For children with achondroplasia[1]

Eve, 3 years old, started VOXZOGO at 16 months as part of a clinical trial

# Treatment with VOXZOGO®

## The only FDA-approved targeted therapy

Indicated to increase linear growth for children with achondroplasia, from as early as birth until growth plates close.[1]

VOXZOGO®
(vosoritide) for injection

**INDICATION AND IMPORTANT SAFETY INFORMATION**

**VOXZOGO®** (vosoritide) is indicated to increase linear growth in pediatric patients with achondroplasia and open growth plates.

- This indication is approved under accelerated approval based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

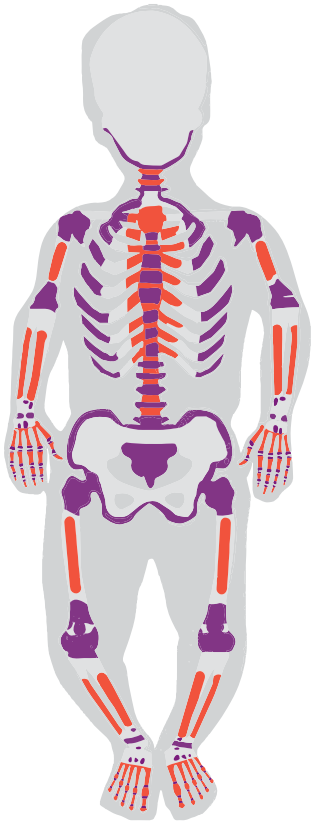
**Warnings and Precautions for Risk of Low Blood Pressure**

Transient decreases in blood pressure were observed in clinical studies. Patients with significant cardiac or vascular disease and patients on anti-hypertensive medicinal products were excluded from participation in VOXZOGO clinical trials. To reduce the risk of a decrease in blood pressure and associated symptoms (dizziness, fatigue, and/or nausea), patients should be well hydrated, have adequate food intake, and drink approximately 8-10 ounces of fluid in the hour prior to VOXZOGO administration.

**Please see additional Important Safety Information presented throughout, and in the full Prescribing Information.**

# Endochondral bone growth is inhibited in achondroplasia[2,3]

Endochondral bone growth occurs at open growth plates where cartilage converts to bone. Most bones start to grow before birth and continue for as long as growth plates remain open.[4,5]



Achondroplasia affects endochondral bones, which make up >90% of the bones in the body[3,6-14]

Endochondral bones

Growth plates

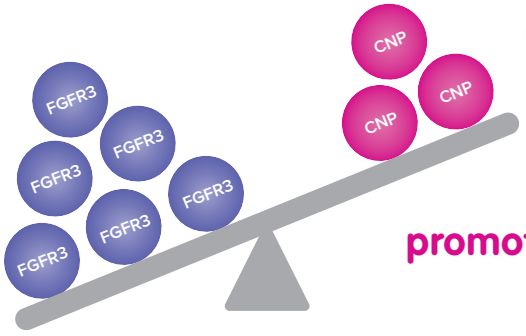
This image is for illustrative purposes only to show areas of endochondral bone growth.

## Bone growth requires a balance of signaling pathways[2]

**In achondroplasia, this balance is disrupted[2]**

**Overactive FGFR3** signaling results in inhibited endochondral bone growth throughout the body.[2,3,6-14]

**FGFR3 signaling slows bone growth.[2]**




**Endogenous CNP** levels cannot adequately regulate overactive FGFR3 signaling.[2]

**CNP signaling promotes bone growth.[2]**

**CNP,** C-type natriuretic peptide; **FGFR3,** fibroblast growth factor receptor 3.

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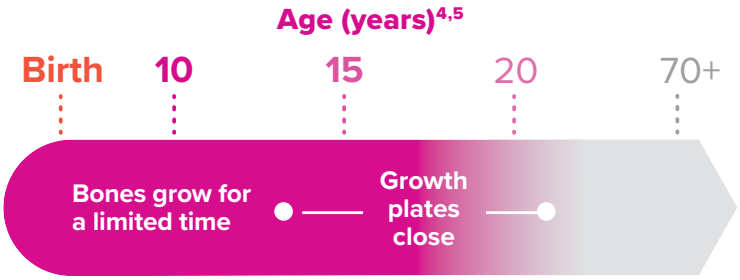
# VOXZOGO promotes endochondral bone growth as early as birth[1]

VOXZOGO (vosoritide) for injection

VOXZOGO targets overactive FGFR3 and works by mimicking the body's natural CNP to increase linear growth*—only while growth plates remain open.[1]

Decreased linear growth in achondroplasia caused by inhibited bone growth is greatest during the first 5 years of life and compounds over time.[15,16]




## Maximize time on treatment by starting early and continuing until growth plates close[1]

### Guidelines support early initiation of VOXZOGO[17]

BioMarin provided funding for this project, including to the participants. BioMarin was not involved in the selection of the guidelines development group, defining the guidelines scope, the voting process, analysis of the results, or preparation of the submitted manuscript. Please see Acknowledgements section of publication for additional detail.


*Linear growth, an increase in length or height, is an indicator of overall health and development.[18]

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions for Risk of Low Blood Pressure (cont'd)**

In a 52-week, randomized, double-blind, placebo-controlled trial in 121 subjects with achondroplasia, subjects aged from 5.1 to 14.9 years, (Study 1) eight (13%) of 60 patients treated with VOXZOGO had a total of 11 events of transient decrease in blood pressure, compared to 3 (5%) of 61 patients on placebo, over a 52-week treatment period. The median time to onset from injection was 31 (18 to 120) minutes, with resolution within 31 (5 to 90) minutes in VOXZOGO-treated subjects. Two out of 60 (3%) VOXZOGO-treated patients each had one symptomatic episode of decreased blood pressure with vomiting and/or dizziness compared to 0 of 61 (0%) patients on placebo.

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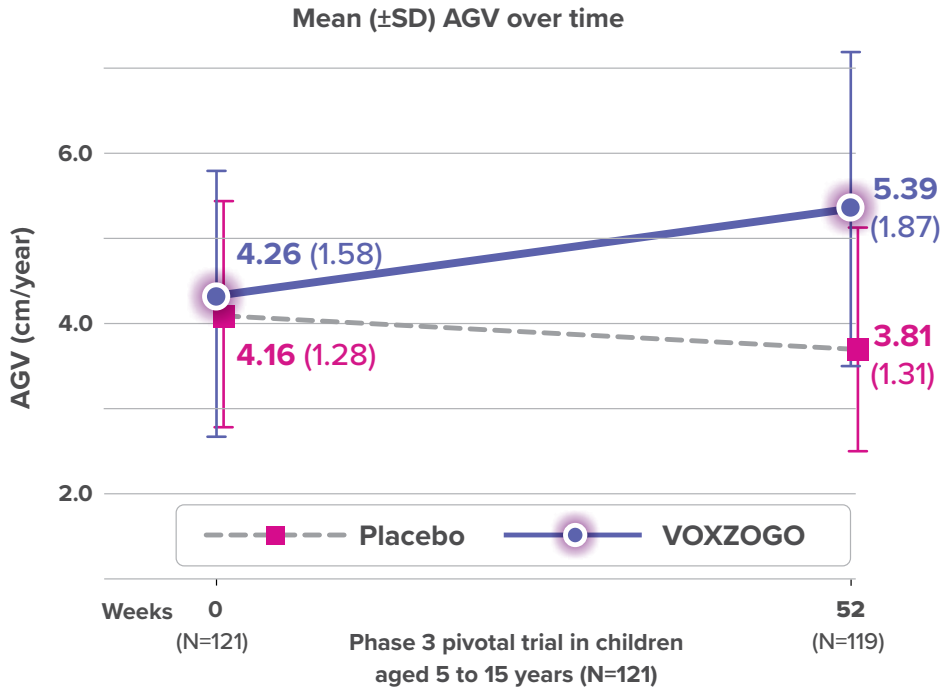
# Children on VOXZOGO can grow faster than without treatment[1,19]




**AGV difference from placebo at 1 year in the primary analysis:**

**+1.57 cm/yr[1*†‡]**

*P*<0.0001 (95% CI: 1.22, 1.93)

**AGV increase maintained over baseline at**

**4 years**

**in VOXZOGO-treated children from the open-label extension study (N=105)[19]**

**Mean (±SD) AGV at 4 years:**
**VOXZOGO (n=49)=4.77 (2.17)**
**Placebo to VOXZOGO (n=56)=4.43 (2.35)**

**97% (58/60) of the patients in the phase 3 pivotal trial remained on treatment during the 1-year study[1]**

## Study design[1,19]

4 years of data were collected from VOXZOGO-treated patients aged 5 to 15 years across the phase 3, randomized, placebo-controlled, double-blind, 52-week pivotal trial and the open-label extension study evaluating the long-term efficacy and safety profile of VOXZOGO.

## Primary endpoint[1]

Change from baseline in AGV at Week 52 compared to placebo.

AGV is a measure of linear growth expressed as the change in height or length units over 1 year.

**AGV,** annualized growth velocity; **CI,** confidence interval; **LS,** least squares; **SD,** standard deviation.

*Improvement in AGV was consistent across all predefined subgroups, including sex, age, and Tanner stage.[1]
†All randomized subjects. Two patients in the VOXZOGO group discontinued from the study before Week 52; the values for these 2 patients were imputed assuming baseline growth rate for the period with missing data.[1]
‡LS means were estimated from the ANCOVA (analysis of covariance) model, which included treatment, stratum defined by sex and Tanner stage, baseline age, baseline AGV, and baseline height Z-score.[1]

### IMPORTANT SAFETY INFORMATION

**Adverse Reactions:**

Adverse reactions that occurred in ≥5% of patients treated with VOXZOGO and at a rate greater than that of placebo in the phase 3 study are injection site reactions (including erythema, swelling, urticaria, pain, bruising, pruritus, hemorrhage, discoloration, and induration), vomiting, arthralgia, decrease in blood pressure, gastroenteritis, diarrhea, dizziness, ear pain, influenza, fatigue, seasonal allergy, and dry skin. VOXZOGO-treated patients had an increase in alkaline phosphatase levels (17%), and was noted as a laboratory abnormality.

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# The safety of VOXZOGO has been rigorously evaluated[1]

VOXZOGO® (vosoritide) for injection

VOXZOGO is a once-daily subcutaneous injection administered at home by a trained caregiver.[1]

## Children 5-15 years old

**Adverse reactions that occurred in ≥5% of patients aged 5 to 15 treated with VOXZOGO and at a percentage greater than placebo over 1 year[1]*:**

| ADVERSE REACTIONS | PLACEBO (n=61) | VOXZOGO (n=60) |
|---|---|---|
| Injection site erythema† | 42 (69%) | 45 (75%) |
| Injection site swelling† | 22 (36%) | 37 (62%) |
| Vomiting | 12 (20%) | 16 (27%) |
| Injection site urticaria† | 6 (10%) | 15 (25%) |
| Arthralgia | 4 (7%) | 9 (15%) |
| Decreased blood pressure | 3 (5%) | 8 (13%) |
| Gastroenteritis‡ | 5 (8%) | 8 (13%) |
| Diarrhea | 2 (3%) | 6 (10%) |
| Dizziness§ | 2 (3%) | 6 (10%) |
| Ear pain | 3 (5%) | 6 (10%) |
| Influenza | 3 (5%) | 6 (10%) |
| Fatigue‖ | 2 (3%) | 5 (8%) |
| Seasonal allergy | 1 (2%) | 4 (7%) |
| Dry skin | 0 (0%) | 3 (5%) |

- Adverse reactions reported in the 1-year phase 3 study are consistent with those seen in the long-term safety study[20]

VOXZOGO may cause serious side effects including a temporary decrease in blood pressure in some patients; to reduce the risk of a decrease in blood pressure and associated symptoms (dizziness, feeling tired, or nausea), patients should be well fed and hydrated in the hour before receiving VOXZOGO.[1]

## Children under 5 years old

**The overall safety profile of VOXZOGO in pediatric patients <5 years was similar to that seen in older pediatric patients.[1]**

- The most common adverse reactions (>10%) reported in pediatric patients <5 years were injection site reactions (86%) and rash (28%)[1]

*Includes adverse reactions occurring more frequently in the VOXZOGO arm and with a risk difference of ≥5% (ie, difference of >2 subjects) between treatment arms.[1]
†Injection site reactions occurring more frequently in VOXZOGO-treated patients than placebo.[1]
‡Includes the preferred terms: gastroenteritis and gastroenteritis, viral.[1]
§Includes the preferred terms: dizziness, presyncope, procedural dizziness, and vertigo.[1]
‖Includes the preferred terms: fatigue, lethargy, and malaise.[1]

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# BioMarin is here to support you every step of the way

## BioMarin RareConnections™

- Assistance navigating financial barriers to treatment by dedicated Case Managers
- Identification of financial assistance programs for eligible patients
- Specialty pharmacy coordination and assistance
- Field Reimbursement Managers (FRMs) can provide product access education and payer requirements for seeking treatment coverage

## BioMarin Clinical Coordinators

- Provide one-to-one product support
- Product education throughout the treatment journey
- Timely reinforcement of injection training and education
- Ongoing product refill reminders and shipment updates

## Help them take the next step

### The Achondroplasia Doctor Finder

Scan the QR code to help your patients find a local specialist with expertise in achondroplasia

# Indication and Important Safety Information

VOXZOGO® (vosoritide) for injection

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**Warnings and Precautions for Risk of Low Blood Pressure**

Transient decreases in blood pressure were observed in clinical studies. Patients with significant cardiac or vascular disease and patients on anti-hypertensive medicinal products were excluded from participation in VOXZOGO clinical trials. To reduce the risk of a decrease in blood pressure and associated symptoms (dizziness, fatigue, and/or nausea), patients should be well hydrated, have adequate food intake, and drink approximately 8-10 ounces of fluid in the hour prior to VOXZOGO administration.

In a 52-week, randomized, double-blind, placebo-controlled trial in 121 subjects with achondroplasia, subjects aged from 5.1 to 14.9 years, (Study 1) eight (13%) of 60 patients treated with VOXZOGO had a total of 11 events of transient decrease in blood pressure, compared to 3 (5%) of 61 patients on placebo, over a 52-week treatment period. The median time to onset from injection was 31 (18 to 120) minutes, with resolution within 31 (5 to 90) minutes in VOXZOGO-treated subjects. Two out of 60 (3%) VOXZOGO-treated patients each had one symptomatic episode of decreased blood pressure with vomiting and/or dizziness compared to 0 of 61 (0%) patients on placebo.

**Adverse Reactions:**

Adverse reactions that occurred in ≥5% of patients treated with VOXZOGO and at a rate greater than that of placebo in the phase 3 study are injection site reactions (including erythema, swelling, urticaria, pain, bruising, pruritus, hemorrhage, discoloration, and induration), vomiting, arthralgia, decrease in blood pressure, gastroenteritis, diarrhea, dizziness, ear pain, influenza, fatigue, seasonal allergy, and dry skin. VOXZOGO-treated patients had an increase in alkaline phosphatase levels (17%), and was noted as a laboratory abnormality.

**Injection site reactions:** In Study 1, injection site reactions occurred in 51 (85%) subjects receiving VOXZOGO and 50 (82%) subjects receiving placebo over a 52-week period of treatment. Patients receiving VOXZOGO experienced a total of 6983 events of injection site reactions, while patients receiving placebo experienced a total of 1776 events of injection site reactions, over a 52-week period, representing 120.4 events per patient/year exposure and 29.2 events per patient/year exposure, respectively. Two patients in the VOXZOGO arm discontinued treatment due to adverse events of pain and anxiety with injections.

**Pediatric Patients 0 to <5 Years:**

The safety of VOXZOGO in pediatric patients 0 to <5 years with achondroplasia was evaluated in a 52-week randomized, double-blind, placebo-controlled study (Study 2). In this study, 64 patients from birth to <5 years of age were randomized to receive either a daily vosoritide dose with similar exposure to that characterized to be safe and effective in children with ACH aged ≥5 years old, or placebo. An additional 11 patients received open-label treatment as part of this study. The most common adverse reactions (>10%) reported in pediatric patients 0 to <5 years were injection site reactions (86%) and rash (28%). The overall safety profile of VOXZOGO in pediatric patients 0 to <5 years was similar to that seen in older pediatric patients.

**Administration and Monitoring:**

VOXZOGO is administered as a daily subcutaneous injection. Prior to use, instruct caregivers on proper preparation and administration of VOXZOGO, and ensure caregivers have demonstrated the ability to perform a subcutaneous injection.

Monitor and assess patient body weight, growth, and physical development regularly every 3-6 months. Adjust dosage according to the patient's actual body weight. Permanently discontinue treatment with VOXZOGO upon confirmation of no further growth potential, indicated by closure of epiphyses.

**Special Populations:**

- There are no available data on the use of VOXZOGO in pregnant women, or data on the presence of VOXZOGO in human milk, the effects on the breastfed infant, or the effects on milk production.
- The influence of renal impairment on the pharmacokinetics of VOXZOGO has not been evaluated. No dosage adjustment is needed for patients with eGFR ≥60 mL/min/1.73 $m^2$. VOXZOGO is not recommended for patients with eGFR <60 mL/min/1.73 $m^2$.

You may report side effects to the FDA at **1-800-FDA-1088** or **www.fda.gov/medwatch**. You may also report side effects to BioMarin at **1-866-906-6100**.

**Please see additional Important Safety Information presented throughout, and in the full Prescribing Information.**

# It's time to talk VOXZOGO

VOXZOGO® (vosoritide) for injection

The **only FDA-approved targeted therapy** to increase linear growth for pediatric patients of all ages with achondroplasia and open growth plates.[1]

## Over 3,800 infants and children with achondroplasia around the world are being prescribed VOXZOGO[21]

**97%** of insured patients have secured coverage for VOXZOGO[22*†]

**96%** of eligible families with commercial insurance paid $0 out of pocket for VOXZOGO[23*‡§]

## Connect with a Local BioMarin Representative

Learn more about VOXZOGO and how it can help your patients by connecting with a dedicated representative.

*BioMarin RareConnections™ Data on File. VOXZOGO patients included are eligible VOXZOGO patients who have enrolled in BioMarin RareConnections and are on commercial therapy.[22,23]

†BioMarin RareConnections data from April through December 2023.[22]

‡BioMarin RareConnections data from January through December 2023.[23]

§Terms and Conditions apply. Valid only for patients with commercial prescription insurance coverage who have a valid prescription for an FDA-approved indication and who meet additional eligibility criteria. Not valid for prescriptions reimbursed, in whole or in part, by any federal, state, or government-funded insurance programs (for example, Medicare, Medicare Advantage, Medigap, Medicaid, VA, DoD, or TRICARE) or where prohibited by law or by the patient's health insurance provider. If at any time a patient begins receiving prescription drug coverage under any federal, state, or government-funded healthcare program, the patient will no longer be able to use the program and patient must notify BioMarin RareConnections at 1-866-906-6100 to stop participation. Patients residing in or receiving treatment in certain states may not be eligible for some or all of the program elements. Patients may not seek reimbursement for value received from the program from any third-party payers. Additional restrictions may apply. Offer subject to change or discontinuance without notice. This assistance offer is not health insurance. Click here for full Terms and Conditions.

**References: 1.** VOXZOGO [package insert]. Novato, CA: BioMarin Pharmaceutical Inc; 2024. **2.** Horton WA, Hall JG, Hecht JT. Achondroplasia. *Lancet*. 2007;370(9582):162-172. **3.** Savarirayan R, Ireland P, Irving M, et al. International Consensus Statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia. *Nat Rev Endocrinol*. 2022;18(3):173-189. **4.** Mackie EJ, Tatarczuch L, Mirams M. The skeleton: a multi-functional complex organ: the growth plate chondrocyte and endochondral ossification. *J Endocrinol*. 2011;211(2):109-121. **5.** Kvist O, Dallora AL, Nilsson O, et al. A cross-sectional magnetic resonance imaging study of factors influencing growth plate closure in adolescents and young adults. *Acta Paediatr*. 2021;110(4):1249-1256. **6.** Breeland G, Sinkler MA, Menezes RG. Embryology, bone ossification. In: StatPearls. StatPearls Publishing; 2023. Accessed March 3, 2025. https://www.ncbi.nlm.nih.gov/books/NBK539718/ **7.** Berendsen AD, Olsen BR. Bone development. *Bone*. 2015;80:14-18. **8.** Cowan PT, Launico MV, Kahai P. Anatomy, bones. In: StatPearls. StatPearls Publishing; 2024. Accessed March 3, 2025. https://www.ncbi.nlm.nih.gov/books/NBK537199/ **9.** Johns Hopkins Medicine. Anatomy of the bone. Accessed March 3, 2025. https://www.hopkinsmedicine.org/health/wellness-and-prevention/anatomy-of-the-bone **10.** Jin SW, Sim KB, Kim SD. Development and growth of the normal cranial vault: an embryologic review. *J Korean Neurosurg Soc*. 2016;59(3):192-196. **11.** Anderson BW, Kortz MW, Black AC, et al. Anatomy, head and neck, skull. In: StatPearls. StatPearls Publishing; 2023. Accessed March 3, 2025. https://www.ncbi.nlm.nih.gov/books/NBK499834/ **12.** Encyclopaedia Britannica. Science & Tech. Skull. Accessed March 3, 2025. https://www.britannica.com/science/skull **13.** Hall R, Beals K, Neumann H, et al. *Introduction to Human Osteology*. Grand Valley State University; 2008. **14.** Encyclopaedia Britannica. Science & Tech. Clavicle. Accessed March 3, 2025. https://www.britannica.com/science/clavicle **15.** Ornitz DM, Legeai-Mallet L. Achondroplasia: development, pathogenesis, and therapy. *Dev Dyn*. 2017;246(4):291-309. **16.** Merker A, Neumeyer L, Hertel NT, et al. Growth in achondroplasia: development of height, weight, head circumference, and body mass index in a European cohort. *Am J Med Genet A*. 2018;176(8):1723-1734. **17.** Savarirayan R, Hoover-Fong J, Ozono K, et al. International consensus guidelines on the implementation and monitoring of vosoritide therapy in individuals with achondroplasia. *Nat Rev Endocrinol*. 2025 Jan 6. doi:10.1038/s41574-024-01074-9 **18.** Wit JM, Himes JH, van Buuren S, et al. Practical application of linear growth measurements in clinical research in low- and middle-income countries. *Horm Res Paediatr*. 2017;88(1):79-90. **19.** Data on file [1]. BioMarin Pharmaceutical Inc; 2025. **20.** Savarirayan R, Tofts L, Irving M, 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):2443-2447. **21.** Data on file [2]. BioMarin Pharmaceutical Inc; 2025. **22.** Data on file [3]. BioMarin Pharmaceutical Inc; 2023. **23.** Data on file [4]. BioMarin Pharmaceutical Inc; 2023.

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