

Transforming Achondroplasia Care: Oral Infigratinib as a Disease-Modifying Therapy for FGFR3-Driven Skeletal Dysplasia

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ABSTRACT

Background: Achondroplasia is the most common genetic skeletal dysplasia and the leading cause of disproportionate short-limb stature in children. It is caused mainly by gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 gene.

Objective: This article reviews the biological rationale, clinical evidence, safety profile, monitoring requirements and future role of oral infigratinib in pediatric achondroplasia.

Methods: The article is narrative review based on recent published literature, clinical trial reports, international guidelines and pediatric medication-administration evidence published mainly within the last five years.

Results: Oral infigratinib represents a major development in the treatment of pediatric achondroplasia. Its scientific strength lies in directly targeting FGFR3-driven pathophysiology, while its practical appeal comes from oral administration.

Conclusion: Although infigratinib remains investigational for achondroplasia until regulatory approval, current evidence suggests that it may become a valuable disease-modifying therapy for children with open growth plates. The next stage of research must move beyond growth velocity alone and determine whether infigratinib improves long-term function, proportionality, quality of life, medical complications and family-centered outcomes.

Keywords: achondroplasia, children, FGFR3, skeletal dysplasia, annualized height velocity, body proportionality

1. INTRODUCTION

Achondroplasia is a lifelong skeletal dysplasia characterized by disproportionate short stature, rhizomelic limb shortening, macrocephaly, frontal bossing, midface hypoplasia, trident hand, lumbar lordosis and several age-dependent complications [1]. It is widely recognized as the most common

genetic form of short-limbed skeletal dysplasia. Recent clinical summaries describe achondroplasia as a condition caused mainly by FGFR3 mutations that impair endochondral ossification and contribute to orthopedic, neurological, respiratory, otolaryngological and functional complications across the lifespan. The clinical significance of achondroplasia extends beyond height [2]. Children may experience foramen magnum stenosis, sleep-disordered breathing, recurrent otitis media, conductive hearing loss, thoracolumbar kyphosis, genu varum, spinal stenosis, delayed motor milestones, functional limitations and psychosocial challenges. Gene Reviews notes that individuals with achondroplasia have characteristic clinical and radiological features and that average adult height is approximately 129.9 cm in males and 122.4 cm in females. Traditional care is multidisciplinary and supportive, involving pediatrics, genetics, endocrinology, orthopedics, neurosurgery, otolaryngology, respiratory medicine, physiotherapy, audiology and psychosocial care. However, disease-modifying therapy has changed the treatment landscape [3]. Vosoritide, a C-type natriuretic peptide analogue, became the first approved precision therapy for achondroplasia, creating the need for practical international treatment and monitoring guidance. Oral infigratinib represents the next major development because it directly targets FGFR signaling and is administered orally [4]. This article critically reviewed the oral infigratinib as a disease-modifying therapy in children with achondroplasia. The article discusses the molecular basis of achondroplasia, the pharmacological rationale for infigratinib, available clinical evidence from the PROPEL programme, safety and monitoring considerations, comparison with existing treatment options, and future research priorities.

2. MATERIAL & METHODS

This article is a narrative review based on recent published literature, clinical trial reports, international guidelines and pediatric medication-administration evidence published mainly within the last five years. Sources included peer-reviewed articles on achondroplasia genetics, PROPEL and PROPEL 2 study data, Phase 3 PROPEL 3 trial reports, international consensus guidance, Gene Reviews, Stat Pearls, Nature Reviews Endocrinology, Orphanet Journal of Rare Diseases. Search concepts included “achondroplasia,” “FGFR3,” “oral infigratinib,” “PROPEL 2,” “PROPEL 3,” “children,” “annualized height velocity,” “body proportionality,” “vosoritide,” “pediatric medication adherence” and “skeletal dysplasia [5].”

3. MOLECULAR BASIS OF ACHONDROPLASIA

Achondroplasia is usually caused by a heterozygous gain-of-function pathogenic variant in FGFR3. Gene Reviews reports that targeted testing commonly identifies c.1138G>A p. Gly380Arg in approximately 98% of affected individuals and c.1138G>C p. Gly380Arg in approximately 1%. A 2024 review of 467 published patients similarly found that p. Gly380Arg was the most common FGFR3 mutation, with c.1138G>A being much more common than c.1138G>C. FGFR3 normally acts as a negative regulator of endochondral bone growth [6]. In achondroplasia, FGFR3 signaling is overactive, suppressing chondrocyte proliferation and maturation in the growth plate. A 2025 review explained that gain-of-function FGFR3 mutations dysregulate endochondral ossification by enhancing FGFR3 signaling, reducing growth plate size and limiting long bone elongation. This mechanism provides the biological rationale for targeted therapies that either counteract FGFR3 downstream signaling or inhibit FGFR3 activity directly [7].

4. INFIGRATINIB: PHARMACOLOGICAL RATIONALE

Infigratinib is an orally bioavailable, selective FGFR1–3 tyrosine kinase inhibitor. The PROPEL and PROPEL 2 publications described infigratinib as an oral FGFR1–3 selective inhibitor being developed as a direct therapeutic strategy to counteract FGFR3 overactivity in children with achondroplasia. The key theoretical advantage of infigratinib is that it targets the primary receptor pathway involved in achondroplasia rather than acting only through compensatory downstream pathways. By inhibiting

FGFR3 tyrosine kinase activity, infigratinib aims to reduce excessive receptor signaling in the growth plate, allowing improved chondrocyte proliferation, maturation and longitudinal bone growth [8]. This is mechanistically different from vosoritide, which activates the CNP-NPR-B pathway to oppose MAPK signaling downstream of FGFR3. Infigratinib is also important because it is oral. Daily injections can be difficult for some children and caregivers, especially when treatment continues for years. A systematic review on pediatric medication administration emphasized that caregiver health literacy, clear dosing instructions, administration tools and patient education are major factors affecting medication safety and adherence at home. These findings are relevant to infigratinib because an oral pediatric therapy still requires accurate dosing, consistent administration, monitoring and caregiver education [9].

5. CLINICAL EVIDENCE: PROPEL AND PROPEL 2

The early PROPEL programme established the clinical development framework for infigratinib in achondroplasia. PROPEL was designed as an observational study, while PROPEL 2 and PROPEL 3 were interventional studies evaluating infigratinib and/or placebo. The Phase 2 PROPEL 2 trials evaluated oral infigratinib in children with achondroplasia aged 3–11 years. In this dose-finding study, 72 children were enrolled into five sequential cohorts receiving daily doses from 0.016 mg/kg to 0.25 mg/kg [10]. The highest-dose cohort, cohort 5, received 0.25 mg/kg daily. The PROPEL 2 findings were clinically meaningful. In cohort 5, annualized height velocity increased and remained improved through 18 months, with a mean change from baseline of 2.50 cm/year at 18 months. Height z-score also improved by 0.54 relative to an untreated achondroplasia reference population, and the upper-to-lower body segment ratio decreased by 0.12, suggesting improved body proportionality. Safety findings in PROPEL 2 were also encouraging [11]. All children experienced at least one adverse event, but most events were mild or moderate, and none resulted in treatment discontinuation. No major safety signal was apparent in the published conclusion. These results supported the movement from Phase 2 dose-finding into Phase 3 confirmatory evaluation.

6. CLINICAL EVIDENCE: PHASE 3 PROPEL 3

The Phase 3 PROPEL 3 trial was designed as a global, one-year, randomized, double-blind, placebo-controlled study evaluating infigratinib in children and adolescents with achondroplasia aged 3 to under 18 years with open growth plates. PROPEL 3 met its primary endpoint. At Week 52, oral infigratinib demonstrated superiority over placebo for change from baseline in annualized height velocity, with a least-squares mean treatment difference of +1.74 cm/year and an observed mean difference of +2.10 cm/year. The trial also met a key secondary endpoint for height z-score, with an LS mean increase of +0.41 SD in the infigratinib arm [12]. A particularly important finding was the signal for improved body proportionality. In a pre-specified exploratory analysis among children younger than 8 years, infigratinib showed a statistically significant treatment difference in upper-to-lower body segment ratio compared with placebo. Additional data presented at the International Congress of Children's Bone Health showed improvement in arm-span z-score versus placebo, suggesting that future studies should evaluate proportionality, reach, function and daily living outcomes rather than height alone. Safety findings in PROPEL 3 were favourable over 52 weeks [13]. The company-reported NEJM publication summary stated that there were no discontinuations related to study drug, no serious adverse events related to study drug, three mild and transient cases of hyperphosphatemia and no retinal or corneal adverse events associated with FGFR1 or FGFR2 inhibition.

7. SAFETY AND MONITORING CONSIDERATIONS

Although current pediatric achondroplasia data are encouraging, infigratinib is still a tyrosine kinase inhibitor, and long-term safety monitoring is essential. FGFR inhibition may theoretically affect phosphate metabolism, ocular tissues, dental development, bone maturation, growth plate biology and

other organ systems. In oncology, higher doses of FGFR inhibitors have been associated with hyperphosphatemia and ocular adverse events, making monitoring especially important in children even when lower doses are used.

Table 01: A practical monitoring framework should include:

Domain	Suggested Monitoring Focus
Growth	Standing height, sitting height, growth velocity, height z-score, arm span, upper-to-lower segment ratio
Skeletal development	Bone age, limb alignment, spine assessment, orthopedic symptoms
Biochemistry	Serum phosphate, calcium, renal function, liver enzymes where clinically appropriate
Ophthalmology	Baseline and periodic eye assessment, especially retinal and corneal evaluation
Neurology	Screening for foramen magnum stenosis symptoms, spinal stenosis, sleep-disordered breathing
ENT and respiratory	Hearing, otitis media, sleep apnea, airway symptoms
Adherence	Caregiver education, oral dosing routine, missed-dose plan, medication storage
Patient-centred outcomes	Mobility, fatigue, pain, school participation, quality of life, family burden

Infigratinib should not be viewed as a replacement for multidisciplinary achondroplasia care. Even with improved linear growth, children still require surveillance for neurological, respiratory, ENT, orthopedic and psychosocial complications.

8. COMPARISON WITH VOSORITIDE AND OTHER EMERGING THERAPIES

Vosoritide changed achondroplasia care by demonstrating that precision therapy could improve growth in children. International consensus guidance recognizes vosoritide as the first pharmacological precision treatment for achondroplasia and provides recommendations for starting, monitoring and stopping therapy. Infigratinib differs from vosoritide in three main ways [14]. First, it is oral rather than injectable. Second, it targets FGFR signaling directly rather than acting through the CNP pathway. Third, current Phase 3 evidence suggests potential improvement in both growth velocity and body proportionality. However, direct comparison between therapies should be cautious because trial populations, ages, endpoints, designs and follow-up durations differ. The future treatment landscape may include multiple options, such as CNP analogues, FGFR3 inhibitors and other pathway-modifying therapies [15]. The central clinical question will not be only “which treatment increases height most?” but “which treatment improves overall health, function, proportionality, safety, independence and quality of life over the long term?”

9. PATIENT SELECTION

Potential candidates for oral infigratinib, once approved by regulators, would likely include children with genetically or clinically confirmed achondroplasia and open growth plates. The strongest current trial evidence applies to children aged 3 years and above, although infant and toddler studies are now part of the wider PROPEL programme. Bridge Bio’s trial information states that the infant and toddler trial is enrolling children from birth to under 3 years. Before treatment, clinicians should confirm

diagnosis, assess baseline growth, evaluate neurological and respiratory risk, review medical history, check concomitant medication, discuss realistic expectations and obtain informed consent from caregivers with age-appropriate assent from the child. Genetic confirmation may be particularly helpful when targeted therapy is being considered, as Gene Reviews notes that molecular confirmation can aid access to targeted therapy [16].

10. ETHICAL AND PSYCHOSOCIAL CONSIDERATIONS

Achondroplasia treatment raises important ethical issues. Some families may value increased height and improved proportionality, while others may worry that treatment reinforces social bias against short stature. Ethical care should avoid framing achondroplasia only as a height disorder. Instead, clinicians should discuss potential benefits in relation to function, reach, independence, mobility, pain, proportionality and medical complications, while respecting the identity and preferences of individuals with dwarfism. Shared decision-making is essential. Families should understand that available data show improved annualized height velocity, but long-term adult height, lifelong functional outcomes, complication reduction and psychosocial effects still require further evidence. Treatment should be offered as an option, not imposed as a social expectation.

11. GLOBAL ACCESS AND IMPLEMENTATION CHALLENGES

If infigratinib receives regulatory approval, global implementation will face several barriers. These include cost, availability, specialist access, genetic testing capacity, monitoring infrastructure, caregiver education, long-term follow-up systems and equity between high-income and low- and middle-income countries. Oral administration may improve convenience, but it does not eliminate access challenges. A safe oral therapy still requires accurate weight-based dosing, adherence support, regular monitoring and clear family education [17].

12. Value-Added Clinical Model for Infigratinib Use

A value-added model for oral infigratinib in children with achondroplasia should include six pillars:

- **Molecular confirmation and baseline risk assessment** Confirm achondroplasia clinically, radiologically and genetically where appropriate, and identify neurological, respiratory, ENT and orthopedic risks.
- **Growth and proportionality tracking** Measure height velocity, sitting height, arm span, upper-to-lower segment ratio and achondroplasia-specific height z-scores [18,19].
- **Safety monitoring** Monitor phosphate, ocular findings, bone development, dental health, adverse events and drug interactions.
- **Function-focused outcomes** Include reach, mobility, daily activity, pain, fatigue, sleep, school participation and caregiver-reported outcomes.
- **Family-centred adherence support** Provide clear oral dosing instructions, missed-dose guidance, visual tools and culturally appropriate counselling [20].
- **Long-term registry participation** Encourage post-marketing registries to track adult height, safety, complications, surgery rates and quality of life.

13. LIMITATIONS OF CURRENT EVIDENCE

Current evidence is promising but not complete. The Phase 2 study had limited cohort sizes, and Phase 3 results currently provide 52-week randomized data. Longer follow-up is required to determine final adult height, durability of proportionality improvements, long-term safety, effect on spinal stenosis,

foramen magnum outcomes, sleep apnea, ENT disease, pain, function and quality of life. Another limitation is that growth velocity is a surrogate endpoint. While important, it does not fully capture meaningful benefit. Future trials should include patient-reported outcomes, caregiver-reported outcomes, functional reach, independence, physical activity, pain, sleep, school participation and psychosocial well-being.

14. FUTURE RESEARCH PRIORITIES

Future studies should address:

- Long-term safety through skeletal maturity and adulthood.
- Final adult height and body proportionality outcomes.
- Impact on functional reach, mobility, pain and daily living.
- Effect on neurological, spinal, respiratory and ENT complications.
- Treatment initiation in infancy and early childhood.
- Comparative effectiveness against approved and emerging therapies.
- Combination or sequencing strategies with CNP-pathway therapies.
- Real-world adherence and caregiver experience with oral therapy.
- Health economics and global access.
- Ethical outcomes and patient-community perspectives.

15. CONCLUSION

Oral infigratinib represents a major development in the treatment of pediatric achondroplasia. Its scientific strength lies in directly targeting FGFR3-driven pathophysiology, while its practical appeal comes from oral administration. Phase 2 data showed sustained improvement in annualized height velocity, height z-score and upper-to-lower body segment ratio without major safety signals. Phase 3 PROPEL 3 data further demonstrated superiority over placebo for annualized height velocity at 52 weeks, with supportive findings for height z-score and proportionality. Although infigratinib remains investigational for achondroplasia until regulatory approval, current evidence suggests that it may become a valuable disease-modifying therapy for children with open growth plates. The next stage of research must move beyond growth velocity alone and determine whether infigratinib improves long-term function, proportionality, quality of life, medical complications and family-centered outcomes.

AUTHOR CONTRIBUTION STATEMENT

Wang Jun & Liu Xiaomei: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, Drafting the work or reviewing it critically for important intellectual content; AND Final approval of the version to be published, and Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data Availability: The datasets and information used in this study are publicly available from the sources cited within the article. No proprietary or restricted data were used.

Trial Registration: Trial registration is not applicable to this study, as it does not involve clinical trials, human participants, or experimental interventions.

Generative AI Disclosure: Generative artificial intelligence tools were not used for generating research data, conducting analyses, or producing scientific conclusions in this study. The authors take full responsibility for the content and accuracy of the manuscript.

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SUPPLEMENTAL MATERIAL

No supplementary files, datasets, figures, or additional materials are associated with this study. Any information necessary to understand and evaluate the work is included in the main article.