Prospective clinical assessment study in children with achondroplasia: the PROPEL trial

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Background

- Achondroplasia (ACH) is the most common non-lethal form of skeletal dysplasia, affecting between 1 in 15,000 to 1 in 30,000 live births.[1,2]
- Clinical features of ACH include:[3]
  - Short stature with short limbs and rhizomelic disproportion.
  - Macrocephaly with variable frontal and parietal bossing.
  - Midfacial retrusion due to the under-development of cartilaginous bones of the face.
  - Thoracolumbar kyphosis and lumbar hyperlordosis.
  - Relatively short chest with overly compliant ribs.
  - Short fingers and trident configuration of the hands.
  - Hypermobile hips and knees and limited elbow extension.
  - Tibial bowing of the mesial segment of the legs.
  - Hypotonia, occurring in most infants with ACH.
- Genetically, ACH is an autosomal dominant disorder characterized by gain of function pathogenic variants in the *FGFR3* gene,[4] of which 99% are *G380R* substitutions in the transmembrane domain of FGFR3. Eighty percent of affected individuals represent a *de novo* event.
- Linear growth is slower in ACH children compared with average stature children (Table 1).
  - Body length at birth is approximately between –1.4 and –2 SDS for non-ACH reference tables.
  - During infancy and childhood, height falls progressively and deviates even further from average stature due to a lack of a pubertal growth spurt.[5–7] Final height is approximately 131 cm for males and 124 cm for females.[8]

Table 1. Growth velocity in patients with ACH compared with those having average stature

Age group	Growth velocity	
	ACH	Average stature
Infants (after birth)	20 cm/year (1.7 cm/month)	44 cm/year (3.7 cm/month)
1 year	10 cm/year (0.8 cm/month)	14.4 cm/year (1.2 cm/month)
2–10 years	4–5 cm/year	5–7 cm/year
10+ years	4–5 cm/year	5.5–7 cm/year
Puberty peak (12–14 years)	5 cm/year	9.3 cm/year (males at 13.5 years) 8.3 cm/year (females at 12 years)

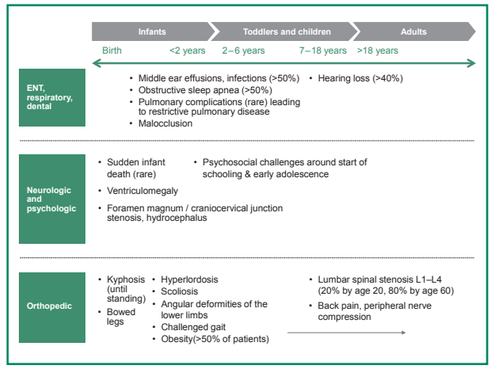
Modified from Hoover-Fong et al. 2008.[6]

- Children and adults with ACH are prone to significant co-morbidities, including obstructive sleep apnea, chronic otitis media with conductive hearing loss, spinal stenosis and a propensity towards obesity (Figure 1). In some infants, narrowing of the foramen magnum may result in compression of the spinal cord (at the craniocervical junction) with neurologic sequelae, requiring timely neurosurgical intervention.

Current treatment options for ACH

- There are currently no approved therapies for the treatment of ACH in either the United States or the European Union, and management is supportive in nature.
- Current treatment options are non-targeted, ineffective, or painful interventions aimed at preventing or treating complications of ACH.[8,9]
  - Recombinant human growth hormone (rhGH) has been studied for the treatment of ACH, although no clear growth effects have been shown after treatment with rhGH.[10] Nevertheless, rhGH is approved for the treatment of achondroplasia in Japan.
  - Limb lengthening procedures can provide 15–30 cm of additional height (~20% increased length of bone segment), but the procedures are painful and have high complication rates.[1]

Figure 1. Medical complications associated with ACH

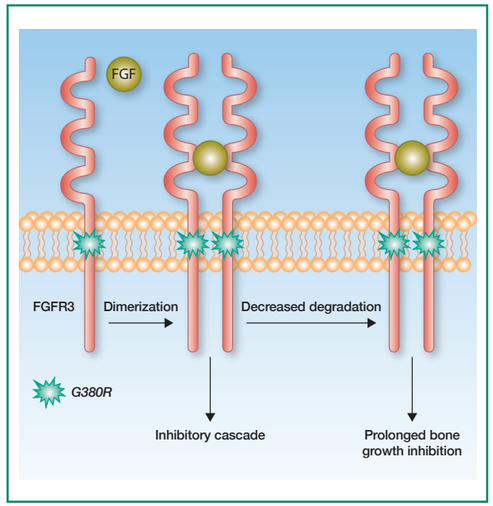


ENT = ear, nose and throat. Modified from Unger et al. 2017.[8]

Rationale for FGFR3-targeted treatment for patients with ACH

- ACH is characterized by defective endochondral ossification resulting from gain of function pathogenic variants in the fibroblast growth factor receptor 3 (*FGFR3*) gene, which is a negative regulator of endochondral bone formation.
- Longitudinal bone growth is driven by the proliferation and differentiation of chondrocytes in the growth plate and activating pathogenic variants of *FGFR3* cause inhibition of chondrocyte proliferation and differentiation (Figure 2).[8]

Figure 2. FGFR3-mediated inhibition of bone growth in ACH



The *G380R* pathogenic variant in ACH extends the signaling cascade, resulting in prolonged bone growth inhibition. Modified from Unger et al. 2017.[8]

Infigratinib

- Infigratinib is an orally bioavailable and selective FGFR1/2/3 selective tyrosine kinase inhibitor in development for FGFR-related diseases.
- Infigratinib inhibits FGFR downstream signaling, offering a direct therapeutic strategy to counteract the hyperactivity of FGFR3 in ACH.[11]
- Preclinical data in a *Fgfr3*$^{Y367C/+}$ mouse model of ACH[11–13] showed that:
  - Low doses of infigratinib (0.2, 0.5 and 2 mg/kg) reduced FGFR3 phosphorylation, restored the activity of FGFR3 downstream signaling pathways to levels observed in wild-type mice.
  - Mice also exhibited substantially improved skeletal parameters in the upper and lower limbs, and improvement in the foramen magnum.
  - No toxic effects were observed at these low but efficacious doses.
- These preclinical data indicate that low doses of infigratinib administered to children with ACH has the potential to ameliorate skeletal abnormalities that can lead to long-term complications and also improve long bone growth that could improve the ability to conduct activities of daily living.

PROPEL study design

- PROPEL is a prospective, non-interventional clinical assessment study to collect serial assessments in order to characterize the natural history of children with ACH.
- The study is designed to evaluate participants over a period of time (minimum of 6 months and maximum of 2 years) and to collect baseline data prior to potential enrollment in a QED-sponsored interventional phase 2 or 3 trial to assess the safety of daily dosing, evidence of efficacy, and dose finding of infigratinib in children with ACH.

Study objectives/endpoints

Table 3. PROPEL objectives and endpoints

Objectives	Endpoints
Primary objective	
Collect baseline height velocity measurements of children with ACH being considered for future enrolment in interventional studies sponsored by QED Therapeutics.	Annualized height velocity.
Other objectives	
Collect other baseline growth measurements of children with ACH being considered for future enrolment in interventional studies sponsored by QED Therapeutics.	Change from baseline in other growth parameters, including but not limited to height Z score, upper to lower body ratio, upper arm to forearm ratio, and upper leg to lower leg ratio.
Exploratory evaluation of biomarker indicators of growth (e.g., type X collagen degradation fragment, collagen X marker [CXM]).	Bone biomarkers (blood).
Assess ACH-related medical events (e.g., obstructive sleep apnea, middle ear infections, lumbar spinal stenosis reported as medical history or non-treatment adverse events [NT-AEs]).	ACH-related NT-AEs.
Assess ACH-related surgical procedures (e.g., tympanostomy tube insertion, orthopedic procedures).	ACH-related surgical procedures.

Patients

- Key inclusion/exclusion criteria are shown in Table 2.

Outcomes

- Objectives and endpoints of the PROPEL trial are shown in Table 3.

Statistics

- Relationships between selected baseline factors and height velocity may be assessed descriptively, and linear regression models may be used to assess the association between baseline factors and growth velocity.
- Descriptive statistics will be provided for demographics, disposition, and other assessments of bone and growth (biomarkers).

Table 2. Key inclusion/exclusion criteria

Key inclusion criteria	Key exclusion criteria
1. Signed informed consent by study participant or parent(s) or legally authorized representative (LAR) and signed informed assent by the study participant (when applicable).	1. Hypochondroplasia or short stature condition other than ACH.
2. Age 2.5 to 10 years (inclusive) at study entry.	2. Females who have had their menarche.
3. Diagnosis of ACH (as confirmed by the Principal Investigator, Co-principal Investigator, or other qualified clinical geneticist).	3. Height < –2 or > +2 standard deviations for age and sex based on reference tables on growth in children with ACH.
4. Ambulatory and able to stand without assistance.	4. Annualized height velocity ≤1.5 cm/year over a period ≥6 months prior to screening.
5. Study participants and parent(s) or LAR(s) are willing and able to comply with study visits and study procedures.	5. Concurrent disease or condition that, in the view of the investigator and/or study sponsor, may impact growth or where the treatment is known to impact growth.
	6. Significant abnormality in screening laboratory results.
	7. Treatment with growth hormone, insulin-like growth factor-1 (IGF-1), or anabolic steroids in the previous 6 months or long-term treatment (>3 months) at any time.
	8. Treatment with a C-type natriuretic peptide (CNP) analog or treatment targeting fibroblast growth factor receptor (FGFR) inhibition at any time.
	9. Regular long-term treatment (>1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma is acceptable).
	10. Any other investigational product or investigational medical device for the treatment of ACH or short stature.
	11. Previous limb-lengthening surgery.

PROPEL trial: current status

- The PROPEL study is underway – the first patient was enrolled in August 2019.
- Planned total enrollment is 200 children with ACH.
- The sample size of approximately 200 study participants is considered enough to characterize the natural history of children with ACH and lead to sufficient enrollment in an interventional phase 2 or 3 trial of infigratinib in children with ACH.

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The data shown in this poster were accepted but not presented at ENDO 2020 as the conference was cancelled amid concerns about COVID-19