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Objectives and design of the Acorn Study: A non-interventional study evaluating long-term safety in achondroplasia patients treated with vosoritide

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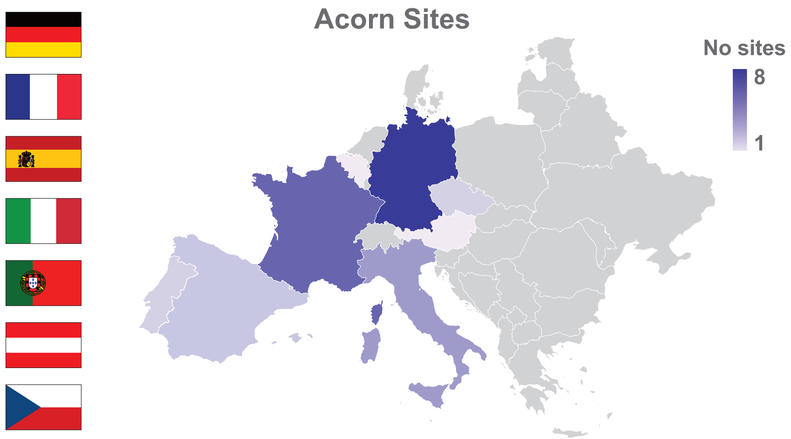
Background and objectives

- Achondroplasia (ACH) is the most common form of disproportionate short stature (approx. 1:25,000 live births)[1]
- ACH is caused by a pathogenic mutation in the *FGFR3* gene, leading to impaired endochondral bone growth and multiple medical complications[2,3]
- Vosoritide, a modified recombinant human C-natriuretic peptide (rhCNP), leverages the CNP pathway to counteract overactive *FGFR3* signaling and stimulate endochondral bone growth[4,5,6]
- Vosoritide was approved by the European Medicines Agency (EMA) in August 2021 for treating achondroplasia in patients aged ≥ 2 years until closure of epiphyses and whose diagnosis was genetically confirmed
- The Acorn study is the first treatment-based registry for achondroplasia, created to monitor long-term safety of vosoritide treatment in real world use
- We describe the objectives and methodology of this post-authorisation safety study (PASS) requested by the EMA as part of the risk management plan (Category 3 per Risk Management Plan, BMN 111-603)

Methods

Acorn study design: Real world, observational, prospective

Setting: Up to 10 European countries. Additional country selection is dependent upon access to commercial vosoritide and site feasibility



*Flags represent countries that are currently being set up

Enrollment: Approximately 330 patients

Broad inclusion and exclusion criteria including limb-lengthened patients will maximize representativeness

Study duration: Up to 12 years

Observational Study Period – 10 years from first patient enrolled (ICF signed)

Post-treatment Follow-up Period – 2 years post-completion of treatment, for the subset of patients who complete or discontinue treatment during the observational period

Data collection: Patients followed per routine clinical practice with clinical outcomes assessed at regular intervals and recorded in the study electronic data capture (EDC) system

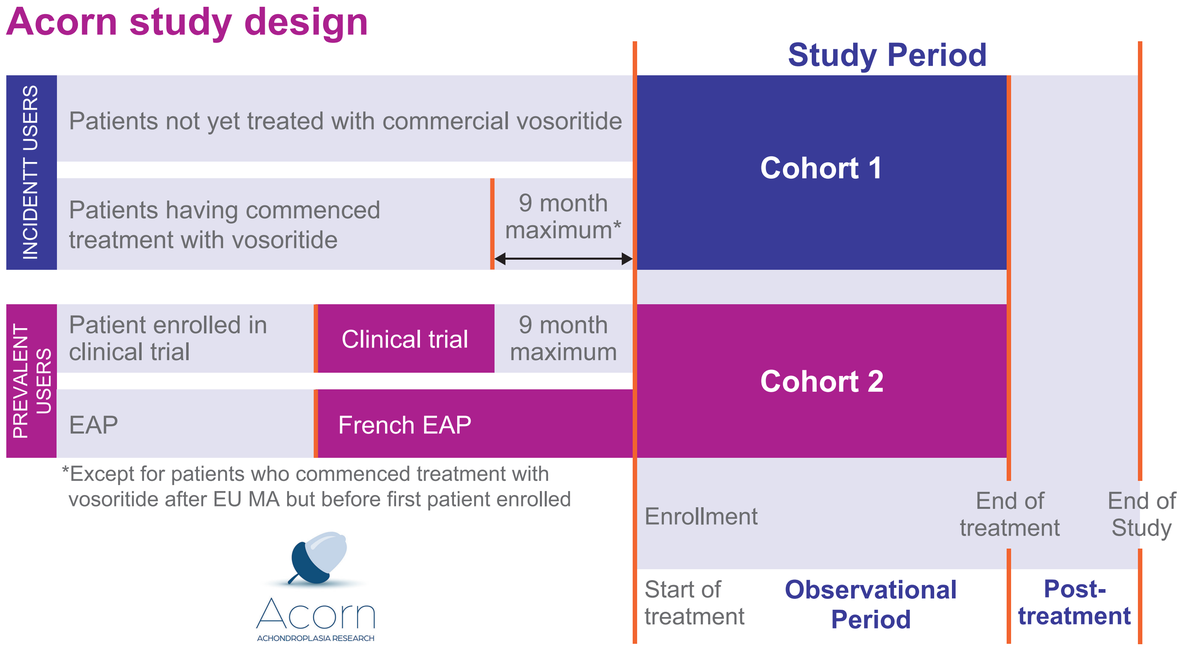
Patient engagement: Utilizing routine care and implementation of patient retention initiatives to minimize early withdrawal and loss to follow-up

	Objectives	Endpoints
Primary	To evaluate the long-term impact of vosoritide treatment on **adverse bone-related safety events**	Incidence of new bone-related safety events of interest: ▪ Fractures ▪ Slipped capital femoral epiphysis ▪ Osteonecrosis or avascular necrosis ▪ Spinal cord and nerve root disorder ▪ Spine and neck deformities ▪ Joint disorder (eg, joint contractures, joint laxity/ hypermobility, genu varum) ▪ Clinically apparent cartilage disorder
Secondary	**To evaluate:** 1) the long-term impact of treatment with vosoritide on **safety and disease related outcomes**	Incidence of: ▪ Serious AEs (SAEs), severe adverse drug reactions (ADRs), and ADRs leading to treatment discontinuation ▪ Surgeries related to bone-related safety events of interest ▪ ACH-related complications and surgeries (excluding elective limb lengthening surgeries) ▪ Changes in anthropometric measures, including height
	2) the **immunogenic potential** of vosoritide treatment	Incidence of: ▪ Severe injection site reactions (ISRs) ▪ Vosoritide-related hypersensitivity events
	3) surgical outcomes and treatment experience in subjects who undergo **elective bone-related surgery**	▪ Treatment interruption or discontinuation ▪ Complications, length of hospital stay and antibiotic use

Summary inclusion criteria

Cohort 1 "incident users"	▪ ≈300 patients (≥2 to ≤ 8 years old) at enrolment or 1st treatment with vosoritide who recently or will soon initiate treatment ▪ In addition, anticipation of at least 36 months of vosoritide treatment during the study
Cohort 2 "prevalent users"	▪ 30 patients (≥2 years) who initiated vosoritide as part of a BioMarin clinical trial or French expanded access program (EAP), have discontinued from those studies, switched or intend to switch to vosoritide treatment and the subject does not meet the Cohort 1 inclusion criteria ▪ In addition, anticipation of at least 36 months of vosoritide treatment, comprising time in prior clinical trials/ French EAP and the current study

Acorn study design



*Except for patients who commenced treatment with vosoritide after EU MA but before first patient enrolled

Data elements of interest

Variable	Baseline	During follow-up	End of treatment	Post-treatment follow-up
Documentation of ACH	X			
Demographics	X			
Medical history	X			
Physical examination	X	X	X	X
Height (standing and seated) and weight	X	X	X	X
Vital signs	X	X	X	X
Safety events, including bone-related safety events of interest (primary endpoint)		X	X	X
ACH and/or skeletal related medical and surgical events	X	X	X	X
Voxzogo administration details	X	X	X	
Concomitant medications	X	X	X	X

Data analysis

- Analyses of Cohort 1 are considered to be the primary (main) analysis
- Safety analyses will be presented by Cohort 1 (incident users) and Cohort 2 (prevalent users) separately
- Evaluation alongside external comparator populations will be conducted as appropriate
  - Exploration of external registries or datasets, is ongoing
  - Use of patient-level data is preferred for external comparison to allow appropriate adjustment methods
- The primary endpoint will include the exposure-adjusted incidence rate (EAIR and 95% confidence interval) of all new bone-related safety events not previously observed in the subject, which emerge during the course of the study
- Time-to-first bone-related safety event of interest will be explored graphically using Kaplan-Meier survival methods and cumulative incidence figures from index date until data cut-off date for interim reporting and/or study end will be provided
- Sensitivity and bias analysis methods will be used to address unknown or unmeasured confounders
- Additional analyses will be specified in the Statistical Analysis Plan

Study status

- The study is registered on the EU post authorization study (PAS) register (EUPAS47514)
- Recruitment began in April 2023
- As of August 2023, 6 participants (2 females and 4 males, aged 4–14) have been enrolled into the study in France, 1 into Cohort 1 and 5 into Cohort 2
- Publication of study results is anticipated in peer-reviewed scientific journals and at conferences

Conclusions

- Vosoritide is the first medicine to be approved to treat children with achondroplasia in Europe
- The Acorn study will collect important long-term, real-world data from patients across Europe
- These data will provide important insights into the impact of long-term vosoritide treatment on safety, effectiveness and the use of vosoritide in context of other interventions

References

1. Foreman PK et al. Birth prevalence of achondroplasia: A systematic literature review and meta-analysis. *Am J Med Genet A*. 2020;182(10):2297-2316. **2.** Horton WA, Hall JG, Hecht JT. Achondroplasia. *Lancet* 2007; 370(9582):162-72. **3.** Hoover-Fong J et al. Lifetime impact of achondroplasia: Current evidence and perspectives on the natural history. *Bone* 2021; 146:115872. **4.** BioMarin Pharmaceutical. Voxzogo: EU summary of product characteristics. 2021. https://www.ema.europa.eu/en/documents/product-information/voxzogo-epar-product-information_en.pdf. Accessed 25 Aug 2022. **5.** Savarirayan R et al. C-type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia. *N Engl J Med.* 2019;381(1):25-35. **6.** Savarirayan R 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):684-692.

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