Oral infigratinib treatment is well tolerated and significantly increases height velocity in children with achondroplasia: Month 6 results from the PROPEL 2 dose-finding study

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Disclaimers

- **Infigratinib has not been approved by the FDA or any other regulatory authority for the treatment of achondroplasia, as its efficacy and safety have not yet been established**

- Dr Melita Irving has the following potential conflicts of interest to disclose:
  - **Advisory board member:** Ascendis Pharma, BioMarin, QED Therapeutics, Sanofi, Therachon/Pfizer
  - **Speaker:** BioMarin, QED

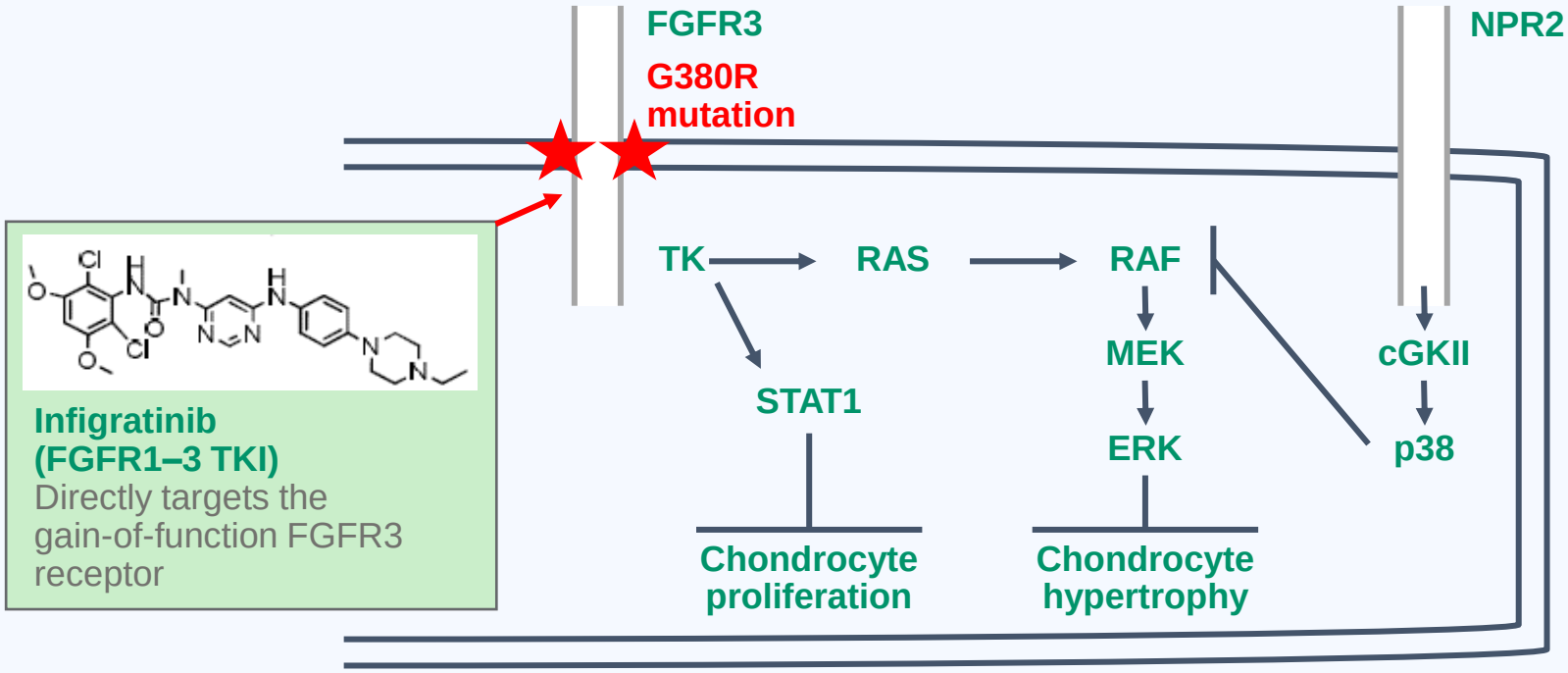
Achondroplasia: the most common short-limbed skeletal dysplasia

- Achondroplasia (ACH) affects between 1 in 15,000 and 1 in 30,000 live births, with an estimated global prevalence of 250,000[1,2]
- Characteristic clinical features include disproportionate short stature, smaller than average chest, macrocephaly with frontal bossing, midface hypoplasia, curvature of the spine, hypermobile joints, leg bowing, and shortening of the fingers and toes[4]
- Individuals with ACH experience a variety of physical, functional, and psychosocial complications and challenges throughout their lifetime[4]
- ACH is characterized by defective endochondral ossification resulting from gain of function pathogenic variants in the fibroblast growth factor receptor-3 gene (FGFR3),[3,4] which is a negative regulator of endochondral bone formation
- Infigratinib is an orally bioavailable, FGFR1–3 selective tyrosine kinase inhibitor being investigated as a direct therapeutic strategy to counteract FGFR3 overactivity in ACH
- Preclinical data in an *Fgfr3*$^{Y367C/+}$ mouse model of ACH showed that low doses of infigratinib resulted in substantial increases in the length of upper and lower limb long bones, and improvement in the shape and size of the foramen magnum, compared with untreated animals

[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]Bellus GA, et al. Am J Hum Genet 1995;56:368–73; [4]Savarirayan R, et al. Nat Rev Endocrinol. 2022 Mar;18:173–89

Infigratinib is an oral, selective FGFR1–3 inhibitor in development as a treatment option for achondroplasia

Mechanism of action



Infigratinib

- **Orally-available, selective**, ATP-competitive **FGFR-selective tyrosine kinase inhibitor**
- Selective for FGFR 1, 2 & 3
- **Inhibits both pathways** responsible for the clinical phenotype associated with achondroplasia

Infigratinib directly targets FGFR3 overactivity, the underlying cause of achondroplasia

Source: Adapted from Ornitz DM et al 2017 Dev Dynamics

Month 6 results from the dose escalation portion of the Phase 2 PROPEL 2 study

- N=72; 42 females
- Mean ± SD (range) age at consent = Mean ± SD (range) age at consent, 7.5 ± 2.2 (3.1–11.5)
- 5 dose levels explored:
  - Cohort 1: 0.016 mg/kg/day
  - Cohort 2: 0.032 mg/kg/day
  - Cohort 3: 0.064 mg/kg/day
  - Cohort 4: 0.128 mg/kg/day
  - Cohort 5: 0.25 mg/kg/day

Additional information about the PROPEL2 study design, disposition and demographics are available in the full poster

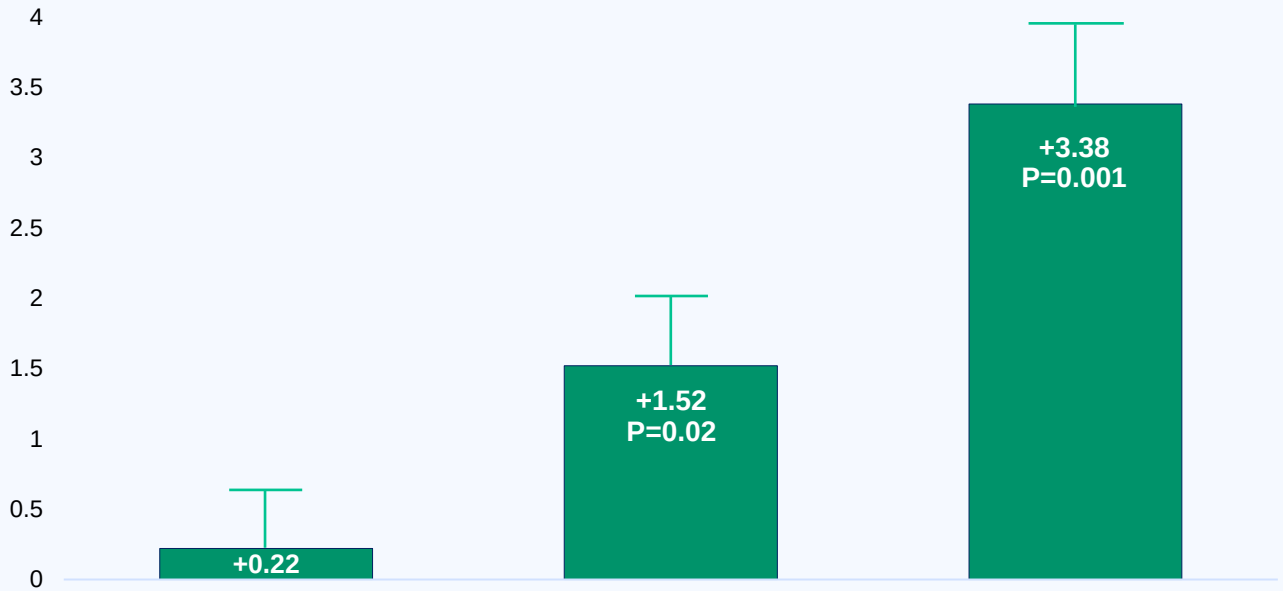
Summary of adverse events

- Treatment with infigratinib was **well tolerated**
- **No serious adverse events (SAEs)** and no AEs that required treatment discontinuation
- 71/72 (98.6%) children presented with at least 1 treatment-emergent AE (TEAE):
  - **Most** TEAEs were **grade 1 (58.3%) and 2 (34.7%)** in severity, and mostly **not related** to study drug
  - Adverse events most frequently reported are considered common conditions in pediatric population, particularly in children with ACH
  - 4 subjects (2 from cohort 2, and 2 from cohort 3) had a **Grade 3 TEAE** assessed as not related to study drug, and represent expected comorbidities in children with ACH:
    - Cholesteatoma, hydrocephalus, severe sleep apnea, worsening of adenoidal hypertrophy
- **At the highest dose level (Cohort 5: 0.25 mg/kg/day)**
  - No serious adverse events (SAEs) and no AE that required treatment discontinuation
  - Most TEAEs were grade 1 in severity and not assessed as related to study drug
  - **0 subjects with grade 3 TEAEs**
  - **0 ocular adverse events**
  - **0 hyperphosphatemia events**
  - No accelerated progression of the bone age and no worsening in body proportions

Source: Data on file

Infigratinib demonstrated significant, dose-responsive increases in annualized height velocity compared with baseline levels

Mean (SE) change from baseline in annualized height velocity at month 6 cm/year



N	37	11	12

Cohort 5 n=12	
Female:Male ratio	**7:5**
Mean age (year)	**7.24**
<5	8%
5 to <8	58%
8 to <11	25%
≥11	8%
BL AHV (cm/year) Mean (SD)	**3.52 (1.3)**
Month 6 AHV (cm/year) Mean (SD) Median	**6.9 (2.06)** **7.58**

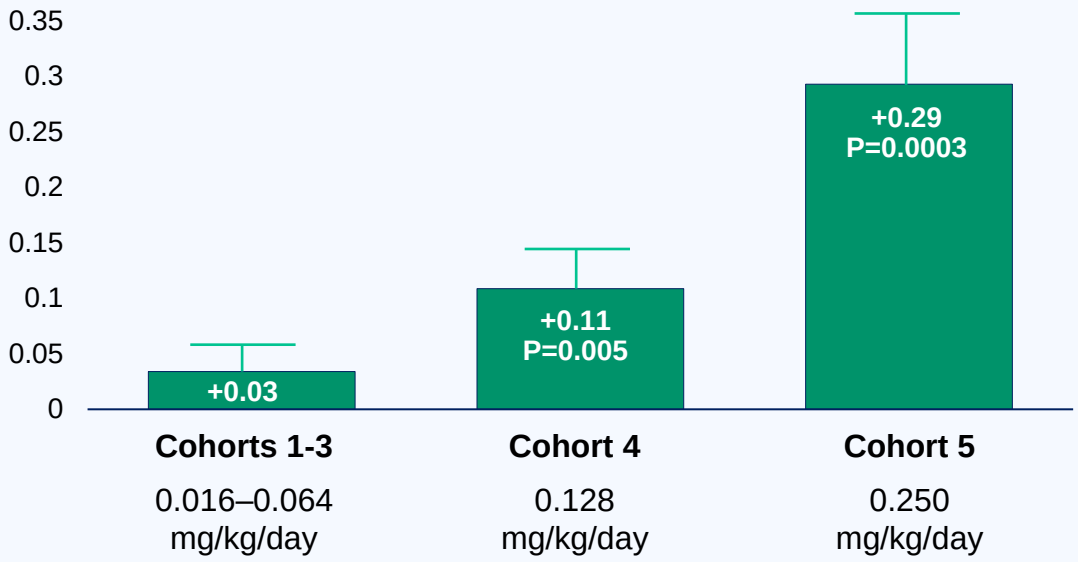
P values: 6-month AHV vs BL AHV

Note: Data shown is restricted to children ages 5 and greater, except in Cohort 5, which includes one child who turned 5 between screening and dosing

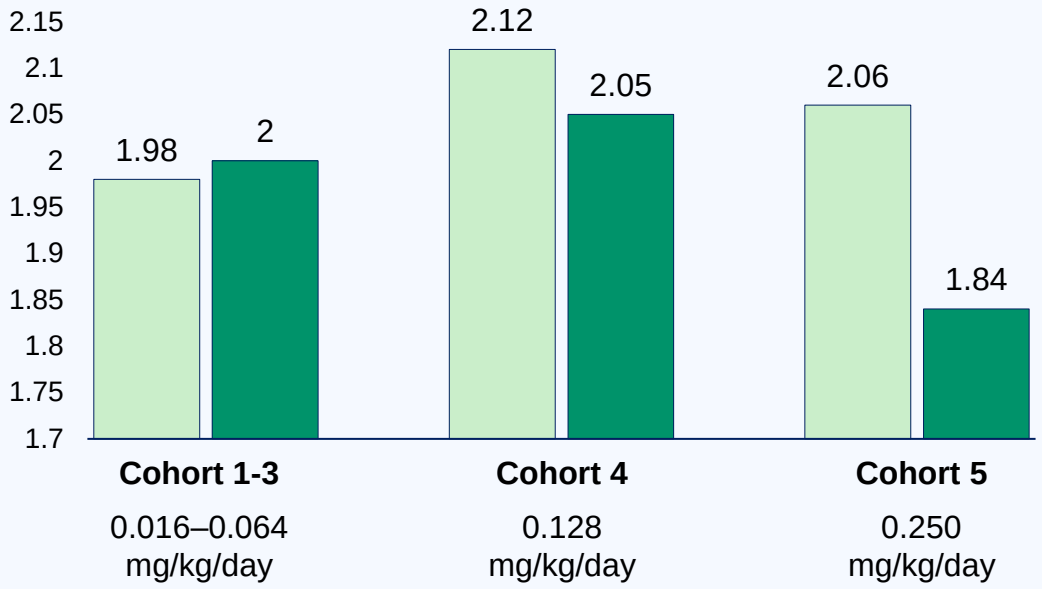
Source: Data on file

Month 6 changes in height z-score and body proportions compared with baseline levels

Height z-score change (ACH growth curve)
Mean (SE)



Mean upper to lower body segment ratio



Cohort 5 dose level resulted in a significant increase in height z-score (for both ACH and non-ACH growth charts) and in a decrease in the upper to lower body segment ratio

P values 6-month z-score vs baseline z-score
Source: Data on file

Summary

- Treatment with oral infigratinib has been **well tolerated**, with no SAEs, or TEAEs that led to treatment discontinuation
- At Cohort 5 dose level, (0.25 mg/kg/day)
  - No hyperphosphatemia
  - No ocular AEs (i.e., no retinal or corneal disorders)
  - No accelerated progression of bone age
  - No worsening of body proportions
    - Preliminary data suggests the Cohort 5 dose level may be having a positive effect on the upper/lower body segment ratio
- Treatment with infigratinib at the Cohort 5 dose level resulted in a significant and robust increase in AHV compared with baseline values, with a change of **+3.38cm/year**
- This increase in growth translates to an increase in z-score of +0.29 standard deviation scores compared with ACH growth charts and +0.25 standard deviation scores compared with average height growth charts
- Changes in linear growth are supported by an increase in CXM, supporting a true biologic effect

Source: Data on file. See full poster for further details

Conclusions

- The safety and efficacy of an oral, once-daily dose of infigratinib at 0.25 mg/kg/day will be explored further in a phase 3, randomized, controlled trial
- The 6-month observational lead-in to the phase 3 trial is open for enrollment
- If these phase 2 data are confirmed, infigratinib could potentially offer children with ACH the first effective oral therapy to improve growth, enhance functionality and decrease medical complications

THANK YOU