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Real-world safety and effectiveness of vosoritide: Results from an early access program in France

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Introduction

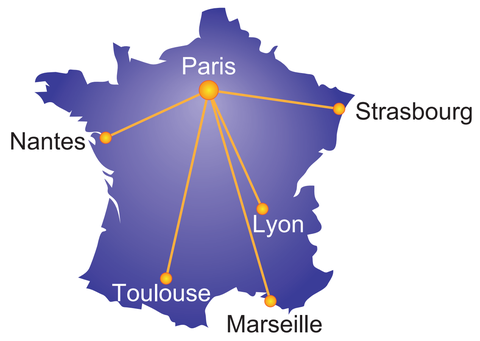
- Achondroplasia (ACH) is the most common form of disproportionate short stature (approx. 1:25,000 live births)[1,2]
- ACH is caused by a pathogenic mutation in the FGFR3 gene, leading to impaired endochondral bone growth and multiple medical complications[1,3]
- Vosoritide is a CNP analogue that counteracts overactive FGFR3 signaling and stimulate endochondral bone growth[4-6]
- On 26 August 2021, the European Medicines Agency (EMA) approved vosoritide for treating ACH in patients aged ≥2 years until closure of epiphyses
- Prior to this, vosoritide was made available in France through a cohort Temporary Authorization for Use (ATUc), approved by the National Agency for the Safety of Medicines and Health Products (ANSM) on 24 June 2021
- After EMA approval, the ATUc transitioned to an Early Access Post-Marketing Authorisation (or AP2) approved by the French Health Authority (HAS) in December 2021
- We report the final findings from this real-world access program for the entire treatment period from 24 June 2021 to 13 December 2022

Methods

- A consortium of French ACH experts (CRMR MOC) reviewed ACH cases followed in the network (6 centres across France) to confirm eligibility for treatment initiation with vosoritide
- The early access to vosoritide was requested for children with achondroplaisa aged 5 years or older with open epiphyses, in line with CRMR MOC to prioritize the enrolment of older patients
- Treatment consisted of once daily, subcutaneous vosoritide at a dose of 15 µg/kg
- After treatment initiation and parent therapeutic education, patients were followed up at months 1, 3 and 6 and at 6-monthly intervals thereafter
- Data were collected to evaluate treatment compliance, adverse events, and growth

Participating centres

ATU centres
Hôpital Necker Enfants Malades, Paris
CHU Toulouse – Hôpital des Enfants, Toulouse
CHU Nantes – Hôpital Hôtel-Dieu, Nantes
CHU de Strasbourg – Hôpital de Hautepierre, Strasbourg
Hôpital de La Timone, Marseille
Hôpital Femme-Mère-Enfant, Lyon



Data collected at each visit

	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 Ach[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[c]		X	X	X	X	X
Vosoritide treatment		X	X	X	X	X
Adverse event data[d]			X	X	X	X

[a]Documentation includes the patient's age at diagnosis, the place and author of the diagnosis, and confirmation of genetic testing.
[b]From 7 years of age. Only if this examination is performed as part of recommended treatment.
[c]Prepubertal stage without closure of the epiphyseal cartilage in patients aged 7 to 12 years.
[d]All safety events were reported within 24 hours of identification.

Results

- The first patient enrolled in the ATUc on 8 September 2021
- A total of 62 patients were enrolled and 57 initiated treatment with vosoritide within the early access period
- Of the 57 patients treated with vosoritide, treatment was initiated during the ATUc for 23 patients (40.4%) and during AP2 for 34 patients (59.6%)
- Among these, 22 patients (38.6%) were treated for 12 months

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%)

Treatment exposure and adherence

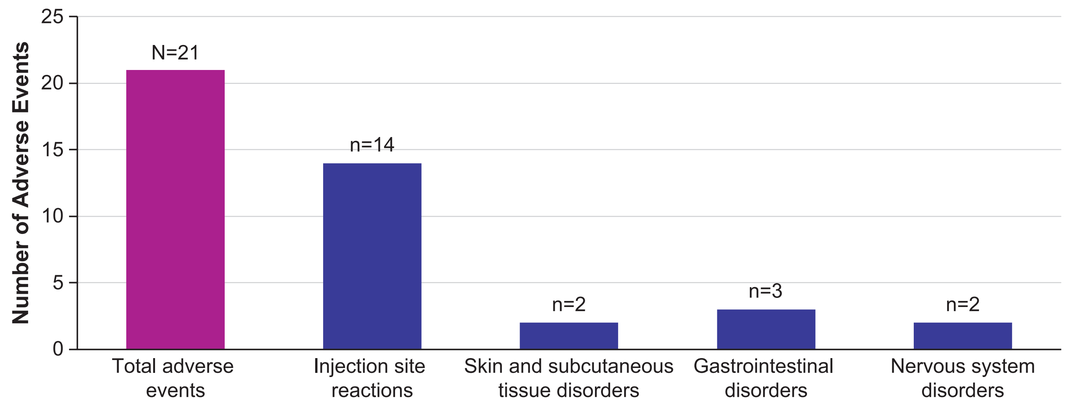
Exposure to vosoritide (days)	Overall treated (n=57)
Cumulative exposure	15,817
Mean (SD)	277.5 (146.24)
Min, Max	32,443

- No patients discontinued treatment
- A total of 14 patients missed a total of 43 doses in the entire treatment period
- 20 missed doses between Month 0 and Month 6
- 23 missed dosed at Month 12
  - One patient was responsible for 16 of the 23 missed doses

Safety

- Among 57 treated patients, 21 adverse events were reported
- All events were mild, and the majority were injection site reactions and vomiting
- There were no serious adverse events related to vosoritide treatment

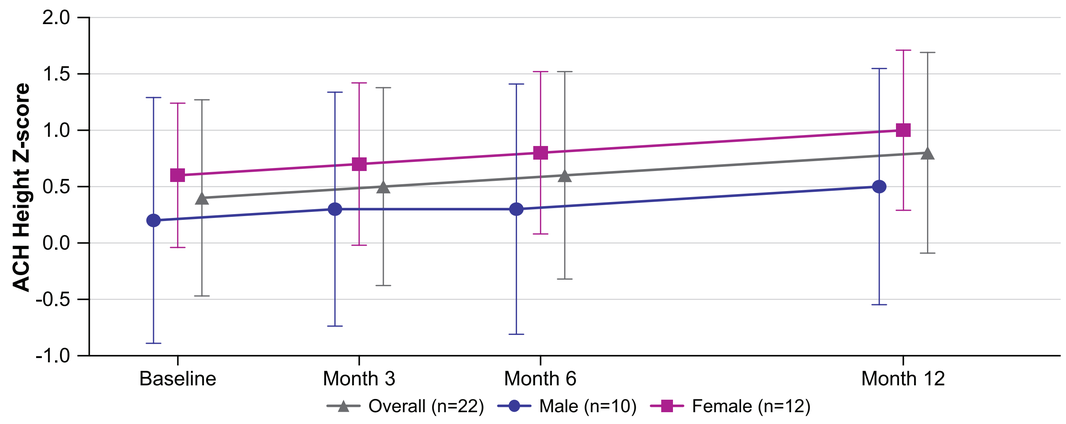
Number of adverse events



Overall treated patients (n=57).

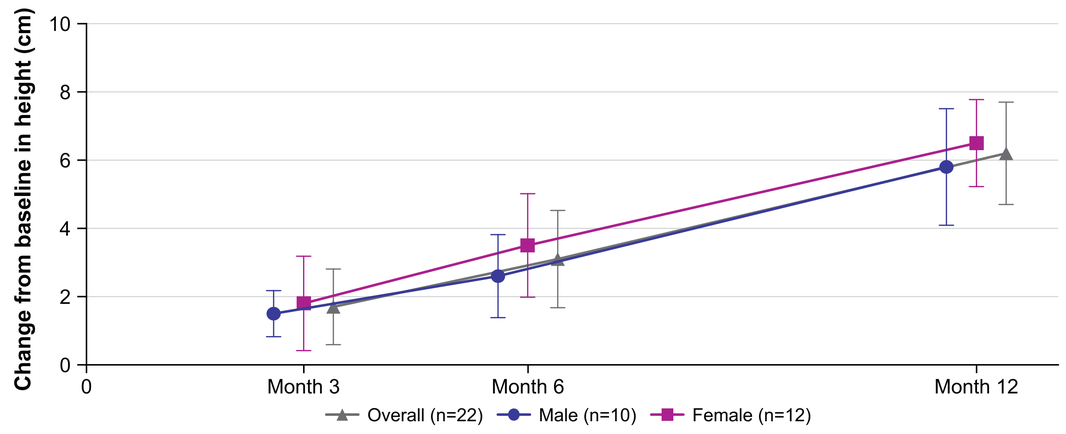
Effectiveness

Height Z-scores of patients treated for 12 months referenced to untreated ACH population[8] over time



- After 12 months of treatment:
  - ACH height Z-scores (SD) increased by 0.3 (0.30) among males, 0.5 (0.21) among females, and 0.4 (0.26) overall
  - Height Z-scores (SD) referenced to average stature using CDC data[9] increased by 0.3 (0.28) among males, 0.4 (0.37) among females, and 0.4 (0.33) overall

Change from baseline in height (cm) in patients treated for 12 months



- After 12 months of treatment, absolute height increased by 5.8 (1.71) cm among males, 6.5 (1.28) cm among females, and 6.2 (1.50) cm overall

Annualized growth velocity (AGV) in patients treated for 12 months

Mean AGV in cm/year (SD)	Male (n=10)	Female (n=12)	Overall (n=22)
6 Months	5.6 (2.14)	6.4 (2.76)	6.1 (2.49)
12 Months	5.7 (1.72)	6.3 (1.17)	6.0 (1.44)

Conclusions

- These data from 57 children with ACH who were treated for up to 14.5 months (443 days) indicate that vosoritide under real-world conditions has a safety and effectiveness profile consistent with outcomes in vosoritide clinical trials[5-7]
- Patients treated in this early access program demonstrated good adherence and remained on treatment
- Long-term data collection for these patients will continue where possible through the EU Voxzogo Post-Authorisation Safety Study (PASS, 111-603) to further establish the safety and effectiveness of vosoritide in the real world

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Disclosures

VCD has received travel support and speakers' fees from BioMarin and is a clinical trial investigator for BioMarin and QED. **TE** has received speakers' fees from Novo Nordisk. **BE** has received honoraria from Genzyme and Sanofi Aventis France and speakers' fees from BioMarin France SAS. **MR** has received travel support, speakers' fees, and consulting fees from BioMarin and is a clinical trial investigator for BioMarin and QED. **SS** has received honoraria from Sanofi Aventis France, BioMarin France SAS, AKCEA Therapeutics France. **SC**, **SM**, and **LL** are employees of BioMarin. **JP** is an employee of BioMarin and owns BioMarin stock. **EMG** is an employee of BioMarin and received payment from Redbock for contract work performed on behalf of BioMarin. All other authors have no disclosures.

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