Therapies in Achondroplasia and Skeletal Dysplasia

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Disclosures

BioMarin Pharmaceutical

Advisory board · 2026

Why This Topic Matters

1 in 4,000 to 5,000

live births affected by a skeletal dysplasia

THE SHIFT

Prognosis. Recurrence. Delivery planning.

Therapeutic eligibility. Subspecialty referral. Timing of intervention. Family decisions.

Prenatal diagnosis has become therapeutically actionable.

From Diagnosis to Decision

Targeted therapy relies on molecular precision. Variant-level information drives eligibility, not just prognosis.

PHENOTYPE

What we see

Ultrasound · MRI

→

GENOTYPE

What it is

Targeted gene panel vs. exome/genome sequencing chosen by phenotype and turnaround

→

DECISION

What we do

Therapy eligibility · referral pathway · delivery setting · counseling

Achondroplasia

Achondroplasia

PREVALENCE

Most common

1 in 10,000 to 1 in 30,000 live births

non-lethal skeletal dysplasia

GENE

FGFR3

gain-of-function

VARIANT

>95% c.1138G>A

p.Gly380Arg

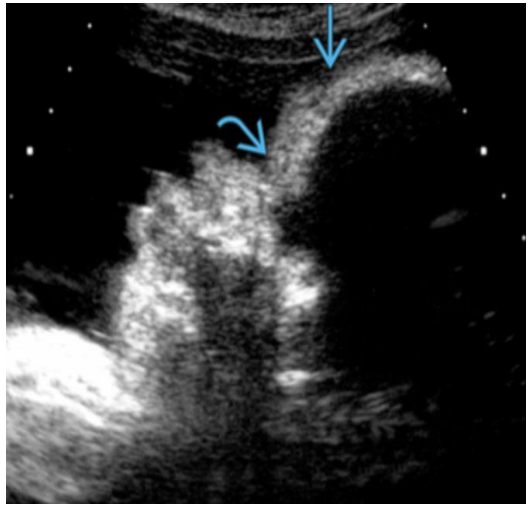
INHERITANCE

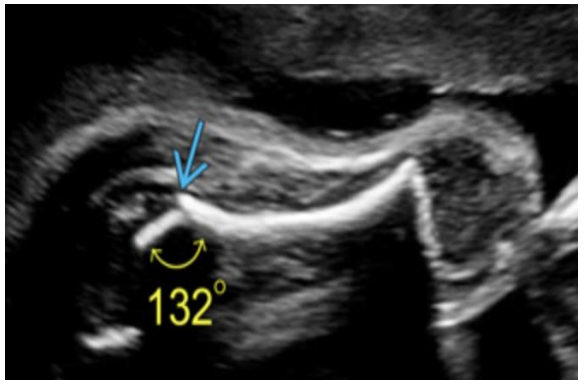
Majority de novo in 80%

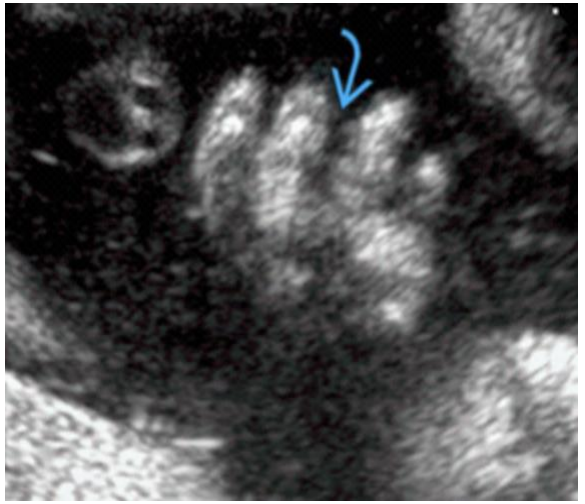
AD if transmitted

Prenatal Imaging Findings

- Rhizomelic limb shortening
- Macrocephaly
- Frontal bossing
- Trident hand configuration







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Standard Postnatal Management

Multidisciplinary surveillance from birth.

Orthopedics

Limb alignment · spine

Neurosurgery

Foramen magnum · hydrocephalus

ENT

Airway · otitis · hearing

Sleep medicine

Central + obstructive apnea

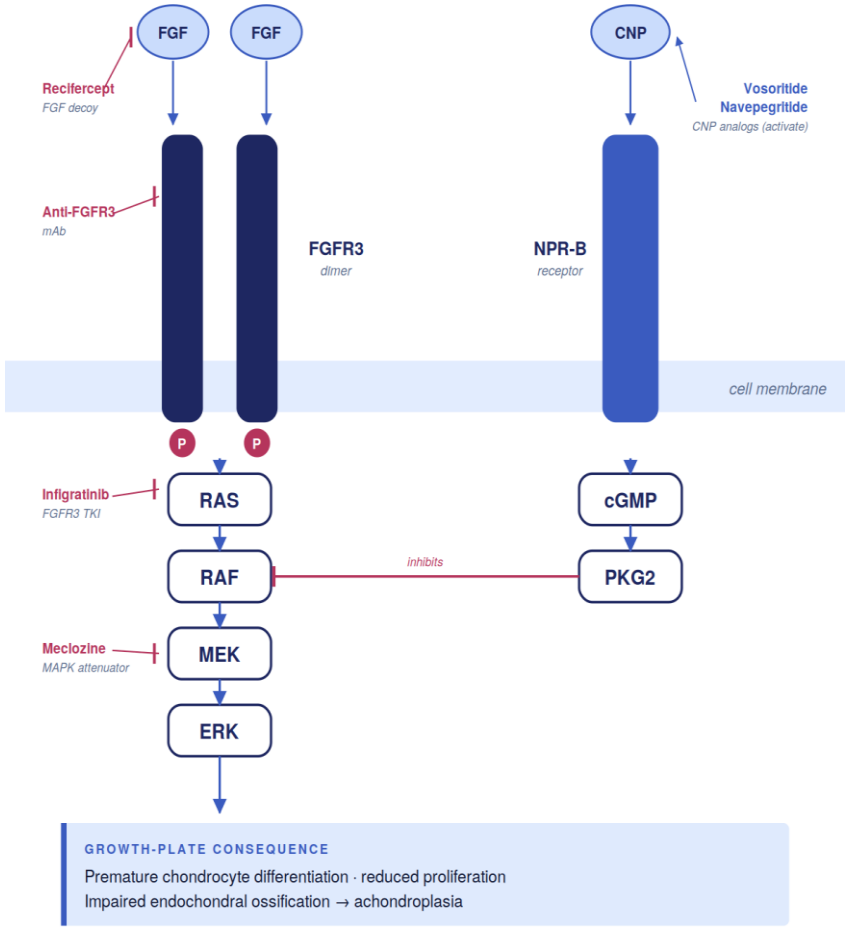
Pulmonology

Thoracic mechanics

Development

Motor + neurocognitive

Mechanism: FGFR3 Overactivation



FGFR3 in the growth plate

Activating FGFR3 variants drive sustained RAS/MAPK signaling, suppressing chondrocyte proliferation and accelerating differentiation.

THE CASCADE

FGFR3 → RAS → RAF → MEK → ERK

THE BRAKE

CNP / NPR-B → cGMP → PKG2 ⊣ RAF

THE TARGETS

Therapies act at the ligand, receptor, kinase, or parallel arm.

Pathway concept based on Fafilek B, Bosakova M, Krejci P. Osteoarthritis Cartilage 2022;30(4):535–544.

Vosoritide

CNP analog

Counters FGFR3 downstream MAPK signaling at the growth plate.

ROUTE

Daily SC injection

FDA APPROVAL

2021

Children ≥5 years, open growth plates

EXPANDED APPROVAL

2023

From birth until growth plate closure

Vosoritide - Trial & Real-World Data

PIVOTAL TRIAL

Savarirayan et al., Lancet 2020

- **Design:** Phase 3, randomized, double-blind, placebo-controlled
- **Population:** n = 121, ages 5–17 with achondroplasia
- **Duration:** 52 weeks (open-label extension ongoing)
- **Primary endpoint:** Change from baseline in annualized growth velocity

PRIMARY OUTCOME

+1.57 cm/yr

vs. placebo (95% CI 1.22–1.93; p<0.0001)

Height Z-score also significantly improved. Effect durable through ≥2 yrs in extension.

SAFETY (PHASE 3)

- Injection-site reactions — *~70–85% vs. 43% placebo*
- Vomiting — *27% vs. 20%*
- Urticaria — *25% vs. 10%*
- Arthralgia — *15% vs. 7%*
- Hypotension (mild, vasodilatory) — *13% vs. 5%*

No deaths; SAEs comparable between arms.

Infant hypotension/vomiting reported post-2023 label expansion (Cureus 2024).

REAL-WORLD CAVEAT

Post-approval registry cohorts suggest effect sizes may be smaller than the pivotal trial — counsel families with a range, not a single number.

Hypochondroplasia phase 3 (CANOPY-HCH-3) hit primary endpoint 2026.

Navepegritide - Trial Data

PIVOTAL TRIAL

ApproaCH (JAMA Pediatrics)

- **Drug class:** Long-acting CNP prodrug (NPR-B agonist)
- **Design:** Phase 3, randomized, double-blind, placebo-controlled
- **Population:** n = 84, ages 2–11 (2:1 randomization)
- **Dosing:** 100 µg/kg once-weekly SC
- **Primary endpoint:** Change from baseline in annualized growth velocity

PRIMARY OUTCOME (AGV at Week 52)

5.42 vs **4.35** cm/yr

Phase 2 ACcomplisH — p=0.022 (eClinicalMedicine 2023)

Phase 3 ApproaCH met primary AGV endpoint; gains sustained through 2 years.

SAFETY & SECONDARY ENDPOINTS

- Overall AE rate — *Similar to placebo*
- Injection-site reactions — *Low frequency (phase 2)*
- Symptomatic hypotension — *None observed*
- Lower-limb alignment — *Improved vs. placebo*
- Body proportionality — *Improved vs. placebo*
- Health-related QoL — *Positive changes reported*

KEY DIFFERENTIATOR

Once-weekly SC dosing

vs. daily injection for vosoritide — meaningful reduction in administration burden.

COACH phase 2 (2025–26): combination with lonapegsomatropin (long-acting GH) shows additive growth at 26 weeks.
Currently investigational — not yet FDA-approved.

Infigratinib - Trial Data

PIVOTAL TRIAL

PROPEL 3

- **Drug class:** Oral selective FGFR1–3 tyrosine kinase inhibitor
- **Design:** Phase 3, randomized, double-blind, placebo-controlled
- **Population:** Children with achondroplasia (>50% < 8 yrs old)
- **Duration:** 52 weeks
- **Primary endpoint:** Change from baseline in annualized height velocity

PRIMARY OUTCOME (Δ AHV vs. placebo)

+2.10 cm/yr *(LS mean +1.74)*

p<0.0001 · Height Z-score +0.41 SD (p<0.0001)

Phase 2 PROPEL 2 (NEJM): +2.5 cm/yr AHV sustained ≥18 months at 0.25 mg/kg/day.

SAFETY (PHASE 3)

- Serious drug-related AEs — *None*
- Discontinuations for AE — *None*
- Hyperphosphatemia (mild, transient) — *3 cases (≈4%); no dose change*
- FGFR1/2 off-target effects — *None (no retinal/corneal events)*
- Bone age / BMD adverse change — *None observed*

HEADLINE SECONDARY ENDPOINT

First statistically significant improvement in body proportionality vs. placebo in any ACH trial.

LS mean treatment difference −0.05 (p<0.05) in children <8 yrs.

FDA Breakthrough Therapy Designation · NDA/MAA planned 2H 2026.

Currently investigational — not yet approved.

Why Some Families Decline Therapy

CLINICAL CONCERNS

- Long-term safety profile remains unclear
- Adult height and morbidity outcomes pending
- Continuous pathway modulation across childhood

WHAT FAMILIES ARE WEIGHING

What is the target of treatment?

Distinguishing complication prevention from height gain.

Pathology or variation?

Whether achondroplasia is something to correct, or to live with.

Disease or identity?

Short stature as a medical problem vs. a way of being.

What Drives Family Decisions

01

Reduce future complications

Spinal stenosis, foramen magnum decompression, joint misalignment , parents most want to avoid surgeries.

02

Height for independence

Height matters as a means to functional independence and participation, not as an end in itself.

03

Acceptable side-effect profile

Families weighed published trial safety carefully; regulatory approval lent confidence.

Parents worry whether their child will later be content with the decision, especially as eligibility expands to ages where the child cannot meaningfully assent.

NiMhurchadha S, et al. Parents' Experience of Administering Vosoritide. Adv Ther 2023;40:2457–2470.

Psychological, Ethical & Social Perspectives

Parent-driven decisions

in early childhood, with future child autonomy at stake

Injection anxiety

and effects on the parent–child relationship

Lived experience

and community identity shape values

Access & coverage

vary widely and constrain real choice

Patient Advocacy & Community

> *The skeletal-dysplasia community is not a passive audience to therapeutic progress - it is an active voice in defining what counts as benefit.*

Little People of America

Long-standing advocacy organization with formal positions on therapy.

Disability identity

Achondroplasia as a way of being, not exclusively a condition to correct.

Heterogeneous views

Within the community there is no single answer on treatment.

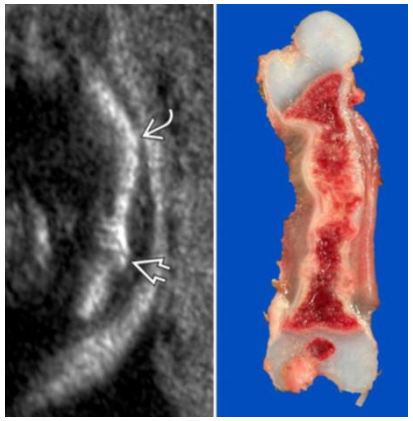
Osteogenesis Imperfecta

Overview & Prenatal Imaging

Type I collagen disorder

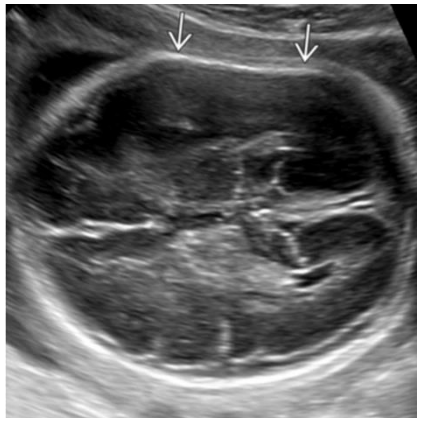
Most cases COL1A1 / COL1A2.

Spectrum from mild to perinatally lethal.



PRENATAL IMAGING

- Fractures (often multiple, varying ages)
- Bowed long bones
- Hypomineralization
- Compressible skull
- Small thorax in severe forms



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Bisphosphonate Therapy

Pamidronate

ROUTE

IV

FREQUENCY

Cycles every 2–4 months

MONITOR FOR

Acute-phase reaction (fever, myalgia) on first infusion · hypocalcemia · monitor renal function

Zoledronic acid

ROUTE

IV

FREQUENCY

Every 6–12 months

MONITOR FOR

More potent acute-phase reaction · hypocalcemia · longer skeletal half-life

Neridronate

ROUTE

IV or IM

FREQUENCY

Quarterly (regional protocols vary)

MONITOR FOR

Similar acute-phase profile · less widely available outside Europe

Shared mechanisms and goals

Inhibit bone resorption

Reduce fracture frequency · improve mobility · improve bone mineral density · reduce pain

Timing & Monitoring

Initiate in infancy for severe disease; tailor by severity and fracture burden.

ROUTINE MONITORING

Calcium	Vitamin D	Renal function	Bone density

Trial Data - Bisphosphonates

FOUNDATIONAL EVIDENCE

Glorieux et al., NEJM 1998

- **Design:** Open-label, cyclical IV pamidronate
- **Population:** n = 30, ages 3–16 with severe OI (types III/IV)
- **Duration:** 1.3 – 5 years
- **Key outcomes:** LS BMD +42%/yr; fracture rate ↓ ~70%; improved vertebral geometry; pain reduction; improved mobility

CONFIRMATORY DATA

Plotkin 2000 (JCEM): children < 3 yrs, BMD ↑86–227%; fracture rate 2.6 vs 6.3/yr ($p<0.01$)

Åström 2016 (Swedish cohort, n=79): fracture reduction across OI types I, III, IV

Zoledronic acid q6–12 mo: similar BMD/fracture benefit, lower infusion burden

ESTABLISHED OUTCOMES

- Lumbar spine BMD — *Substantial increase across age groups*
- Vertebral compression — *Improved height/geometry*
- Long-bone fracture rate — *Reduced (especially severe OI)*
- Bone pain — *Often relieved within first cycle*
- Mobility / function — *Improved in most cohorts*

- Optimal duration — long-term continuation vs. discontinuation
- Adult outcomes — fewer prospective data beyond adolescence
- Mild OI (type I) — clearest benefit in severe disease
- Growth plate effects — generally reassuring but actively studied

No bisphosphonate is FDA-approved for pediatric OI - all pediatric use is off-label.

Emerging Therapies

LEAD CANDIDATE

Setrusumab (UX143)

Fully human anti-sclerostin monoclonal antibody : anabolic, distinct from bisphosphonates.

- **ORBIT (Ph 3):** Adults & adolescents vs. placebo
- **COSMIC (Ph 3):** Pediatric vs. bisphosphonates
- **Primary endpoint:** Annualized clinical fracture rate
- **Result:** Both missed primary endpoint (Dec 2025)
- **Secondary endpoint:** BMD significantly improved in both trials

METHODOLOGICAL LESSON

BMD improvement did not translate to fracture reduction.

Raises questions about BMD as a surrogate endpoint in OI. Ultragenyx pursuing additional analyses.

OTHER APPROACHES

Anti-TGF-β therapies

Fresolimumab and related agents target dysregulated TGF-β signaling in OI matrix. Early-phase studies; rationale strongest in moderate–severe disease.

Mesenchymal stem cell therapy

BOOSTB4 trial — fetal liver-derived MSCs delivered prenatally and/or postnatally. First-in-human prenatal cell therapy for OI; safety data emerging.

Gene therapy / editing

Conceptual. Most OI mutations are dominant-negative, so allele-specific silencing or correction is needed. No clinical trials yet.

Combination strategies

Sequential or combined antiresorptive + anabolic regimens; under study post-setrusumab results.

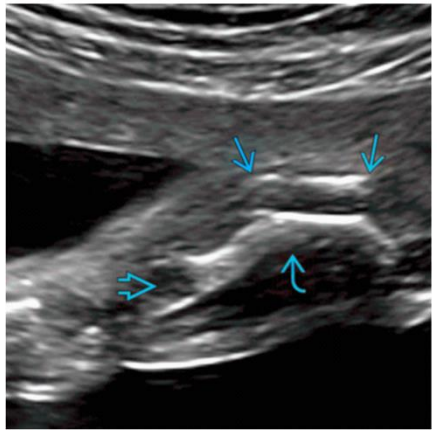
Hypophosphatasia

Overview & Prenatal Imaging

Hypophosphatasia

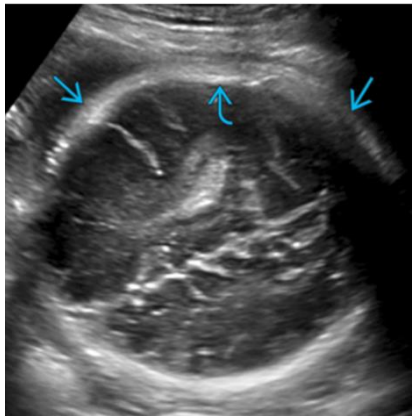
ALPL-related

Defective mineralization due to deficient tissue-nonspecific alkaline phosphatase activity (TNSALP).



PRENATAL IMAGING

- Severe undermineralization
- Bowed long bones
- Poor skull ossification
- Fractures



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Clinical Manifestations

PERINATAL SEVERE (HISTORICALLY LETHAL)

- Profound in-utero hypomineralization
- Hypoplastic lungs · restrictive chest deformity
- Respiratory failure (leading cause of death)
- Vitamin B6–dependent seizures (sign of impending death)
- Hypercalcemia · hyperphosphatemia
- Skin-covered osteochondral spurs (pathognomonic)
- Bowed long bones · short limbs

PRE-ERT MORTALITY

58–100% in the first year of life

Perinatal & infantile forms, pre–enzyme replacement era.

INFANTILE (ONSET < 6 MONTHS)

- Irritability · poor feeding · failure to thrive
- Hypotonia
- Premature craniosynostosis (raised ICP risk)
- Rachitic chest · recurrent respiratory infections
- Nephrocalcinosis from hypercalciuria
- Premature loss of deciduous teeth

DIAGNOSTIC BIOCHEMISTRY

↓ **Alkaline phosphatase** : *for age and sex*

↑ **Pyridoxal-5-phosphate (PLP)** : *accumulated TNAP substrate*

↑ **Urine phosphoethanolamine** : *accumulated TNAP substrate*

↑ **Calcium, ↑ phosphate** : *with hypercalciuria*

Asfotase Alfa

Enzyme replacement therapy

Whyte et al. landmark trial transformed a previously lethal perinatal phenotype.

ADMINISTRATION

ROUTE

Subcutaneous injection

FREQUENCY

Three or six times per week

MONITOR FOR

Injection-site reactions (very common) · ectopic calcification (eye, kidney) · hypersensitivity · anti-drug antibody formation

KEY OUTCOMES

- **Survival**
  Dramatic improvement in perinatal-onset HPP
- **Respiratory**
  Reduced ventilatory support
- **Skeletal**
  Improved mineralization
- **Mobility**
  Improved motor function

XLH & Burosumab

THE DISORDER

PHEX-related · excess FGF23 activity · bowing, rickets, short stature, dental disease

BUROSUMAB

Anti-FGF23 monoclonal antibody

ADMINISTRATION

ROUTE

Subcutaneous injection

FREQUENCY

Every 2 weeks (pediatric); every 4 weeks (adult)

MONITOR FOR

Fasting serum phosphate · injection-site reactions · ectopic mineralization · hypersensitivity

KEY OUTCOMES

- Improved phosphate homeostasis
- Reduced rickets severity
- Improved growth & physical function

Thanatophoric Dysplasia

Severe FGFR3 activating variants - same gene as achondroplasia, a different end of the spectrum.

PRENATAL FEATURES

- **Severe micromelia**
- **Narrow thorax**
- **Cloverleaf skull (type II)**
- **Polyhydramnios**

Current Management & Counseling

> **No approved disease-modifying therapy.**

WHERE PRENATAL DIAGNOSIS STILL CHANGES CARE

- Neonatal respiratory support decisions
- Palliative care planning
- Delivery setting and mode
- Family counseling and support

Future Therapeutic Directions

Earlier intervention

Including prenatal or perinatal therapy concepts

Combination therapy

Targeting multiple pathway nodes

Precision modulation

Variant-specific pharmacology

Stem cell approaches

Investigational across multiple dysplasias

Gene editing

Conceptual in this space; mechanism-dependent

Key Takeaways

01

Therapeutically actionable

Skeletal dysplasia diagnosis now drives downstream therapy decisions.

02

Molecular precision matters

Variant-level information is increasingly a prerequisite for eligibility.

03

Outcomes are changing

Multiple targeted therapies - with effect sizes still being refined in the real world.

04

Counseling

Efficacy, uncertainty, identity, autonomy, and lived experience all belong on the table.

Questions?

Thank you.