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From a Recurrent FGFR3 Variant to Isoform-Selective Kinase Inhibition: A Critical Appraisal of Targeted Therapy in Paediatric Achondroplasia

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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Abstract

Achondroplasia arises almost invariably from a single recurrent gain-of-function variant in the gene encoding fibroblast growth factor receptor 3, and has therefore become a reference case for genotype-directed drug development in paediatric rare disease. Within five years the field has moved from a single approved subcutaneous peptide analogue to a competitive landscape containing long-acting prodrugs of C-type natriuretic peptide, an orally administered pan-fibroblast growth factor receptor 1 to 3 tyrosine kinase inhibitor with pivotal placebo-controlled data, and receptor-selective inhibitors designed to spare the remaining receptor isoforms. This critical narrative review examines whether the evidence supporting these strategies has advanced at the same pace as the pharmacology. Literature was identified through structured searching of bibliographic and scholarly indexes, trial registries and institutional sources, complemented by citation tracking, and appraised for design adequacy, endpoint validity, consistency and translational reach rather than catalogued study by study. Three interpretive conclusions emerge. First, the

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mechanistic case for receptor-level inhibition is strong, yet the clinical case for isoform selectivity remains an inference from adult oncology dosing rather than a demonstrated paediatric advantage, because the doses used in skeletal dysplasia are far below those at which class toxicity is observed. Second, the apparent superiority of any single agent rests on indirect comparison across trials that differ in age range, baseline growth, imputation strategy and duration, and the differences in reported effect on annualised growth velocity are small relative to these design differences. Third, the endpoint on which the entire field depends is a one-year surrogate, and effects on body proportionality, foramen magnum development, functional capacity and adult stature remain inconsistent, exploratory or unmeasured. Selective inhibitors such as dabogratinib, and the oncology-developed compound vepugratinib, are best understood at present as pharmacological demonstrations that isoform-restricted inhibition is achievable, not as therapies of established paediatric benefit. Priorities include head-to-head or platform designs, growth-plate-relevant pharmacodynamic biomarkers, prospective imaging of the craniocervical junction, and outcome sets defined with affected families.

Keywords: Achondroplasia; fibroblast growth factor receptor 3; tyrosine kinase inhibitors; vosoritide; infigratinib; skeletal dysplasia; paediatric drug development.

1. Introduction

Achondroplasia is the most frequent form of disproportionate short stature and the best characterised of the fibroblast growth factor receptor 3 (FGFR3) related chondrodysplasias (Ornitz & Legeai-Mallet, 2017; Savarirayan et al., 2022). Its clinical definition extends well beyond stature. Affected children experience foramen magnum stenosis with the attendant risk of cervicomedullary compression, obstructive and central sleep-disordered breathing, recurrent otitis media and conductive hearing loss, thoracolumbar kyphosis followed by lumbar lordosis and symptomatic spinal stenosis, genu varum, and elevated rates of obesity and hypertension that persist into adult life (Hoover-Fong, Cheung, et al., 2021; Lo et al., 2026; Murton et al., 2023; Stender et al., 2022). Adults report reduced physical functioning and a higher burden of mental health conditions than the general population (Fagereng et al., 2025). The condition is therefore best framed as a multisystem disorder of endochondral ossification in which short stature is the most visible but not necessarily the most consequential feature. Recent paediatric cohorts from Japan and Türkiye have likewise documented early neurological, respiratory, otolaryngological and orthopaedic morbidity, reinforcing the need for longitudinal multidisciplinary surveillance and outcome assessment extending beyond linear growth (Saitou et al., 2024; Soğukpınar et al., 2024).

The molecular basis is unusually simple. A recurrent heterozygous substitution in the transmembrane domain of FGFR3, p.Gly380Arg, accounts for the overwhelming majority of cases and arises predominantly as a *de novo* paternal event subject to selfish spermatogonial selection (Goriely & Wilkie, 2012; Shiang et al., 1994). The substitution stabilises receptor dimers and produces ligand-independent constitutive kinase activity (He et al., 2010; Webster & Donoghue, 1996). Because FGFR3 acts as a negative regulator of chondrocyte proliferation and differentiation, the consequence of activation is inhibition rather than acceleration of growth, a relationship established by the skeletal overgrowth phenotype of receptor-null mice (Colvin et al., 1996). This inversion of the usual oncogenic logic is the conceptual foundation of every targeted strategy currently in development.

Translation of that logic has proceeded along two distinct routes. The first bypasses the receptor and antagonises its downstream mitogen-activated protein kinase output through the natriuretic peptide receptor B axis, an approach validated in transgenic and pharmacological mouse studies (Lorget et al., 2012; Yasoda et al., 2004) and realised clinically in vosoritide, the first agent approved for the condition (Savarirayan et al., 2020). The second inhibits the receptor itself. Preclinical demonstration that a tyrosine kinase inhibitor could rescue FGFR3-related dwarfism in mice (Komla-Ebri et al., 2016) led to the clinical development of infigratinib, an orally bioavailable inhibitor of fibroblast growth factor receptors 1 to 3, which has now reported placebo-controlled pivotal results (Savarirayan, De Bergua, et al., 2025; Savarirayan, Hoover-Fong, et al., 2026). A third generation of compounds, designed to inhibit FGFR3 while sparing the other isoforms, has entered clinical evaluation: dabogratinib, formerly designated TYRA-300, is in paediatric study for achondroplasia, and vepugratinib is in advanced oncology development for FGFR3-altered urothelial carcinoma (L. Chen, 2025; Hudkins et al., 2024; Starrett et al., 2025). Beyond these pharmacological routes, experimental reduction of Fgfr3 expression in a mouse model carrying the orthologue of the recurrent human variant improved long-bone, vertebral, craniofacial and foramen magnum phenotypes, supporting partial normalisation of receptor signalling as a mechanistically plausible but still preclinical strategy (Angelozzi et al., 2025).

The pace of this expansion has outstripped the pace of critical appraisal. Existing reviews are informative but largely descriptive, and most were written before pivotal randomised data for oral receptor inhibition were available (Fafilek et al., 2022; Ozono et al., 2024; Savarirayan, Hoover-Fong, et al., 2024; Taylor-Miller & Savarirayan, 2024). Contemporary clinical overviews concentrate on implementation of the approved agent rather than on comparative evaluation of the emerging classes (Merchant et al., 2025; Savarirayan, Hoover-Fong, et al., 2025). Quantitative syntheses have been confined to vosoritide and have pooled single-arm estimates from heterogeneous designs, including case reports, which limits the inferences that can be drawn (Albuquerque et al., 2026; Alfaraj et al., 2026). No published synthesis has examined the specific proposition on which the newest compounds depend, namely that restricting inhibition to a single receptor isoform will improve the therapeutic ratio in a growing child. That proposition is asserted frequently and tested nowhere.

Several features of the evidence base complicate interpretation and are rarely addressed together. Trials of different agents are routinely compared on annualised growth velocity despite enrolling different age ranges and applying different analytical conventions. Effects on body proportionality, arguably more relevant to function than height alone, have been reported inconsistently and often as exploratory or externally controlled analyses. Safety inferences for receptor inhibitors are drawn partly

from adult oncology experience at doses two orders of magnitude higher than those used in children, a comparison that cuts in both directions and is seldom examined carefully. Skeletal complications that dominate early morbidity, particularly at the craniocervical junction, are supported by imaging series of fewer than ten children. Recent orthopaedic appraisal further indicates that growth-promoting therapies may alter the timing and interpretation of spinal and limb interventions, while evidence-based algorithms for integrating pharmacological and surgical care remain underdeveloped (Mindler et al., 2024).

1.1 Scope, Research Gap and Objectives

This review addresses pharmacological interventions that act on the FGFR3 signalling axis in children with achondroplasia, from the level of the receptor variant to the level of downstream pathway antagonism. It covers the mechanistic rationale, the clinical trial evidence for C-type natriuretic peptide analogues and prodrugs, the evidence for pan-receptor and isoform-selective tyrosine kinase inhibition, the safety framework applicable to chronic inhibition of a developmental receptor in growing children, and the adequacy of the outcome measures on which regulatory and clinical decisions currently rest. Surgical limb lengthening and multidisciplinary supportive care are considered only where they bear on the interpretation, sequencing or comparative evaluation of pharmacological therapy.

The knowledge gap addressed is threefold. There is no critical synthesis that evaluates receptor-level and pathway-level strategies against one another using explicit appraisal of design comparability rather than juxtaposition of headline effect estimates. There is no published appraisal of the selectivity hypothesis that underpins the newest inhibitors, including whether the dose separation between paediatric and oncological use undermines the premise of that hypothesis. There is no integrated assessment of whether the surrogate endpoints in current use can support the claims of clinical benefit increasingly attached to them.

The objectives are to define what the mechanistic evidence does and does not license; to appraise the strength, consistency and comparability of the randomised evidence across therapeutic classes; to evaluate the selectivity argument on its own terms and identify what evidence would confirm or refute it; to examine the validity of the endpoints in use and the fragility of secondary findings; and to derive prioritised, design-specific research recommendations. Genetic and cell-based correction strategies are discussed only as future prospects. Adult-onset management, hypochondroplasia and other FGFR3-related dysplasias are outside the primary scope and are referenced only where they inform inference about achondroplasia itself.

2. Methods for Literature Selection

2.1 Review Design and Rationale

A critical narrative design was selected because the review question requires interpretive comparison across heterogeneous evidence types that cannot be pooled meaningfully. The relevant literature spans structural and cell biology, murine pharmacology, phase 1 to phase 3 clinical trials of three mechanistically distinct classes, pharmacovigilance datasets from an unrelated adult population, imaging case series and consensus statements. Populations, comparators, dosing conventions and outcome definitions differ to an extent that would render a pooled effect estimate uninterpretable, and the central questions concern the validity of inference rather than the magnitude of a common effect. Narrative synthesis is appropriate where the objective is to interrogate assumptions and explain disagreement rather than to estimate a parameter (Ferrari, 2015; Greenhalgh et al., 2018). Narrative design does not exempt a review from methodological transparency, and the conduct reported here was structured to satisfy the domains of the Scale for the Assessment of Narrative Review Articles, covering justification of importance, statement of aims, description of searching, referencing of statements, evidence-appropriate presentation and adequate presentation of data (Baethge et al., 2019).

2.2 Information Sources

Searching was conducted using the PubMed and MEDLINE interface of the United States National Library of Medicine through its programmatic retrieval service, the Crossref metadata index, and general scholarly web searching. Trial-level information was obtained from the ClinicalTrials.gov registry maintained by the same institution. Institutional and regulatory material was consulted where it established the developmental status of an investigational compound that had not yet generated peer-reviewed clinical publications. Subscription-restricted databases including Web of Science, Scopus and Embase were not accessible during the preparation of this review, and no search of those resources is claimed. Supplementary retrieval used backward citation searching of recent reviews and consensus statements, forward citation inspection of pivotal trial reports through publisher citation listings, and targeted searching for corrections and errata affecting included studies.

2.3 Search Strategy and Search Period

Search concepts were constructed around four axes: the condition and its allelic relatives; the molecular target and its signalling output; the therapeutic modalities under evaluation; and the outcome domains of interest. Representative strings combined controlled and free-text terms, for example achondroplasia AND (FGFR3 OR fibroblast growth factor receptor 3) AND (inhibitor OR tyrosine kinase OR targeted therapy); achondroplasia AND (vosoritide OR navepegritide OR C-type natriuretic peptide); achondroplasia AND (infigratinib OR TYRA-300 OR dabogratinib OR recifercept OR meclizine); (vepugratinib OR LOXO-435 OR LY3866288) AND FGFR3; and achondroplasia AND (foramen magnum OR body proportionality OR quality of life OR growth velocity). Compound-specific searches were run separately for each named agent rather than combined, to avoid the loss of sensitivity that occurs when rare investigational names are conjoined.

The search period opened in 1994, the year in which the causative variant was identified and the field acquired a defined molecular target (Shiang et al., 1994). Publications predating that boundary were admitted only where they established a foundational biological principle. The final search date was 2 June 2026. Publications identified after that date through citation alerts were considered only when they reported pivotal outcomes bearing directly on the review question, and such instances are identifiable from the reference list.

2.4 Eligibility Criteria

Eligible material comprised peer-reviewed original research and high-quality reviews addressing the pathogenesis of FGFR3-related chondrodysplasia, preclinical or clinical evaluation of agents acting on the FGFR3 axis, natural history and disease burden relevant to endpoint selection, safety data for fibroblast growth factor receptor inhibition, and consensus guidance on management. Interventional studies were eligible irrespective of phase, provided the population comprised children with genetically or clinically confirmed achondroplasia or an animal model of an FGFR3 gain-of-function allele. Trial registry records were admitted only to establish the existence, design and status of studies without published results, and were not used as evidence of efficacy. Publications in languages other than English were not retrievable in full text and were excluded, with the consequence noted among the limitations. Excluded were commercial promotional material, unrefereed conference abstracts, preprints where peer-reviewed evidence on the same question existed, and any source whose bibliographic identity could not be independently confirmed.

2.5 Screening, Duplicate Handling and Study Selection

Records were screened by title and abstract against the eligibility criteria, and full texts or full abstracts were examined for all records retained at that stage. Duplicates arising from retrieval of the same article through different indexes were identified by digital object identifier and by matched title and first-author pairing, and were collapsed to a single record. Where a study was represented by more than one publication, for example a dose-finding report and a subsequent pivotal trial of the same compound, each was retained and treated as reporting distinct data. Selection was purposive rather than exhaustive, prioritising studies that defined a mechanism, provided the strongest available evidence for a therapeutic claim, contradicted a prevailing interpretation, or exposed a methodological constraint. No record counts are reported, because the selection process was interpretive and iterative and did not follow a documented systematic screening protocol; presenting counts would imply a procedural rigour that was not applied.

2.6 Critical Appraisal and Evidence Synthesis

Each included clinical study was appraised for the appropriateness of its design to the question asked, the adequacy of randomisation and masking where applicable, the size and representativeness of the sample, the pre-specification and hierarchy of endpoints, the handling of missing data, the distinction between confirmatory and exploratory analyses, and the transparency of funding and sponsor involvement. Preclinical studies were appraised for the fidelity of the model to the human allele, the relevance of the dosing regimen, the blinding of morphometric assessment where reported, and the extent to which conclusions were confined to the outcomes measured. No formal risk-of-bias instrument was applied, because the heterogeneity of study types precluded consistent use of any single validated tool and partial application would generate misleading scores. Themes were developed inductively from recurring points of agreement and disagreement across the literature, then organised around the mechanistic, comparative, safety and endpoint questions posed in Section 1.1. Where studies disagreed, the synthesis sought explanations in design and population differences before attributing disagreement to genuine biological heterogeneity.

3. The Molecular Target and the Limits of Mechanistic Inference

3.1 A Recurrent Variant with an Unusually Well-Defined Consequence

The identification of a recurrent transmembrane-domain substitution in FGFR3 as the cause of achondroplasia established a degree of genetic homogeneity rare among skeletal disorders (Shiang et al., 1994). Subsequent structural and biophysical work clarified the mechanism: the substituted arginine promotes dimer stabilisation and ligand-independent transphosphorylation, producing constitutive kinase activity rather than augmented ligand responsiveness (He et al., 2010; Webster & Donoghue, 1996). Comparable transmembrane and kinase-domain substitutions in the same receptor generate a graded severity spectrum extending through hypochondroplasia to thanatophoric dysplasia, and the correlation between the degree of constitutive activation and phenotypic severity is one of the more robust genotype-phenotype relationships in human skeletal genetics (Foldynova-Trantirkova et al., 2012).

The direction of the effect is decisive for drug design. Receptor-null mice display skeletal overgrowth together with cochlear abnormalities and deafness, confirming that FGFR3 restrains rather than promotes endochondral bone growth and that its physiological role is not confined to the growth plate (Colvin et al., 1996). Therapeutic benefit therefore requires attenuation of signalling, which is achievable either by reducing receptor output directly or by opposing its downstream consequences. Both routes have been pursued, and their comparative merits form the substance of Sections 4 and 5.

3.2 Downstream Signalling and the Multisystem Phenotype

Activated FGFR3 in growth-plate chondrocytes signals principally through the mitogen-activated protein kinase cascade, with contributions from signal transducer and activator of transcription proteins and from phosphoinositide 3-kinase, the relative weighting of which varies with cell type and allele (H. Chen et al., 2025; Foldynova-Trantirkova et al., 2012; Ornitz & Itoh, 2015).

Suppression of the mitogen-activated protein kinase arm by C-type natriuretic peptide signalling through natriuretic peptide receptor B provides the mechanistic basis for the peptide analogue class, and transgenic overexpression of the peptide in chondrocytes rescues the murine achondroplasia phenotype in a manner dependent on that pathway (Yasoda et al., 2004).

Recent work has complicated the conventional account in a way that has direct therapeutic implications. Using a knock-in model carrying the human p.Gly380Arg allele, Horike et al. (2026) demonstrated expansion of the resting zone of the growth plate, with lineage tracing and proliferation labelling indicating disrupted turnover and impaired stem-cell-like behaviour of resting-zone chondrocytes, mediated in part through cyclic adenosine monophosphate response element-binding protein signalling. Administration of a small-molecule inhibitor of that transcription factor restored growth-plate architecture and bone length in the model. If the primary lesion involves the stem-cell-like compartment rather than only the proliferative column, then the therapeutic window may be defined less by the magnitude of pathway suppression than by the developmental timing of intervention, and agents that promote proliferative-zone activity may not fully correct the underlying defect. This finding is recent, derives from a single laboratory, and requires independent replication, but it identifies a plausible reason why growth-promoting effects observed in the first year of treatment might not translate proportionately into adult stature.

The systemic distribution of receptor expression explains why achondroplasia manifests as more than a growth disorder, and why complications arise at sites where endochondral ossification and synchondrosal fusion are critical. Premature fusion of the skull base synchondroses underlies foramen magnum stenosis, midface hypoplasia contributes to upper airway obstruction, and vertebral body and pedicle abnormalities underlie spinal stenosis (Ornitz & Legeai-Mallet, 2017; Savarirayan et al., 2022). Any therapeutic strategy assessed only by linear growth of the long bones therefore measures a fraction of what the receptor does.

3.3 Physiological Receptor Function and the Ceiling on Inhibition

The therapeutic proposition is not the elimination of receptor signalling but its partial normalisation. This distinction is frequently blurred. The receptor contributes to cochlear development, to the maintenance of bone in adult life and to the regulation of chondrocyte differentiation in a manner that is dose-dependent rather than binary (Colvin et al., 1996; Ornitz & Itoh, 2015). Complete inhibition in a child with an open growth plate is neither achievable with the doses in use nor obviously desirable, and the relevant question for each agent is whether the achieved degree of suppression sits within a window that improves skeletal outcomes without disturbing other receptor-dependent processes. No clinical study in achondroplasia has yet reported a pharmacodynamic measure of receptor pathway suppression in a growth-plate-relevant compartment, which means that the position of any given dose within that window is inferred from growth response rather than measured directly.

The evidence base offers a partial natural experiment. Fibroblast growth factor receptor inhibitors used in oncology are administered at doses selected for maximal pathway suppression in tumour tissue, and the resulting toxicity profile of hyperphosphataemia, nail and skin changes, mucositis and ocular events reflects inhibition across receptor isoforms in adults (Subbiah & Verstovsek, 2023). Infigratinib in achondroplasia is administered at 0.25 mg per kilogram daily, roughly two orders of magnitude below the exposure used in cholangiocarcinoma and urothelial carcinoma. Whether the favourable paediatric tolerability observed to date reflects the low dose, the short duration of observation, or a genuinely different pharmacology cannot be resolved from the available data, and this ambiguity is central to the appraisal of isoform selectivity developed in Section 5.3.

Table 1 organises the principal points at which the axis has been targeted, distinguishing the level of intervention, the strongest supporting evidence and the current translational status. The table makes explicit that mechanistic plausibility is distributed far more evenly across the strategies than clinical evidence is, and that several approaches with compelling preclinical rescue have not progressed, a pattern examined further in Section 5.1.

Table 1. Points of pharmacological intervention in the fibroblast growth factor receptor 3 axis, with the strongest available supporting evidence and current translational status

Level of intervention	Representative approach	Strongest evidence available	Translational status	Supporting references
Ligand trapping upstream of the receptor	Recombinant soluble FGFR3 decoy (recifercept)	Rescue of skeletal phenotype and prevention of premature synchondrosal fusion in mouse models; acceptable juvenile toxicology in non-clinical species	Clinical development not advanced beyond early-phase evaluation; efficacy inference constrained by absence of a randomised comparator	Campion et al. (2023); Garcia et al. (2013); Gonçalves et al. (2020); Qiao et al. (2024)
Receptor kinase inhibition, non-selective across isoforms 1 to 3	Infigratinib	Placebo-controlled randomised trial in children aged 3 to 17 years reporting a significant increase in annualised height velocity at 52 weeks	Pivotal data published; regulatory submissions announced by the sponsor	Komla-Ebri et al. (2016); Savarirayan, De Bergua, et al. (2025); Savarirayan, Hoover-Fong, et al. (2026)
Receptor kinase inhibition restricted to FGFR3	Dabogratinib (TYRA-300); vepugratinib in oncology	Structure-based design confirming isoform selectivity; growth promotion and	Paediatric phase 2 dose-finding under way; no human efficacy data in	L. Chen (2025); Hudkins et al. (2024); Starrett et al. (2025, 2026)

Level of intervention	Representative approach	Strongest evidence available	Translational status	Supporting references
		improvement of foramen magnum and vertebral morphology in two FGFR3-driven mouse models	achondroplasia; vepugratinib developed only for FGFR3-altered malignancy	
Receptor trafficking and degradation	Histone deacetylase 6 inhibition	Blockade of mutant receptor accumulation with improved bone growth in a murine model	Preclinical only; no registered clinical programme identified	Ota et al. (2016)
Downstream antagonism through natriuretic peptide receptor B	Vosoritide; navepegritide	Randomised placebo-controlled trials in children, with open-label extension exposure exceeding six years for the approved agent	Vosoritide approved in multiple jurisdictions; navepegritide has completed a pivotal randomised trial	Savarirayan et al. (2020); Savarirayan, Irving, et al. (2025); Savarirayan, McDonnell, et al. (2026); Yasoda et al. (2004)
Downstream antagonism through other intracellular nodes	Statins; meclizine; CREB inhibition	Phenotypic rescue in cellular or murine systems; small single-arm clinical evaluation for meclizine showing no meaningful height-velocity gain	Repurposing attempts have not produced convincing clinical benefit; CREB inhibition is preclinical	Horike et al. (2026); Matsushita et al. (2023, 2025); Yamashita et al. (2014)
Correction of the causative allele	Genome editing; correction in patient-derived pluripotent stem cells	Precise correction of the murine equivalent allele and functional recovery in patient-derived chondrogenic cells	Preclinical; delivery to growth-plate chondrocytes unresolved	Miao et al. (2019); Zou et al. (2021)

Note. CREB = cyclic adenosine monophosphate response element-binding protein; FGFR3 = fibroblast growth factor receptor 3. Translational status reflects information available to the final search date. The table lists representative rather than exhaustive approaches within each level of intervention.

4. Bypassing the Receptor: The C-Type Natriuretic Peptide Axis

4.1 Preclinical Foundations and the Logic of Downstream Antagonism

The rationale for the peptide class rests on an antagonistic relationship between two signalling systems that converge on the same effector. Chondrocyte-specific overexpression of C-type natriuretic peptide rescued the dwarfism phenotype of a murine achondroplasia model through suppression of mitogen-activated protein kinase signalling, establishing that the receptor need not be inhibited directly for the phenotype to be corrected (Yasoda et al., 2004). Because the native peptide is rapidly cleared by neutral endopeptidase, therapeutic translation required an analogue resistant to that degradation while retaining receptor selectivity and avoiding the vasodilatory effects mediated by natriuretic peptide receptor A. Modified analogues achieved this profile and produced dose-dependent growth in the *Fgfr3*$^{Y367C/+}$ mouse (Lorget et al., 2012; Wendt et al., 2015).

Two features of this preclinical package deserve critical attention. The murine models used carry alleles that are not the human p.Gly380Arg substitution, and the *Fgfr3*$^{Y367C/+}$ allele in particular produces a more severe phenotype resembling thanatophoric dysplasia in its cellular consequences. Rescue in a severe model does not establish the magnitude of benefit achievable in a milder human phenotype, and may overstate it because the scope for correction is larger. In addition, the murine growth plate closes differently from the human growth plate and murine growth continues far longer relative to lifespan, which limits inference about effects on final stature. These constraints apply equally to the receptor-inhibitor literature discussed in Section 5 and are among the recurrent limitations summarised in Table 4.

4.2 Vosoritide: What the Randomised Evidence Supports

An open-label phase 2 study first demonstrated that daily administration of the analogue increased growth velocity in children with achondroplasia and established the dose taken forward (Savarirayan et al., 2019). The pivotal randomised, double-blind, placebo-controlled trial enrolled 121 ambulatory children aged 5 to less than 18 years across 24 sites in seven countries, all of whom had completed at least six months of prospective baseline growth observation. The adjusted mean difference in annualised growth velocity at 52 weeks was 1.57 cm per year in favour of vosoritide, with a 95% confidence interval of 1.22 to 1.93 (Savarirayan et al., 2020). Adverse events were reported in 98 per cent of participants in both groups and were dominated by injection-site reactions; no serious adverse event was judged treatment related. The design was strong: prospective baseline growth data reduced regression-to-the-mean effects, randomisation was stratified by sex and pubertal stage, and masking extended to the sponsor.

Three caveats temper the interpretation, and the trial investigators stated the first of them explicitly. Whether adult height is increased was not established, and the treatment period was too short to detect changes in quality of life, activities of daily living or the frequency of medical and surgical interventions (Savarirayan et al., 2020). Second, upper-to-lower body segment ratio, the

standard measure of disproportion, did not improve significantly during the trial, which matters because disproportion contributes to functional limitation independently of absolute stature. Third, the enrolled population was ambulatory, aged five years or older, and had tolerated six months of observational participation, which selects for families able to sustain a demanding daily injection regimen and limits generalisability to the youngest children in whom complication risk is highest.

4.3 Extension, Younger-age and Real-World Evidence

Two-year results from the open-label extension indicated that the growth-promoting effect persisted without new safety concerns (Savarirayan et al., 2021), and the extension now provides the longest continuous exposure data available for any agent in this condition. Among 119 participants followed for up to six years, representing 464.05 person-years of exposure, annualised growth velocity approximated that of the average-stature population before puberty, and comparison with the untreated CLARITY cohort indicated an additional height gain of 5.75 cm over three years, with a 95% confidence interval of 4.93 to 6.57 (Savarirayan, Irving, et al., 2025). A significant improvement in upper-to-lower body segment ratio emerged at three years relative to age-matched untreated controls, confined to females younger than 11 years and males younger than 12 years. No long-term harms or deaths were observed.

The strength of the extension is its duration; its weakness is its comparator. Once all participants receive active treatment, the counterfactual is an external cohort assembled under different conditions, and confounding by secular trends in supportive care, by differential ascertainment and by the health characteristics that permitted continued trial participation cannot be excluded. The proportionality finding illustrates the difficulty precisely. It was observed in a subgroup defined by age, against an external control, after three years, and did not appear in the randomised phase. That pattern is compatible with a genuine effect requiring time to emerge and with a chance finding among multiple comparisons, and the available data do not distinguish between these explanations.

Extension of treatment to children younger than five years, where the rationale is strongest because craniocervical complications cluster in infancy, produced a more equivocal result. In a randomised placebo-controlled trial in children aged 3 to 59 months, the least-squares mean difference in change from baseline height Z score was 0.25, with a 95% confidence interval of −0.02 to 0.53, which does not exclude the null (Savarirayan, Wilcox, et al., 2024). Adverse events occurred in all participants, and serious adverse events were reported in three children receiving vosoritide and six receiving placebo, including one death from sudden infant death syndrome in the treated group that was not attributed to the intervention. The trial is frequently cited as supporting early initiation; the primary efficacy result does not establish that, and the honest summary is that the study demonstrated acceptable tolerability in infants while leaving the efficacy question open.

Real-world evidence has been synthesised twice, with results that agree on direction and differ instructively in method. Albuquerque et al. (2026) pooled ten studies comprising 696 children and reported a height Z score change of 0.32 at 12 months, an annualised growth rate 1.82 cm per year higher after treatment, and a reduction in the ratio of sitting height to height of 0.0089. Alfaraj et al. (2026) pooled 13 studies and reported an annualised growth velocity of 5.72 cm per year at 12 months and a height Z score improvement of 0.28, together with injection-site reactions in 51 per cent and gastrointestinal symptoms in 50 per cent. Both are single-arm syntheses. The second explicitly incorporated case reports and case series alongside randomised trials, a decision that inflates apparent precision, since the reported confidence interval around annualised growth velocity is narrower than the confidence interval around the randomised treatment difference from the pivotal trial despite resting on weaker designs. Pooled single-arm growth velocities also cannot be interpreted as treatment effects, because untreated children with achondroplasia grow, and the appropriate comparison is with a contemporaneous or matched untreated trajectory rather than with zero.

4.4 Long-acting Prodrugs and Combination Strategies

Weekly administration addresses the principal burden of the approved agent. In a dose-escalation randomised trial, navepegritide at 100 µg of C-type natriuretic peptide per kilogram weekly increased annualised growth velocity relative to placebo, 5.42 against 4.35 cm per year, with mild or moderate treatment-emergent adverse events, few injection-site reactions and no symptomatic hypotension (Savarirayan et al., 2023). The pivotal randomised trial in 84 children aged 2 to 11 years confirmed superiority on annualised growth velocity, with a least-squares mean treatment difference of 1.49 cm per year and a 95% confidence interval of 1.05 to 1.93 (Savarirayan, McDonnell, et al., 2026). That trial is notable for reporting radiographically assessed skeletal outcomes alongside growth: tibial-femoral angle improved by 1.81 degrees, mechanical axis deviation by 2.78 mm and the fibula-to-tibia length ratio by 0.016, and physical functioning measured by the Achondroplasia Child Experience Measures improved by 11.1 points in children younger than five years. These are among the few pre-specified non-growth outcomes reported in the field, although the confidence interval for the physical functioning result approaches the null and the analysis was confined to a subgroup.

Combination with growth hormone has been evaluated on the reasoning that the two agents act through independent mechanisms. Fifty-two-week results from a randomised phase 2 evaluation of navepegritide with lonapegsomatropin have been reported (McDonnell et al., 2026). Combination approaches raise a question that the field has not yet confronted: if additive growth can be obtained by combining agents that each act at a different point in the axis, then the comparative evaluation of single agents may become secondary to the evaluation of regimens, and trial designs adequate for that purpose do not currently exist.

Table 2 summarises the randomised placebo-controlled evidence across all classes. The comparison it permits is deliberately structured to expose non-comparability: the trials differ in age range, in whether the primary endpoint was velocity or Z score, in trial phase, and in the width of the confidence intervals reported. Reading the effect estimates as a ranking of agents is not supportable, and the table is presented to demonstrate why.

Table 2. Randomised placebo-controlled trials of growth-promoting agents in children with achondroplasia, with design features relevant to cross-trial comparability

Agent and mechanism	Trial identity and phase	Population and duration	Primary efficacy result	Features limiting cross-trial comparison	Supporting references
Vosoritide, C-type natriuretic peptide analogue, daily subcutaneous	Phase 3 randomised, double-blind, placebo-controlled	121 children aged 5 to <18 years, ambulatory, 52 weeks	Annualised growth velocity difference 1.57 cm/year (95% CI 1.22 to 1.93)	Older age range; requirement for 6 months of prior observational participation; no significant change in body segment ratio	Savarirayan et al. (2020)
Vosoritide, as above	Phase 2 randomised, double-blind, placebo-controlled	75 children aged 3 to 59 months, 52 weeks	Height Z score difference 0.25 (95% CI −0.02 to 0.53); interval includes the null	Primary efficacy endpoint expressed as Z score rather than velocity; sentinel dosing within cohorts; small strata	Savarirayan, Wilcox, et al. (2024)
Navepegritide, C-type natriuretic peptide prodrug, weekly subcutaneous	Phase 2 randomised, double-blind, placebo-controlled, dose escalation	57 prepubertal children aged 2 to 10 years, 42 receiving active treatment across four dose levels and 15 placebo, 52 weeks	Annualised growth velocity 5.42 versus 4.35 cm/year at the highest dose (p = 0.0218)	Dose-escalation design with small groups per dose; comparison confined to the top dose level	Savarirayan et al. (2023)
Navepegritide, as above	Phase 2b randomised, double-blind, placebo-controlled, pivotal	84 children aged 2 to 11 years, 52 weeks	Annualised growth velocity difference 1.49 cm/year (95% CI 1.05 to 1.93)	Younger age range than the vosoritide phase 3 trial; radiographic and functional endpoints reported as secondary or subgroup analyses	Savarirayan, McDonnell, et al. (2026)
Infigratinib, oral inhibitor of receptors 1 to 3	Phase 2 dose finding, open label, five sequential cohorts	72 children aged 3 to 11 years, 6 months plus 12-month extension	Cohort 5 change in annualised height velocity 2.50 cm/year (95% CI 1.22 to 3.79) at 18 months	No concurrent control; within-participant comparison; effect reported for a single dose cohort at 18 rather than 12 months	Savarirayan, De Bergua, et al. (2025)
Infigratinib, as above	Phase 3 randomised, double-blind, placebo-controlled	114 children aged 3 to 17 years randomised 2:1, 52 weeks	Annualised height velocity difference 1.74 cm/year (95% CI 1.31 to 2.17); height Z score difference 0.32 (96% CI 0.23 to 0.41)	Wide age range spanning pre-pubertal and pubertal growth; pre-specified imputation for missing data; body segment ratio difference −0.02 (96% CI −0.06 to 0.01)	Savarirayan, Hoover-Fong, et al. (2026)

Note. CI = confidence interval. Confidence intervals are reproduced at the level reported in the source publication; the 96% intervals reflect the multiplicity adjustment applied in that trial. The table is restricted to randomised placebo-controlled trials and to the phase 2 dose-finding study that determined the dose carried forward for oral receptor inhibition; it is not an exhaustive listing of all clinical studies of these agents.

5. Inhibiting the Receptor: From Pan-Receptor Chemistry to Isoform-Restricted Inhibition

5.1 Proof of Concept and the Compounds that did not Progress

Direct inhibition of the mutant receptor was first demonstrated pharmacologically in the *Fgfr3*$^{Y367C/+}$ mouse, in which the pan-receptor inhibitor then designated NVP-BGJ398 reduced receptor phosphorylation, improved growth-plate organisation and produced functional improvement in skull and axial morphology in addition to long-bone growth (Komla-Ebri et al., 2016). That study is the pivot on which the entire oral inhibitor programme rests, and its finding that craniofacial and foramen magnum abnormalities responded is the origin of the expectation, still largely untested in humans, that receptor inhibition might modify complications rather than only stature.

A parallel strategy sought to intercept ligand upstream of the receptor. A recombinant soluble receptor ectodomain rescued the phenotype of an achondroplasia mouse model and restored bone growth when administered postnatally (Garcia et al., 2013), with subsequent characterisation confirming target engagement and demonstrating prevention of premature skull base synchondrosal ossification (Gonçalves et al., 2020). Juvenile toxicology in a non-clinical species did not identify barriers to paediatric administration (Campion et al., 2023). Despite this coherent package, clinical development did not advance to a pivotal randomised trial, and the efficacy analysis that was attempted relied on modelling of the natural disease course in the absence of a placebo arm (Qiao et al., 2024). The episode is instructive in two ways. It demonstrates that strong preclinical rescue is not sufficient for clinical success, and it illustrates the analytical consequences of designs that dispense with concurrent controls, since inference then depends entirely on the fidelity of the external growth model.

Repurposing has produced a comparable pattern. Statins rescued cartilage phenotypes in cellular and murine systems of FGFR3-related dysplasia (Yamashita et al., 2014), yet no adequately powered clinical evaluation in achondroplasia has followed. Meclizine, identified as an inhibitor of the relevant signalling output, progressed through pharmacokinetic and phase 1b evaluation in children (Matsushita et al., 2023) to an open-label single-arm phase 2 study in nine children aged 5 to 10 years receiving concurrent growth hormone. Height velocity changed from 4.35 to 4.46 cm per year, with one participant reaching the pre-specified threshold of 6 cm per year, while arm-span velocity averaged 6.93 cm per year and six participants exceeded the threshold on that measure (Matsushita et al., 2025). The authors appropriately concluded that an additive effect on height was not observed. The arm-span signal derives from an *ad hoc* analysis in nine children receiving a concomitant growth-promoting agent and should not be treated as evidence of segmental benefit. A subsequent correction to the primary publication was also issued (Matsushita et al., 2026). The study remains a useful reminder that small single-arm designs in a condition with substantial individual variation in growth cannot distinguish treatment effect from noise.

5.2 Infigratinib: Dose Selection and Pivotal Evidence

The clinical programme for infigratinib in achondroplasia selected doses far below oncological exposure. In the open-label phase 2 dose-finding study, 72 children aged 3 to 11 years received one of five daily doses ascending from 0.016 to 0.25 mg per kilogram. In the highest cohort, the mean change from baseline in annualised height velocity at 18 months was 2.50 cm per year, with a 95% confidence interval of 1.22 to 3.79, accompanied by a height Z score change of 0.54 and a reduction in upper-to-lower body segment ratio of 0.12 (Savarirayan, De Bergua, et al., 2025). All participants experienced at least one adverse event, most mild or moderate, and none discontinued because of an adverse event.

The proportionality result from that study attracted particular attention, because reduction of disproportion had not been achieved by the peptide class within a randomised comparison. Its interpretive weight is limited by the design. The comparison is within participants and against a historical reference population rather than a concurrent control, the estimate derives from a single dose cohort at a timepoint 18 months into an open-label extension, and the analysis population is small. Dose-finding studies are not constructed to support efficacy claims, and the appropriate reading is that the result generated a hypothesis for the pivotal trial to test.

The pivotal trial tested it and did not confirm it. In a randomised, double-blind, placebo-controlled study, 114 children aged 3 to 17 years were assigned in a 2:1 ratio to infigratinib 0.25 mg per kilogram daily or placebo for 52 weeks. The difference in least-squares mean change from baseline in annualised height velocity was 1.74 cm per year, with a 95% confidence interval of 1.31 to 2.17, and the difference in height Z score was 0.32, with a 96% confidence interval of 0.23 to 0.41. The difference in upper-to-lower body segment ratio was −0.02, with a 96% confidence interval of −0.06 to 0.01, an interval that includes the null. Adverse events occurred in 96 per cent of the infigratinib group and 95 per cent of the placebo group, serious adverse events in 5 per cent and 3 per cent respectively, and no serious adverse event or discontinuation was attributed by investigators to either treatment (Savarirayan, Hoover-Fong, et al., 2026).

The divergence between the open-label proportionality signal of −0.12 and the randomised estimate of −0.02 is the most consequential internal inconsistency in the current literature on oral receptor inhibition, and it has received little critical attention. Several explanations are compatible with the data. The open-label estimate may have been inflated by measurement expectation in an unmasked setting, since segment ratios depend on sitting-height measurement that is sensitive to technique. The timepoints differ, and proportionality may require longer than 52 weeks to change detectably. The populations differ in age range, and the pivotal trial extended to 17 years, encompassing adolescents in whom the scope for altering segmental proportion is smaller. What the data do not support is the continued citation of the dose-finding estimate as though the randomised comparison had confirmed it. On present evidence, no agent in any class has demonstrated a statistically significant improvement in upper-to-lower body segment ratio within a randomised, concurrently controlled 52-week comparison.

5.3 Dabogratinib and the Selectivity Hypothesis

Dabogratinib, developed under the designation TYRA-300, was designed through a structure-based approach to inhibit FGFR3 while sparing receptors 1, 2 and 4, and to retain activity against gatekeeper substitutions that confer resistance to earlier inhibitors (Hudkins et al., 2024). The stated purpose of the selectivity is to avoid the toxicities attributed in oncology to inhibition of the other isoforms, principally the hyperphosphataemia associated with receptor 1 inhibition and the hepatotoxicity associated with receptor 4 inhibition (L. Chen, 2025; Subbiah & Verstovsek, 2023).

The preclinical skeletal package is the most thorough yet reported for any receptor inhibitor in this condition. In wild-type mice and in both the *Fgfr3*$^{Y367C/+}$ model of achondroplasia and the *Fgfr3*$^{N534K/+}$ model of hypochondroplasia, treatment increased nasoanal

length and tibial and femoral length, and in the two mutant models partially restored the disproportionality of long-bone growth. Histological analysis of the growth plate indicated increased chondrocyte proliferation and differentiation, providing a cellular correlate for the morphometric findings. Treatment improved the size and shape of the skull and foramen magnum in the achondroplasia model, increased lumbar vertebral length and improved intervertebral disc morphology in both models (Starrett et al., 2025). Effects were also observed in wild-type animals, which confirms that the compound engages physiological receptor signalling and is not conditional on the mutant allele, a point with obvious implications for chronic administration to children.

Two features of that package temper the enthusiasm it has generated. Neither mutant model carries the human p.Gly380Arg allele, and the *Fgfr3*$^{Y367C/+}$ allele produces a more severe phenotype than achondroplasia. The claim that the compound partially restores proportionality is therefore a claim about the severe model, and the newly available knock-in model carrying the human allele (Horike et al., 2026) would provide a more direct test. Comparative dosing against the pan-receptor inhibitor within the same experimental system has not been reported in the peer-reviewed literature retrieved for this review, which means that the central premise, namely that selectivity confers a wider therapeutic window, has not been tested even preclinically in a head-to-head design.

Clinical evidence in achondroplasia does not yet exist. The phase 2 dose-finding study in children aged 3 to 10 years with open growth plates began enrolment in March 2025, with co-primary outcomes of treatment-related adverse events and change from baseline in annualised growth velocity, an estimated enrolment of 92 participants, and estimated primary completion in 2030 (Tyra Biosciences, 2025). Oncological data for the same molecule are confined to preclinical characterisation and three individual case reports from an early-phase solid-tumour study (Starrett et al., 2026). Descriptions of the compound as first in class are accurate with respect to design and regulatory sequence, and uninformative with respect to paediatric benefit.

The selectivity hypothesis merits examination on its own terms. Its premise is that adverse effects attributable to inhibition of receptors 1, 2 and 4 constrain the dose of a pan-receptor inhibitor and therefore its efficacy. In adult oncology that premise is well supported, because dosing targets maximal pathway suppression and the resulting toxicity is dose limiting (Subbiah & Verstovsek, 2023). In paediatric achondroplasia the premise is untested, because the dose in use is approximately two orders of magnitude lower and the reported adverse event profile in the pivotal trial did not differ materially from placebo (Savarirayan, Hoover-Fong, et al., 2026). If the pan-receptor inhibitor is not dose limited by isoform-related toxicity at the doses that produce growth, then selectivity removes a constraint that is not currently binding. Selectivity might nonetheless prove valuable for reasons less often articulated: it could permit dose escalation above the current ceiling should greater pathway suppression prove beneficial; it could reduce the probability of latent effects emerging over the decade or more of exposure that treatment from early childhood to skeletal maturity implies; and it could matter disproportionately in the youngest children, in whom receptor 1 and receptor 2 dependent processes in the developing skeleton and central nervous system are most active. None of these possibilities has been tested, and the field would benefit from stating the hypothesis in a falsifiable form rather than presenting selectivity as a self-evident advantage.

5.4 Vepugratinib and the Oncology-derived Selectivity Toolkit

Table 3. Small-molecule fibroblast growth factor receptor inhibitors of relevance to achondroplasia, ordered by breadth of isoform coverage

Compound	Isoform coverage	Primary development context	Highest level of evidence in a skeletal indication	Supporting references
Erdafitinib, pemigatinib, futibatinib	Receptors 1 to 4, broadly equipotent	Adult oncology; approved in defined indications	None; cited only as the source of the class toxicity profile against which selectivity is argued	L. Chen (2025); Pant et al. (2023); Subbiah & Verstovsek (2023)
Infigratinib	Receptors 1 to 3	Adult oncology, subsequently repositioned to skeletal dysplasia at approximately one-hundredth of the oncological dose	Randomised, double-blind, placebo-controlled phase 3 trial in 114 children over 52 weeks	Komla-Ebri et al. (2016); Savarirayan, De Bergua, et al. (2025); Savarirayan, Hoover-Fong, et al. (2026)
Dabogratinib (TYRA-300)	Receptor 3 selective; retains activity against gatekeeper substitutions	Dual development in urothelial carcinoma and paediatric achondroplasia	Preclinical efficacy in two mutant mouse models; open-label phase 2 dose finding in children under way with no results published	Hudkins et al. (2024); Starrett et al. (2025, 2026); Tyra Biosciences (2025)
Vepugratinib (LOXO-435, LY3866288)	Receptor 3 selective	Adult oncology only; phase 1 in FGFR3-altered solid tumours and randomised phase 3 in urothelial carcinoma	None; no skeletal dysplasia programme identified and no peer-reviewed primary clinical report retrieved	L. Chen (2025); Eli Lilly and Company (2022, 2025)

Note. Isoform coverage reflects the selectivity profile reported by the developers and independently summarised in the cited review. Dose comparisons are approximate and are drawn from the dosing regimens reported in the cited clinical studies. Absence of evidence in a skeletal indication denotes that no such study was identified to the final search date and should not be read as evidence of absence of effect.

Vepugratinib, also designated LOXO-435 and LY3866288, is an orally administered, isoform-selective FGFR3 inhibitor developed for malignancies driven by receptor 3 alterations, principally urothelial carcinoma, in which such alterations occur in a substantial minority of cases (L. Chen, 2025; Hudkins et al., 2024). It is under evaluation in a phase 1 study in FGFR3-altered advanced solid tumours (Eli Lilly and Company, 2022) and in a randomised phase 3 study in previously untreated locally advanced or metastatic urothelial carcinoma with an FGFR3 genetic alteration (Eli Lilly and Company, 2025). No study of this compound in achondroplasia or any other skeletal dysplasia was identified, and no peer-reviewed primary clinical report of its efficacy or safety was retrieved within the search period; the clinical evidence available at the final search date consisted of conference presentations, which were excluded under the eligibility criteria set out in Section 2.4.

The relevance of the compound to paediatric achondroplasia is therefore indirect and should be stated precisely. It establishes, alongside dabogratinib, that medicinal chemistry can achieve meaningful isoform discrimination within a receptor family whose kinase domains are highly conserved, and that such compounds can be administered orally to humans (L. Chen, 2025). It does not establish that isoform-selective inhibition is safe or effective in children, and the pharmacological objective in oncology is close to opposite to that required in skeletal dysplasia. Oncological dosing seeks maximal and sustained suppression of a driver pathway in tumour tissue; paediatric dosing in achondroplasia seeks partial, chronic attenuation of a physiological signal in a tissue that must continue to function normally for a decade or more. Tolerability at oncological exposure in adults with limited life expectancy carries almost no information about tolerability at low exposure in children with normal life expectancy, and the inference in the reverse direction is equally weak. Presenting the oncology programme as evidence bearing on paediatric use conflates the demonstration that a molecular property is achievable with the demonstration that it is clinically advantageous.

Table 3 sets out the small molecules of relevance with their isoform coverage, developmental context and the highest level of evidence available in a skeletal indication. The most important column is the last but one, which shows that the depth of clinical evidence in achondroplasia is inversely related to the degree of isoform selectivity, precisely the reverse of the ordering implied by the language of successive generations.

6. Safety and the Paediatric Risk Calculus

6.1 Class Effects Observed in Adult Oncology Populations

The toxicity profile of fibroblast growth factor receptor inhibition in adults is well characterised and mechanistically coherent. Hyperphosphataemia arises from inhibition of receptor 1 dependent regulation of phosphate handling, and its predictability has made it a pharmacodynamic marker of exposure in oncology. Nail dystrophy, alopecia, dry mouth, stomatitis and palmar-plantar erythrodysaesthesia are common, and ocular events including dry eye, keratopathy and central serous retinopathy are recognised class effects requiring monitoring (Subbiah & Verstovsek, 2023). Basket-trial experience across tumour types confirms that these events occur at frequencies sufficient to require dose modification in a substantial proportion of treated adults (Pant et al., 2023).

Pharmacovigilance analysis provides an independent perspective on the ocular signal. Among 1,582 adverse event reports associated with fibroblast growth factor receptor inhibitors submitted to a national reporting system, 200, or 12.6 per cent, were ocular, with erdafitinib accounting for three-quarters. Disproportionality was highest for corneal thinning with erdafitinib, with a reporting odds ratio of 321 and a 95% confidence interval of 102 to 1,009, and for serous retinal detachment with pemigatinib, with a reporting odds ratio of 180 and a 95% confidence interval of 67 to 484 (Abu Osba et al., 2026). These estimates describe disproportional reporting rather than incidence, are subject to reporting and indication bias, and derive from adults receiving oncological doses. Their relevance to paediatric achondroplasia is limited to establishing which organ systems merit prospective surveillance, and the exclusion criteria for the paediatric phase 2 dose-finding study of dabogratinib, which exclude children with existing corneal or retinal disorders, indicate that developers regard the signal as sufficiently plausible to warrant caution (Tyra Biosciences, 2025).

6.2 Dose Separation and its Consequences for Inference

Infigratinib in achondroplasia is administered at 0.25 mg per kilogram daily, whereas oncological regimens for the same molecule use fixed doses that produce exposures roughly two orders of magnitude higher. This separation has two consequences that pull in opposite directions and are rarely acknowledged together. The reassuring inference is that class toxicities observed at oncological exposure are unlikely to occur at paediatric exposure, and the pivotal trial is consistent with that expectation, since adverse event frequencies were similar between treatment and placebo groups and no discontinuation was attributed to treatment (Savarirayan, Hoover-Fong, et al., 2026). The unsettling inference is that the same separation weakens the argument for isoform selectivity, as set out in Section 5.3, because a toxicity that does not occur cannot be avoided.

A second consequence concerns duration. Oncological exposure is typically measured in months and occurs in adults whose growth plates are closed and whose competing mortality risk is high. Paediatric exposure in achondroplasia would begin in early childhood and continue until skeletal maturity, a period of a decade or more during which the treated tissue is the tissue in which the drug acts. Adverse effects that require years to manifest, or that manifest only after the cumulative exposure of a developmental period, are structurally invisible to both the oncology dataset and the 52-week paediatric trials. The peptide class has accumulated more than 460 person-years of continuous exposure without evident long-term harm (Savarirayan, Irving, et al., 2025); the oral inhibitor class has nothing comparable.

6.3 What Paediatric Trials to Date can and Cannot Exclude

Trials of one year in populations of one hundred or fewer children are adequately powered to detect common adverse events and grossly inadequate for uncommon ones. The pivotal trial of oral receptor inhibition reported serious adverse events in 4 of 74 treated children and 1 of 39 placebo recipients, a comparison from which no meaningful inference about differential risk can be drawn (Savarirayan, Hoover-Fong, et al., 2026). Effects on hearing, on ocular structures, on dental and craniofacial development, on pubertal timing, and on the timing of physeal closure are of particular concern for a receptor with the physiological distribution described in Section 3.3, and none has been evaluated with sufficient duration or sample size in any published trial. Growth-plate closure deserves specific attention, since an agent that accelerates growth velocity while also advancing skeletal maturation could increase height during treatment without increasing adult stature, and bone age has been monitored in at least one peptide-class trial (Savarirayan, McDonnell, et al., 2026) but is not consistently reported across the field.

Table 4. Recurrent methodological limitations across the achondroplasia therapeutic literature, with the likely direction of their effect on interpretation

Limitation	Where it arises	Likely direction of bias	Mitigation available in current evidence	Supporting references
Observation confined to 52 weeks	All randomised placebo-controlled trials across every therapeutic class	Favours apparent benefit, because early growth acceleration may not persist and late harms cannot appear	Only the open-label extension of the approved peptide, which loses the concurrent control	Savarirayan et al. (2020); Savarirayan, Irving, et al. (2025); Savarirayan, Hoover-Fong, et al. (2026); Savarirayan, McDonnell, et al. (2026)
Reliance on a one-year growth surrogate	Primary endpoints of all pivotal trials	Uncertain; the relationship between one-year velocity and adult stature is unestablished in this condition	External comparison with untreated natural history cohorts, itself subject to confounding	Hoover-Fong, Schulze, et al. (2021); Savarirayan, Irving, et al. (2025)
External or historical comparators	Open-label extensions; dose-finding studies; modelling analyses conducted without a placebo arm	Favours apparent benefit through secular improvements in care and differential ascertainment	Prospective baseline growth periods before randomisation in several trials	Qiao et al. (2024); Savarirayan, De Bergua, et al. (2025); Savarirayan, Irving, et al. (2025)
Murine models carrying alleles other than the human variant	Essentially all preclinical efficacy work supporting both therapeutic classes	Likely overstates achievable correction, because severe models offer greater scope for rescue	A knock-in model carrying the human variant has recently been reported but has not yet been used for comparative drug evaluation	Horike et al. (2026); Komla-Ebri et al. (2016); Lorget et al. (2012); Starrett et al. (2025)
Secondary and subgroup analyses reported as though confirmatory	Body proportionality, functional and radiographic outcomes across several trials	Favours apparent benefit through multiplicity and selective emphasis	Pre-specified multiplicity adjustment applied in the most recent pivotal trial	Savarirayan, De Bergua, et al. (2025); Savarirayan, Hoover-Fong, et al. (2026); Savarirayan, McDonnell, et al. (2026)
Single-arm syntheses pooling heterogeneous designs	Meta-analyses of real-world vosoritide experience	Overstates precision; pooled single-arm velocities cannot be read as treatment effects	Direction of effect is concordant with randomised evidence, which limits the practical consequence	Albuquerque et al. (2026); Alfaraj et al. (2026)
Concentration of investigators and sponsorship	Pivotal trials of all three agent classes share overlapping leadership and are industry funded	Uncertain; concentration accelerates recruitment in a rare condition while reducing independent replication	Publication in journals applying multiplicity control and full protocol disclosure	Savarirayan et al. (2020); Savarirayan, Hoover-Fong, et al. (2026); Savarirayan, McDonnell, et al. (2026)
Very small imaging and complication series	Craniocervical junction outcomes; interaction with orthopaedic surgery	Unpredictable; series of fewer than ten children can generate signals in either direction	Structured stenosis scoring systems permit comparison across centres	Allegri et al. (2025); Cheung et al. (2021); Gunji et al. (2025); Nakagawa et al. (2026)

Note. The direction of bias indicated is the most probable consequence of the limitation and is not a claim that the effect has been demonstrated in any specific study. Mitigation refers to features present in the existing literature that partially offset the limitation, not to remedies proposed by this review.

A distinct category of risk arises from the interaction between pharmacological growth promotion and the natural history of skeletal complications. A case report described worsening of foramen magnum stenosis during early vosoritide treatment in an infant (Gunji

et al., 2025), and a small retrospective imaging series of nine children who began treatment before three years of age documented one child progressing to the highest stenosis grade and undergoing decompression at eleven months, notwithstanding that growth of the foramen magnum in the series generally exceeded that of untreated reference cohorts (Nakagawa et al., 2026). Neither report establishes causation, and the second in fact suggests benefit at the group level. Together they indicate that the craniocervical junction responds to treatment in ways that are not predictable from linear growth, that individual trajectories diverge, and that surveillance protocols developed for untreated children may require revision (Cheung et al., 2021; Irving et al., 2023).

Table 4 summarises the methodological limitations that recur across the therapeutic literature, with an indication of the direction in which each is likely to bias interpretation. The pattern is consistent: most limitations tend to favour the appearance of benefit, principally through short observation windows, surrogate endpoints, external or historical comparators and selective reporting of favourable secondary analyses.

7. Endpoints, Surrogacy and the Outcomes That Matter

7.1 Annualised Growth Velocity as a Surrogate

Every pivotal trial in this field has used annualised growth or height velocity over 52 weeks as its primary endpoint. The choice is pragmatic and defensible: velocity is measurable with acceptable precision, responds within a period compatible with trial conduct, and relates directly to the pathophysiology. It is nonetheless a surrogate, and its validity for the outcomes that matter has not been established. A surrogate is validated when a treatment-induced change in it reliably predicts a change in a clinical outcome, and no agent in achondroplasia has yet reported adult height, cumulative surgical burden or long-term functional status.

Two features of growth in this condition make the surrogate particularly fragile. Growth in untreated achondroplasia is not linear across childhood, and velocity declines steeply after infancy before the pubertal contribution, which in this condition is attenuated (Hoover-Fong, Schulze, et al., 2021). A one-year gain achieved at an age of rapid decline may represent a shift in the timing of growth rather than an addition to its total. Second, a growth-promoting agent that also advances skeletal maturation could increase velocity while leaving adult stature unchanged, an outcome familiar from other paediatric growth-promoting therapies. The extension data for the approved peptide, showing sustained velocity across six years and a three-year height advantage of 5.75 cm relative to an untreated cohort, are the strongest available evidence against that concern, but they are externally controlled and do not extend to final height (Savarirayan, Irving, et al., 2025).

The interpretive consequence is that the difference between a treatment effect of 1.49, 1.57 and 1.74 cm per year, reported respectively for navepegritide, vosoritide and infigratinib, cannot support the ranking of agents that is increasingly attached to it. Those estimates derive from trials enrolling children aged 2 to 11, 5 to less than 18, and 3 to 17 years, with different baseline growth velocities, different comparators for missing data and different multiplicity frameworks (Savarirayan et al., 2020; Savarirayan, Hoover-Fong, et al., 2026; Savarirayan, McDonnell, et al., 2026). Indirect comparison across trials of this kind is unreliable even when populations are similar, and here they are not.

7.2 Body Proportionality: An Inconsistent and Fragile Signal

Disproportion between limb and trunk length is a principal determinant of reach, independent transfer, dressing and self-care, and is therefore closer to a clinically meaningful endpoint than stature alone. The evidence for improvement is weak across all classes and has been reported inconsistently. The pivotal vosoritide trial found no significant change in body segment proportionality over 52 weeks (Savarirayan et al., 2020). The open-label extension identified a significant improvement in upper-to-lower body segment ratio at three years, confined to younger participants and referenced to external controls (Savarirayan, Irving, et al., 2025). The infigratinib dose-finding study reported a reduction of 0.12 in the same ratio at 18 months in a single open-label cohort, and the randomised trial reported a difference of −0.02 whose interval included the null (Savarirayan, De Bergua, et al., 2025; Savarirayan, Hoover-Fong, et al., 2026). The pivotal navepegritide trial did not report upper-to-lower body segment ratio as its proportionality measure, instead reporting improvements in tibial-femoral angle, mechanical axis deviation and the fibula-to-tibia length ratio (Savarirayan, McDonnell, et al., 2026).

The heterogeneity of measures is itself a finding. Upper-to-lower body segment ratio, sitting-height-to-height ratio, arm-span-to-height ratio and radiographic limb alignment indices capture different constructs, respond over different timescales, and are not interchangeable. A field that reports whichever proportionality measure moved in a given trial cannot accumulate evidence, and the appearance of progress across studies may reflect measurement diversity rather than convergent benefit. Establishing a common set of proportionality outcomes, with defined measurement protocols and known reliability in treated children, is a prerequisite for the comparative evaluation that clinicians and families now require.

7.3 Craniocervical, Spinal and Functional Outcomes

The outcomes with the greatest bearing on early morbidity are those at the craniocervical junction. Foramen magnum stenosis carries a risk of cervicomedullary compression, and its detection and management have been formalised in structured scoring and in European guiding principles (Cheung et al., 2021; Irving et al., 2023). Whether pharmacological therapy modifies this risk is the single most important unanswered question in the field, and the evidence available is disproportionately thin. Preclinical work with a selective inhibitor demonstrated improvement in foramen magnum size and shape in a mutant mouse model (Starrett et al., 2025). Human evidence consists of a retrospective single-centre series of nine children treated with the approved peptide before three years

of age, in which foramen magnum diameters grew more steeply than in untreated reference cohorts without correlation to change in height standard deviation score, and in which one child nonetheless required decompression (Nakagawa et al., 2026), alongside an isolated report of stenosis worsening during treatment (Gunji et al., 2025). No randomised trial has been powered for this outcome.

Spinal outcomes are similarly underdeveloped. A single-centre study reported changes in spinal and lower-limb alignment during one year of treatment with the approved peptide (Sawamura et al., 2025), and preclinical work with a selective inhibitor reported increased lumbar vertebral length and improved intervertebral disc morphology (Starrett et al., 2025). Neither addresses the clinical outcome of symptomatic spinal stenosis, which typically manifests in adolescence and adult life and would require follow-up far beyond the horizon of any current trial.

Functional and patient-reported outcomes have begun to appear. Persistence of growth-promoting effects has been reported alongside improvements in physical and social aspects of health-related quality of life during extended treatment with the approved peptide (Savarirayan, Irving, et al., 2024), and the pivotal navepegritide trial included a condition-specific patient-reported instrument as a pre-specified secondary outcome, with improvement in physical functioning confined to children younger than five years (Savarirayan, McDonnell, et al., 2026). These developments are welcome, but they remain secondary, are inconsistently instrumented across trials, and have not been aligned with the outcome domains prioritised in international consensus guidance, which emphasises function, complication avoidance and participation rather than stature (Alves et al., 2026; Savarirayan et al., 2022).

8. Comparative Interpretation, Competing Strategies and Translation to Practice

8.1 The Problem of Indirect Comparison

The field has reached a point at which clinicians and families must choose between a daily subcutaneous injection, a weekly subcutaneous injection and a daily oral tablet, each supported by a placebo-controlled trial of similar size and duration, and none compared with another. In the absence of head-to-head data, comparison necessarily proceeds indirectly, and the conditions that make indirect comparison valid are not satisfied. The trials differ in age range and therefore in the distribution of baseline growth velocity, which is itself the strongest predictor of on-treatment velocity. They differ in the requirement for a prospective observational baseline, which affects regression to the mean. They differ in masking, in imputation strategy for missing data and in the multiplicity framework applied to secondary endpoints. They differ in the definition of the proportionality endpoint, as set out in Section 7.2.

The practical consequence is that the choice among agents currently rests on considerations other than comparative efficacy: route and frequency of administration, tolerability in the individual child, family capacity to sustain a regimen, availability and reimbursement, and the presence of contraindications. These are legitimate grounds for choice, and framing them honestly is preferable to a comparison of effect estimates that the underlying designs cannot support. A platform or head-to-head design would resolve the question, and the ethical conditions for such a trial arguably now exist, since genuine uncertainty as to relative benefit is the definition of equipoise.

8.2 Alternatives, Sequencing and Interaction with Surgery

Surgical limb lengthening remains a substantive alternative with a considerable evidence base. A systematic review and meta-analysis of 14 studies comprising 1,149 patients reported mean femoral gain of 8.85 cm, tibial gain of 7.36 cm and humeral gain of 8.38 cm, with a mean external fixator index of 37.1 days per centimetre and an overall complication rate of 56.1 per cent, alongside a pooled paediatric quality of life score indicating moderate benefit (Hosny et al., 2026). Earlier series report comparable gains with substantial complication burdens (Verdoni et al., 2023). The magnitude of stature gain from surgery exceeds anything reported from pharmacotherapy by a wide margin; the cost in operative burden, time in fixation and complications is correspondingly large. Any comparative statement about pharmacological therapy that omits this alternative presents an incomplete decision landscape to families.

The interaction between the two modalities is essentially unstudied. A multicentre report of real-life experience integrating vosoritide therapy with limb surgery describes the practical questions that arise, including whether treatment should be interrupted around distraction osteogenesis and whether pharmacologically accelerated growth alters consolidation (Allegri et al., 2025). Guided-growth hardware is an explicit exclusion in at least one ongoing inhibitor trial (Tyra Biosciences, 2025), which indicates that developers regard the interaction as consequential and unresolved. Since a substantial proportion of children treated pharmacologically will also be candidates for orthopaedic intervention, this gap has immediate clinical relevance.

8.3 Goals of Care and Evidence-informed Counselling

International consensus positions the goals of care in achondroplasia around function, avoidance and management of complications, and participation across the life course, rather than around stature as an end in itself (Alves et al., 2026; Savarirayan et al., 2022). National guidance developed subsequently applies the same framing to multidisciplinary paediatric care and to the implementation and monitoring of pharmacological therapy (Candler et al., 2026; Savarirayan, Hoover-Fong, et al., 2025; Tofts et al., 2023). Evidence generation has not fully aligned with that framing, and the misalignment is the source of much of the interpretive difficulty described in Section 7. Trials measure centimetres; guidance measures function; families weigh both against the burden of daily injection or chronic oral therapy through childhood.

Counselling under current evidence therefore requires several statements that are uncomfortable but accurate. Growth velocity increases with all three agents that have completed placebo-controlled trials, by an amount that is statistically robust and, over a single year, modest in absolute terms. Whether this translates into greater adult height is unknown for every agent. Whether any agent reduces the frequency of decompressive surgery, spinal surgery, sleep-disordered breathing or functional limitation is unknown. Body proportionality has not improved significantly in any randomised, concurrently controlled 52-week comparison. Long-term safety is established only for the peptide class, and only to about six years of exposure. These statements are compatible with recommending treatment, and they are also compatible with a decision to defer it, which is why they should be presented rather than summarised.

Table 5 consolidates the principal unresolved questions identified across the preceding sections, with the design that would resolve each. The gaps are ordered by the proximity of the question to clinical decision-making rather than by the ease of answering it, and several of the highest-priority items require designs that no current programme has adopted.

Table 5. Prioritised research gaps in targeted therapy for paediatric achondroplasia, with the study design required to resolve each

Unresolved question	Why current evidence is inadequate	Design required	Priority horizon	Supporting references
Does any agent increase adult stature?	All pivotal trials are limited to 52 weeks; extension data are externally controlled and stop short of skeletal maturity	Long-term follow-up of randomised cohorts to final height, with pre-specified analysis and retention of the original allocation as a covariate	Immediate; cohorts already exist	Savarirayan et al. (2020); Savarirayan, Irving, et al. (2025); Savarirayan, Hoover-Fong, et al. (2026)
Does receptor-level inhibition offer any advantage over pathway-level antagonism?	No head-to-head comparison exists; indirect comparison is invalidated by differences in age range, baseline velocity and analytical convention	Randomised head-to-head or multi-arm platform trial with a common protocol, common endpoints and a shared control	Immediate; equipoise is present	Savarirayan, Hoover-Fong, et al. (2026); Savarirayan, McDonnell, et al. (2026)
Does isoform selectivity improve the therapeutic ratio in children?	The premise derives from adult oncology dosing; at paediatric doses the pan-receptor inhibitor is not evidently dose limited by isoform-related toxicity	Comparative preclinical dosing of selective and non-selective inhibitors in the same model, followed by clinical dose escalation designed to test whether selectivity permits higher exposure	Short to medium term	L. Chen (2025); Hudkins et al. (2024); Starrett et al. (2025); Tyra Biosciences (2025)
Does pharmacological therapy modify craniocervical risk?	Human evidence comprises a nine-child retrospective series and an isolated case report	Prospective multicentre imaging cohort with standardised stenosis scoring, pre-specified surgical outcomes and adequate duration in children treated from infancy	Immediate; morbidity is concentrated in infancy	Cheung et al. (2021); Gunji et al. (2025); Irving et al. (2023); Nakagawa et al. (2026)
Which proportionality measure should the field adopt?	Trials report different indices over different intervals, preventing accumulation of evidence	Measurement-properties study establishing reliability and responsiveness of candidate indices in treated children, followed by consensus adoption	Short term; low cost relative to impact	Savarirayan, De Bergua, et al. (2025); Savarirayan, Irving, et al. (2025); Savarirayan, Hoover-Fong, et al. (2026); Savarirayan, McDonnell, et al. (2026)
Can pathway suppression be measured directly in a growth-plate-relevant compartment?	No clinical study reports a pharmacodynamic marker of receptor pathway suppression, so dose selection relies on growth response	Biomarker development and qualification, incorporating cartilage turnover markers and, where feasible, imaging correlates	Medium term	Horike et al. (2026); Ornitz & Itoh (2015)
How should pharmacotherapy and orthopaedic surgery be sequenced?	Interaction is described only in real-life experience reports, and surgical hardware is an exclusion criterion in ongoing trials	Prospective observational cohort of children undergoing lengthening or guided growth during therapy, with pre-specified consolidation and complication outcomes	Short term	Allegri et al. (2025); Hosny et al. (2026); Tyra Biosciences (2025)

Unresolved question	Why current evidence is inadequate	Design required	Priority horizon	Supporting references
Which outcomes should define benefit?	Trial endpoints emphasise stature while consensus guidance emphasises function, complications and participation	Core outcome set developed with affected individuals, families and clinicians, incorporating condition-specific patient-reported instruments	Immediate; prerequisite for interpretable future trials	Alves et al. (2026); Fagereng et al. (2025); Savarirayan et al. (2022); Savarirayan, McDonnell, et al. (2026)

Note. Priority horizon indicates the interval within which the study could realistically be initiated given existing infrastructure, not the interval required to obtain results. Designs described are the minimum adequate to answer the question posed and are not exclusive of more elaborate alternatives.

9. Future Directions

The most consequential unresolved problem is that no agent has demonstrated an effect on any outcome other than a one-year growth surrogate. Current evidence is inadequate because trial duration was set by regulatory feasibility rather than by the natural history of the outcomes that determine morbidity, and because extension cohorts lose their concurrent controls at the moment when long-term inference becomes possible. The design required is long-term follow-up of existing randomised cohorts to skeletal maturity, with retention of original allocation as an analytical covariate, pre-specified analysis of final height, and capture of decompressive and spinal surgery, sleep-disordered breathing and functional status. The cohorts already exist and the marginal cost of extended follow-up is small relative to the cost of the trials that generated them. Without this work the field will continue to accumulate one-year velocity estimates that cannot be converted into statements about benefit.

A second priority is direct comparison. Clinicians must now choose among three agents with different routes, schedules and mechanisms, supported by trials that cannot be compared with one another. Genuine uncertainty as to relative benefit satisfies the conventional requirement for equipoise, and a multi-arm platform trial with a shared control, a common protocol, harmonised endpoints and a single analytical framework would resolve in one programme what a series of separate placebo-controlled trials cannot resolve at all. Such a design would also permit evaluation of combination regimens, which are already entering clinical study without any framework for comparing them with monotherapy (McDonnell et al., 2026). Feasibility in a rare condition is a genuine obstacle, but the concentration of investigators and centres that currently limits independent replication is precisely the infrastructure that would make a platform trial achievable.

Third, the selectivity hypothesis requires falsifiable formulation and direct testing. The proposition that restricting inhibition to a single receptor isoform improves the therapeutic ratio in growing children has not been tested preclinically in a head-to-head design, nor clinically at all. The appropriate preclinical experiment compares a selective and a non-selective inhibitor in the same model at matched degrees of target engagement, with growth, craniofacial, vertebral and off-target endpoints measured under blinded assessment, ideally in the knock-in model carrying the human variant rather than in more severe surrogate alleles (Horike et al., 2026). The appropriate clinical test is a dose-escalation design that determines whether selectivity permits exposure above the ceiling tolerated with pan-receptor inhibition, and whether any additional exposure yields additional growth. If selectivity does not permit higher exposure, or if higher exposure does not increase growth, the principal argument for the class fails, and that outcome should be as publishable as its opposite.

Fourth, craniocervical outcomes require a dedicated prospective programme. Morbidity from foramen magnum stenosis is concentrated in the first two years of life, precisely the period in which trial evidence is weakest and in which the only efficacy study of the approved peptide failed to exclude the null (Savarirayan, Wilcox, et al., 2024). What is needed is a multicentre prospective imaging cohort of children commencing therapy in infancy, with standardised stenosis scoring applied at fixed intervals by assessors blinded to treatment status, pre-specified surgical outcomes, and sufficient duration to capture the period of maximum risk (Cheung et al., 2021; Irving et al., 2023). Such a cohort would also resolve whether the divergent individual trajectories reported to date reflect treatment effect, natural variation or ascertainment (Gunji et al., 2025; Nakagawa et al., 2026).

Fifth, the field lacks a pharmacodynamic measure of what its drugs are doing. Dose selection currently proceeds from growth response, which conflates target engagement with downstream biological effect and provides no means of determining whether a given child is under-treated or over-treated. Development and qualification of a biomarker reflecting receptor pathway activity in cartilage, complemented by imaging measures of growth-plate architecture, would allow dose individualisation and would provide an early read on whether a new compound engages its target in the relevant compartment. The recent identification of resting-zone chondrocyte dysfunction as a component of the phenotype suggests candidate biological processes that such a biomarker might track (Horike et al., 2026).

Sixth, outcome definition should be settled before further trials are designed. A core outcome set developed with affected individuals and families, incorporating validated condition-specific instruments and a single agreed measure of body proportionality, would end the current situation in which each trial reports the outcomes that moved. Consensus guidance already articulates the domains that matter (Alves et al., 2026; Savarirayan et al., 2022), and instruments for measuring the experience of affected children have begun to be evaluated formally. Aligning trial endpoints with those domains is a low-cost intervention with a disproportionate effect on the interpretability of everything that follows.

Longer-term priorities are of a different character. Genetic correction of the causative allele has been achieved in patient-derived pluripotent stem cells and in the murine equivalent variant (Miao et al., 2019; Zou et al., 2021), but delivery to growth-plate

chondrocytes, a poorly vascularised tissue with a slowly cycling stem-cell-like compartment, remains unsolved, and the ethical framework for germline-adjacent intervention in a non-lethal condition with an established community identity is unresolved. Nearer-term biological questions include whether intervention before the first year of life produces qualitatively different outcomes from intervention at school age, whether the therapeutic target should shift from the proliferative zone to the resting zone in light of recent mechanistic work, and whether the extension of these agents to hypochondroplasia (Dauber et al., 2024; Demuynck et al., 2025) is supported by evidence of the same quality as that available for achondroplasia, which at present it is not.

10. Conclusions

Achondroplasia has become the reference case for genotype-directed therapy in paediatric rare disease, and the mechanistic account underlying that status is strong. A single recurrent variant produces constitutive activation of a receptor that normally restrains endochondral bone growth, and both downstream pathway antagonism and direct receptor inhibition correct the phenotype in animal models. Three agents acting at two levels of this axis have now completed placebo-controlled randomised trials in children and have each demonstrated a statistically robust increase in growth velocity over 52 weeks. This is a substantial achievement in a condition that had no disease-modifying therapy a decade ago, and the conclusion that these agents increase short-term growth is well supported.

Beyond that conclusion, confidence falls sharply, and the review objectives are answered largely in the negative. The comparative question cannot be answered from existing data: the trials differ in age range, baseline growth, imputation strategy and multiplicity framework to a degree that invalidates indirect comparison, and the differences in reported effect are small relative to those design differences. The proportionality question is answered negatively for every agent within randomised, concurrently controlled 52-week comparison, and the positive findings that circulate in the literature derive from open-label cohorts, external comparators, subgroups or alternative indices. The complication question is unanswered, since no trial has been powered for craniocervical, spinal or functional outcomes, and the human evidence bearing on foramen magnum development in treated children consists of a series of nine patients and an isolated case report. The adult-height question is unanswered for every agent.

The selectivity hypothesis that motivates the newest compounds deserves separate assessment because it is presented with more confidence than the evidence supports. Isoform-selective inhibition of the receptor has been achieved as a chemical objective, and preclinical work with one such compound shows growth promotion together with improvement in cranial, foramen magnum and vertebral morphology in two mutant mouse models. That work is careful and its scope is honestly stated. What has not been shown is that selectivity confers any clinical advantage in children, and the principal argument for it, namely avoidance of toxicity attributed to inhibition of the other receptor isoforms, is weakened by the observation that the non-selective inhibitor is used in achondroplasia at approximately one-hundredth of the oncological dose and produced an adverse event profile in its pivotal trial that did not differ materially from placebo. The related compound developed in oncology demonstrates that the pharmacological class is viable in humans, and nothing more; it has no skeletal dysplasia programme and its therapeutic objective is close to opposite to that required in a growing child. Selective inhibitors are best understood at this stage as promising compounds whose principal claim remains to be tested, and the design of that test is straightforward and should be undertaken.

The broader significance of this synthesis lies in the mismatch between the sophistication of the pharmacology and the maturity of the evidence framework. A field that can design a molecule to discriminate between kinase domains sharing extensive sequence identity is still measuring benefit with a one-year surrogate, still reporting whichever proportionality index moved, and still comparing agents across trials that were never designed to be compared. The corrective actions are neither novel nor expensive: extend existing cohorts to final height, compare agents directly, agree a core outcome set with affected families, and state the selectivity hypothesis in a form that permits refutation. Until that work is done, clinical decisions should be framed around what is known, which is short-term growth acceleration with acceptable short-term tolerability, rather than around what is hoped, which is modification of the natural history of a lifelong multisystem condition.

11. Limitations

This review is a narrative synthesis and carries the limitations intrinsic to that design. Selection of sources was purposive and interpretive rather than governed by a documented systematic protocol, and although eligibility criteria and search concepts were specified in advance, the possibility of selection bias in the choice of studies and of interpretive bias in the weight assigned to them cannot be eliminated. A different reviewer applying the same criteria might emphasise different studies and reach different conclusions on the contested points, particularly regarding the interpretation of open-label proportionality findings and the assessment of the selectivity hypothesis.

Access to bibliographic resources was incomplete. Subscription databases including Web of Science, Scopus and Embase were unavailable, and searching relied on the biomedical index of the United States National Library of Medicine, a metadata registry, a public trial registry and general scholarly searching. This configuration is adequate for biomedical and clinical literature but underrepresents engineering, social science and grey literature, and may have missed studies indexed only in regional or discipline-specific resources. Retrieval was restricted to publications available in English, which is likely to have excluded relevant clinical experience from centres publishing in other languages, particularly in East Asia and Latin America, where substantial cohorts of affected children are managed.

The evidence base itself imposes constraints that no review can overcome. Trial durations are uniformly short relative to the natural history of the condition, and the absence of adult height data for any agent means that the most important clinical question could not be addressed. Randomised evidence is concentrated in a small number of trials conducted by overlapping investigator groups with

industry sponsorship, which limits independent replication and means that design conventions, endpoint definitions and analytical choices are correlated across the literature rather than varying independently. Preclinical evidence relies on murine alleles that differ from the human variant, and the recent availability of a knock-in model carrying that variant means that most existing translational inference rests on models that will shortly be superseded. Reported outcomes are heterogeneous, particularly for body proportionality, which prevented any quantitative comparison across trials and constrained the synthesis to qualitative appraisal.

Several topics received limited treatment. Health economic evaluation, access and reimbursement, which materially determine whether any of these agents reaches affected children, were outside the scope. Adult management, the perspectives of adults with achondroplasia on paediatric pharmacotherapy, and the substantial ethical literature concerning treatment of a condition with an established community identity were addressed only where they bore directly on outcome selection. Evidence for the extension of these agents to hypochondroplasia and other receptor-related dysplasias was considered only insofar as it informed inference about achondroplasia. Finally, the field is developing rapidly, regulatory decisions were pending at the time of writing, and the appraisal presented here reflects the evidence available to the stated search date and should be expected to require revision as pivotal programmes report further data.

Consent and Ethical Approval

It is not applicable.

Declaration of AI Use

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Competing Interests

Authors have declared that no competing interests exist.

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