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

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Background

Achondroplasia (ACH) is the most common non-lethal form of skeletal dysplasia, affecting between 1 in 15,000 to 20,000 live births in the US, with an estimated global prevalence of 250,000.1,2 Longitudinal bone growth is driven by the proliferation and differentiation of chondrocytes in the growth plate and achieving pathogenic variants of FGFR3 cause inhibition of chondrocyte proliferation and differentiation.3

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.

To evaluate changes in ACH condition burden, including quality of life.

Key inclusion criteria


Key exclusion criteria

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 notclinically relevant and will be used as the null hypothesis.

Data review committee and cohort escalation/de-escalation

• 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 PaedQoL (generic core scale short form, child and parent reports).

• Baseline change in motion and PaedQoL 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).

Methods

PROPEL2 is a prospective, 2-phase 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 the dose-expansion phase.

To evaluate the changes in PK and pharmacodynamic (PD) profile of infigratinib in children with ACH after administration of oral infigratinib.

PK parameters (e.g., Cmax, and t1/2).

Changes in PD parameters: biomarkers of bone turnover that may include type X collagen degradation fragment, collagen X marker (CMX).

Table 2. Key inclusion/exclusion criteria

Key inclusion criteria

1. Children 3–11 years old.

2. Clinical and molecular ACH diagnosis.

3. Cognitive status and adequate upper extremity strength.

4. Willingness to comply with study visits and procedures; signed informed consent.

5. At least 6 month of prior growth in PROPEL study before entry study.

Key exclusion criteria

1. Height <2 or >2 standard deviations for age and sex based on reference tables on growth in children with ACH.

2. Prior treatment with C-type natriuretic peptide analog or FGFR inhibitor, or any other drug that may interact with infigratinib.

3. Subjects with prior treatment with C-type natriuretic peptide analog or FGFR inhibitor.

4. Prior treatment with C-type natriuretic peptide analog or FGFR inhibitor, or any other drug that may interact with infigratinib.

5. In females, having had their menstrual cycles. Children with 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

• TEAEs that lead to dose decrease or discontinuation.

• Changes from baseline in height velocity that may include a velocity of 0.5 cm/year (to confirm the selected dose and to provide evidence of efficacy). A pharmacokinetic (PK) sub-study is also included.

• Children (age ≤4) 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 (extension period).

• When the children reach the lower dose levels (cohorts 1 to 3) and may have their dose increased at Month 6 and if there are no safety concerns and IF 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-expansion phase for a total duration of 12 months.

• 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 dose cohort based on the originally dosed and in toto.

• 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 parameters will be performed in an intent-to-treat analysis set and will include all baseline at post-dose baseline growth parameter assessment.

PROPEL2 trial (NCT04265561): 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.

References


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