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Design and objectives of the Acorn study: a non-interventional study evaluating long-term safety in achondroplasia children treated with vosoritide

Jeanne M. Pimenta[1], Fiona Fettes[1], Swati Mukherjee[1], Sheetal Ingole[1], Veronika Horvathova[1], Ekkehart Lausch[2]

[1]BioMarin (U.K.) Limited, London, UK; [2]Section of Pediatric Genetics, Center for Pediatrics, University of Freiburg, Freiburg, Germany

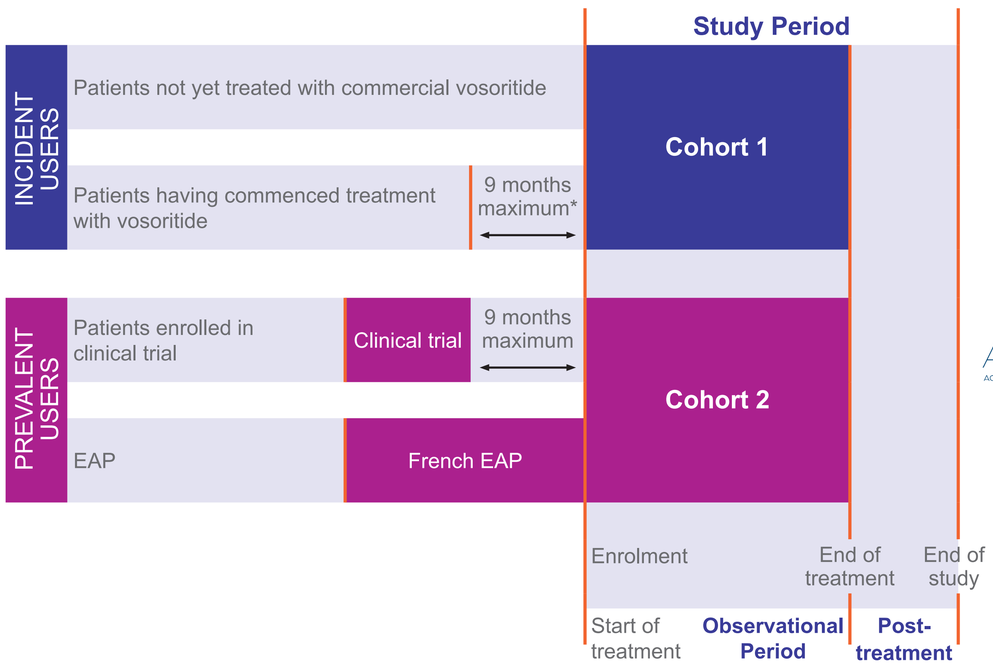
Background

- Achondroplasia (ACH) is the most common form of disproportionate short stature, with a global birth prevalence of 4.6 per 100,000 births[1]
- ACH is a rare skeletal dysplasia caused by a pathogenic variant in the fibroblast growth factor receptor 3 gene (*FGFR3*), leading to impaired endochondral bone growth and multiple medical complications[2,3]
- Vosoritide, a modified recombinant human C-type natriuretic peptide, is approved by the European Medicines Agency (EMA) for treating ACH in patients aged ≥4 months with a genetically confirmed diagnosis until closure of epiphyses[4]
- A post-authorisation safety study (BMN 111-603, Acorn) was requested by the EMA as part of the vosoritide Risk Management Plan
- The Acorn study is the first treatment-based registry for ACH that monitors real-world, long-term use of vosoritide
- Here we describe methodology, objectives, and preliminary data from the Acorn study

Methods

Acorn study design

- Real-world, observational, prospective, multicentre, non-interventional, post-authorisation, Category 3 safety study (European post-authorisation study registration: EUPAS47514)



*Except for patients who commenced treatment with vosoritide after European Union marketing authorisation but before first patient enrolled
EAP, expanded access program

Summary of inclusion criteria

Cohort 1 "Incident Users"	▪ Aged ≥4 months to ≤8 years old ▪ Either recently started vosoritide treatment or plan to start treatment within 3 months of enrolment ▪ Anticipation of ≥36 months of vosoritide treatment during the study
Cohort 2 "Prevalent Users"	▪ Initiated treatment in the French EAP or vosoritide open-label clinical trials and have discontinued from those studies and switched to commercial vosoritide treatment, and do not meet Cohort 1 inclusion criteria ▪ Anticipation of ≥36 months of vosoritide treatment, comprising time in French EAP/prior clinical trials and the current study

EAP, expanded access program

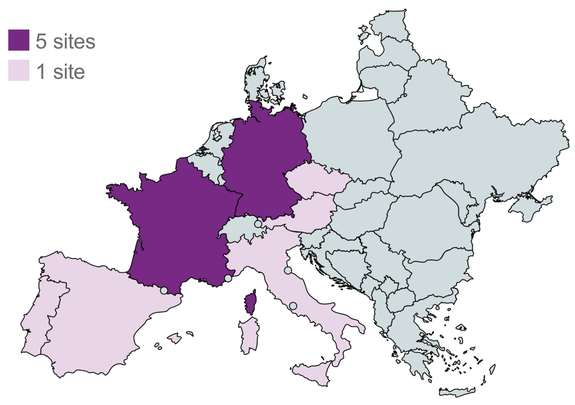
- Study duration:
  - Observational study period: 10 years from first patient enrolled
  - Post-treatment follow-up period: an additional follow-up after 2 years among patients who complete or discontinue treatment during the observational period
- Data collection:
  - Patients followed per routine clinical practice with clinical outcomes assessed at regular intervals and recorded in the electronic data capture system
  - A patient questionnaire will be used to capture data at the post-treatment follow-up
- Data analyses:
  - Incidence rates (95% confidence interval) will be calculated for the primary endpoint (new bone-related safety events)
  - Time to first bone-related safety event will be explored graphically using Kaplan-Meier survival methods and cumulative incidence figures
  - Additional sensitivity and bias analysis methods will be used to address unknown or unmeasured confounders
  - Analyses of Cohort 1 (incident users) will be considered as the primary analysis; all safety analyses will be stratified by cohort

	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: ▪ SAEs, severe 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 ▪ Vosoritide-related hypersensitivity events
	3. Surgical outcomes and treatment experiences in patients who undergo **elective bone-related surgery**	▪ Treatment interruption or discontinuation ▪ Complications, length of hospital stay, infections, and antibiotic use

ADR, adverse drug reaction; SAE, serious adverse event

Results

- As of 5 April 2024, 66 participants were enrolled from 15 sites in 7 countries



Characteristics of enrolled participants*

Characteristic	Enrolled participants (N=66)
Sex, n (%)	
Male	32 (48)
Female	34 (52)
Cohort†, n	
Cohort 1	52
Cohort 2	10
Age at enrolment (n=61), years	
Mean (SD)	6.89 (3.19)
Min, Max	2.1, 14.0
Duration of treatment (n=45), days	
Mean (SD)	445.7 (266.0)
Min, Max	19, 892

*Data cut-off: 5 April 2024; †4 participants had no data entered on the cohort form and remained unassigned at the time of data cut-off
Max, maximum; Min, minimum

- No participants have discontinued treatment
- Among those with treatment data currently available (n=45), there have been no reported treatment interruptions or missed doses*
- There have been no adverse bone-related safety events reported

*Missed dose defined as: no dose for 7 consecutive days

Conclusions

- Vosoritide is the first approved medicinal treatment for children with ACH
- Acorn is collecting real-world data across Europe and will provide important insights on long-term safety and effectiveness of vosoritide and use in the context of other interventions
- Expansion of the indication to ≥4 months will now allow enrolment of younger patients
- Vosoritide treatment is well tolerated, with no reported discontinuations or interruptions

References

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Disclosures

- JMP, FF, SM, SI, and VH are employees of BioMarin (U.K.) Limited. EL has received honoraria from BioMarin for advisory boards and travel.
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