

Little People of America's (LPA) Biotech Industry Liaison Committee has established a comprehensive overview of the latest biotechnology developments in skeletal dysplasias or dwarfisms. Prior to any interaction with LPA, pharmaceutical companies began developing pharmacologic therapies. This review will focus on achondroplasia but will evolve to include developments for other conditions as they advance. The LPA Biotech Industry Liaison Committee was formed to process these ongoing research efforts to ensure the LPA community, as well as those just being introduced to dwarfism, have access to objective and easy to understand information in which to base healthcare decisions. In this review, we break down the latest data and identify questions that still need to be answered.

LPA's Formal Stance

LPA recognizes the complexity and sensitivity of this topic for our community. We maintain that LPA's organizational role is to provide social support and advocacy. This role does not mean that LPA is categorically opposed to all medical research, especially if it holds the potential to improve the quality of life of our members by treating symptoms that can range from uncomfortable to lethal. As medical science moves forward, we will continue to advocate for researchers to be mindful of our commitment to the value of dwarf pride and its contributions to human biological, social, and cultural diversity.

In our mission to support the community of people with dwarfism, LPA respects the choices of parents or individuals regarding healthcare decisions. We welcome all individuals and families to be part of LPA, regardless of medical decisions and outcomes. LPA aims to help provide accurate information to make these complex, emotionally charged, and potentially life-altering choices. We hope to help our members better understand their rights while advocating for researchers to focus on healthcare outcomes beyond growth velocity. **As a support organization, we believe that focusing on growth velocity is a pharmaceutical solution for a societal problem. We want to reframe these priorities in research to the most meaningful ones to our members, such as reducing spinal stenosis, sleep apnea, corrective surgeries, and other interventions that would improve quality of life.**

What is achondroplasia:

Achondroplasia is the most common form of skeletal dysplasia or dwarfism. It is a condition of abnormal bone growth that is caused by a mutation or alteration to the gene that encodes for fibroblast growth factor receptor 3 (FGFR3). This mutation causes the signaling pathway of the cells within the cartilage growth plate of the bones to be overactive, incorrectly telling the body to “slow down” growing.^{1,2}

The majority of individuals with achondroplasia are diagnosed based on clinical characteristics and X-rays prior to birth or shortly after birth, although genetic testing can be done to remove any uncertainty. These characteristic features include short stature with disproportionately short arms and legs, large head (macrocephaly), prominent forehead (frontal bossing) and mid-face hypoplasia. Most individuals with achondroplasia are able to live independent and productive lives.^{1,2}

Potential complications associated with achondroplasia include bowing of the legs, recurrent ear infections, leg & back pain due to spinal stenosis, delays in walking & motor skills, neck compression, and breathing problems, particularly sleep apnea. To learn more about achondroplasia, more information can be [found here](#) and [here](#).^{2,3}

Medical management of achondroplasia:

Medical management is focused on preventing, anticipating, identifying, and correcting complications as they arise and encouraging a healthy lifestyle, positive self-esteem, and mental health.² The complications associated with achondroplasia can vary greatly in comparison to others with achondroplasia and across one’s lifetime.^{2,5}

Some individuals experience very minor complications and require little to no medical intervention, while others will require more intensive management, including interventions such as spinal decompression, leg straightening, spinal fusion, and ear tubes. Additionally, the type of complications individuals with achondroplasia may face can change throughout one’s life. As a baby, the major complications include constriction of the nerves in the neck (i.e. foramen magnum) and breathing restrictions. Ear infections, obesity, obstructive apnea, orthopedic concerns, and other complications may also arise throughout childhood & adulthood.²

Until recently, there have been no pharmaceutical therapies approved for achondroplasia. Human growth hormone has been used previously but is not recommended as it does not reduce any of the complications associated with achondroplasia. Furthermore, the small 1 to 1.5 inch increase in height requires years of injections.^{2,4} Development of targeted therapies designed specifically for achondroplasia is ongoing. Vosoritide is the first FDA approved therapy for achondroplasia and was

approved under accelerated approval for use in the United States in November 2021. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory studies. This paper summarizes the research process and the therapies in development.⁴

Research overview:

In order for a drug or therapy to receive regulatory approval and be available on the market, each must go through a series of steps or phases to evaluate whether it is safe and effective.⁶ The different phases are:

1. **Pre-clinical:** Important safety, toxicity, and preliminary efficacy testing conducted using tissue and animal models. This phase helps researchers characterize the drug and is required before a drug can be studied in humans.
2. **Phase I:** Once a drug completes all of the pre-clinical testing, the drug is given to humans for the first time in a phase I trial. This typically involves a small group of normal, healthy adult volunteers to assess the safety of the drug.
3. **Phase II:** If the safety assessment in phase I is acceptable, the drug can then be studied in the target population (in this case achondroplastic children). Safety continues to be assessed, while also beginning to assess efficacy.
4. **Phase III:** Now that the drug has demonstrated to be relatively safe and effective for further testing, a phase III trial is completed to compare the safety and effectiveness of the new treatment against the current standard treatment. In cases where there is no standard treatment like with achondroplasia, a placebo (an inactive substance like distilled water) can be used as a reference to compare the safety and efficacy of the study drug.
5. **Regulatory approval:** If successful in phase III, a regulatory agency, like the Food and Drug Administration (FDA), reviews all of the data collected from the different research phases to evaluate the risks and efficacy to determine if the drug should be approved for general use by the public.
 - a. **Accelerated approval:** The FDA instituted its Accelerated Approval Program to allow for earlier approval of drugs that treat serious conditions, and that fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Drug companies are still required to conduct studies to confirm the anticipated clinical benefit, which will determine whether the drug receives a traditional approval or is removed from the market.

6. **Phase IV:** If approved, research on the drug is not stopped. The drug continues to be studied to understand the long-term safety and efficacy outcomes.

Current development:

Currently, there are 6 different drugs in clinical development (being studied in humans) for achondroplasia. Each target the overactive FGFR3 pathway, which if successful would allow the bones to grow and develop more ordinarily. While the therapies have the potential to impact the symptoms and complications of achondroplasia, they will not impact any genetic factors. For the purpose of this review, we will focus on the 4 therapies and companies furthest in development (phase II and beyond).⁷

The 4 therapies and companies are:

- Vosoritide (Biomarin)
- TransCon CNP (Ascendis)
- Recifercept (Theracon, acquired by Pfizer)
- Infigratinib (QED Therapeutics).

Voxzogo (vosoritide) - Biomarin

Biomarin's vosoritide is the furthest in development and is currently approved under accelerated approval for use in the United States in November 2021. Vosoritide is a c-type natriuretic peptide (CNP) analog that bolsters CNP signaling in the bone to improve the balance of overactive FGFR3 signaling, allowing bones to grow.^{3,4,8} In the US, vosoritide, is approved in children with achondroplasia who are 5 years of age and older with open growth plates.

Vosoritide's phase III trial studied children with achondroplasia aged 5 to 14 years. In this trial, vosoritide improved growth velocity or height by 1.39 inches over 2 years, a roughly 0.7 inch benefit per year versus placebo.^{9,10} While the trial met its primary endpoint (growth velocity), these studies are limited in their ability in determining whether improvements in growth will translate to benefits of functionality, quality of life, activities of daily living, and/or reducing any of the major complications associated with achondroplasia. Vosoritide was found to improve upper-to-lower body segment proportionality, a secondary endpoint of the trial, however key secondary endpoints such as the impact to quality of life, developmental status, and functional independence are inconclusive and are continuing to be assessed. More data and longer follow-up is needed to determine the exact impact vosoritide has on these endpoints. Additionally, the impact of vosoritide on other meaningful outcomes such as reduction in spinal

stenosis, sleep apnea, and medical interventions is not known and are also continuing to be evaluated.^{9,10}

Overall, vosoritide was well tolerated with the majority of adverse events or side effects being mild and no serious adverse events being reported. The most common side effects were injection site reactions such as redness and swelling of the skin.^{9,10}

- **Phase in development:** Accelerated approval November 2021; confirmatory studies ongoing
- **Administration:** Once daily subcutaneous shot under the skin and will likely be taken until the growth plates close, which is determined by your doctor.
- **Cost:** Patient costs will be influenced by the type of insurance & coverage. The wholesale price (without insurance) for a 1 year supply of vosoritide is \$328,000. Access and patient support programs can be found at BioMarin Rare Connections.
- **Ongoing studies:**
 - Phase III extension: Continuing to follow the children from the phase III trial to assess the secondary endpoints
 - Phase II: Children at risk of life-threatening foramen magnum compression
 - Phase II: Infants and young children ages 0 to 5 years old

Questions about vosoritide and its clinical development can be addressed at Biomarin.com/contact-us/global-medical-information.

TransCon CNP - Ascendis Pharma

Similar to vosoritide, Ascendis Pharma's TransCon CNP is also a c-type natriuretic peptide and works similarly. One difference is that it has a different formulation that allows the drug to stay in the body longer, leading to less frequent administrations. Overall, there is a lot of information still to be determined for TransCon CNP, which is to be expected since it is still only in phase II development.¹¹

TransCon CNP is being studied in children 2 to 10 years of age. Currently, there is little data on the efficacy and safety of TransCon CNP, although the results from this phase II trial will provide an initial understanding.¹²

- **Phase in development:** Phase II ongoing
- **Administration:** Once weekly subcutaneous shot under the skin and will likely be taken until the growth plates close (typically in the teenage years)
- **Cost:** TBD; patient costs will be influenced by the type of insurance & coverage
- **Ongoing studies:**

- TBD

Questions about TransCon CNP and its clinical development can be addressed at atascendispharma.com/contact-us.

Truseltiq (Infigratinib) - QED Therapeutics

Infigratinib is already approved as a treatment for bile duct & bladder cancer and is in phase II development for achondroplasia with results expected in the second half of 2021. Infigratinib is a tyrosine kinase inhibitor which alters the FGFR3 receptor, reducing the ability of ligands or molecules from activating FGR3. This leads to a reduction in both of the overactive signaling mechanisms, allowing bones to grow.¹³

Similar to TransCon CNP, there is a lot of information to be determined for Infigratinib. What is known is that the phase II trial is being studied in children 3 to 11 years of age and is administered as oral tablets. Results from this study will provide an initial glimpse at the efficacy and safety of Infigratinib in achondroplasia.¹⁴

- **Phase in development:** Phase II ongoing
- **Administration:** TBD; Oral tablets
- **Cost:** TBD; patient costs will be influenced by the type of insurance & coverage
- **Ongoing studies:**
 - TBD

Questions about infigratinib and its clinical development can be addressed at qedtx.com/#contact.

Recifercept - Recifercept

Lastly, we have Pfizer's recifercept, which is a FGFR3 decoy. It works by tricking the ligands or molecules that normally bind to FGR3 to bind to the drug instead. This reduces the FGFR3 activation and both overactive signaling mechanisms, leading to bone growth.¹⁵ The administration will likely be a subcutaneous injection, although the frequency is not known. Like TransCon CNP and Infigratinib, there is a lot to be determined with recifercept. What is known is that the phase II trial is being studied in 2 groups: children under the age of 2 years old and children 2 to 10 years old. The results from this study will provide initial understanding on the safety & efficacy of recifercept.^{15,16}

- **Phase in development:** Phase II ongoing
- **Administration:** TBD; likely subcutaneous injection under the skin
- **Cost:** TBD; patient costs will be influenced by the type of insurance & coverage
- **Ongoing studies:**
 - TBD

Questions about recifercept and its clinical development can be addressed at [Pfizer.com/products/information](https://www.pfizer.com/products/information).

Conclusion:

We recognize that this is a sensitive and difficult topic for many individuals with dwarfism. As part of our mission to support the community of people with dwarfism, LPA will continue to advocate for researchers to be mindful of our commitment to the value of dwarf pride and its contributions to human biological, social, and cultural diversity. Furthermore, we will continue to strongly push for research efforts to focus beyond growth velocity, but instead on the outcomes most meaningful to our community, such as reducing spinal stenosis, sleep apnea, corrective surgeries, and/or improving quality of life. Currently, vosoritide is the first drug to meet its primary endpoint for achondroplasia, however, we do not know yet whether this improvement in growth velocity will translate to improving more meaningful outcomes.

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About LPA's Biotech Industry Liaison Committee:

This committee is a diverse, well-rounded group of LPA members that was formed to provide objective, unbiased interpretation and analysis of the ongoing research efforts in skeletal dysplasias. Our committee includes both the short statured and average height perspective including lifetime LPA members, new parents, as well as caregivers to children who have participated in some of the clinical trials. Together, we bring a robust knowledge in healthcare, pharmaceutical industry, legal, and executive board experience.

Committee Members:

- Ashley Grist
- Colleen Giofreda
- Deb Himsel
- Dianna Carda
- Josh Maudlin
- Karen McDonnell
- Kelsie Hankins Hughes
- Mark Povinelli
- Michael Hughes
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Glossary:

Efficacy: In medicine, the ability of an intervention (for example, a drug or surgery) to produce the desired effect.

Growth Velocity: The change in measurements or increments in weight and length/height over time. It indicates the velocity or the rate of growth per unit of time.

Open/Closed Growth Plates: Growth plates are areas of cartilage located near the ends of bones. Open growth plates are still in the process of growing. Closed growth plates have hardened into solid bone and indicate that the bones are no longer growing.

Primary Endpoint: The main result that is measured at the end of a study to see if a given treatment worked.

Sleep Apnea: Sleep apnea is a potentially serious sleep disorder in which breathing repeatedly stops and starts.

Spinal Stenosis: Spinal stenosis is a narrowing of the spaces within your spine, which can put pressure on the nerves that travel through the spine.

Subcutaneous: Beneath, or under, all the layers of the skin.