Plain Language Summary of Publication

Future Rare Diseases

# Vosoritide treatment accelerates bone growth in children with achondroplasia

Ravi Savarirayan[1], Melita Irving[2], Julie Hoover-Fong[3], Carlos A Bacino[4], Keiichi Ozono[5], Klaus Mohnike[6], Valerie Cormier-Daire[7], Antonio Leiva-Gea[8], Yasemin Alanay[9], Mary Andrews (patient author)[10], Chandler Crews (patient author)[11], Cristina Klafehn[12], Kala Jayaram[12], George S Jeha[12], Elena Fisheleva[13], Alice Huntsman-Labed[13] & Jonathan Day[13]

[1]Murdoch Children's Research Institute, Royal Children's Hospital, and University of Melbourne, Parkville, VIC, Australia
[2]Guy's and St. Thomas' NHS Foundation Trust, Evelina Children's Hospital, London, UK
[3]McKusick-Nathans Department of Genetic Medicine, Johns Hopkins University, Baltimore, MD, USA
[4]Baylor College of Medicine, Houston, TX, USA
[5]Osaka University Hospital, Osaka, Japan
[6]Otto-von-Guericke-Universität, Magdeburg, Germany
[7]Clinical Genetics Department, Université de Paris, INSERM Unite Mixte de Recherche 1163, Institut Imagine, Assistance Publique–Hopitaux de Paris, Hopital Necker–Enfants Malades, Paris
[8]Hospital Universitario Virgen de la Victoria, Málaga, Spain
[9]Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey
[10]The Magic Foundation, Warrenville, IL, USA
[11]The Chandler Project, Little Rock, AR, USA
[12]BioMarin Pharmaceutical Inc, Novato, CA, USA
[13]BioMarin (UK), London, UK

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## Summary

Vosoritide is a drug developed for the treatment of achondroplasia and has demonstrated increases in the growth velocity of children with this condition. Achondroplasia is a skeletal dysplasia (a condition affecting children's bones and joints meaning they do not grow in the typical way) and is also referred to as dwarfism. There are currently no approved treatments for achondroplasia, except for growth hormone in Japan. When a new drug is being developed, it is essential to conduct clinical studies after many other steps to assess how well the drug works and whether it has any side effects[§]. These studies of new drugs are carried out before the drug is approved to treat, improve, or reduce physical problems of certain conditions. This summary reports the results from two clinical studies looking at vosoritide as a potential treatment for children with achondroplasia. Study A compared different doses of vosoritide to find out which is the safest and shows the best results with the fewest side effects[§]. Study B looked at how well vosoritide works compared with a nonactive medicine (known as a placebo) and the side effects[§]. In these studies, vosoritide increased bone growth velocity in children with achondroplasia. Children receiving the drug every day generally only had mild side effects[§]. Serious health complications[¶] were generally medical events seen in children with achondroplasia even if they do not take vosoritide. No children stopped taking vosoritide during the studies due to safety* reasons. How well vosoritide works and the side effects[§] in children over a longer period of time are still being studied.

### How to say (double click to play sound)...

- **Achondroplasia:** <Ay-kon-droh-play-zee-ah>
- **Dysplasia:** <Diss-play-zee-ah>
- **Vosoritide:** <Vo-sor-it-ide>

## Glossary of terms used in this summary

*__Safety__ looks at the side effects of a medicine or drug (in this case, vosoritide) | †__Efficacy__ is how well a drug produces a desired effect (in this case, increasing the amount of growth over a defined period of time) within a clinical trial | §A __side effect__ is something (expected or unexpected) that you feel was caused by a medicine or treatment you take and is not always a bad or negative effect | ¶A health complication is considered '__serious__' when it is life threatening, needs hospital care, or causes lasting problems | ‖A __gene__ is a section of DNA that contains the instructions for how to make a specific biological substance, such as a protein | #A type of study in which both health providers and patients are aware of the drug or treatment being given.

## Who should read this article?

This summary may be helpful for individuals with achondroplasia and parents of children and adolescents with achondroplasia. It may also be helpful for patient organization representatives, patient advocates, and healthcare professionals.

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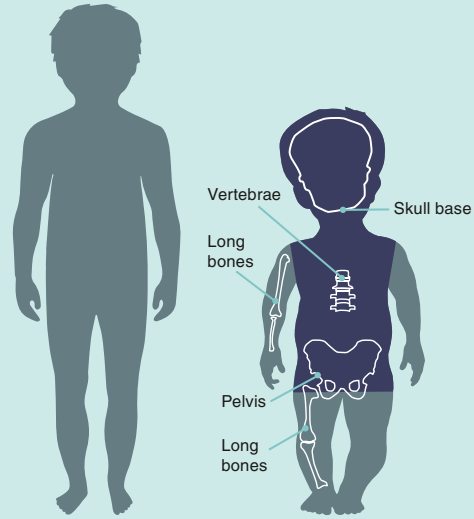
## What is achondroplasia?

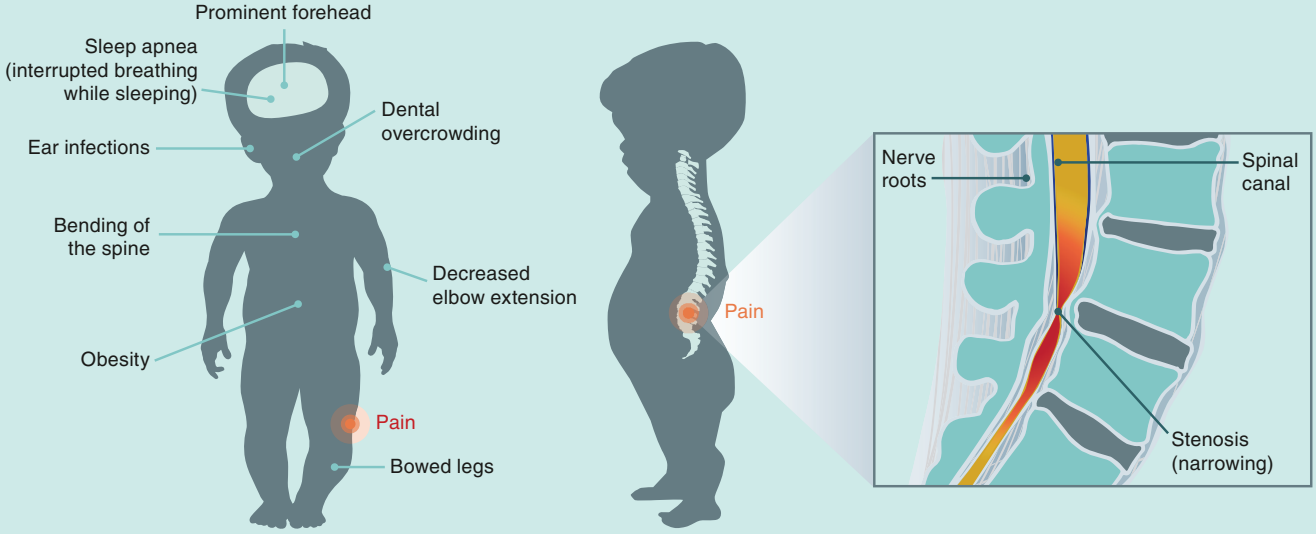
Achondroplasia is a rare genetic condition affecting children's bones and joints meaning they do not grow in the typical way or as fast. This leads to the bones being wrongly shaped.

- While the most visible effects are in the arms, legs, spine, hands, feet, face, and head, many of the bones in the body are affected.
- Individuals with achondroplasia have a close to average-sized torso but short arms and legs. This is why achondroplasia is known as a disproportionate dysplasia.
- Achondroplasia is the most common type of skeletal dysplasia (a condition that affects cartilage and bone growth and development).




Individuals with achondroplasia typically have other, less visible health complications.

### Other features of achondroplasia that may be present




Individuals with achondroplasia have a change in their DNA, called a 'mutation' within the fibroblast growth factor receptor 3 (shortened to *FGFR3*) gene[ll].

- This gene holds instructions for making the *FGFR3*. Growth is a balanced process with acceleration and braking, and *FGFR3* is a natural brake of growth.
- Changes in the gene cause the 'brake' to be very active, slowing bone growth.

## What is vosoritide?

Vosoritide is similar to a natural substance that exists in the human body (C-type natriuretic peptide; shortened to CNP).

- Vosoritide works by supplementing the body's existing CNP to increase bone growth velocity during the time of life when most growth usually occurs (most growth occurs until puberty).
- Children receive vosoritide as a daily injection with a very small needle, for an administration of the medicine under the skin.
  - Injections were given to children at their homes by a trained caregiver.

## What did these studies look at?

This summary looks at the **safety*** and **efficacy**† of vosoritide from two studies in children with achondroplasia.

Children between the ages of 5 and 18 years took part in the studies.

Researchers (clinicians and nurses responsible for conducting these studies in each clinical center) measured how much vosoritide increased bone growth over 42 months in children with achondroplasia.

Researchers measured the children several times over the course of the studies. Based on these measures, researchers did calculations to predict how much children would grow during a year. This is known as 'annualized growth velocity' (see below).

They also looked at how many children experienced **side effects**,§ what types, and how **serious**¶ these were.

## Annualized growth velocity (growth rate)

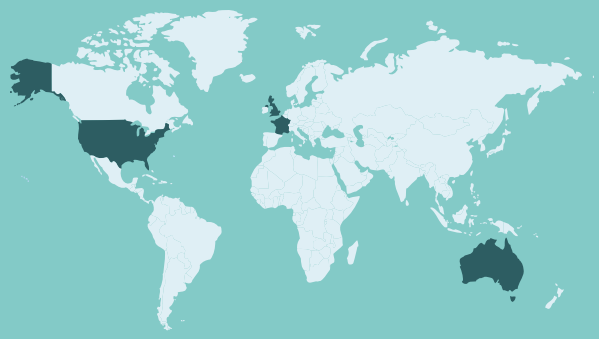
Growth was measured at different times during the study. The annualized growth velocity represents the increase in growth rate over a year.

## What was Study A?

- Phase 2 study
- Researchers looked at the safety* and efficacy† of vosoritide in 35 children aged 5–14 years with achondroplasia.
  - Children were measured for height and other body dimensions for 6 months before starting Study A.
  - Approximately the same number of children were put randomly in different groups, with each group getting a daily injection of 2.5, 7.5, 15 or 30 micrograms of vosoritide per kilogram of body weight.

The study took place in several hospitals in:

Australia France
UK USA



### Who took part in Study A?

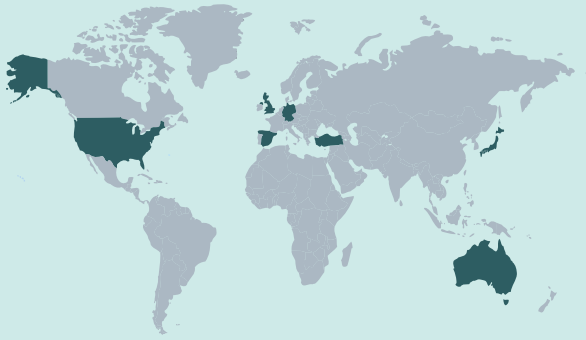
**Characteristics of children at start of study**

## What was Study B?

- Phase 3 study
- Researchers looked at the safety* and efficacy† of vosoritide in children aged 5 up to 18 years with achondroplasia.

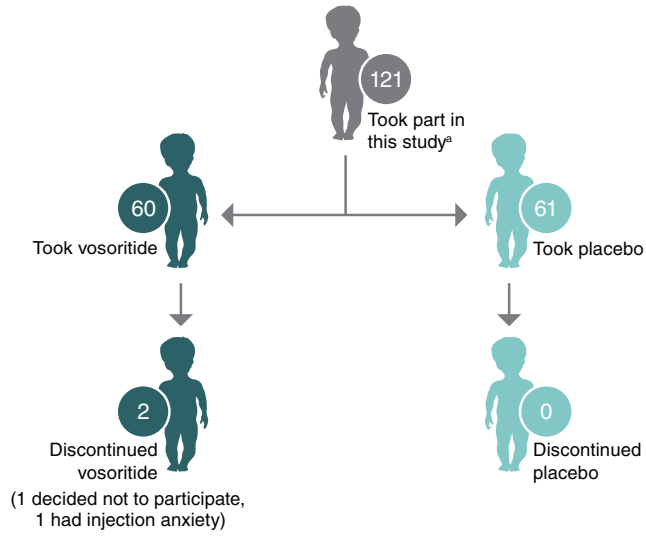
The study took place in several hospitals in:

Australia Germany Japan Spain
Turkey USA UK



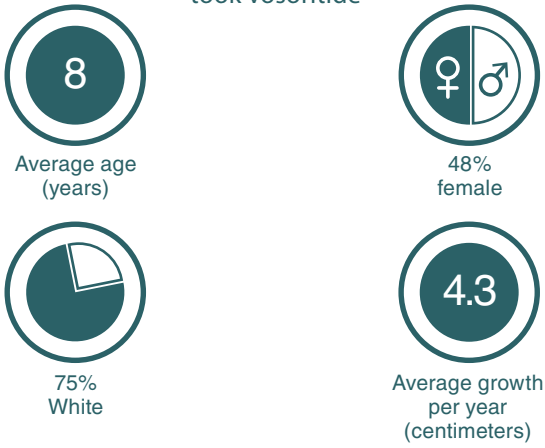
- Children were measured for height and other body dimensions for 6 months before starting Study B.
  - 60 children received vosoritide.
  - 61 children received a placebo‡.

### Who took part in Study B?

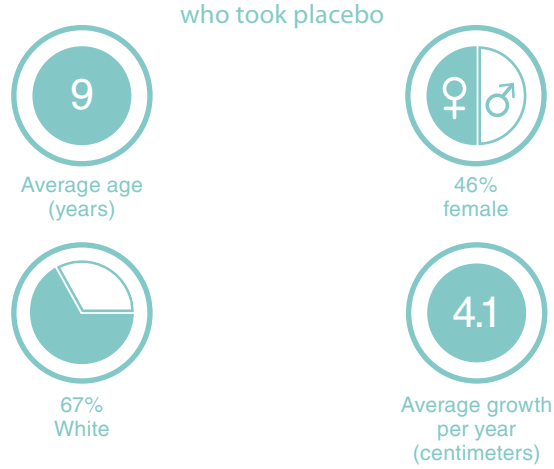



[a]Children were assigned to receive vosoritide or placebo randomly. None of the children, parents, or healthcare professionals knew which group the children were assigned to (this is called a 'closed-label' or 'double-blind' study).

### Characteristics of children at start of study who took vosoritide




### Characteristics of children at start of study who took placebo



## What were the safety* findings from both of these studies?

- Following a daily injection of vosoritide or placebo, the most common side effects[§] that children developed were skin reactions at the injection site, such as redness.
  - All of these symptoms were mild, and children got better quickly.
- Most side effects[§] were generally mild and improved without children needing to stop treatment.
- No children stopped taking vosoritide during the study due to safety* reasons.
- Vosoritide did not cause additional disproportionate bone growth or bone changes and no improvement or worsening of body proportions was observed.

## What were the safety* results of Study A?

- All 35 children experienced mild side effects[§] when taking vosoritide.

**The most common side effects[§] of vosoritide among 35 children were:**

86%

Inflammation or rash at the injection site (injection-site reaction)

86%

Redness at the injection site

54%

Fever

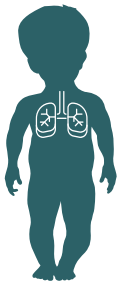
49%

Cough

- 4 children experienced serious health complications during the study[¶].
  - Doctors did not consider these to be due to taking vosoritide.
  - These health complications are sometimes seen in children with achondroplasia.
- 6 children stopped the treatment during the study for different reasons unrelated to vosoritide. 1 child stopped treatment due to the diagnosis of a syndrome that was not thought to be caused by treatment.

## Serious health complications[¶] experienced by children while taking part in Study A

*Researchers did not consider these to be due to taking vosoritide*



1 Interrupted breathing (apnea) when they slept

1 Enlarged tonsils

1 Cyst on their neck

1 Fluid-filled cyst in their spinal cord

## What were the safety* results of Study B?

- There was no difference in the total number or overall severity of side effects[§] in children receiving vosoritide or placebo.
  - Nearly all (98%) children had at least 1 side effect[§] at 1 point during the study.
  - Some injection-site reactions (like inflammation/rash or swelling) were more common in children taking vosoritide than in those taking placebo.
  - Most side effects[§] were mild.

### The most common side effects[§] of treatment in 121 children were:

Vosoritide (60 children)

73%

Inflammation or rash at the injection site (injection-site reaction)

68%

Redness at the injection site

38%

Swelling at the injection site

27%

Swelling of the nasal passages/ throat (naso-pharyngitis)

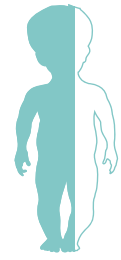
27%

Vomiting

Placebo (61 children)

48%

Inflammation or rash at the injection site (injection-site reaction)



66%

Redness at the injection site

10%

Swelling at the injection site

30%

Swelling of the nasal passages/ throat (naso-pharyngitis)

20%

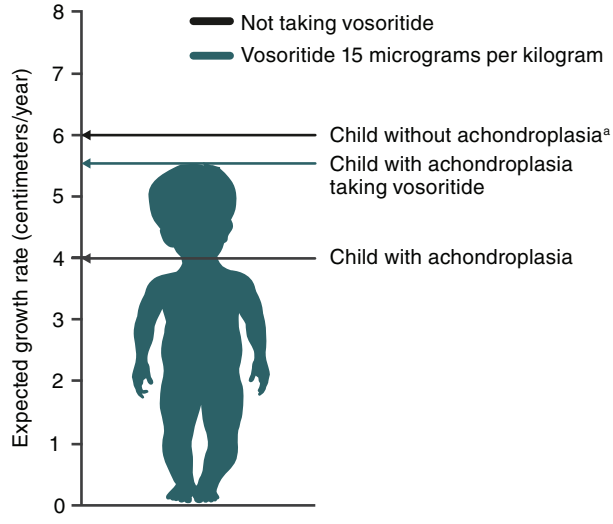
Vomiting

- 7 children had serious health complications[¶]; 3 of these children were taking vosoritide and 4 were taking placebo.
  - None of these serious health complications[¶] were thought to be due to treatment.
  - 2 children stopped the treatment during the study. 1 child stopped treatment due to feeling more pain from the injection and 1 stopped due to fear of needles.

## What were the efficacy† results of Study A?

- In the first 6 months of treatment, the velocity of growth (growth rate) of the children increased with all doses of vosoritide greater than 2.5 micrograms per kilogram.
  - Doses of 15 micrograms per kilogram of body weight of vosoritide increased the growth rate of children by 2 cm per year from study start.
  - Children who took higher doses (30 micrograms per kilogram) of vosoritide grew at similar rates to children taking the 15-microgram dose.
- The increases in growth rate seen at 6 months were observed over the first 24 months (dose-finding part) of the study.
- Overall, researchers took measurements over a total of 42 months (months 30 to 42 were part of an extension study).
- An increased growth rate for children taking the drug persisted over the 42 months of treatment.
- Between 30 and 42 months of treatment, children who took 15 micrograms per kilogram of vosoritide had an average growth rate of 5.5 cm per year (this includes natural growth + vosoritide effect).
  - Vosoritide increased growth rate by roughly 1.5 cm per year from the start of the study.
    - As this is an average, some children grew more and some grew less than 1.5 cm per year.
- After 42 months of treatment, children with achondroplasia taking vosoritide grew at a rate closer to children without achondroplasia, who were of similar age and sex.

### Expected growth rate for children with achondroplasia receiving vosoritide for 42 months

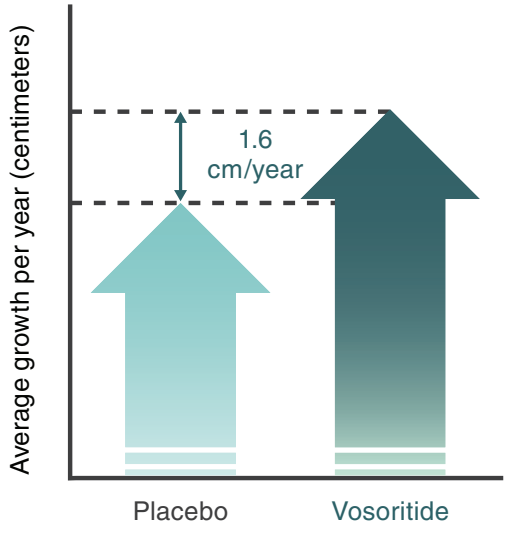



[a]Average annual growth of a child without achondroplasia per year before reaching adolescence.

## What were the efficacy† results of Study B?

- After 1 year of treatment, the growth rate for children receiving 15 micrograms per kilogram vosoritide was 1.6 cm per year higher on average than for children receiving placebo.

### After 1 year



## What do the results of these studies mean?

- In these studies, vosoritide increased bone growth in children with achondroplasia.
- The body proportionality (legs and arms versus the length of the torso) did not worsen during the studies.
- Receiving the drug every day at an effective dose generally only caused mild side effects[§].
- Serious health complications[¶] observed in children while taking vosoritide were mostly those sometimes seen in children with achondroplasia even if they do not take vosoritide.
- In the long term, with continuous administration of vosoritide for several years until the child's growth plates close and the child stops growing naturally, it is not yet known if vosoritide will:
  - Increase children's final adult height
  - Change body proportions (i.e., increase arm or leg length relative to the torso)
  - Reduce other complications that are related to achondroplasia.
- The side effects[§] of long-term treatment are also unknown.
  - There will be other studies to look at the long-term effects of the treatment.
  - Ongoing studies are analysing the effects of vosoritide in children between the ages of 0 and 5 years old to see if bone growth is greater if children receive vosoritide when they are younger.

## Are there any plans for future studies?

- Both Study A and Study B have an extension period. This means researchers will continue to look at the effects of vosoritide until the children reach their final adult height (i.e., after their growth plates close).
- All children in Study B changed to vosoritide after 1 year of placebo[‡] when starting the long-term extension study.
  - Title: A Phase 3, open-label[#] long-term extension study to evaluate the safety* and efficacy[†] of BMN 111 (vosoritide) in children with achondroplasia (https://clinicaltrials.gov/ct2/show/NCT03424018).
  - The extension study will continue to collect information on how vosoritide affects children in diverse aspects that include:
    - Quality of life
    - Ability to perform daily activities independently
    - The frequency and type of medical or surgical treatments
    - Final adult height.

- A second Phase 2 study is now underway to assess the safety* and efficacy[†] of vosoritide in younger children (between the ages of 0 and 5 years old).
  - Title: A randomized, double-blind, placebo[‡]-controlled clinical trial to evaluate the safety* and efficacy[†] of BMN 111 (vosoritide) in infants and young children with achondroplasia, age 0 to <60 months (5 years) (https://clinicaltrials.gov/ct2/show/NCT03583697).

- A third Phase 2 study is currently underway to assess the safety* of vosoritide in children (up to 1 year old) who are at risk of requiring cervicomedullary decompression surgery for foramen magnum stenosis or cervicomedullary compression.
  - Title: A randomized, controlled, clinical trial with an open-label[#] extension to investigate the safety* of vosoritide in infants and young children with achondroplasia at risk of requiring cervicomedullary/foramen magnum decompression surgery (https://clinicaltrials.gov/ct2/show/NCT04554940).

## Who sponsored these studies?

These studies were sponsored by BioMarin Pharmaceutical Inc.

## FAQs

**What is achondroplasia?**

- Achondroplasia is a condition that affects bone growth and can lead to diverse physical challenges and health issues. It is the most common type of skeletal dysplasia with disproportionate short stature, also known as dwarfism.

**What is vosoritide?**

- Vosoritide is a drug developed to increase growth in children with achondroplasia.

**What does vosoritide do?**

- Vosoritide improves bone growth by compensating for the reduced growth effects of the changed *FGFR3* gene[‖] in achondroplasia.

**Is vosoritide safe?**

- The most common side effects[§] of vosoritide are skin reactions at the injection site. These are typically mild and get better quickly.

**Does vosoritide increase final adult height?**

- Vosoritide increased bone growth velocity in children during the studies, but more time taking vosoritide is needed to confirm the increase in final adult height. An extension study is investigating this.

## Where can readers find more information on these studies?

The original article of Study A was published in the *New England Journal of Medicine* and is called 'C-type natriuretic peptide analogue therapy in children with achondroplasia' (Savarirayan R *et al. N. Engl. J. Med.* 381, 25–35 [2019]).

You can access the full article for free here: https://www.nejm.org/doi/pdf/10.1056/NEJMoa1813446

The original article of Study B was published in *The Lancet* and is called 'Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, Phase 3, placebo-controlled, multicentre trial' (Savarirayan R *et al. Lancet* 396, 684–692 [2020]).

You can access the abstract for free, or pay a small fee for the full article here:
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31541-5/fulltext

**For additional information on BioMarin clinical studies** visit www.clinicaltrials.gov and type in study code 'BMN 111'.
For inquiries or to provide feedback from advocacy organizations, please contact patientadvocacy@bmrn.com.
Contact BioMarin Medical Information at https://www.biomarin.com/contact-us/global-medical-information/.

**For additional information on vosoritide clinical trials** visit https://www.biomarin.com/clinical-trials/achondroplasia/

### Disclaimer

Please note that this summary only contains information from the full scientific articles.

### Acknowledgments

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