study (NCT03424018), in which all participants received daily subcutaneous injections of vosoritide at a dose of 15 µg/kg. HRQoL data were collected in both studies. Race and ethnicity were determined for participating children at enrollment through specific questioning of parents or guardians by the investigators. Race and ethnicity data were not collected for parents or guardians. The current analysis focuses on a data cutoff of February 25, 2023, at which time data collection was complete to year 3 for all participants (barring discontinuation), although for those participants randomized to vosoritide in 111-301 data were complete (barring discontinuation) up to 4 years. Baseline was defined as the assessment on the first day of vosoritide administration (in 111-301 or 302).

A secondary outcome in the 111-302 study was evaluation of change from baseline in HRQoL measured using the Quality of Life of Short Stature Youth (QoLISSY),[13] a multidimensional, participant- and caregiver-reported outcome measure developed to assess HRQoL in children with short stature and suitable for use in children with achondroplasia.[14,15] The Quality of Life of Short Stature Youth (QoLISSY) has a caregiver-report version (from age 4) and self-report version (from age 8) and comprises 3 core domains (physical, social, and emotional), which are summed and averaged to create the total score, and 5 additional domains (coping, belief, treatment, future, and effects on parents) (Supplemental Methods). Raw QoLISSY scores were transformed on a scale of 0 to 100, with higher values representing higher HRQoL. Children and/or their caregivers completed the QoLISSY at baseline and at 6-monthly intervals. Only the caregiver version was administered among all participants at baseline.

Statistical analysis

These analyses are based on on-treatment data (up to 45 days posttreatment discontinuation). Data are presented as mean with standard deviation (SD) or standard error (SE) or as median (25th and 75th percentiles).

Descriptive summary statistics are provided for mean annual change from baseline for each of the domains and for QoLISSY total score for caregiver- and self-reported questionnaires for all children with an assessment at baseline and up to the week 234 (4.5 years). Subgroup analyses for all domains (except treatment, which was not used in this study) were conducted at year 3 in children with <1 SD change in achondroplasia height *z*-score at this time point and in those with ≥1 SD change (whereby an increase of change in achondroplasia height *z*-score indicates an improvement).[16] Similarly, subgroup analyses for participants with a change in upper-to-lower body ratio of <–0.2 (which indicates a greater improvement) and in those with a change of ≥–0.2 at year 3 were conducted for all domains (except treatment, which was not used in this study).

To facilitate the interpretation of the results in the treated population, in which the treatment effect would be confounded with increase in age, models were produced to determine the effect of increase in age using observational data from completed BioMarin (BMN) 111-901 (ClinicalTrials.gov number, NCT01603095)[17] and placebo data from BMN 111-301 (ClinicalTrials.gov number, NCT03197766).[8] Mixed models were fitted for each domain

score, including fixed effects for age and sex and random participant effects. Each model provided an estimate for the change in a score associated with a 1-year increase in age for each domain score in the untreated setting.[8,17]

Statistical analyses were performed with SAS version 9.4 (SAS Institute). ProPhase Labs, Inc were contracted by BioMarin to collect and score the QoLISSY data.

Results

Mean (SD) age at baseline (start of active vosoritide treatment) of the 119 participants receiving vosoritide was 9.2 (2.6), 47.1% were female and 71.4% were white (Table 1). Twenty-nine participants (24.4%) had a baseline Tanner score >I. Mean (SD) height *z*-score—referenced to average stature children using data from Centers for Disease Control and Prevention—was −5.12 (1.09), and upper-to-lower body ratio was 1.98 (0.19) (median 1.99, 25th, 75th percentile 1.88, 2.11). Mean (SD) baseline caregiver-reported QoLISSY total score was 57.46 (19.03) (n = 113), and self-reported total score was 64.50 (18.44) (n = 73) (Supplemental Table 1). At the time of the data cut (February 25, 2023), data collection was complete to year 3 for all participants. Some participants had up to 6 years of follow-up; however, summary tables included only up to 4.5 years of follow-up because the data were too sparse to summarize after this point. Mean (SD) treatment duration was 4 (0.78) years.

QoLISSY total score at year 3 increased relative to baseline, as reported by caregivers (mean change 3.25 [15.48]) and participants (5.43 [17.74]) (Supplemental Table 1), and to a greater extent, in the subgroup (47/113; 42%), with ≥1 SD increase in achondroplasia height *z*-score (6.94 [13.13] for caregiver reported [n = 38] and 8.31 [19.75] for self-reported [n = 27]) (Figure 1, Supplemental Table 2). Among participants with a decrease change in upper-to-lower body ratio of <–0.2, mean changes in total score were 5.58 (13.00) for caregiver-reported score (n = 19) and 4.93 (24.82) for self-reported (n = 7) score (Supplemental Table 3).

The greatest changes over time were observed for QoLISSY physical and social scores (Supplemental Tables 3-9). Specifically, mean changes from baseline for QoLISSY physical score at 3 years were 5.99 (19.41) for caregiver reported and 6.32 (20.15) for self-reported scores (Supplemental Table 4). These changes were driven primarily by participants with a ≥1 SD increase in achondroplasia height *z*-score, in whom the mean changes were 11.36 (19.51) for caregiver-reported (n = 38) and 8.48 (21.83) for self-reported (n = 28) scores (Supplemental Table 5). Summaries are provided for participants with a change in upper-to-lower body ratio of <–0.2, for which mean changes were 12.67 (16.42) for caregiver reported (n = 19) and 10.71 (29.55) for self-reported (n = 7) scores (Supplemental Table 6). Mixed models for the untreated achondroplasia population provided an estimated annual slope [mean (SE)] for the physical domain score of 0.16 (0.55) for caregiver-reported outcomes and 1.45 (0.77) for self-reported outcomes (Supplemental Table 10).

Table 1 Participant characteristics

Characteristic	Vosoritide Treated (n = 119)
Age at first assessment (years)	
Mean (SD)	9.2 (2.6)
Median (Min, Max)	9.22 (5.1, 15.9)
Age subgroup (%)	
≥5 to <8 years	46 (38.7)
≥8 to <11 years	37 (31.1)
≥11 to <15 years	35 (29.4)
≥15 to <18 years	1 (0.8)
Female sex (%)	56 (47.1)
Race (%)	
Asian	21 (17.6)
Black or African American	5 (4.2)
White	85 (71.4)

Race and ethnicity were determined for participating children at enrollment through specific questioning of parents or guardians by the investigators. Race and ethnicity data were not collected for parents or guardians.

QoLISSY, Quality of Life of Short Stature Youth.

Similar changes from baseline were observed for QoLISSY social score (Supplemental Table 7). Mean changes from baseline for QoLISSY social score at 3 years were 2.85 (18.29) for caregiver-reported score and 6.76 (22.64) for self-reported score. These changes were driven primarily by participants with a ≥1 SD increase in achondroplasia height *z*-score, in whom the mean changes were 5.84 (15.45) (caregiver reported; n = 38) and 9.79 (22.80) (self-reported; n = 27) (Supplemental Table 8). Caregiver-reported social scores improved in children with a <–0.2 change in their upper-to-lower body ratio (1.88 [17.24]; n = 19), whereas self-reported social score did not show improvement (−0.77 [35.60]; n = 7) (Supplemental Table 9). Mixed models for the untreated achondroplasia population provided an estimated annual slope [mean (SE)] for the social domain score of 0.16 (0.50) for caregiver-reported outcomes and 1.92 (0.77) for self-reported outcomes (Supplemental Table 10).

The results for the other domain scores did not demonstrate such clear and consistent trends at the 3-year time point (Supplemental Tables 11-25) as shown in the physical scores.

No serious treatment-related adverse effects were reported and vosoritide was well tolerated.[8,11]

Discussion

In children with achondroplasia aged 5 to 15 years enrolled in this open-label extension study, 3 years of daily vosoritide treatment resulted in consistent improvements in

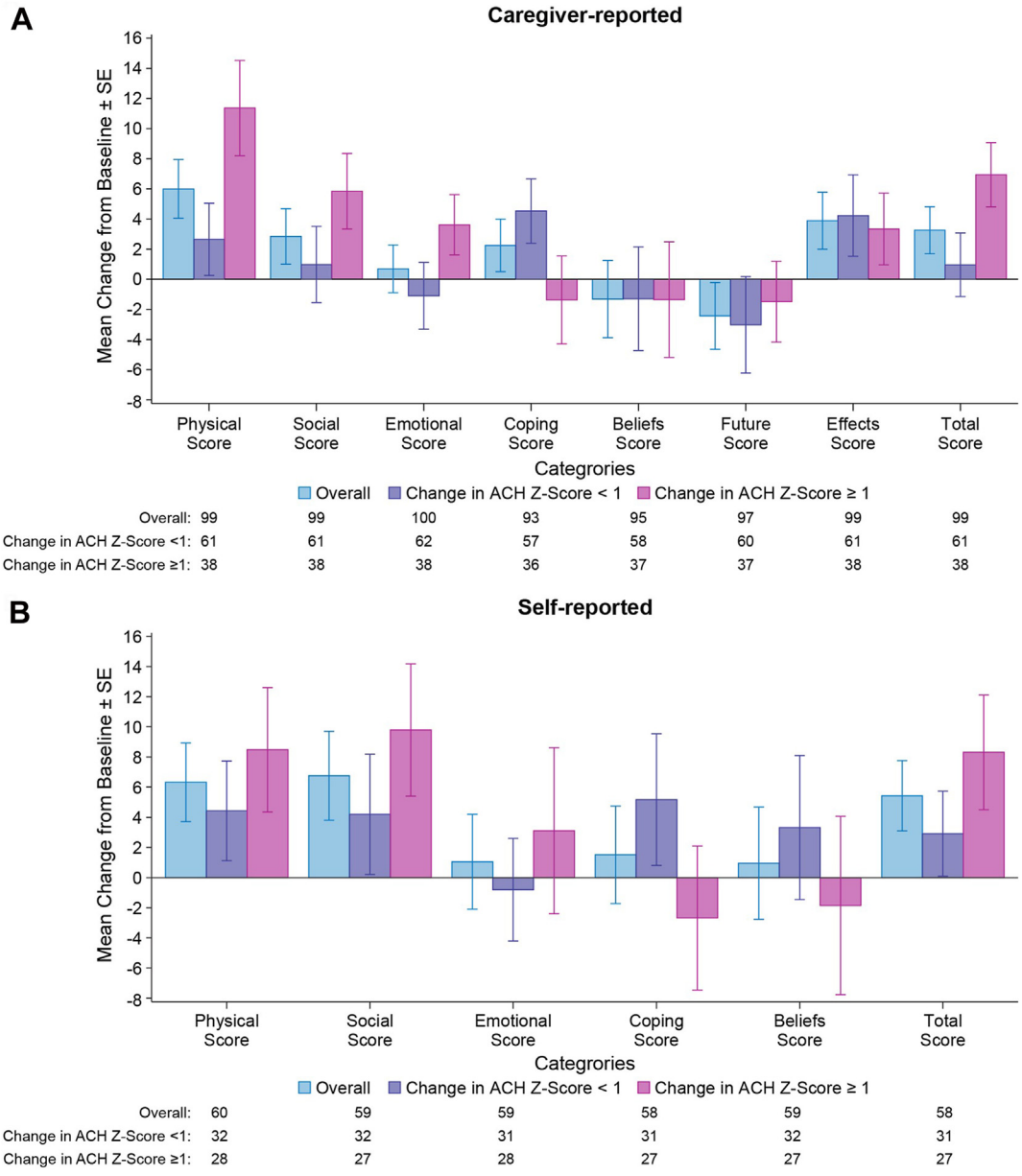

Figure 1 Mean change from baseline in Quality of Life of Short Stature Youth (QoLISSY) at year 3, overall and by change in achondroplasia height *z*-score (treated participants). *Effects on parents.

QoLISSY physical and generally for the social domain scores. This was broadly consistent between self-reported and caregiver-reported scores. Changes in the scores for the caregiver assessments at year 3 for treated participants were greater than the expected changes in the untreated setting, as determined from models produced from a similar untreated achondroplasia population.[8,11] The changes generally correlated with greater increases in height in participants with a ≥1 increase in their achondroplasia height *z*-score. By contrast, for the assessments on the body proportion subgroup, the results were unclear. The sample size was small ($N = 7$), and further follow-up is warranted for these analyses.

These preliminary results suggest a positive treatment effect of vosoritide on HRQoL in children with achondroplasia, as assessed by the QoLISSY physical and social domains. It is unsurprising that changes in the physical domain have emerged because these items assess concepts most closely relate to physical changes observed because of treatment (height gain and improved proportionality). Improvements in social domain scores also reflect the downstream benefits of treatment, although individual and environmental confounders could affect the rate of change over time. Remaining domains (emotional, coping, belief, future, and effects on parents) assess concepts disproportionately affected by confounding factors (eg, psychological and environmental, caregiver perception of their own well-being rather than the child's); therefore, marked improvements in these domains were not expected within the context of a trial as a result of treatment. The data suggest that those who had the largest

improvement in their height deficit experienced the greatest treatment impact to date, as reflected by their (and their caregiver's) QoLISSY physical scores. In the cross-sectional observational Lifetime impact of achondroplasia study in Europe study,[6] height *z*-score was a key factor deemed to be meaningfully associated with HRQoL. Consistent with the findings reported here and in other studies,[18,19] children in the Lifetime impact of achondroplasia study in Europe study scored their own HRQoL higher than their parents across most domains.

The results from this study suggest that there are quality-of-life benefits related to improved height deficit observed in children with achondroplasia treated with vosoritide, which take time to accumulate.[11] These findings support the argument for early initiation of treatment, in line with current global approvals, so that children can achieve the maximum functional and HRQoL benefits from their increased stature and improved proportionality. Early initiation of treatment might also lead to beneficial effects on other aspects of achondroplasia, such as foramen magnum stenosis, a major risk factor for sudden death in children under the age of 5.[5,6] The impact of these changes, clinically and in terms of HRQoL, will be investigated in ongoing studies (NCT03989947 and NCT04554940[20]).

These are preliminary analyses, and further follow-up is required to assess these preliminary trends, particularly for the subgroups for which the sample sizes were small. The study is limited because of the absence of a control group; however, the results from the models help to interpret the results and draw conclusions on the potential effect of vosoritide. It is also acknowledged that, for some analyses, the sample sizes were small, particularly for subanalyses stratified by change in upper-to-lower body ratio. However, these are preliminary analyses to identify potential trends, and we would expect these subgroups to increase in size in large data cuts. In addition, some participants were pubertal at initiation of treatment with vosoritide and therefore less likely to see improvements in height deficit and HRQoL than younger children. In spite of this, we believe the breadth of the analyses described here offer important insights into the impact of vosoritide on different aspects of HRQoL that were previously not available. Another potential limitation of this study is that participants and their caregivers all chose to receive long-term treatment with vosoritide, which could be a source of confirmation bias.

Self-reported data in these analyses were limited to participants aged ≥8 years at the start of treatment. Further work is ongoing to better understand the clinical meaningfulness of these improvements.

Conclusions

The results from this study suggest that 3 years of treatment with vosoritide may translate into improvements in the HRQoL of children with achondroplasia, as shown by increased caregiver-reported and self-reported QoLISSY scores over time. Changes were most marked in physical and social domain scores, with the most pronounced effects reported in participants who had more marked improvements in height deficit and reductions in body proportionality for the physical domain. This study adds to the growing body of evidence that the established positive effects of vosoritide treatment on growth velocity, height, and body proportionality in children with achondroplasia may translate into positive effects on participants' functioning and HRQoL. With the accumulation of longer-term follow-up data, the cumulative effects of vosoritide on other medical, functional, and psychosocial challenges experienced by children with achondroplasia will become clearer.

Data Availability

The deidentified individual participant data that underlie the results reported in this article (including text, tables, figures, and supplemental material) will be made available together with the research protocol and data dictionaries, for noncommercial, academic purposes. Additional supporting documents may be available upon request. Investigators will be able to request access to these data and supporting documents via a website (BioMarin.com) beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of the relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria at www.BioMarin.com to determine if access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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Author Contributions

Conceptualization: R.S., A.H.-L., J.D.; Data Curation: R.S., R.R., A.H.-L., J.D., K.J., E.F.; Formal Analysis: R.R., A.H.-L.; Funding Acquisition: J.D.; Investigation: R.S., M.I., W.R.W., C.A.B., J.E.H.-F., P.H., C.E.P., T.K., P.A., A.L.-G.; Methodology: R.S., A.L., I.S., J.D.; Project Administration: A.L., I.S.; Resources: J.D.; Software: A.H.-L.; Supervision: R.S., A.L., I.S., J.D.; Validation: R.S., A.L., I.S., A.H.-L., J.D.; Visualization: R.S., J.D.; Writing-original draft: R.S., J.D.; Writing-review and editing: R.S., M.I., W.R.W., C.A.B., J.E.H.-F., P.H., C.E.P., T.K., P.A., A.L.-G., R.R., A.L., I.S., A.H.-L., J.D.

Ethics Declaration

This study received ethics approval from the Royal Children's Hospital Melbourne Human Research Ethics Committee (HREC) with reference number HREC/37252. All other institutions represented in this paper received local institutional review board approval before enrollment of the first participant at their institute. Written, informed consent was obtained from all parents/caregivers of enrolled participants as per protocol and institutional review board requirements.

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Conflict of Interest

All authors were investigators in this clinical trial except for Richard Rowell, Andrea Low, Ian Sabir, Alice Huntsman-Labed, and Jonathan Day, who are employees of the funder (BioMarin). Antonio Leiva-Gea has received consulting fees from BioMarin, has participated as a clinical trial investigator for BioMarin and QED Therapeutics, has received speaker fees from BioMarin, MBA, and EAF, and has received travel support from BioMarin and MBA. Carlos A. Bacino has received consulting fees from BioMarin and has participated as clinical trial investigator for Roche, BioMarin and Ascendis. Carlos E. Prada has received consulting fees from BioMarin, Sanofi, and Takeda, has participated as a clinical trial investigator for BioMarin, Sanofi, Hemoshear, and Prevail, and has received speaker payments from Sanofi. Julie E. Hoover-Fong has received consulting fees from BioMarin, Ascendis, QED Therapeutics, Innoskel, and Tyra, has received research grants from Alexion, has participated as a clinical trial investigator for BioMarin, QED Therapeutics, and Pfizer/Therachon, has received speaker fees from Medscape, and has received travel support from BioMarin, QED Therapeutics, and Tyra. Klaus Mohnike has received consulting payments from BioMarin, QED Therapeutics and Novo Nordisk, has participated as a clinical trial investigator for BioMarin, and has received speaker fees and travel support from BioMarin and Novo Nordisk. Lynda E. Polgreen has received consulting fees from BioMarin, Lysogene, and Denali, has participated as a clinical trial investigator for BioMarin, Pfizer, and Takeda, and has received travel support from BioMarin. Melita Irving has received consulting fees from BioMarin, QED Therapeutics/Bridge Bio, Ascendis, Sanofi, and Tyra, has participated as a clinical trial investigator for BioMarin, QED Therapeutics/Bridge Bio, and Ascendis, has received speaker fees from BioMarin, QED Therapeutics/Bridge Bio, Ascendis, Ipsen, and Sandoz, and has received travel support from BioMarin, QED Therapeutics/Bridge Bio, and Ascendis. Paul Harmatz has received consultancy fees from Grace Science, Rallybio, Neurogene, Novel Pharma, and Orchard Therapeutics, has received speaker fees, travel support, and travel grants from BioMarin, has received research funding from Adrenas, Amicus, Ascendis, ASPA, Azafaros, BioMarin, Calcilytics, Denali, Homology, JCR Pharmaceuticals, Orphazyme, QED Therapeutics, RegenXbio, Sangamo, Takeda, Idorsia, Prevail,and Allievex, and has participated as a clinical trial investigator for BioMarin. Ravi Savarirayan has received consulting fees and travel support from BioMarin, QED Therapeutics, and Ascendis, and has participated as a clinical trial investigator for BioMarin, QED Therapeutics, Ascendis, and Sanofi. Takuo Kubota has received speaker payments from BioMarin and Novo Nordisk and research grants from Eli Lilly. William R. Wilcox has received consulting fees from BioMarin and has participated as a clinical trial investigator for BioMarin. All other authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2024.101274) contains supplemental material, which is available to authorized users.

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