Infigratinib in children with achondroplasia: Design of the PROPEL, PROPEL 2, and PROPEL OLE studies

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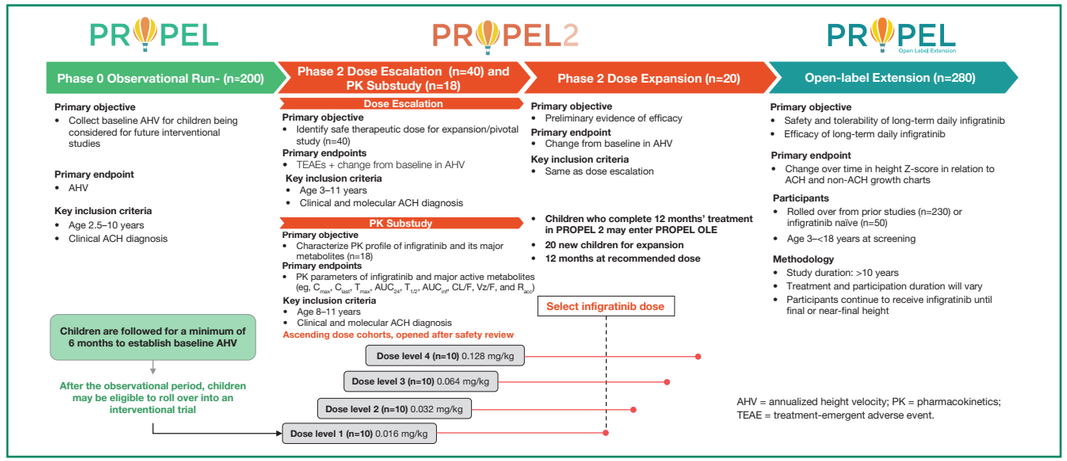
#PSAT106

Background

- Achondroplasia (ACH) is the most common non-lethal form of short-limbed skeletal dysplasia, affecting between 1 in 15,000 and 1 in 30,000 live births in the USA, with an estimated global prevalence of 250,000.[1,2]
- Children and adults with ACH are prone to significant comorbidities, including obstructive sleep apnea, chronic otitis media with conductive hearing loss, spinal stenosis, foramen magnum stenosis, and a propensity towards obesity.
- Currently, there is no widely accepted consensus about treatment. Vosoritide is the only drug targeting the underlying causes of ACH that has been approved to date, although additional agents are in development for this indication.
- 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.[3]
- Infigratinib is an orally bioavailable and selective FGFR1/2/3 selective tyrosine kinase inhibitor in development for ACH. Infigratinib inhibits FGFR downstream signaling, offering a direct therapeutic strategy to counteract the hyperactivity of FGFR3 in ACH.[3]



Summary

- Children with ACH currently have few treatment options for the management of their condition. Infigratinib, an FGFR1–3 selective tyrosine kinase inhibitor, is the only agent currently in clinical development for the treatment of children with ACH that is orally administered.
- The ongoing PROPEL program is intended to provide key evidence on the safety and efficacy of oral infigratinib in children with ACH and will inform the design of future studies in this setting:
  - The initial observational PROPEL study will lay down a benchmark against which the interventional PROPEL 2 and PROPEL OLE studies can measure the potential benefit of infigratinib.

References

1. Horton WA, et al. Lancet 2007;370:162–72.
2. Waller DK, et al. Am J Med Genet A 2008;146A:2385–9.
3. Hoover-Fong J, et al. Bone 2021;146:115872.

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PROPEL

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 Harmonisation 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.

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, participant disposition, and other assessments of bone and growth (biomarkers). The sample size of approximately 200 children is considered large enough to characterize the natural history of ACH in children.

Table 1. PROPEL key inclusion/exclusion criteria

Key inclusion criteria
• Signed informed consent by study participant or parent(s) or legally authorized representative (LAR) and signed informed assent by the study participant (when applicable)
• Age 2.5–10 years (inclusive) at study entry
• Diagnosis of ACH (as confirmed by the Principal Investigator, Co-principal Investigator, or other qualified clinical geneticist)
• Ambulatory and able to stand without assistance
• Study participants and parent(s) or LAR(s) are willing and able to comply with study visits and study procedures
Key exclusion criteria
• Hypochondroplasia or short stature condition other than ACH
• Females who have had their menarche
• Height <–2 or >+2 standard deviations for age and sex based on reference tables on growth in children with ACH
• AHV ≤1.5 cm/year over a period ≥6 months prior to screening
• 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
• Significant abnormality in screening laboratory results
• 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
• Treatment with a C-type natriuretic peptide analog or treatment targeting FGFR inhibition at any time
• Regular long-term treatment (>1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma is acceptable)
• Use of any other investigational product or investigational medical device for the treatment of ACH or short stature
• Previous limb-lengthening surgery

Current status

- The PROPEL study is ongoing.
- The estimated primary completion date of PROPEL is June 2026.
- Please refer to poster #RF26 | PMON326 for baseline medical history data for participants who have been enrolled into PROPEL to date.

PROPEL 2

Design

- PROPEL 2 (NCT04265651) is a prospective, phase 2, open-label study designed to provide preliminary evidence of safety and efficacy of oral infigratinib in children with ACH, and to identify the dose of infigratinib to be explored in future studies. Children aged 3–11 years with ACH who have completed ≥6 months of observation in PROPEL are eligible to participate in PROPEL 2.
- PROPEL 2 consists of:
  - Dose-escalation phase with extended treatment (N≈40, 10 participants/cohort, 4 cohorts planned)
  - Dose-expansion phase to confirm the selected dose and to provide evidence of efficacy (N=20)
  - PK substudy (N=18, 6 participants/cohort, 3 cohorts planned; no PK Cohort 1), same doses as in the Dose-Escalation phase
  - Children enrolled in the dose-escalation phase will be treated for 6 months at their assigned dose, continuing for an additional 12 months (extended-treatment period). Children enrolled in cohorts 1 and 2 may have their dose increased at Months 6 and 12 if there are no safety concerns and height velocity does not increase by >25% compared with baseline.
  - Enrollment of new dose cohorts may continue if the maximum dose (based on safety and efficacy) has not been reached.
- Children enrolled in the dose-expansion phase (n≈20) will receive treatment with infigratinib at the dose identified in the dose-escalation phase for a total duration of 12 months.
- A Data Review Committee is responsible for monitoring participant safety and key efficacy data and will provide recommendations to the Sponsor regarding dose escalation, dose de-escalation, and/or expansion of dose cohorts. The recommendation for dose escalation, de-escalation, or expansion is made following rules pre-specified in the protocol, which are based on the Bayesian optimal interval design with a target toxicity level of 25%.

Eligibility criteria and objectives/endpoints

- Eligibility criteria are summarized in Table 2.

Table 2. PROPEL 2 key inclusion/exclusion criteria

Key inclusion criteria
Age 3–11 years (inclusive)
Clinical and molecular diagnosis of ACH
Ambulatory and able to stand without assistance
Willingness to comply with study visits and study procedures; signed informed consent
Growth assessment for ≥6 months in PROPEL before study entry
Negative pregnancy test in girls aged ≥10 years
Key exclusion criteria
Height <–2 or >+2 standard deviations for age and sex based on reference tables on growth in children with ACH
AHV ≤1.5 cm/year over a period ≥6 months prior to screening
Prior treatment with growth hormone in previous 6 months or long-term treatment (>3 months) at any time.
Prior treatment with C-type natriuretic peptide analog, FGFR inhibitor, or other investigational product or medical device for treatment of ACH or short stature at any time
Previous limb-lengthening procedure
Having had menarche (females)
Severe sleep apnea, having had guided growth surgery, or recent fracture (within 6 months of screening)

Statistics

- Selection of the dose for the dose-expansion phase will be based on efficacy and safety data of approximately 10 participants per cohort, which will allow observation of at least of one AE with 94.4% confidence.
- In the dose-expansion phase, ≈ 20 participants will be enrolled at the selected dose level. An AHV increase of ≤0.5 cm/year will be considered not clinically relevant and will be used as the null hypothesis. For dose escalation, all analyses will be performed separately for each dosing cohort based on the originally received dose and in total.
- All safety analyses will be performed using the safety analysis set, defined as participants who have received at least one dose of study drug. Analyses on growth parameter endpoints will be performed for participants who have a baseline and at least one post-baseline growth parameter assessment.

Current status

- The PROPEL 2 study is underway and enrolling participants.
- Following completion of PROPEL 2, participants have the opportunity to enroll in an open-label, long-term expansion study.

PROPEL OLE

Design

- PROPEL OLE (NCT05145010) is a prospective, phase 2, long-term OLE study of infigratinib in children with ACH designed to:
  - Collect long-term safety data
  - Confirm that changes observed during the first or second year of treatment with infigratinib will continue during the growth period resulting in a clinically relevant improvement in final height
  - Evaluate potential improvements in other clinically relevant parameters such as complications associated with ACH.
- Study duration will be >10 years. Individual treatment and study participation durations will vary. Participants will receive treatment with study drug until they reach final or near-final height.
- Approximately 230 participants will roll over into PROPEL OLE after completion of a previous interventional study sponsored by QED. Up to 50 additional, infigratinib-naïve participants may also be enrolled.
- A Safety Monitoring Committee will monitor safety during the first 5 years of the study.

Eligibility criteria and objectives/endpoints

- Eligibility criteria are summarized in Table 3.

Statistics

- All safety analyses will be performed using the safety analysis set. Analyses on growth parameter endpoints will be performed using the efficacy analysis set.

Table 3. PROPEL OLE key inclusion/exclusion criteria

Key inclusion criteria	
Rollover participants	**Treatment-naïve participants**
Completed study activities in a previous QED-sponsored interventional study with infigratinib	Age 3 – <18 years (inclusive) at screening, with growth potential as defined for the study
Participants and LARs willing to comply with study visits and procedures; signed informed consent	Participants and LARs willing to comply with study visits and procedures; signed informed consent
Able to swallow oral medication	Able to swallow oral medication; ambulatory and able to stand without assistance
Negative pregnancy test in girls aged ≥10 years or girls of any age who have experienced menarche	Clinical diagnosis of ACH confirmed by genetic testing
Willing to use a highly effective method of contraception while taking study drug and for 1 month afterwards if sexually active	Growth assessment for >6 months in PROPEL before study entry
	Negative pregnancy test in girls aged ≥10 years or girls of any age who have experienced menarche
	Willing to use a highly effective contraception while taking study drug and for 1 month afterwards if sexually active
Key exclusion criteria	
Concurrent circumstance, disease, or condition that, in the view of the Principal Investigator and/or Sponsor, would interfere with study participation or safety evaluations	Hypochondroplasia or short stature condition other than ACH
Development of a medical condition that will require the initiation of treatment with a prohibited medication	Concurrent disease or condition that would interfere with study participation or safety evaluations
Prematurely discontinued a prior QED-sponsored interventional study with infigratinib	History of or current extensive ectopic tissue calcification; history of malignancy; evidence of endocrine alterations of calcium/phosphorus homeostasis
Reached final height or near-final height	Prior growth hormone, insulin-like growth factor-1, anabolic steroids, investigational treatments for ACH in the 6 months before screening

Current status

- The PROPEL OLE study is underway and enrolling participants.
- PROPEL OLE is due to complete in February 2032.

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