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Real-world safety of vosoritide in children with achondroplasia in Japan

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Introduction

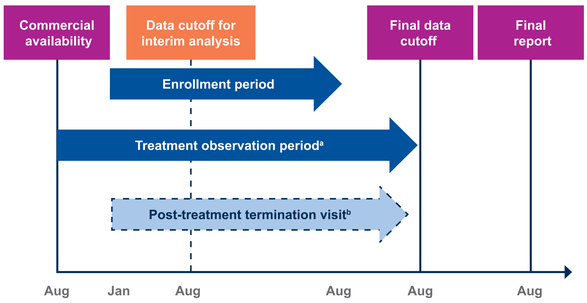
- Achondroplasia (ACH) is a rare skeletal dysplasia caused by a pathogenic variant of the fibroblast growth factor receptor 3 gene (*FGFR3*) that impairs endochondral bone growth[1,2]
- Vosoritide, a recombinant C-type natriuretic peptide, potently stimulates endochondral bone growth by inhibiting FGFR3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

- Real-world data on vosoritide use 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

Methods

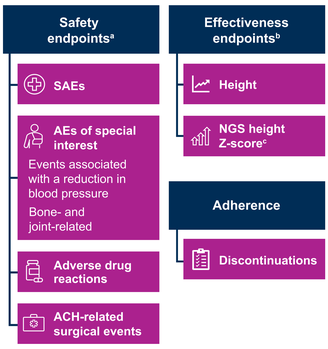
Study design



[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 the long-term safety and effectiveness of vosoritide in children with ACH
  - As vosoritide is an orphan drug, all exposed participants are included in the survey

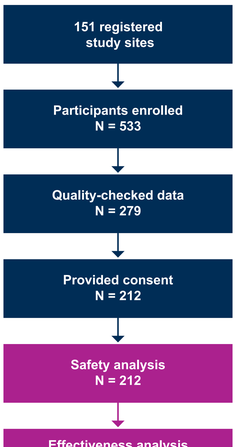
Endpoints



[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 NGS references.[6]
ACH, achondroplasia; AE, adverse event; MedDRA/J, Japanese translation of Medical Dictionary for Regulatory Activities; NGS, National Growth Survey; SAE, serious AE.

Results

Participants



At the data cutoff (August 25, 2024), 533 participants were enrolled and 212 provided consent for publication (**Table 1**). Of these, **212** were available for safety analysis and **74** available for effectiveness analysis.

Table 1. Overall participant characteristics at enrollment

Characteristic	Total (N = 212)
Sex, n (%)	
Male	116 (54.72)
Female	96 (45.28)
Age at treatment initiation, years	
Mean (SD)	6.13 (4.09)
Min, max	0, 16.6
Height, cm	
Mean (SD)	88.54 (22.52)
Min, max	46.5, 134.8
NGS height Z-score	
Mean (SD)	−4.32 (1.32)
Min, max	−8.16, −0.1

NGS, National Growth Survey; max, maximum; min, minimum; SD, standard deviation.

Safety

Of the total population, 2 participants reported a serious adverse event (SAE), both viral infections (gastroenteritis and respiratory syncytial virus infection) likely unrelated to vosoritide treatment

There were 3 patients who reported adverse drug reactions, though all were deemed non-serious (nausea and malaise, pruritus and urticaria, and injection site pain)

There have been no adverse events of special interest related to bones or joints and only 1 non-serious event (nausea) associated with a reduction in blood pressure

ACH-related surgical procedures were reported in 24 (11.32%) participants. The most common were

- Limb lengthening/elongation (7)
- Foremen magnum decompression (6)
- Myringotomy tubes (3)
- Surgery for limb deformity (3)

Adherence

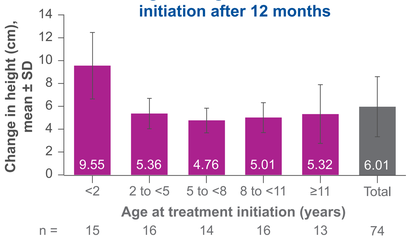
Among the total population (N = 212), mean (standard deviation) duration of treatment exposure was 17.45 (4.86) months

There were 9 discontinuations due to

- Occurrence of AEs, pruritus and urticaria (1)
- Doctor's judgment (5)
- Other (3)

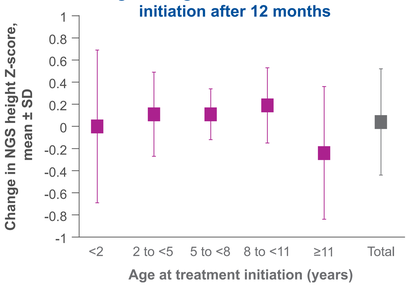
Effectiveness

Change in height from treatment initiation after 12 months



- Participants experienced increased growth after 12 months[a] of treatment, with the greatest numerical height gains in children <2 years of age

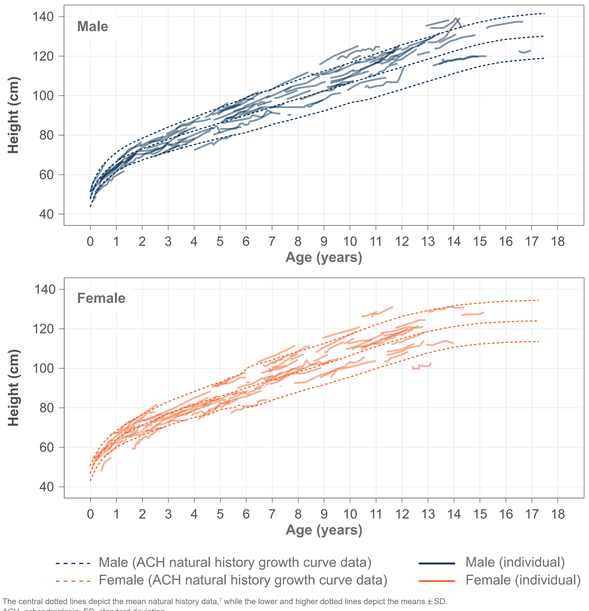
Change in height Z-score from treatment initiation after 12 months



- Height Z-score increased in the total population in 12 months[a]
- In those <2 years old, where rapid Z-score decreases are expected, height Z-score change was similar to the NGS population
- In those ≥11 years old, height Z-score was slightly lower than the NGS population, possibly due to lack of a growth spurt

Data are presented as mean ± SD.
[a]Effectiveness data are changes in measurements from −1 month of baseline to 12 months (± 2 months).
NGS, National Growth Survey; SD, standard deviation.

Spaghetti plot of height by sex



The central dotted lines depict the mean natural history data,[7] while the lower and higher dotted lines depict the means ± SD.
ACH, achondroplasia; SD, standard deviation.

Discussion

- Overall, the safety profile of vosoritide among children with ACH from age <1 to 17 years remains favorable in real-world clinical practice in Japan, with low adverse drug reaction frequency
- Vosoritide treatment adherence was high throughout Japan, with <5% discontinuations
- Vosoritide long-term safety and efficacy has been demonstrated in the clinical trials 111-206 for children aged <5 years[8] and in 111-301/302 for children aged ≥5 years,[9,10] and these real-world data demonstrate consistent results and restoration of growth deficits

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.** Isojima T, et al. *Clin Pediatr Endocrinol.* 2016;25(2):71–6. **7.** Tachibana, et al. *The Journal of Pediatric Practice.* 1997;8(125):1363–9. **8.** Savarirayan R, et al. *Lancet Child Adolesc Health.* 2024;8:40–50. **9.** Savarirayan R, et al. *Lancet.* 2020;396(10252):684–92. **10.** Savarirayan R, et al. *Genet Med.* 2021;23(12):2443–7.

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Disclosures

Taichi Kitaoka, Jeanne M Pimenta, Veronika Horvathova, Hirofumi Tokuoka, and Toshimi Michigami:

1. **Employment/leader position/advisory role:** BioMarin (UK) Ltd., BioMarin Pharmaceutical Japan KK
2. **Stock ownership or options:** BioMarin (UK) Ltd., BioMarin Pharmaceutical Japan KK
3. **Honoraria (eg, lecture fees):** Alexion Pharma Japan, BioMarin Pharmaceutical Inc., BioMarin Pharmaceutical Japan, and Kyowa Kirin

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