Study design and baseline characteristics of children enrolled in PROPEL: A prospective clinical assessment study in children with achondroplasia

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#P1-130

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 in the US, with an estimated global prevalence of 250,000.[1,2]
- Characteristic clinical features of ACH are as follows:[3]
  - Disproportionately short stature.
  - Smaller than average chest.
  - Macrocephaly with frontal bossing.
  - Midface hypoplasia.
  - Curvature of the spine.
  - Hypermobile joints.
  - Leg bowing.
  - Shortening of the fingers and toes.
- Individuals with ACH experience a variety of physical, functional, and psychosocial complications and challenges (see Figure 1).

Figure 1. Medical complications associated with ACH

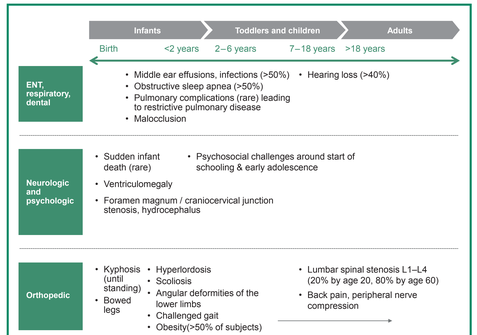
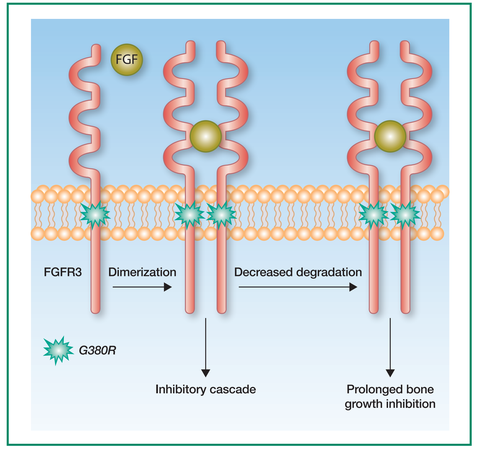


Figure 2. FGFR3-mediated inhibition of bone growth in ACH



The *G380R* pathogenic variant in ACH extends the signaling cascade, resulting in prolonged bone growth inhibition. Modified from Unger et al. 2017[4]

- ACH is characterized by defective endochondral ossification resulting from gain of function pathogenic variants in the fibroblast growth factor receptor-3 gene (*FGFR3*),[5,6] which is a negative regulator of endochondral bone formation.
- FGFR3 is particularly prevalent on the surface of chondrocytes that give rise to cartilaginous bone.[7]
- 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).[4]
- ACH results in most cases from either a G to A or G to C substitution at nucleotide position 1,138 in the *FGFR3* gene.[5] Both mutations pathogenic variants result in the same glycine to arginine amino acid (Gly380Arg) point mutation in the transmembrane domain of FGFR3; notably, 80% of affected individuals have a de novo event.

Current treatment options for ACH

- No therapies for the treatment of ACH are currently marketed in the United States or 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.[4,8]
- Infigratinib is an orally bioavailable and selective FGFR1–3 tyrosine kinase inhibitor in development for conditions related to *FGFR* genetic alterations, including cholangiocarcinoma and bladder cancer.[9,10]
- In ACH, infigratinib inhibits FGFR downstream signalling, potentially offering a direct therapeutic strategy to counteract the hyperactivity of FGFR3.[4]
- Preclinical data in an *Fgfr*$^{G367C/+}$ mouse model of ACH showed that low doses of infigratinib (0.2, 0.5, and 2 mg/kg/day) reduced FGFR3 phosphorylation and restored activity of FGFR3 downstream signalling pathways to levels observed in wild-type mice.[11–13]
- Infigratinib-treated mice exhibited substantially improved skeletal parameters in the upper and lower limbs, and improvement in the foramen magnum, compared with untreated animals.[11]

PROPEL study design

Design

- PROPEL (NCT04035811) is an ongoing, prospective, non-interventional clinical assessment study designed to collect baseline growth data and to characterize the natural history of ACH in children being considered for future enrollment in interventional studies sponsored by QED Therapeutics.
- Children will participate for a minimum of 6 months and a maximum of 2 years.
- PROPEL is being conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and all relevant human clinical research and data privacy regulations in the countries in which the study is being undertaken.
- The protocol has been approved by local ethics committees and institutional departments as applicable.

Eligibility criteria and objectives/endpoints

- Eligibility criteria are summarized in Table 1.
- PROPEL objectives and endpoints are summarized in Table 2.

Statistics

- No formal statistical hypothesis will be tested.
- Relationships between selected baseline factors and height velocity will be assessed descriptively.
- Descriptive statistics will be provided for demographics, subject disposition, and other assessments of bone and growth (biomarkers).
- The sample size of approximately 200 children is considered adequate to characterize the natural history of ACH in children.

Table 1. 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). 2. Age 2.5 to 10 years (inclusive) at study entry. 3. Diagnosis of ACH (as confirmed by the Principal Investigator, Co-principal Investigator, or other qualified clinical geneticist). 4. Ambulatory and able to stand without assistance. 5. Study participants and parent(s) or LAR(s) are willing and able to comply with study visits and study procedures.	1. Hypochondroplasia or short stature condition other than ACH. 2. Females who have had their menarche. 3. Height < –2 or > +2 standard deviations for age and sex based on reference tables on growth in children with ACH. 4. Annualized height velocity ≤1.5 cm/year over a period ≥6 months prior to screening. 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, 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 analog or treatment targeting 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. Use of any other investigational product or investigational medical device for the treatment of ACH or short stature. 11. Previous limb-lengthening surgery.

Table 2. 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 (AHV).
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).	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).	ACH-related non-treatment adverse events.
Document ACH-related surgical procedures (e.g., tympanostomy tube insertion, orthopedic procedures).	ACH-related surgical procedures.

Results

- A total of 79 children have been enrolled as of June 2021 at 19 sites in Europe, Australia and North America. The study is ongoing.
- Baseline characteristics of the participants are shown in Table 3.
- The heights of the 79 participants at study entry were within ±2 standard deviations when compared with growth charts for children with ACH, with a median height for age percentile of 47.0% (range 5.0–95.0%), indicating that the participating children are a good representation of the population of interest.
- 90.5% of cases were sporadic while 9.5% had another family member with diagnosis of ACH.
- Of the 79 subjects enrolled, 85% had molecular confirmation of their diagnosis.
- The most common conditions reported in the medical histories of subjects are summarized in Table 4.

Current status

- The PROPEL study is underway and enrolling participants as of 22 September 2020.
- The estimated primary completion date of PROPEL is June 2026.
- The planned total enrollment is 200 children with ACH.
- This sample size is considered adequate to characterize the natural history of the condition and lead to sufficient enrollment in Phase 2 (PROPEL2) and/or Phase 3 interventional trials of infigratinib in children with ACH.
- Please refer to ESPE poster #P1-125 for further details on the PROPEL2 study.

Table 3. Baseline demographics and participant characteristics

Characteristic	Total (n=79)
Median age, years (range)	6.3 (2.5–10.8)
Age group, n (%)	
<3 years	11 (14)
3–<5 years	18 (23)
5–<8 years	27 (34)
≥8 years	23 (29)
Sex, n (%)	
Male	29 (37)
Female	50 (63)
Race, n (%)	
White	50 (63)
Asian	5 (6)
Black or African American	4 (5)
Other	5 (6)
Not reported	15 (19)
Median height, cm (range)	90.6 (70.1–111.2)
Median height for age percentile, % (range)	47.0 (5.0–95.0)
Median weight, kg (range)	16.8 (9.2–30.8)
Median Body Mass Index, kg/m^2 (range)	20.9 (16.8–26.2)

Table 4. Common conditions/complications from medical histories

Characteristic	Number (%)
Surgical and medical procedures	52 (66)
Infections and infestations	42 (53)
Respiratory, thoracic and mediastinal disorder	31 (39)
Musculoskeletal and connective tissue disorders	27 (34)

- Children with surgical and medical procedures underwent 1–11 interventions per child, with a total of 152 events (mean 3 surgeries per individual). The most common types of surgery were:
  - Adenoidectomy, adenotonsillectomy and tonsillectomy (n=30; 38%; 48 procedures), with 1-4 surgeries per individual.
  - Ear tube insertion/removal/myringotomy/ear tube replaced/tympanostomy tube insertion, etc. (n=28; 35%; 48 procedures) with 1-5 procedure per individual.
  - Spinal and foramen magnum decompression (n=17; 22%; 24 procedures) with 1-5 procedures per individual.
- The most common infection was otitis media (n=26; 33%).
- The most common respiratory, thoracic and mediastinal disorder was mild, moderate, obstructive or central, mild, moderate, sleep apnea (n=27; 34%).
- The most common musculoskeletal and connective tissue disorder reported as MH was kyphosis (n=18; 23%).
- Other clinically important conditions/complications were nervous system disorder (hydrocephalus, ventriculomegaly, paresthesia, cervical cord compression, foramen magnum compression) (n=12; 15%) and ear and labyrinth disorders (hearing loss) (n=12; 15%).

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