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 10,000 to 1 in 20,000 live births in the US, with an estimated prevalence of 350,000.1

Children and adults with ACH have profound cognitive, behavioral, and physical disabilities and a shortened life expectancy compared to non-ACH tables.2

No therapies for the treatment of ACH are currently marketed in either the US or Europe, although there is evidence of some benefit from biphosphonates and denosumab.3

The pathogenic variant in ACH extends the signaling cascade, resulting in prolonged bone growth.4

Infigratinib is an orally bioavailable and selective FGFR1/2/3 tyrosine kinase inhibitor that has shown antitumor activity in preclinical models and phase I trials.5

Infigratinib inhibits FGFR signaling, offering a direct therapeutic opportunity to correct the ACH phenotype by targeting the FGFR1/2/3 signaling pathway.6

FGFRs are expressed in cells of osteoblastic lineage and inhibit the FGFs signaling pathway that controls bone growth.7

Rationale for the use of infigratinib in ACH

The rationale for the use of infigratinib in ACH is based on the following:

- Phospho-FGFR, the downstream target of FGFR activation, is upregulated in ACH.8
- In vitro studies have shown that infigratinib inhibits phosphorylation of FGFR in osteoblasts, resulting in reduced bone growth.9
- In vivo studies have shown that infigratinib reduces bone growth in mouse models of ACH.10

Methods

Achondroplasia is an irritable bone marrow and selective FGFR1/3 tyrosine kinase inhibitor in development for ACH.

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In vivo studies have shown that infigratinib reduces bone growth in mouse models of ACH.10

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

Figure 2. PROPEL and PROPEL2 study design

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Table 1. Objectives and endpoints (cont'd)

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Table 2. Key inclusion/exclusion criteria

Key inclusion criteria

1. Children ≥11 years old.
2. Clinical and molecular ACH diagnosis.
3. Inability to control bone growth with existing therapies.
4. Willingness to comply with study visits and procedures and signed informed consent.
5. At least 6-month period of growth assessment in PROPEL before study entry.

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. Annualized height velocity >0.5 cm/year over a period ≥12 months prior to screening.
3. Prior treatment with growth hormone in previous 6 months or long-term treatment with thyroid hormone.
4. Prior treatment with CYP3A4 selective peptide analog or FGFR inhibitor, or any other investigational product or investigational medical device for the treatment of ACH or other 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 failed growth surgery, or a recent fracture (within 6 months of screening) will also be excluded.

In the dose expansion phase, up to 20 subjects will be enrolled at the selected dose. An elevated height velocity >0.5 cm/year will be continued at a clinically relevant dose and will be used to identify the dose that will provide antitumor activity.11

Dose escalation

In the dose escalation phase, all subjects will be performed separately for each dosing cohort based on the same dose schedule.12

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Data review committee and cohort escalation/dose-expansion

A Data Review Committee (DRC) is responsible for monitoring subject treatment effects and providing 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 DRC's recommendations.13

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 a check of the review of safety data from approximately 10 subjects in each cohort after they complete at least 4 weeks of treatment and safety assessment.

Cohort dose-de-escalation at any point in the study: the need for a cohort dose-escalation will be determined by the DRC based on the safety assessment and incidence of TEAEs that lead to dose decrease/ discontinuation for an individual subject.

Dose reduction/discontinuation for an individual subject: during the dose escalation phase, objectives will be the number of subjects who are reduced or discontinued the dose.

Dose reduction/discontinuation for an individual subject: during the dose escalation phase, the DRC will review safety data from approximately 10 subjects in each cohort after they complete at least 4 weeks of treatment and safety assessment.

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Table 1. Objectives and endpoints (cont’d)

Objectives

Endpoints

Phase 2-3 dose-finding phase (approx. n=40)

- Dose escalation
- Cohort dose escalation can proceed or if a dose de-escalation is needed, a cohort dose de-escalation can proceed.

Phase 2 expansion phase (approx. n=20)

- Dose de-escalation
- Dose de-escalation can proceed if the DRC recommends a dose de-escalation.

Secondary (cont’d)

- PK parameters (e.g., Cmax, AUC and tmax)
- Changes in P2 protein biomarkers: biomarkers of tumour growth that may include type X collagen, degradation fragment, collagen X marker (COMP).

Exploratory

- Table 1. Key inclusion/exclusion criteria

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Table 2. Sample size calculation

Sample size

Selection of the dose for the dose expansion phase will be based on the evaluation of the median change in height velocity per year, which will allow observation of at least one AE with >4% confidence.

References