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

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Infragratinib is an orally bioavailable and selective FGFR-3 kinase inhibitor in development for ACH. Infragratinib inhibits FGFR downstream signaling, offering a direct therapeutic strategy to counteract the hyperactivity of FGFR3 in ACH.

Study design

Phase 2 Dose Expansion (n~20)

- Primary objective: (1) determine safety and tolerability; (2) characterize the pharmacokinetic profile; (3) assess activity in patients who have progressed or are refractory to prior treatment; and (4) determine the dose to be used in the dose-escalation phase.
- Dose-escalation phase: patients will receive the lowest dose identified in the dose-escalation phase for 12 months or until progression.

Phase 2 Dose-Escalation (n=20)

- Primary objective: (1) determine safety, tolerability, pharmacokinetics, and activity of infragratinib in patients with ACH; (2) determine the dose to be used in the dose-escalation phase; and (3) determine the optimal dose for Phase 3 trials.

Phase 2, Open-Labeled Extension (n=280)

- Primary objective: (1) continue the evaluation of safety and tolerability of infragratinib in patients with ACH; (2) determine the optimal dose for Phase 3 trials; and (3) assess the long-term efficacy of infragratinib in patients with ACH.

Key inclusion criteria

- Age ≥ 1 year and < 22 years.
- Clinical and molecular diagnosis of ACH confirmed by the Principal Investigator, Co-principal Investigator, or other qualified individual.
- Patients who are able to stand without assistance.
- Patients who are receiving hormone treatment (GH, rhIGF1, or both).
- At least one post-baseline growth parameter assessment.

Key exclusion criteria

- History of malignancy.
- History of extensive ectopic tissue calcification.
- History of or current coagulopathy.
- History of or current compromise of lung function.
- History of or current cardiac disease.

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Summary

- Children with ACH currently have few treatment options for the management of their condition; infragratinib, an FGFR-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 infragratinib in children with ACH and will inform the design of future studies in this setting.

- The initial observational PROPEL study will study a back-and-forward regimen with the interventional PROPEL 2 and PROPEL OLE studies can measure the potential benefit of infragratinib.
- The run-in for the pivotal PROPEL 3 study is underway and enrolling.

References


Acknowledgements

- The authors acknowledge the support of study participants, parents, and adults, together with participating sites, investigators, and study staff involved in the PROPEL program.
- Financial support for this paper was provided by Miller Medical Communications Ltd. This work was undertaken by the study monitor (QED Therapeutics Inc.).

Table 1. PROPEL 1 key inclusion/exclusion criteria

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Table 2. PROPEL 2 key inclusion/exclusion criteria

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Table 3. PROPEL OLE key inclusion/exclusion criteria

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Background

- Achondroplasia (ACH) is the most common non-lamellar form of short-limbed skeletal dysplasia, affecting between 1 in 15,000 and 1 in 30,000 births in the USA, with an estimated global prevalence of 250,000.3
- Children and adults with ACH are prone to serious complications, including bony magnification, spinal stenosis, obstructive sleep apnea, chronic otitis media with conductive hearing loss, and a propensity towards obesity.
- ACH is characterized by skeletal disorganization resulting from gain of function mutations in the fibroblast growth factor receptor 3 (FGFR3), which is a negative regulator of endochondral bone formation.6
- Currently, there is no widely accepted consensus about treatment. To date, only one drug targeting ACH is characterized by defective endochondral ossification resulting from gain of function FGFR3 mutations.7
- FGFR3 alteration in ACH affects between 1 in 15,000 and 1 in 30,000 live births in the USA, with an estimated global prevalence of 250,000.3

- Infragratinib is orally bioavailable and selective FGFR-3 kinase inhibitor in development for ACH.
- Infragratinib inhibits FGFR downstream signaling, offering a direct therapeutic strategy to counteract the hyperactivity of FGFR3 in ACH.

Design

PROPEL (NCT04303161) is an ongoing, open-label, multinational, randomized, double-blind, placebo-controlled phase 2 dose-escalation study designed to assess baseline growth and characteristics of the natural history of ACH in children being considered for enrollment in future sponsored interventional studies sponsored by QED Therapeutics.

- Children will participate for a minimum of 6 months and a maximum of 4 years.
- Children will be randomized to the ACHV arm in a 2:1 ratio.
- The protocol is 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 protection laws in the countries in which the Study is being undertaken.

- Eligibility criteria and endpoints
  - Key inclusion criteria
    - Age ≥ 6 months prior to screening
    - Height <–2 or >+2 standard deviations for age and sex based on reference tables on growth in children with ACH
    - Clinical and molecular diagnosis of ACH confirmed by the Principal Investigator, Co-principal Investigator, or other qualified individual.
    - Patients who are able to stand without assistance.
    - Patients who are receiving hormone treatment (GH, rhIGF1, or both).
    - At least one post-baseline growth parameter assessment.

- Key exclusion criteria
  - History of malignancy
  - History of extensive ectopic tissue calcification
  - History of or current coagulopathy
  - History of or current compromise of lung function
  - History of or current cardiac disease

- Study duration: >10 years
- Rollover participants may also be enrolled.
- Participants will receive treatment with infragratinib while taking study drug and for 1 month after the final dose.
- Treatment will vary. Participants will receive treatment with infragratinib at the selected dose for the dose-escalation phase for a minimum of 12 months or until progression.
- All safety analyses will be performed using the safety analysis set, defined as one post-baseline growth parameter assessment.
- Willing to use a highly effective method of contraception for at least 1 year during study participation.
- Girls of any age who have experienced menarche ≥ 6 months prior to screening.
- Females who have had their menarche ≥ 6 months prior to screening.
- Negative pregnancy test in girls aged 12–17 who are sexually active.
- Contraindication to use of hormone treatment (GH, rhIGF1, or both).

- Statistics
  - Measurement of growth will be performed. Growth assessment for 10 participants at baseline.
  - Key efficacy endpoints will include change in height Z-score in relation to age and sex based on reference tables on growth in children with ACH.
  - Clinical efficacy endpoints will include change in ACHV Z-score in relation to age and sex.

- Safety
  - All safety analyses will be performed using the safety analysis set, defined as one post-baseline growth parameter assessment.
  - Safety analyses will include the evaluation of safety, tolerability, and dose-modifying events.
  - Safety analysis will be performed for demographic, participants, and safety data in an exploratory manner.
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- Pharmacokinetics
  - PK parameters will be performed for demographic, participants, and safety data in an exploratory manner.
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- Monitoring
  - A Data Review Committee is responsible for monitoring participant safety and key efficacy data.
  - A Safety Monitoring Committee will monitor participant safety and key efficacy data.
  - Studies will be 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 protection laws.

- Quality assurance
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