Safety profile, effectiveness, and adherence of vosoritide in young children with achondroplasia in Japan

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Introduction

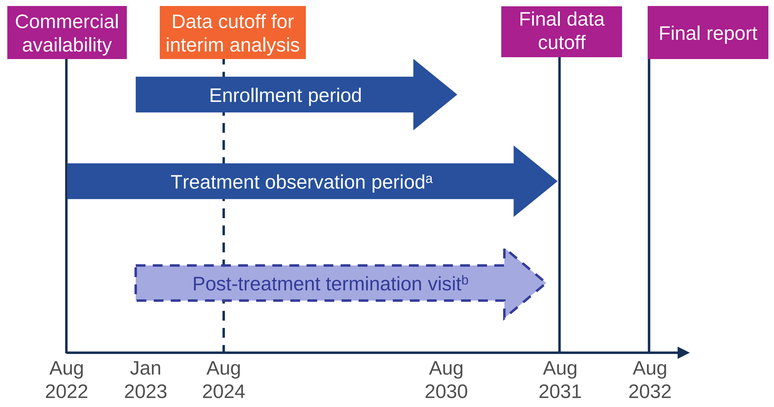
- Achondroplasia (ACH) is a rare skeletal dysplasia caused by a pathogenic variant of the fibroblast growth factor receptor 3 gene (*FGFR3*) that impairs endochondral bone growth[1,2]
- Vosoritide, a recombinant C-type natriuretic peptide, potently stimulates endochondral bone growth by inhibiting FGFR3 signaling and is approved in several countries for the treatment of ACH[3,4]

In June 2022, Japan became the first country to approve vosoritide treatment in children with ACH **from birth** until the closure of epiphyses[5]

- Data from vosoritide use in young children are limited. Here, we present interim analyses from an ongoing drug use survey in Japan reporting real-world vosoritide safety, effectiveness, and adherence in children with ACH aged ≤3 years

Methods

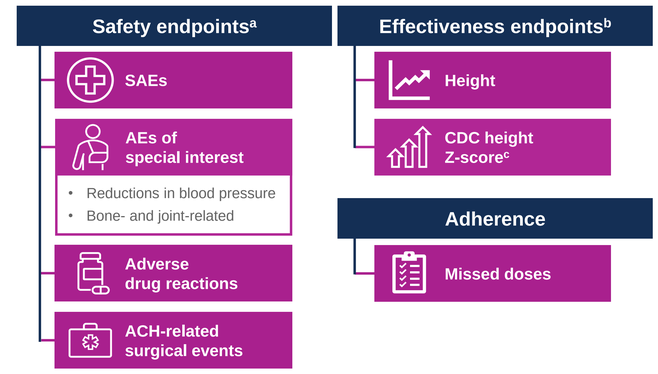
Study design



[a]Data will be collected from first dosing to withdrawal or data cutoff for reporting (whichever is first). Retrospective data will be collected for study participants who started vosoritide prior to study start in January 2023.
[b]Participants who stop treatment before August 2031 (withdraw or reach final adult height) will have a 1-year follow-up after the end of treatment or at the end of the observation period (whichever comes first).

- Drug use survey 111-604 was required by the Japanese Pharmaceuticals and Medical Devices Agency as a condition of approval to evaluate long-term safety and effectiveness of vosoritide in children with ACH
  - As vosoritide is an orphan drug, all exposed cases are included in the survey
- Safety, effectiveness, and adherence are presented from survey initiation to August 2024 from young children across 2 age groups who began treatment at ≤36 months (≤3 years) or ≤12 months (≤1 year) of age

Endpoints



[a]Safety events were coded with MedDRA/J version 27.0 and assessed by incidence.
[b]Effectiveness on-treatment data were available from −1 month of baseline to 12 (± 2) months.
[c]Change in height Z-scores over time. Z-scores were calculated by converting standing height to an age- and sex-appropriate standard deviation score and compared to CDC references.
ACH, achondroplasia; AE, adverse event; CDC, US Centers for Disease Control and Prevention; MedDRA/J, Japanese translation of Medical Dictionary for Regulatory Activities; SAE, serious AE.

Results

Participants

At the data cutoff (August 25, 2024), 533 participants were enrolled and 212 provided consent for publication; 63 (29.7%) were aged ≤3 years **at treatment initiation.** Of these, 63 were available for safety analysis and 20 available for effectiveness analysis (**Figure 1, Table 1**).

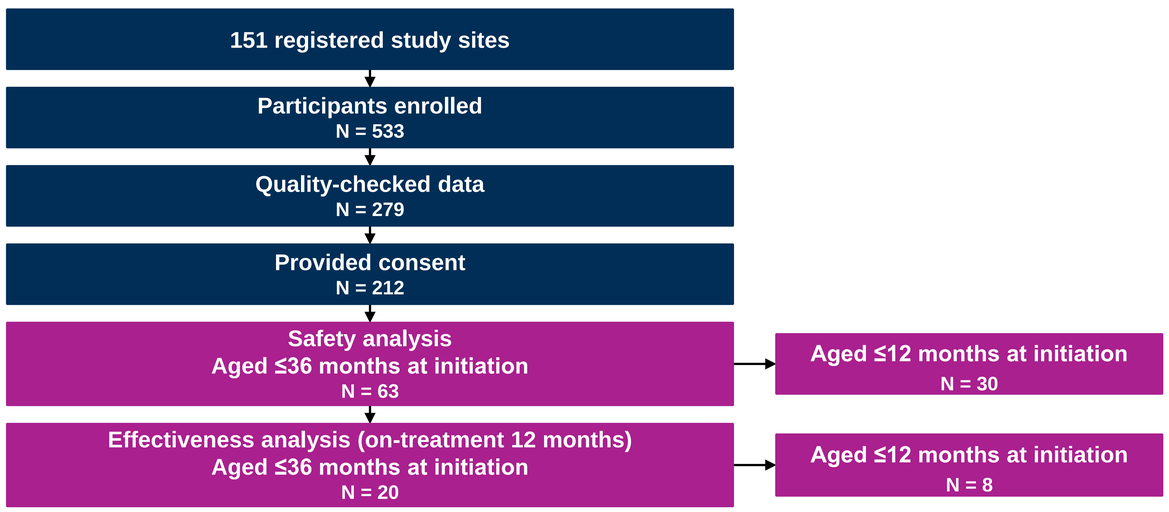
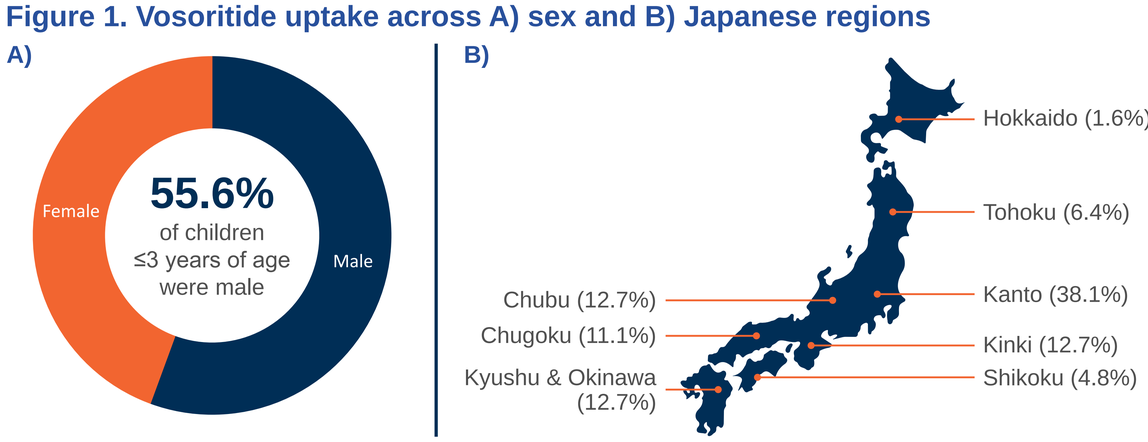


Figure 1. Vosoritide uptake across A) sex and B) Japanese regions



Data are percentages from children aged ≤3 years (n = 63).

Table 1. Participant characteristics at enrollment

	≤36 months (≤3 years) (n = 63)	≤12 months (≤1 year) (n = 30)
Age at treatment initiation, months		
Mean (SD)	15.4 (11.3)	5.6 (3.6)
Min, max	0, 36	0, 12
Height, cm		
Mean (SD)	63.3 (8.8)	55.7 (5.3)
Min, max	46.5, 80.4	46.5, 66.2
CDC height Z-score		
Mean (SD)	−3.75 (1.44)	−3.03 (1.36)
Min, max	−7.0, −0.6	−6.0, −0.6

CDC, US Centers for Disease Control and Prevention; max, maximum; min, minimum; SD, standard deviation.

Safety

Since the start of commercial availability, only 1 serious adverse event (AE) deemed unrelated to vosoritide has been reported (respiratory syncytial virus infection in a child ≤1 years of age at initiation)

There have been no AEs of special interest related to bones or joints or associated with reductions in blood pressure

ACH-related surgical procedures have been reported in 10 (15.87%) children aged ≤3 years at initiation; 4 (13.33%) children were ≤1 year of age

- 6 foramen magnum decompressions[a]
- 2 adenoidectomies
- 2 myringotomy tube surgeries
- 1 hydrocephalus-related surgery

[a]Four reported in children ≤1 year of age

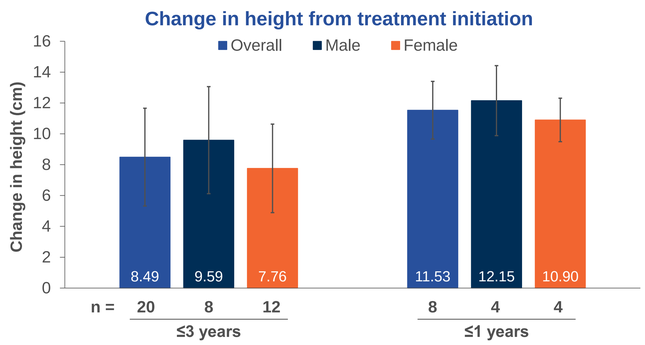
There have been no reports of adverse drug reactions

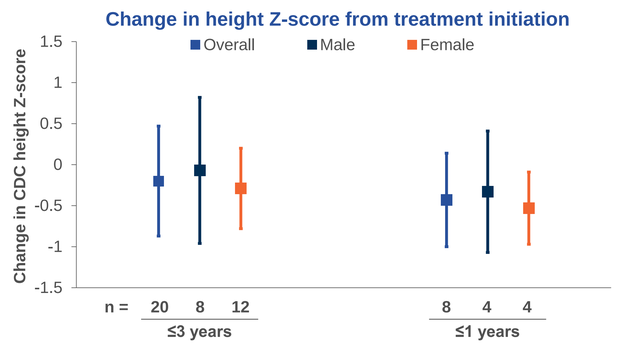
Effectiveness

Figure 2. Effect of vosoritide treatment on height and height Z-scores after 12 months of exposure in children with ACH ages ≤3 (N = 20) and ≤1 (N = 8) years at first dose

Participants experienced rapid growth after 12 months[a] of treatment, with greater numerical height gains in children ≤1 year of age

In a young population where rapid decreases in height Z-score are expected, mean Z-score change in treated participants remained stable over 12 months[a]





Data are presented as mean ± SD. [a]Effectiveness data are changes in measurements from −1 month of baseline to 12 months (± 2 months).
ACH, achondroplasia; CDC, US Centers for Disease Control and Prevention; SD, standard deviation.

Adherence

- Cumulative mean (standard deviation [SD]) duration of treatment exposure was 17.97 (4.76) months and 16.00 (5.48) months for children aged ≤3 and ≤1 years at treatment initiation, respectively
- No dose interruptions were reported for any children
- There was 1 non-safety-related discontinuation after genetic testing revealed a variant in *FGFR3* for hypochondroplasia

Discussion

- Overall, the safety profile of vosoritide in children ≤3 years of age remains favorable in real-world clinical practice in Japan
- Vosoritide treatment adherence was high throughout Japan, even in children ≤1 year of age, with no reported dose interruptions
- Benefits of early intervention have been shown in the vosoritide clinical trial 111-206 in children aged <5 years,[6] and these real-world data demonstrate consistent results and restoration of growth deficits
- Data collection in this survey is ongoing and will strengthen the body of evidence on the impact of starting vosoritide treatment among infants and young children

References

1. Pauli RM, et al. *Orphanet J Rare Dis.* 2019;14(1):1. **2.** Savarirayan R, et al. *Nat Rev Endocrinol.* 2022;18(3):173-89. **3.** Lorget F, et al. *Am J Hum Genet Rep.* 2012;91:1108-14. **4.** U.S. Food and Drug Administration approved BioMarin's VOXZOGO® (vosoritide) for children under 5 years with achondroplasia. BioMarin Pharmaceutical Inc. October 20, 2023. Accessed December 26, 2024. https://investors.biomarin.com/news/news-details/2023/U.S.-Food-and-Drug-Administration-Approves-BioMarins-VOXZOGO-vosoritide-for-Children-Under-5-Years-with-Achondroplasia-10-20-2023/default.aspx. **5.** BioMarin announces the Ministry of Health, Labor and Welfare (MHLW) in Japan granted approval for VOXZOGO® (vosoritide) for injection for the treatment of children with achondroplasia, whose growth plates are not closed. BioMarin Pharmaceutical Inc. June 21, 2023. Accessed December 26, 2024. https://www.biomarin.com/news/press-releases/biomarin-announces-the-ministry-of-health-labor-and-welfare-mhlw-in-japan-granted-approval-for-voxzogo-vosoritide-for-injection-for-the-treatment-of-children-with-achondroplasia-whose-grow/. **6.** Savarirayan R, et al. *Lancet Child Adolesc Health.* 2024;8:40-50.

Acknowledgements

The principal investigators thank the reporting physicians and patients. Funding for this study was provided by BioMarin Pharmaceutical Inc. Medical writing support was provided by Rachel Corrigan, PhD, of AlphaBioCom, a Red Nucleus company, and funded by BioMarin Pharmaceutical Inc.

Disclosures

TM received lecture fees from Kyowa Kirin, Alexion Pharma Japan, and BioMarin Pharmaceutical Japan K.K. **TK** has received honoraria from BioMarin Pharmaceutical Inc. **JMP and VH** are employees and stockholders of BioMarin (UK), Ltd. **HT** is an employee and stockholder of BioMarin Pharmaceutical Japan K.K. **SM** has no disclosures to report.

Presented at ACMG Annual Clinical Genetics Meeting: March 18–22, 2025, Los Angeles, CA.