PROPEL2: a phase 2, open-label, dose-escalation and dose-expansion study of infigratinib in children with achondroplasia

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#P1-125

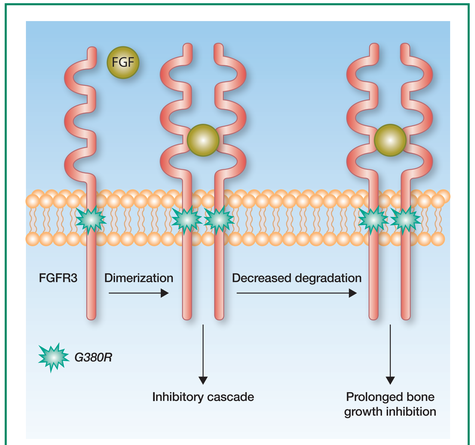
Background

- 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]
- Children and adults with ACH are prone to significant co-morbidities, including obstructive sleep apnea, chronic otitis media with conductive hearing loss, spinal stenosis, foramen magnum stenosis and a propensity towards obesity.
- No therapies for the treatment of ACH are currently marketed 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.[3,4]
- 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.[3]

Rationale for the use of infigratinib in ACH

- Infigratinib is an orally bioavailable and selective FGFR1/2/3 tyrosine kinase inhibitor in development for FGFR-related conditions.
- Infigratinib inhibits FGFR downstream signaling, offering a direct therapeutic strategy to counteract the hyperactivity of FGFR3 in ACH.[3]
- Preclinical data in a *Fgfr3*$^{Y367C/+}$ mouse model of ACH[5,6] showed that:
  - Low doses of infigratinib (0.2, 0.5 and 2 mg/kg/day) 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 preclinical 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.

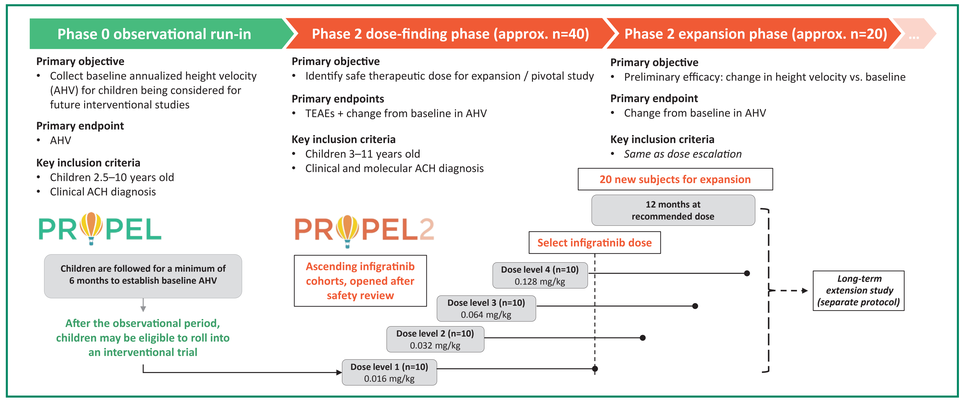
Figure 1. FGFR3-mediated inhibition of bone growth in ACH



The *G380R* pathogenic variant in ACH extends the signaling cascade, resulting in prolonged bone growth inhibition. Modified from Unger et al. 2017[3]

Methods

Figure 2. PROPEL and PROPEL2 study design



- PROPEL2 is a prospective, phase 2, open-label study, which is 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 3–11 years of age with ACH who have completed at least 6 months of observation in PROPEL are eligible to participate in PROPEL2.
- PROPEL2 consists of dose escalation with an extended treatment phase, designed as dose finding, followed by a dose-expansion phase to confirm the selected dose and to provide evidence of efficacy. A pharmacokinetic (PK) sub-study is also included.
- Children (approx. n=40) will be enrolled in ascending dose cohorts of approximately 10 subjects/cohort (4 cohorts planned) and treated for 6 months at their assigned dose, continuing for an additional 12 months (extended-treatment period).
- Children enrolled at the two lower dose levels (cohorts 1 and 2) may have their dose increased at Months 6 and 12 if there are no safety concerns and HV does not increase at least 25% compared with baseline.
- Children enrolled in the dose-expansion phase (approx. n=20) will receive treatment with infigratinib at the dose identified in the dose-escalation phase for a total duration of 12 months.

Table 1. Objectives and endpoints

Objectives	Endpoints
Primary	
Dose-escalation phase: to identify a dose of oral infigratinib for children with ACH to be used for further study.	• TEAEs that lead to dose decrease or discontinuation. • Change from baseline in height velocity (annualized to cm/year). Baseline defined as annualized height velocity obtained from at least 6 months of observation in PROPEL study.
Dose-expansion phase: to provide preliminary evidence of efficacy for oral infigratinib in the treatment of ACH.	• Change from baseline in height velocity (annualized to cm/year).
PK sub-study: to evaluate the PK profile of infigratinib and major active metabolites in children with ACH after administration of oral infigratinib.	• PK parameters of infigratinib and major active metabolites (e.g. C_{max}, C_{last}, T_{max}, AUC_{24}, $T_{1/2}$, AUC_{inf}, CL/F, Vz/F, and R_{acc}).
Secondary	
To evaluate the safety and tolerability of oral infigratinib in children with ACH.	• Safety evaluations by incidence, type, severity, and causality of AEs, SAEs, laboratory test results (urinalysis, chemistry, hematology), clinically significant changes in vital signs, physical examination (including ophthalmic and dental evaluation), electrocardiograms, and imaging.
To evaluate changes from baseline in anthropometric parameters after administration of oral infigratinib.	• Absolute height velocity (annualized to cm/year), expressed numerically and as Z-score in relation to non-ACH tables. • Absolute (expressed as absolute value and Z-score in relation to ACH and non-ACH standardized pediatric growth curves) and change from baseline in anthropometric parameters, including body proportions. Anthropometric measurements may include standing height, sitting height, weight, head circumference, upper and lower arm length, thigh length, knee height, and arm span. Body proportion measurement ratios may include upper to lower body segment ratio, upper arm to forearm length ratio, upper leg to lower leg length ratio, arm span to standing height ratio, and head circumference to standing height ratio.

Table 1. Objectives and endpoints (cont'd)

Objectives	Endpoints
Secondary (cont'd)	
To evaluate the PK and pharmacodynamic (PD) profile of infigratinib in children with ACH after administration of oral infigratinib.	• PK parameters (eg, C_{max} and t_{max}). • Changes in PD parameters: biomarkers of bone turnover that may include type X collagen degradation fragment, collagen X marker (CXM).
Exploratory	
To evaluate changes in ACH condition burden, including quality of life.	• Changes in condition-specific complications, such as changes in mobility (assessed by elbow, hip, and knee range of motion), changes in the number of episodes of otitis media per year, changes in number of episodes and/or severity of sleep apnea, and changes in quality of life (QoL) as assessed by PedsQL (generic core scale short form, child and parent reports): – Baseline for range of motion and PedsQL will correspond to the values obtained at the baseline visit. – Baseline for the number of episodes of otitis media will be the number of episodes recorded during the PROPEL study (expressed as episodes/year). – Baseline for sleep apnea, will correspond to the polysomnogram performed at screening (to rule out severe sleep apnea).

Table 2. Key inclusion/exclusion criteria

Key inclusion criteria	Key exclusion criteria
1. Children 3–11 years old. 2. Clinical and molecular ACH diagnosis. 3. Ambulatory and able to stand without assistance. 4. Willingness to comply with study visits and procedures; signed informed consent. 5. At least a 6-month period of growth assessment in PROPEL before study entry.	1. Height < –2 or > +2 standard deviations for age and sex based on reference tables on growth in children with ACH. 2. Annualized height growth velocity ≤1.5 cm/year over a period ≥6 months prior to screening. 3. Prior treatment with growth hormone in previous 6 months or long-term treatment (>3 months) at any time. 4. Prior treatment with C-type natriuretic peptide analog or FGFR inhibitor, or any other investigational product or investigational medical device for the treatment of ACH or short stature at any time. 5. Prior limb-lengthening procedure. 6. In females, having had their menarche. Children with severe sleep apnea, children who have had guided growth surgery, or a recent fracture (within 6 months of screening) will also be excluded.

Data review committee and cohort escalation/de-escalation

- **Data Review Committee (DRC):** a DRC is responsible for monitoring subject safety and key efficacy data and 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 are made following rules pre-specified in the protocol, which are based on the Bayesian optimal interval (BOIN) design with a target toxicity level of 25%.
- **Cohort dose escalation:** each cohort will commence after safety of the prior dose cohort has been reviewed and confirmed by the DRC. The opening of a new ascending dose cohort will be decided by the DRC based on review of safety data from approximately 10 subjects in each cohort after they complete at least 4 weeks of treatment and safety assessments.
- **Cohort dose de-escalation at any point in the study:** the need for a cohort dose de-escalation will be determined by the DRC based on the safety assessment and incidence of TEAEs that leads to dose decrease/discontinuation for an individual subject.
- **Dose reduction/discontinuation for an individual subject:** although the DRC monitors subject safety and will consider the number of subjects meeting the dose-reduction/discontinuation criteria to determine whether a cohort dose escalation can proceed or if a dose de-escalation is needed at the cohort level, dose modifications in an individual subject is managed by the Investigator. Clear guidance on dose modification/discontinuation are included in the study protocol.

Statistical methods

Sample size

- Selection of the dose for the dose-expansion phase will be based on the assessment of approximately 10 subjects per cohort, which will allow observation of at least of one AE with 94.4% confidence.
- In the dose-expansion phase, approx. 20 subjects will be enrolled at the selected dose level. An annualized height velocity increase of ≤0.5 cm/year will be considered not clinically relevant and will be used as the null hypothesis.

Dose escalation

- For dose escalation, all analyses will be performed separately for each dosing cohort based on the originally received dose and in total.

Dose expansion

- Subjects enrolled in dose expansion will be analyzed for both safety and efficacy.

Statistical analyses

- All safety analyses will be performed using the safety analysis set, defined as subjects who have received at least one dose of study drug. Analyses on growth parameter endpoints will be performed for subjects who have a baseline and at least one post-baseline growth parameter assessment.

PROPEL2 trial (NCT04265651): current status

- The PROPEL2 study is currently enrolling. The first subject was enrolled in July 2020.
- Following completion of PROPEL2, subjects have the opportunity to enroll in an open-label long-term extension study to assess the safety and efficacy of long-term administration of infigratinib in children with ACH.
- Please refer to ESPE poster #P1-130 for further details on the phase 0 observational run-in study (PROPEL), which feeds into PROPEL2.

References

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