Hormone Research in Paediatrics

Research Article

Horm Res Paediatr
DOI: 10.1159/000543743

Received: November 5, 2024
Accepted: January 10, 2025
Published online: January 25, 2025

Real-World Safety and Effectiveness of Vosoritide in Children with Achondroplasia: French Early Access Program

Valérie Cormier-Daire[a] Thomas Edouard[b] Bertrand Isidor[c] Swati Mukherjee[d] Jeanne M. Pimenta[d] Massimiliano Rossi[e] Elise Schaefer[f] Sabine Sigaudy[g] Geneviève Baujat[a]

[a]INSERM UMR 1163, Imagine Institute, Centre of Reference for Constitutional Bone Diseases (MOC), Necker-Enfants malades Hospital, Paris Cité University, Paris, France; [b]Endocrine, Bone Diseases and Genetics Unit, Reference Centre for Rare Diseases of Calcium and Phosphate Metabolism, OSCAR Network, ERN BOND, Children's Hospital, Toulouse University Hospital, INSERM U1301, Toulouse, France; [c]Centre Hospitalier Universitaire de Nantes, Nantes, France; [d]BioMarin (UK) Limited, London, UK; [e]Genetic department, Referral Centre for Constitutional Bone Diseases, Hospices Civils de Lyon, INSERM U1028, CNRS UMR5292, CRNL, GENDEV Team, UCBL1, Lyon, France; [f]Service de génétique médicale, institut de génétique médicale d'Alsace , hopitaux universitaires de Strasbourg, Strasbourg, France; [g]Département de Génétique Médicale, Hôpital Timone Enfant, Marseille, France

Keywords
Achondroplasia · Vosoritide · Early access program · Growth · Safety

Abstract

Introduction: Vosoritide is the first approved treatment for achondroplasia, a rare genetic disorder that results in disproportionate short stature. In clinical trials, vosoritide has shown a positive safety profile and increased height in children with achondroplasia. This article shares the organizational structure, initiation, follow-up protocol, and findings of a vosoritide early access program (EAP) conducted in France. ***Methods:*** Participants aged ≥5 years with achondroplasia and open epiphyses were eligible for enrollment in the EAP, conducted by six centers within the French national rare disease reference center for constitutional bone diseases network, from 24 June 2021 to 13 December 2022. Treatment consisted of once-daily subcutaneous vosoritide 15 µg/kg. Safety and effectiveness (height, height *Z*-score, annualized growth velocity [AGV]) data over a 12-month follow-up period were collected. ***Results:*** Among 62 enrolled participants, 57 started treatment with vosoritide within the EAP period with 38 completing at least 6 months and 22 at least 12 months of treatment. After 12 months of treatment, participants achieved a mean AGV of 6.0 cm/year, absolute gain in height of 6.2 cm, and increase in height *Z*-score referenced to the average stature population of 0.38. All adverse events were mild (mainly injection site reactions) and there were no discontinuations related to vosoritide treatment. ***Conclusions:*** In this first use of vosoritide in a real-world setting, vosoritide had a positive benefit-risk ratio similar to that observed in vosoritide clinical trials. The French EAP provides a model that may be adapted and adopted for use in other countries.

karger@karger.com
www.karger.com/hrp

Correspondence to:
Valérie Cormier-Daire, valerie.cormier-daire@inserm.fr

Introduction

Achondroplasia is a rare genetic autosomal dominant condition with an estimated birth prevalence of 4.6 per 100,000 worldwide and 3.9–6.6 per 100,000 in France [1]. The disease is caused by a pathogenic gain-of-function variant in the fibroblast growth factor receptor 3 (*FGFR3*) gene and at least 80% of cases are spontaneous (de novo) [2]; this leads to constitutive activation of the downstream inhibitory signaling pathway in chondrocytes, overwhelming the counteracting signaling from the endogenous natriuretic peptide receptor B (NPR-B) pathway, and resulting in impaired endochondral bone growth [3, 4]. Growth of the long bones is particularly affected, resulting in disproportionate short stature, characteristic of achondroplasia [5]. Abnormal linear bone growth significantly contributes to the medical, functional, and psychosocial challenges faced by people with achondroplasia throughout their lifespan [6, 7]. In addition to these growth anomalies, individuals may present with a number of other defects, including bone deformity (e.g., spinal deformity, *genu varum*), ear, nose, and throat (ENT) problems (e.g., recurrent ear infections and sleep apnea), and neurological complications (e.g., foramen magnum stenosis, narrow lumbar canal).

Vosoritide, the first-targeted treatment for achondroplasia, is a recombinant C-type natriuretic peptide (CNP) analog that binds to NPR-B, counteracts FGFR3 downstream signaling and acts as a positive regulator of endochondral bone growth as it promotes chondrocyte proliferation and differentiation. Favorable findings from studies of vosoritide in achondroplasia mouse models [8, 9], and a phase 2, open-label, dose-finding study in children with achondroplasia [10] provided support for a phase 3, randomized, double-blind, placebo-controlled, multicenter trial and open-label extension study that evaluated the safety and efficacy of once-daily subcutaneous 15 μg/kg vosoritide in children with achondroplasia aged 5 to <18 years [11, 12]. During the 52-week phase 3 trial, vosoritide was well tolerated with mainly mild adverse events (AEs) and no serious AEs attributable to treatment or on bone maturation [11]; no treatment-limiting AEs emerged after 4 years of continuous treatment in the extension study [13]. After 1 year of vosoritide treatment, mean annualized growth velocity (AGV) in treated children was 5.61 cm/year, representing a statistically significant increase of 1.57 cm/year compared with placebo ($p < 0.0001$) [11], which was maintained after 4 years [13]. A phase 2, randomized, double-blind, placebo-controlled study of vosoritide in 75 infants and young children (aged 3 months to <5 years) with achondroplasia found that vosoritide was well tolerated and yielded a gain in least-squares mean height *Z*-score from baseline to 52 weeks of 0.25 (95% CI: −0.02 to 0.53) relative to placebo [14].

The European Medicines Agency (EMA) designated vosoritide an orphan drug in 2013, issued marketing approval (MA) on 26 August 2021 for its use for the treatment of achondroplasia in patients aged ≥2 years until closure of epiphyses and expanded the indication to treat children with achondroplasia aged ≥4 months on 14 September 2023 [15].

France was the first country globally that treated patients with vosoritide outside a study since approval of an early access program (EAP) by Health Authorities in June 2021 as a pre-marketing authorization EAP (formerly called Cohort Temporary Authorization for Use or cATU) followed by a post-marketing authorization or AP2 in December 2021. In France, EAP prioritized vosoritide treatment to patients aged ≥5 years and ran until commercialization started on 13 December 2022. This manuscript aimed to share the organizational model and follow-up protocol implemented in France for individuals with achondroplasia receiving early access to vosoritide treatment and describe the efficacy and safety of vosoritide in a real-world setting.

Methods

French EAP Implementation, Common Preparation, and Organization at a National Level

The vosoritide EAP was carried out through a consortium of achondroplasia experts within the French national rare disease reference center (CRMR) for constitutional bone diseases (MOC) network. The MOC network consists of a coordinating center (Necker-Enfants Malades Hospital) and 22 rare disease competence centers (CCMRs) which are intended to provide care and monitoring of patients as close as possible to their homes. The vosoritide EAP was conducted by the coordinating center and five CCMRs in France (University Hospitals of Lyon, Marseille, Nantes, Strasbourg, and Toulouse). The consortium was established in January 2021 and met every 3 months to prepare the organization of the EAP, including discussing enrollment criteria, defining baseline and follow-up assessments and visits, and the organization of the EAP; after enrollment began, the consortium continued to meet periodically to share their experiences and follow-up.

Medical experts at the six centers reviewed each case of a child with achondroplasia to confirm eligibility for

treatment initiation with vosoritide. Children with genetically confirmed achondroplasia aged 5 years or older with open epiphyses were eligible for enrollment in the French EAP from 24 June 2021 to 13 December 2022. Initially, older participants (age >7 years) were prioritized for enrollment. Prior to the initiation of treatment, each participant's parent or legal representative/proxy was informed by the prescriber about the medicinal product, the exceptional access procedure, and reporting of adverse effects. Written informed consent was obtained from the participant's parent or legal representative/proxy. Enrollment also required sufficient motivation from the participant and family, commitment to the treatment regimen and follow-up visits, and residing within a reasonable distance from a center providing treatment.

Prior to initiating vosoritide, the treating center checked the results of recent tests (e.g., ENT examination, sleep study, X-rays including bone age, spinal cord magnetic resonance imaging) and conducted teleconsultation visits with the child and parents to assess readiness for treatment, provide caregiver information and training, and ensure that support from healthcare professionals was readily available. Concurrently, participating centers prepared by establishing a well-connected multidisciplinary team, procedures for performing routine follow-up visits, and the logistics and storage arrangements for vosoritide by pharmacies and families.

Treatment of once-daily subcutaneous vosoritide at a dose of 15 μg/kg was initiated in a hospital setting (day hospital or specialized consultation) and subsequently self-administered at home by parents/caregivers. Initially, during the first month of treatment, the parents were offered home nursing visits to ensure they were educated on subcutaneous injection procedures until they were completely independent.

Communication with Participants and Families

Participants were monitored by the achondroplasia referring medical expert (clinical geneticist or pediatric endocrinologist within the CRMR MOC network) and clinical team at each center. Parents were given a booklet that included instructions for daily parental monitoring of AEs (e.g., documenting symptoms and the associated vosoritide lot number), a list of medical contacts, a certificate of education from the hospital nurse attesting and confirming that the caregiver received the required education, and a letter for the general practitioner and multidisciplinary team informing them that the participant was currently being treated with vosoritide which may require particular vigilance. The follow-up of participants enrolled in the EAP integrated conventional follow-up according to the guidelines of good practice established by the CRMR MOC network over 10 years with more specific follow-up linked to the new treatment.

Motivation and adherence, which are affected by the participant, parent, and caregiver/family context, were assessed and discussed at every visit. Ongoing discussions between the clinical team and participants/parents/caregivers managed expectations by acknowledging that there is individual variability in response to vosoritide; clear stopping criteria based on clinical trial experience (fused epiphysis and AGV <1.5 cm); uncertainty regarding benefits of treatment beyond an increase in height at that time; evidence of good tolerability and safety but a degree of uncertainty regarding long-term adverse effects. Specific strategies to help motivate participants/families to adhere with treatment and maintain good adherence included initiating treatment with several children in tandem on the same day at the hospital; conducting therapeutic education workshops for older participants; communicating with family associations; showing measurable benefit on growth parameters; and providing additional support from nurses or other healthcare personnel at participants homes in the early days of home treatment.

Data Collection, Monitoring, and Follow-Up

Participants were followed up via clinic visits at months 1, 3, and 6 and at 6-monthly intervals thereafter. Month 1 visit was a virtual visit. Table 1 summarizes the schedule of data collection, monitoring, and follow-up. Baseline characteristics and data on treatment compliance were collected for all enrolled participants. Safety and effectiveness (height, height *Z*-score, AGV) data over a 12-month follow-up period were collected for participants enrolled during the EAP, including assessment of any missed doses. Furthermore, additional height data were collected post hoc at 18-month follow-up. Height *Z*-scores referenced to the average stature population were derived from data from the Centers for Disease Control and Prevention (CDC) [16], hereafter referred to as CDC height *Z*-scores. Height *Z*-scores referenced to the untreated achondroplasia population were derived from a natural history study in that population [17], hereafter referred to as achondroplasia (ACH) height *Z*-scores.

All treated participants were included in safety analyses. During the cATU, all AEs were reported by physicians, inputted into the study database, and coded using the MedDRA system organ class and preferred term.

Table 1. Data collection schedule

	Treatment access request	Day 0 visit (start of treatment)	Month 1	Month 3	Month 6, then every 6 months	End of follow-up
Documentation of achondroplasia[a]	X					
Demographics	X		X		X	
Physical examination	X			X (annual examination)		
Anthropometric and morphological measurements		X		X (annual examination)		
X-ray of the left hand and/or knee[b]	X			X (annual examination)		
Tanner stage		X[c]		X	X	X
Vosoritide treatment[d]		X	X	X	X	X
Adverse event data[e]			X	X	X	X

[a]Documentation included the participant's age at diagnosis, the place, date and author of the diagnosis, and confirmation of genetic testing. [b]From 7 years of age. Only if this examination was performed as part of recommended treatment. [c]Prepubertal stage without closure of the epiphyseal cartilage in participants aged 7–12 years. [d]Including dose monitoring. [e]All safety events were reported to vosoritide sponsor within 24 h of identification.

During the AP2, study centers reported de-identified AEs directly to BioMarin as part of routine vosoritide pharmacovigilance. Hence, we summarize the frequency of all AEs reported during the entire EAP (ATUc and AP2) but do not report AEs at the patient level. Data analyses were descriptive and included the mean, standard deviation (SD), and range for continuous variables and the sample size (*N*), frequency, and percentage for categorical variables.

Results

Baseline Characteristics

A total of 62 participants were enrolled with 57 starting treatment within EAP period and 5 starting vosoritide during commercialization (i.e., after 13 December 2022). Of the 57 participants who initiated vosoritide during EAP, 23 (40.4%) began treatment during cATU and 34 (59.6%) during AP2. About half of participants (29/57; 50.9%) were male and the mean (range) age at treatment initiation was 8.6 (5–13) years. Baseline characteristics (Table 2) of the overall sample and subgroup that reached 12 months of treatment during EAP (n = 22, 38.6%) were similar except that, as expected, the subgroup with the longest follow-up were slightly older at vosoritide initiation as enrollment of older participants was prioritized early in the EAP (9.6 years [range, 7.7–11.5 years]).

Treatment Exposure and Adherence

The mean (SD) exposure to treatment was 277 (146) days (range, 32–443 days) for all participants who initiated vosoritide (n = 57) during the EAP period. Exposure for the subgroups that completed ≥6 months (n = 38) and ≥12 months (n = 22) of treatment are shown in Table 3.

No patient discontinued treatment. Over 12 months, 14 participants missed a total of 43 doses with 20 missed doses occurring between Month 0 and Month 6 and 23 missed doses between Month 6 and Month 12. One patient was responsible for 16 of the 23 missed doses at Month 12.

Growth Outcomes

Participants with ≥6 months of Treatment

By the end of EAP, a total of 38 participants (21 males, 17 females) completed at least 6 months of treatment; 36 participants had data on height *Z*-score and AGV available at Month 6. The mean (SD) change from

Table 2. Baseline demographics and characteristics

	Overall treated (*n* = 57)	Treated for 12 months (*n* = 22)
Sex, *n* (%)		
Male	29 (50.9)	10 (45.5)
Female	28 (49.1)	12 (54.5)
Age at first dose, years		
Mean (SD)	8.6 (2.0)	9.5 (1.9)
Range	5–13	7–13
Height *Z*-score, mean (SD)		
Male	−5.2 (1.11)	−5.1 (1.11)
Female	−5.0 (0.96)	−4.9 (0.75)
Overall	−5.1 (1.04)	−5.0 (0.91)
Tanner stage, *n* (%)		
I	31 (54.4)	13 (59.1)
II	2 (3.5)	0 (0.0)
Missing	24 (42.1)	9 (40.9)

SD, standard deviation.

Table 3. Vosoritide exposure

Exposure to vosoritide, days	Overall (*n* = 57)	≥6 months (*n* = 38)	≥12 months (*n* = 22)
Cumulative exposure	15,817	15,203	9,802
Mean (SD)	277.5 (146.24)	400.1 (81.20)	445.5 (15.90)
Min, Max	32, 443	226, 463	421, 463

SD, standard deviation.

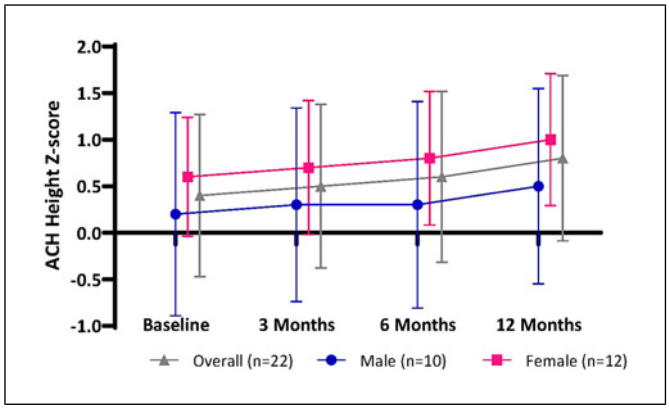

Fig. 1. Height *Z*-scores change from baseline for participants treated for 12 months referenced to untreated achondroplasia (ACH) population. Error bars represent standard deviation.

baseline to Month 6 in CDC height *Z*-score and ACH height *Z*-score, respectively, was 0.20 (0.20) and 0.17 (0.16) in males, 0.27 (0.27) and 0.24 (0.23) in females, and 0.23 (0.23) and 0.20 (0.19) overall. Height increased from baseline to Month 6 by a mean (SD) of 3.0 (0.89) cm in males, 3.4 (1.46) cm in females, and 3.2 (1.19) cm overall. After 6 months of treatment, the mean (SD) AGV was 5.9 (1.65) cm/year in males, 6.5 (2.64) cm/year in females, and 6.2 (2.13) cm/year overall.

Participants with ≥12 Months of Treatment

A total of 22 participants (10 males, 12 females) completed at least 12 months of treatment by the end of the EAP. The mean (SD) increase in CDC height *Z*-score from baseline to Month 12 was 0.38 (0.33) overall with both sexes showing similar improvement (males: 0.33 [0.28], females: 0.42 [0.37]). Figure 1 shows the mean ACH height *Z*-scores over time by sex. At Month 12, mean (SD) ACH height *Z*-scores had increased from baseline by 0.30 (0.30) in males, 0.46 (0.21) in females, and 0.39 (0.26) overall. Figure 2 shows absolute height over time by sex. From baseline to month 12, absolute height increased by a mean (SD) of 5.8 (1.71) cm, 6.5 (1.28) cm, and 6.2 (1.50) cm, respectively, in males,

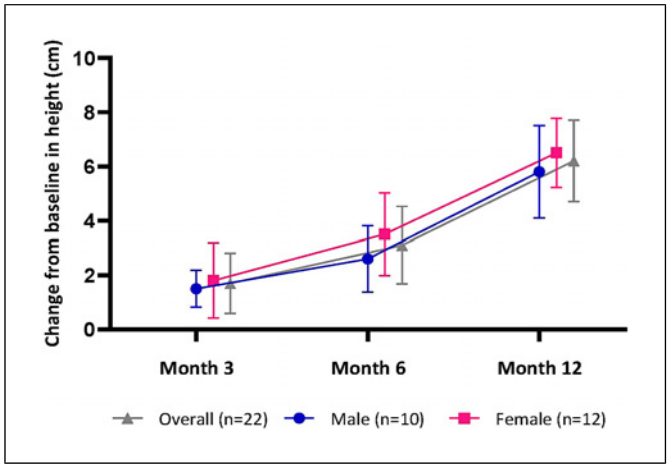

Fig. 2. Change in baseline in height for participants treated for 12 months. Error bars represent standard deviation.

Table 4. Number of adverse events

System organ class/preferred term	Events, *n*
All adverse events	21
Injection site reaction	14
Injection site erythema	4
Injection site papule	3
Injection site rash	4
Injection site pain	2
Injection site swelling	1
Gastrointestinal disorders	3
Vomiting	3
Skin and subcutaneous tissue disorders	2
Contact dermatitis	1
Erythema	1
Nervous system disorders	2
Headache	1
Presyncope	1

females, and overall. After 12 months of treatment, the mean (SD) AGV was 5.7 (1.72) cm/year in males, 6.3 (1.17) cm/year in females, and 6.0 (1.44) cm/year overall.

After the EAP had ended, additional height data at 18 months were available for 17 of 22 participants, collected post hoc during commercial routine treatment. The 17 participants (5 male, 12 female) with 18 months of follow-up height data had a mean (range) age of 9.6 (7.7–11.5) years at initiation of vosoritide. The mean (SD) exposure to treatment was 583 (61) days (range, 390–665 days). From baseline to month 18, height increased by a mean (SD) of 7.5 (1.19) cm, 9.3 (1.33) cm, and 8.8 (1.51) cm, respectively, in males, females, and overall. The mean (SD) increase in CDC height *Z*-score from baseline to Month 18 was 0.40 (0.30) for males, 0.45 (0.63) for females, and 0.44 (0.55) overall. At Month 18, mean (SD) ACH height Z-scores had increased from baseline by 0.35 (0.28) in males, 0.64 (0.23) in females, and 0.56 (0.27) overall. After 18 months of treatment, the mean (SD) AGV was 5.4 (1.31) cm/year in males, 6.0 (1.00) cm/year in females, and 5.9 (1.10) cm/year overall.

Safety

Among 57 treated participants, a total of 21 AEs were reported. All AEs were mild, and the majority were injection site reactions (Table 4). There were no serious AEs or discontinuations related to vosoritide treatment.

Discussion

Results from the French EAP, during which vosoritide was administered under real-world conditions to children with achondroplasia aged 5 years or more and open epiphyses, confirm the positive benefit-risk ratio of vosoritide established in clinical trials [10–12, 14, 18, 19]. A total of 57 participants started vosoritide within the EAP period, at a mean (range) age of 8.6 (5–13) years. After 6 months of vosoritide treatment, 36 participants had anthropometric follow-up measurements showing a mean increase of 3.2 cm in height and 0.23 in CDC height Z-score. The 22 participants who reached 12 months of treatment during the EAP period achieved a mean increase of 6.2 cm in height and 0.38 in CDC height *Z*-score, with a mean AGV of 6.0 cm/year. The descriptive post hoc 18-month outcomes available for 17 participants were in line with earlier findings.

These real-world French EAP outcomes are consistent with the results of a phase 3, randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of vosoritide in children with achondroplasia aged 5 to <18 years [11]. In the phase 3 trial, children treated for 12 months with vosoritide obtained a mean (SD) increase from baseline of 0.24 (0.32) in CDC height *Z*-score versus 0.00 (0.28) for placebo reaching a mean (SD) AGV of 5.61 (1.05) cm/year [11]. The ongoing open-label phase 3 extension study (study 111–302) showed that growth is sustained over 4 years, with no evidence of tachyphylaxis [13]. A phase 2 clinical trial with vosoritide in children aged 3 months to <5 years showed encouraging results: after 12 months of treatment with vosoritide, there was a 0.25 gain in least-squares mean height *Z*-score change from baseline in the

vosoritide group relative to the placebo group (206 study) [14].

Safety findings of mild and transient drug-related AEs (mostly injection site reactions) during the EAP are also consistent with clinical trial data [10, 11, 14], and no new safety signals were observed. As has been reported in vosoritide clinical trials [10–14, 20], participants enrolled in the EAP demonstrated good adherence and none discontinued treatment, improving patients' ability to carry out everyday activities such as self-care. Furthermore, patients and caregivers report consistent improvements from baseline in health-related quality of life, particularly in domains focused on physical function [21]. Additionally, trends toward improvement in foramen magnum area, craniofacial growth, and sinus volume were also demonstrated in infants <6 months of age [14].

American (2005; 2016; 2020) [22–25], Australian (2023) [26], European (2021) [27], Japanese (2020) [28], Spanish (2022) [29], and international (2021; 2022) [30, 31] guidelines for the management of achondroplasia have been published. Early real-world experience with vosoritide, including the French EAP, may help support practical guidance for the optimal use of vosoritide [32]. A recent article provided comprehensive considerations for the use of vosoritide in clinical practice based on the early experience of international experts who collectively manage more than 220 patients receiving vosoritide, including suggestions for site preparation, preparation for treatment initiation, support for patients and families, clinical assessments, treatment response, and follow-up [32]. In this article, the monitoring and follow-up protocol used in the French EAP was cited as an example that could be adopted by other settings with revisions based on patient age and the availability of healthcare resources [32]. We also propose that the CRMR MOC infrastructure used to deliver the French vosoritide EAP offers an organizational model of rare disease management that may be adopted by other countries.

Long-term data on the effectiveness and safety of vosoritide are needed to fully understand the risk-benefit profile of this treatment under real-world conditions. Participants who initiated vosoritide during the French EAP are being invited to enroll in a post-authorization safety study (111–603; EUPAS47514; ACORN) to evaluate the long-term safety of vosoritide. ACORN is a European multicenter, non-interventional, retrospective, and prospective cohort study that will assess the impact of vosoritide on adverse bone-related safety events, anthropomorphic measures, and achondroplasia-related complications over 10 years [33]. Data from CrecsNet (www.crescnet.org), a German prospective patient registry that has incorporated an achondroplasia diagnosis-specific data set, show that 85 patients treated with vosoritide attained an increase of 0.45 in ACH height *Z*-score during the first year of treatment [34]. As prospective registries will be an important source of long-term data for vosoritide and emerging therapeutic approaches for achondroplasia, capturing data in a standardized manner is essential to allow pooling of datasets from different centers, regions, and countries [35].

Conclusion

Outcomes reported in this first worldwide use of vosoritide in real-world settings indicate that vosoritide has a positive benefit-risk profile consistent with clinical trial data. The French rare disease management organizational structure and EAP initiation and follow-up protocol provide models that may be adapted and adopted for use in other countries. The specificity of the French network of MOC centers ensured the organization and implementation of a common process on early access to vosoritide treatment to avoid loss of opportunity for children with achondroplasia in France, in an equitable manner at national level, optimizing compliance and follow-up. Real-world studies designed to evaluate the long-term effectiveness and safety of vosoritide are underway and will enable a more complete picture of vosoritide's impact on patients with achondroplasia.

Acknowledgments

The authors would like to thank the participants, their families, and staff of each center that contributed to the generation of these data; in particular, we thank Dr. Soo Kim at Necker Hospital for her commitment during recruitment and patient care. We also thank the following employees of BioMarin: Erin Goodman and Anne Dee for statistical analyses, Shelda Cohen and Michelle Ford for operationalizing the study, and Valeria Marcos and Sara Dosenovic for manuscript review.

Statement of Ethics

The EAP was approved by HAS France (Haute Autorité de Santé – VOXZOGO (has-sante.fr) and carried out under the conditions authorized by the European General Data Protection Regulation (GDPR) and the amended law of 6 January 1978 known as the "Informatique et Libertés" law, in compliance with CNIL French formalities on the French Public Health Code

concerning early access to medicines (Référentiel "accès précoce" | CNIL).

Prior to the initiation of treatment, each participant's parent or legal representative/proxy was informed by the prescriber about the medicinal product, the exceptional access procedure, and reporting of adverse effects. Written informed consent was obtained from the participant's parent or legal representative/proxy.

Conflict of Interest Statement

V.C.-D.: consultant/speaker honoraria from IPSEN Pharma, BioMarin, and Mereo BioPharma. T.E. and B.I.: consultant/speaker honoraria from BioMarin. M.R.: consultant/speaker honoraria from BioMarin. E.S.: hospitality from Abbott Medical France SAS, speaker honoraria and hospitality from Sanofi Aventis France, and speaker honoraria from BioMarin. S.S.: consultant/speaker honoraria and hospitality from Sanofi Aventis France and BioMarin. G.B.: consultant/speaker honoraria from IPSEN Pharma, Inozyme Pharma Inc., and Exafield and consultant/speaker honoraria from BioMarin. S.M. and J.M.P. are full-time employees of BioMarin and own stocks in the company.

Funding Sources

The EAP protocol was developed by BioMarin Pharmaceutical Inc. in collaboration with MOC participating centers; it received the HAS authorization. Manuscript writing support was financed by BioMarin and provided by Amy Bronstone, PhD (AB Medical Communications Inc.). Except for S.M., J.M.P., and L.L., who are formal employees at BioMarin, authors received no financial support for the research, authorship, and/or publication of this article.

Author Contributions

V.C.-D., T.E., B.I., M.R., E.S., S.S., and G.B. were investigators in the E.A.P., S.M., and J.M.P. are employees of the funder (BioMarin Pharmaceutical Inc.). V.C.-D., T.E., B.I., S.M., J.M.P., M.R., E.S., S.S., and G.B. participated in the interpretation of data and article development.

Data Availability Statement

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for non-commercial, academic purposes. Additional supporting documents may be available upon request to the corresponding author. Investigators will be able to request access to these data and supporting documents via www.BioMarin.com beginning 6 months and ending 2 years after publication. An official report of EAP is already publicly available at the HAS site: https://www.has-sante.fr/jcms/p_3385532/en/voxzogo-0-4-0-56-1-2-mg-vosoritide-achondroplasie#ancreDocAss.

References

1 Foreman PK, van Kessel F, van Hoorn R, van den Bosch J, Shediac R, Landis S. Birth prevalence of achondroplasia: a systematic literature review and meta-analysis. Am J Med Genet. 2020;182(10):2297–316. https://doi.org/10.1002/ajmg.a.61787
2 Shiang R, Thompson LM, Zhu YZ, Church DM, Fielder TJ, Bocian M, et al. Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. Cell. 1994;78(2):335–42. https://doi.org/10.1016/0092-8674(94)90302-6
3 Vasques GA, Arnhold IJ, Jorge AA. Role of the natriuretic peptide system in normal growth and growth disorders. Horm Res Paediatr. 2014;82(4):222–9. https://doi.org/10.1159/000365049
4 Pauli RM. Achondroplasia: a comprehensive clinical review. Orphanet J Rare Dis. 2019;14(1):1. https://doi.org/10.1186/s13023-018-0972-6
5 Ornitz DM, Legeai-Mallet L. Achondroplasia: development, pathogenesis, and therapy. Dev Dyn. 2017;246(4):291–309. https://doi.org/10.1002/dvdy.24479
6 Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet. 2007;370(9582):162–72. https://doi.org/10.1016/S0140-6736(07)61090-3
7 Hoover-Fong J, Cheung MS, Fano V, Hagenas L, Hecht JT, Ireland P, et al. Lifetime impact of achondroplasia: current evidence and perspectives on the natural history. Bone. 2021;146:115872. https://doi.org/10.1016/j.bone.2021.115872
8 Yasoda A, Komatsu Y, Chusho H, Miyazawa T, Ozasa A, Miura M, et al. Overexpression of CNP in chondrocytes rescues achondroplasia through a MAPK-dependent pathway. Nat Med. 2004;10(1):80–6. https://doi.org/10.1038/nm971
9 Lorget F, Kaci N, Peng J, Benoist-Lasselin C, Mugniery E, Oppeneer T, et al. Evaluation of the therapeutic potential of a CNP analog in a Fgfr3 mouse model recapitulating achondroplasia. Am J Hum Genet. 2012;91(6):1108–14. https://doi.org/10.1016/j.ajhg.2012.10.014
10 Savarirayan R, Irving M, Bacino CA, Bostwick B, Charrow J, Cormier-Daire V, et al. C-Type natriuretic peptide analogue therapy in children with achondroplasia. N Engl J Med. 2019;381(1):25–35. https://doi.org/10.1056/NEJMoa1813446
11 Savarirayan R, Tofts L, Irving M, Wilcox W, Bacino CA, Hoover-Fong J, et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. Lancet. 2020;396(10252):684–92. https://doi.org/10.1016/S0140-6736(20)31541-5
12 Savarirayan R, Tofts L, Irving M, Wilcox WR, Bacino CA, Hoover-Fong J, et al. Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study. Genet Med. 2021;23(12):2443–7. https://doi.org/10.1038/s41436-021-01287-7
13 Savarirayan R, Tofts L, Irving M, Wilcox WR, Bacino CA, Hoover-Fong JE, et al. Persistent growth-promoting effects of vosoritide in children with achondroplasia for up to 4 years: update from phase 3 extension study. JBMR Plus. 2024;8(Suppl 2):ii176.
14 Savarirayan R, Wilcox WR, Harmatz P, Phillips J 3rd, Polgreen LE, Tofts L, et al. Vosoritide therapy in children with achondroplasia aged 3-59 months: a multinational, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Child Adolesc Health. 2024;8(1):40–50. https://doi.org/10.1016/S2352-4642(23)00265-1

15 European Medicines Agency. Voxzogo. Amsterdam, The Netherlands: European Medicines Agency; 2024.
16 Centers for Disease Control and Prevention NCfHS. CDC growth charts. United States.
17 Hoover-Fong JE, Schulze KJ, Alade AY, Bober MB, Gough E, Hashmi SS, et al. Growth in achondroplasia including stature, weight, weight-for-height and head circumference from CLARITY: achondroplasia natural history study-a multi-center retrospective cohort study of achondroplasia in the US. Orphanet J Rare Dis. 2021;16(1):522. https://doi.org/10.1186/s13023-021-02141-4
18 Hoover-Fong J, Irving M, Bacino C, Charrow J, Polgreen L, Cormier-Daire V, et al. Vosoritide for children with achondroplasia: a 60-month update from an ongoing phase 2 clinical trial. Mol Genet Metab. 2021;132:S101. https://doi.org/10.1016/s1096-7192(21)00236-5
19 Hoover-Fong J, Savarirayan R, Tofts L, Irving M, Wilcox W, Bacino C, et al. P193: persistent growth-promoting effects of vosoritide in children with achondroplasia for up to 3.5 years: update from phase 3 extension study. GIM Open. 2023;1(1):100222. https://doi.org/10.1016/j.gimo.2023.100222
20 Savarirayan R, Tofts L, Irving M, Wilcox W, Bacino C, Hoover-Fong J, et al. P139: persistent growth-promoting effects of vosoritide in children with achondroplasia for up to 4 years: update from phase 3 extension study. GIM Open. 2024;2:101036. https://doi.org/10.1016/j.gimo.2024.101036
21 Savarirayan R, Tofts L, Irving M, Wilcox W, Bacino C, Hoover-Fong J, et al. P141: persistent growth-promoting effects of vosoritide in children with achondroplasia is accompanied by improvement in physical aspects of quality of life. GIM Open. 2024;2(Suppl 1):101038. https://doi.org/10.1016/j.gimo.2024.101038
22 Trotter TL, Hall JG; American Academy of Pediatrics Committee on Genetics. Health supervision for children with achondroplasia. Pediatrics. 2005;116(3):771–83. https://doi.org/10.1542/peds.2005-1440
23 White KK, Bompadre V, Goldberg MJ, Bober MB, Campbell JW, Cho TJ, et al. Best practices in the evaluation and treatment of foramen magnum stenosis in achondroplasia during infancy. Am J Med Genet. 2016;170a(1):42–51. https://doi.org/10.1002/ajmg.a.37394
24 Hoover-Fong J, Scott CI, Jones MC; COMMITTEE ON GENETICS. Health supervision for people with achondroplasia. Pediatrics. 2020;145(6):e20201010. https://doi.org/10.1542/peds.2020-1010
25 White KK, Bober MB, Cho TJ, Goldberg MJ, Hoover-Fong J, Irving M, et al. Best practice guidelines for management of spinal disorders in skeletal dysplasia. Orphanet J Rare Dis. 2020;15(1):161. https://doi.org/10.1186/s13023-020-01415-7
26 Tofts LJ, Armstrong JA, Broley S, Carroll T, Ireland PJ, Koo M, et al. Australian guidelines for the management of children with achondroplasia. J Paediatr Child Health. 2023;59(2):229–41. https://doi.org/10.1111/jpc.16290
27 Cormier-Daire V, AlSayed M, Ben-Omran T, de Sousa SB, Boero S, Fredwall SO, et al. The first European consensus on principles of management for achondroplasia. Orphanet J Rare Dis. 2021;16(1):333. https://doi.org/10.1186/s13023-021-01971-6
28 Kubota T, Adachi M, Kitaoka T, Hasegawa K, Ohata Y, Fujiwara M, et al. Clinical practice guidelines for achondroplasia. Clin Pediatr Endocrinol. 2020;29(1):25–42. https://doi.org/10.1297/cpe.29.25
29 Leiva-Gea A, Martos Lirio MF, Barreda Bonis AC, Marín Del Barrio S, Heath KE, Marín Reina P, et al. Achondroplasia: update on diagnosis, follow-up and treatment. An Pediatr. 2022;97(6):423.e1–1. https://doi.org/10.1016/j.anpede.2022.10.004
30 Savarirayan R, Tunkel DE, Sterni LM, Bober MB, Cho TJ, Goldberg MJ, et al. Best practice guidelines in managing the craniofacial aspects of skeletal dysplasia. Orphanet J Rare Dis. 2021;16(1):31. https://doi.org/10.1186/s13023-021-01678-8
31 Savarirayan R, Ireland P, Irving M, Thompson D, Alves I, Baratela WAR, et al. International Consensus Statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia. Nat Rev Endocrinol. 2022;18(3):173–89. https://doi.org/10.1038/s41574-021-00595-x
32 Semler O, Cormier-Daire V, Lausch E, Bober MB, Carroll R, Sousa SB, et al. Vosoritide therapy in children with achondroplasia: early experience and practical considerations for clinical practice. Adv Ther. 2024;41(1):198–214. https://doi.org/10.1007/s12325-023-02705-9
33 Pimenta J, Cohen S, Mukherjee S, Fettes F, Jayaram K, Lausch E. P338: objectives and design of the Acorn Study: a non-interventional study evaluating long-term safety in achondroplasia patients treated with vosoritide. GIM Open. 2023;1:100366. https://doi.org/10.1016/j.gimo.2023.100366
34 Kunkel P, Al Halak M, Bechthold-Dalla Pozza S, Grasemann C, Keller A, Muschol N, et al. Multidisciplinary approach in achondroplasia: real world experience after drug approval of vosoritide. In: Poster presented at the 2023 ESPE European society for paediatric endocrinology. The Hague, Netherlands. 2023.
35 Alanay Y, Mohnike K, Nilsson O, Alves I, AlSayed M, Appelman-Dijkstra NM, et al. Real-world evidence in achondroplasia: considerations for a standardized data set. Orphanet J Rare Dis. 2023;18(1):166. https://doi.org/10.1186/s13023-023-02755-w