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

Ravi Savarirayan[1], Josep Maria De Bergua[2], Paul Arundel[3], Jean Pierre Salles[4], Vrinda Saraff[5], Borja Delgado[6], Antonio Leiva-Gea[6], Helen McDevitt[7], Marc Nicolino[8], Massimiliano Rossi[8], Maria Salcedo[9], Valerie Cormier-Daire[10], Mars Skae[11], Peter Kannu[12], Michael B. Bober[13], John Phillips III[14], Howard Saal[15], Paul Harmatz[16], Christine Burren[17], Toby Candler[17], Terry Cho[18], Elena Muslimova[18], Richard Weng[18], Supriya Raj[1], Julie Hoover-Fong[19], Melita Irving[20], and Daniela Rogoff[18]

[1]Murdoch Children's Research Institute, Melbourne, Australia; [2]Hospital Vithas San José, Vitoria-Gasteiz, Spain; [3]Sheffield Children's NHS Foundation Trust, Sheffield, UK; [4]Hôpital des Enfants – Toulouse, Toulouse, France; [5]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK; [6]Hospital Universitario Virgen de la Victoria, Malaga, Spain; [7]NHS Greater Glasgow and Clyde, Glasgow, UK; [8]Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Lyon, France; [9]Hospital Universitario La Paz, Madrid, Spain; [10]Hôpital Necker-Enfants Malades, Paris, France; [11]Manchester University NHS Foundation Trust, Manchester, UK; [12]University of Alberta – Stollery Children's Hospital, Edmonton, Canada; [13]Nemours/Alfred I. duPont Hospital for Children, Wilmington, USA; [14]Vanderbilt University Medical Center Nashville, USA; [15]Cincinnati Children's Hospital Medical Center, Cincinnati, USA; [16]Benioff Children's Hospital Oakland, Oakland, USA; [17]University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK; [18]QED Therapeutics, a BridgeBio company, San Francisco, USA; [19]Johns Hopkins University, Baltimore, USA; [20]Guy's and St Thomas' NHS Foundation Trust, London, UK

SCAN ME

Disclaimers

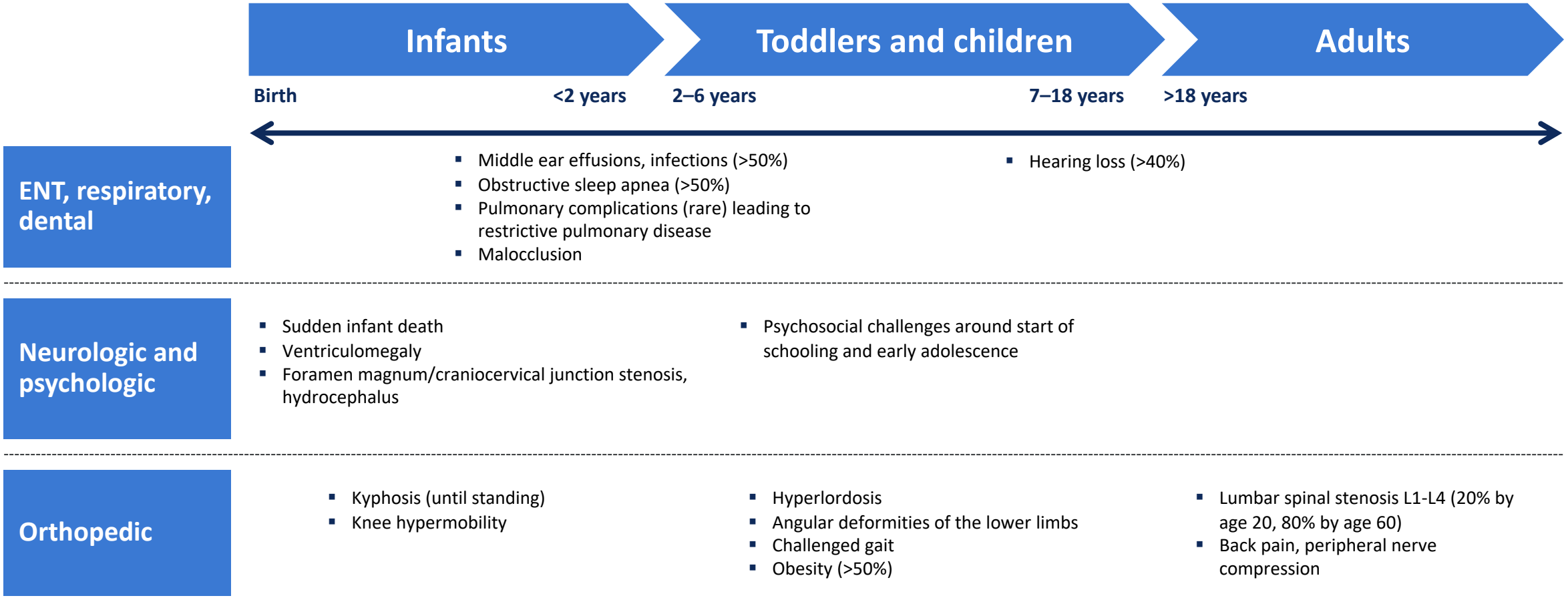
- **Infigratinib has not been approved by the FDA or any other regulatory authority for treatment of achondroplasia, as its efficacy and safety have not yet been established.**
- Dr Ravi Savarirayan received honoraria from QED/BridgeBio, all disclosed.

Achondroplasia (ACH) is the most common short-limbed skeletal dysplasia

- ACH affects between 1 in 15,000 and 1 in 30,000 live births, with an estimated global prevalence of 250,000[1,2]
- 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
- 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]

Source: [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(3):173-189

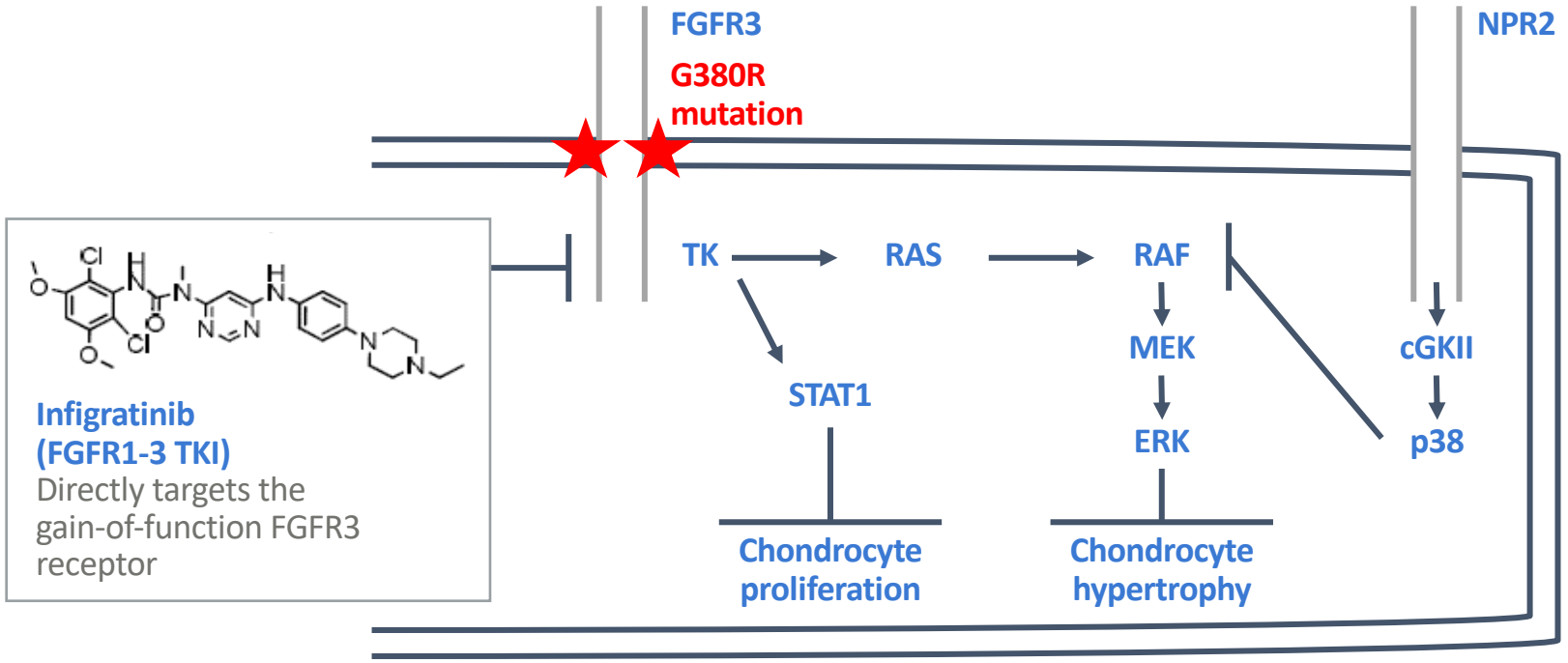
Achondroplasia is associated with multiple medical complications throughout the lifetime of affected individuals



Note: Schematic represents the approximate age at start or presentation of medical complications
Source: Adapted from Unger S, et al. Curr Osteoporos Rep 2017;15:53–607

Infigratinib is an oral, selective FGFR 1-3 inhibitor in development as a treatment option for achondroplasia

Mechanism of action



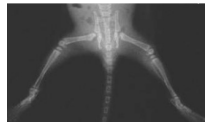
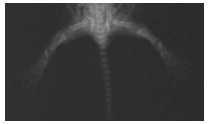
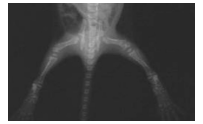
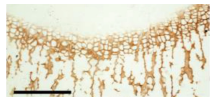
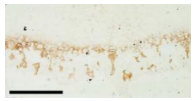
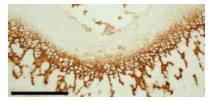
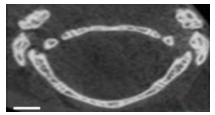
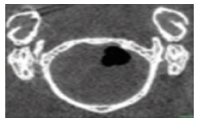
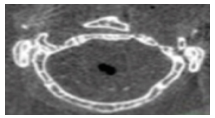
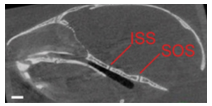
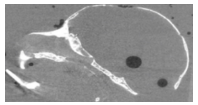
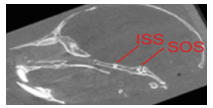
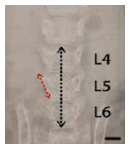
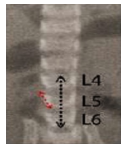
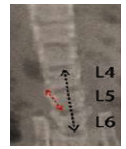
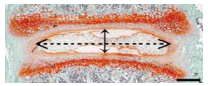
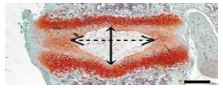
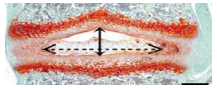
Infigratinib

- **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

Infigratinib demonstrated a robust response on long bone, foramen magnum and spine in a mouse model of achondroplasia

ACH (*Fgfr3*$^{Y367C/+}$) mouse model data		FGFR3 Wild Type	FGFR3 Mutant Mouse No treatment	FGFR3 Mutant Mouse Infigratinib Treatment	Key Results
Fgfr3$^{Y367C/+}$ Mice showed a robust long bone response to infigratinib of >20%	Xray				**21%** increase in femur length **33%** increase in tibia length
	Collagen X immunostaining				Improvement in impaired differentiation of hypertrophic chondrocytes
Infigratinib reduced foramen magnum defects and increased craniofacial skeleton growth in FGFR3$^{Y367C/+}$ mice	Foramen magnum area				**17%** mean increase in foramen magnum area
	Craniofacial skeleton				**6%** mean increase in AP skull length
The spine of mice treated with infigratinib was longer compared to those without treatment	Vertebral body length				**12 %** mean increase in L4-L6 length
	Intervertebral disk width				**73%** mean increase in intervertebral disk width

The foramen magnum & spinal impact of infigratinib in preclinical models suggests potential benefit in the most severe medical complications of achondroplasia

Source: Komla-Ebri, et al. J Clin Invest. 2016 May 2;126(5):1871-84

Infigratinib in achondroplasia is being evaluated in the PROPEL program

PROPEL observational run-in

Key inclusion criteria

- Children 2.5 – 17 years old
- Clinical and molecular ACH diagnosis
- Ambulatory and able to stand without assistance

Key exclusion criteria

- Hypochondroplasia
- AHV ≤1.5 cm/year over ≥6 months prior to screening
- Previous treatment with GH, IGF1, anabolic steroids in the past 6 months, or CNP analog at any time
- Concurrent disease or condition which may impact growth

Children are followed for at least six months to collect BL data, including annualized height velocity (AHV)

PROPEL2 Dose-finding (n=70+)

- Cohort 5:0.25 mg/kg ✓
- Cohort 4: 0.128 mg/kg ✓
- Cohort 3: 0.064 mg/kg ✓
- Cohort 2: 0.032 mg/kg ✓
- Cohort 1: 0.016 mg/kg ✓

PROPEL open-label long-term extension

- Will enroll children that completed other interventional studies with potential for a naïve to treatment cohort
- Long- term safety and efficacy until closure of growth plates
- Key to evaluate the potential benefit of infigratinib in outcomes that will require longer time to present, such as changes in QoL, functional abilities, pain and complications associated with achondroplasia

Primary endpoints

PROPEL2

- Change from baseline annualized height velocity (AHV)
- Safety and tolerability

PROPEL OLE

- Changes over time in height z-score
- Long term safety

Secondary endpoints

- Change in upper body to lower body segment proportionality
- Patient-reported outcome measures: PedsQoL, QoLISSY, Pain-NRS
- Height-for-age z-score (PROPEL2); Change over time in HV Z-score (PROPEL OLE)

PROPEL2: Study design

- Phase 2, open-label study, designed to provide preliminary evidence of safety and efficacy of oral infigratinib in children with achondroplasia, and to identify the dose of infigratinib to be explored in Phase 3.
- PROPEL2 consists of 3 parts:
  - Dose Escalation with Extended treatment Period Phase; PK Sub-study:
    - 5 ascending-dose cohorts (doses 0.016-0.25mg/kg/day)
    - Treatment for 6 months at their assigned dose, continuing for an additional 12 months of treatment (extended-treatment period).
      - Dose increases (at M6 and M12) were allowed in children enrolled in cohorts 1 and 2 if height velocity had not increased by >25% compared with baseline and if no safety concerns were observed
  - Dose Expansion period:
    - Confirmatory phase, where additional children will enroll and receive 12 months of treatment with infigratinib at the dose selected from the dose escalation portion
- Enrolls children 3-<11yo, with confirmed molecular diagnosis of achondroplasia and who have completed at least 6 months of observation in PROPEL.*

Source: Savarirayan R, et al. Ther Adv Musculoskelet Dis. 2022, Mar 21; NCT04265651
*Complete Inclusion/Exclusion criteria described on clinicaltrials.gov

Month 6 Results

Subject disposition and demographics

Disposition

- 72 children enrolled
- Early discontinuation: 4
  - 3 Withdrawal of consent (personal circumstances that would interfere with complying with study activities)
  - 1 subject required a procedure that would confound the efficacy and safety assessments
- Study completion: 39
  - All subjects continued treatment in the OLE

Demographics

- Females: 42 (58.3%); Males: 30 (41.7%)
- Ages (at consent): Mean: 7.5 ± 2.2
  - Range: 3.1– 11.5 years old
    - <8 yo: 37 (51.4%)
    - 3 - <5 yo: 12 (16.7%)
    - ≥8 yo: 35 (48.6%)
- Race:
  - White: 44 (61.1%)
  - Black or African American: 4 (5.6%)
  - Asian: 6 (8.3%)
  - Multiple: 2 (2.8%)
  - Other: 3 (4.2%); Not reported: 13 (18.1%)

Source: Data on file. Race information not collected in France.

Safety – Summary of AEs

- Treatment with infigratinib has been **well tolerated**
- **No serious adverse events (SAEs),** no AE that required treatment discontinuation
- 71/72 (98.6%) children presented at least 1 TEAE
  - **Most** TEAEs **grade 1 (58.3%) and 2 (34.7%)** in severity, and mostly **not related** to study drug
  - 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 - 0.25mg/kg/day)**
  - No serious adverse events (SAEs), no AE that required treatment discontinuation
  - Most TEAEs grade 1 in severity **and none of the TEAEs** were 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

AEs reported in ≥10%

AE	Total (%) N = 72
Vomiting	20 (27.8%)
Abdominal pain	11 (15.3%)
Diarrhea	10 (13.9%)
Abdominal pain upper	8 (11.1%)
Pyrexia	16 (22.2%)
Nasopharyngitis	29 (40.3%)
COVID-19	22 (30.6%)
Ear infections	18 (25.0%)
Rhinitis	11 (15.3%)
Upper respiratory tract infections	10 (13.9%)
Viral infection	9 (12.5%)
Pain in extremity	20 (27.8%)
Headache	21 (29.2%)
Cough	10 (13.9%)

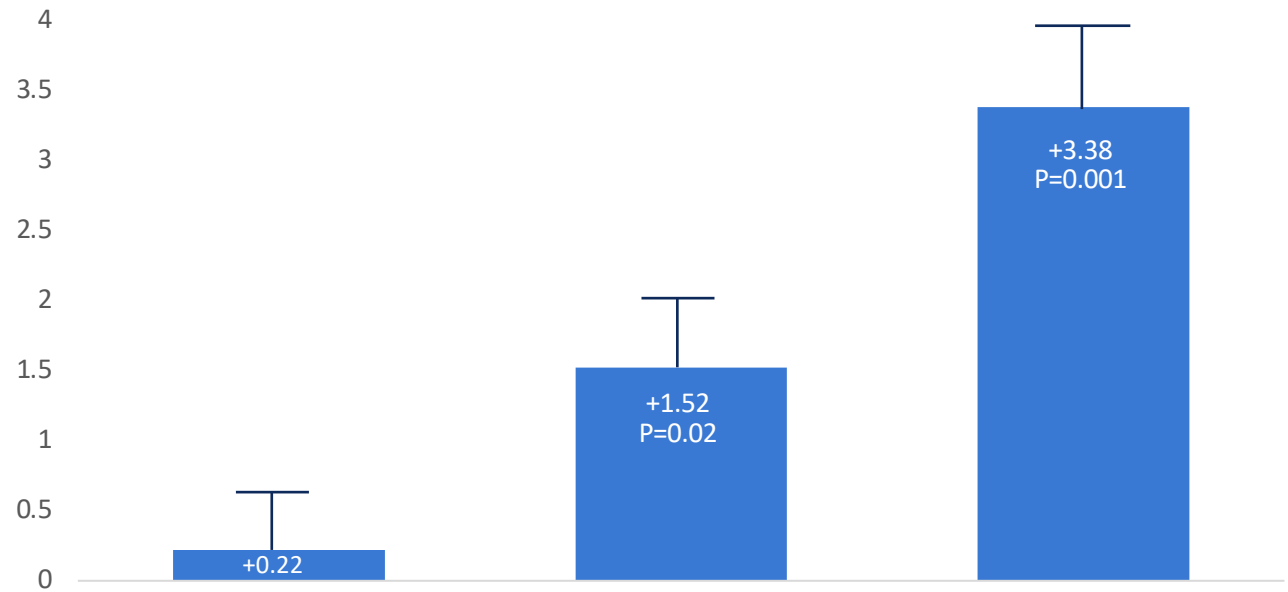
AEs most frequently reported are considered common conditions in pediatric population, particularly in children with achondroplasia.

Source: Data on file

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

Mean (SE) change from baseline in annualized height velocity at M6

cm/yr



N	37	11	12

Cohort 5

N = 12

Female:Male ratio	**7:5**
Mean age (yr) <5 5 - <8 8 - <11 >=11	**7.24** 8% 58% 25% 8%
BL AHV (cm/yr) Mean (SD)	**3.52 (1.3)**
Month 6 AHV (cm/yr) Mean (SD) Median	**6.9 (2.06)** **7.58**

P values 6M AHV vs BL AHV

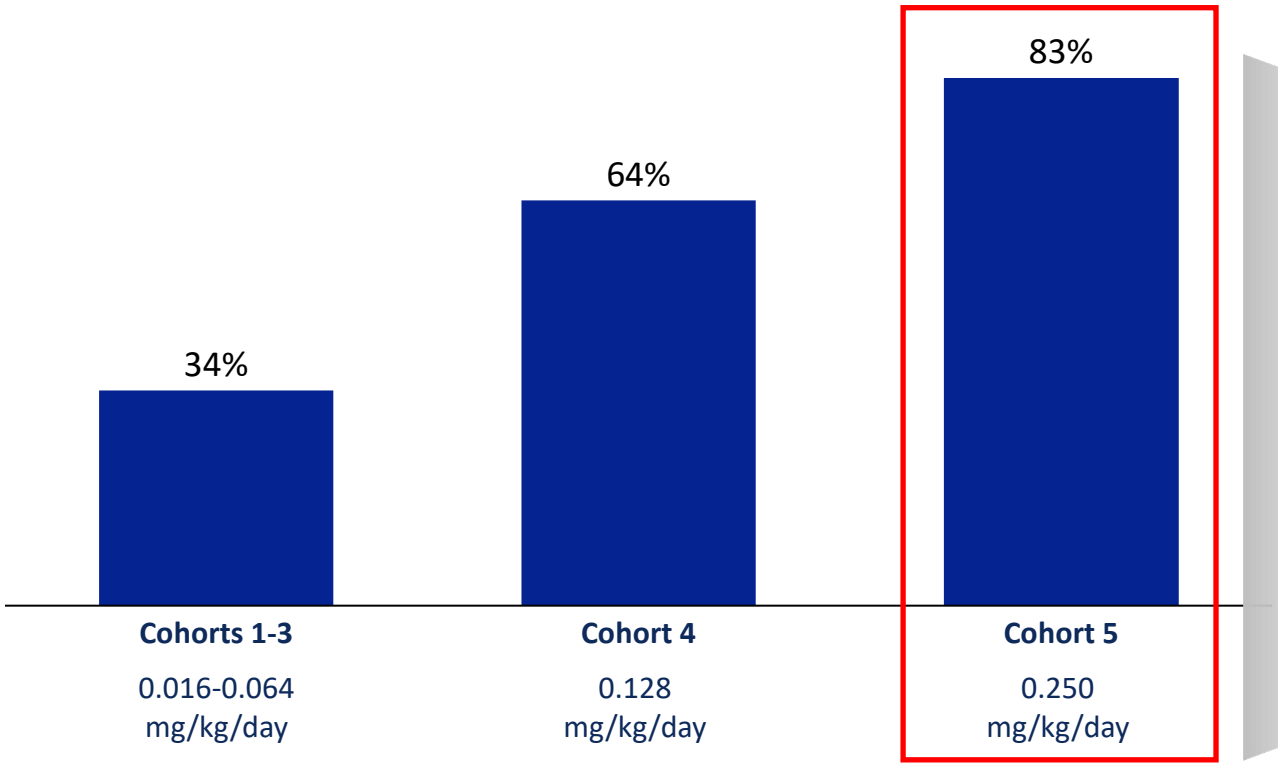
Note: Data shown is restricted to children ages 5 and greater, except in Cohort 5– cohort 5 includes one child who turned 5 between screening and dosing

Source: Data on file

83% of children in cohort 5 responded to infigratinib with an increase in AHV ≥25% over BL

Responder rate[1] at M6

% with an AHV increase of >25% from baseline



Across cohort 5 responders (10 out of 12):

+4.08 cm/yr

mean increase in AHV (±2.4) with a median of **+4.14cm/year**

[1]Responder defined as having a change from baseline AHV of 25% or greater

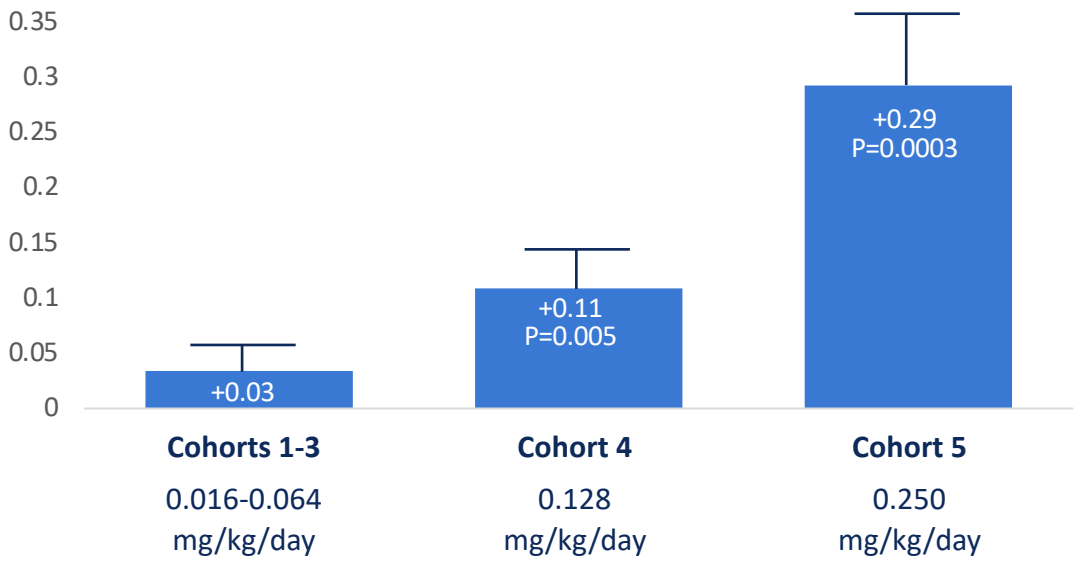
Note: Data shown is restricted to children ages 5 and greater, except in Cohort 5– cohort 5 includes one child who turned 5 between screening and dosing

Source: Data on file.

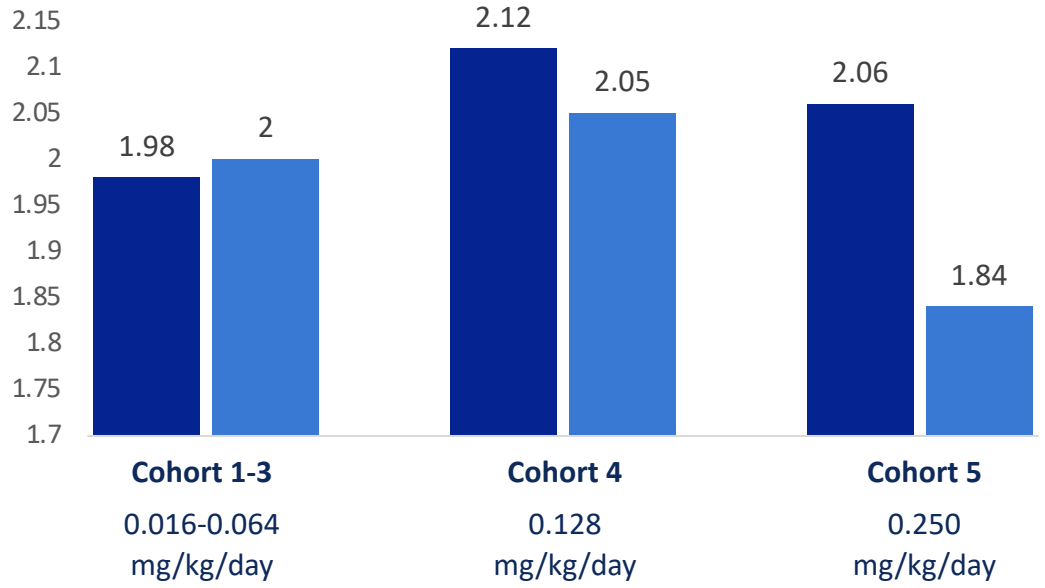
Changes at M6 in height z-score and body proportions compared to baseline

Height z-score change (ACH growth curve)

Mean (SE)



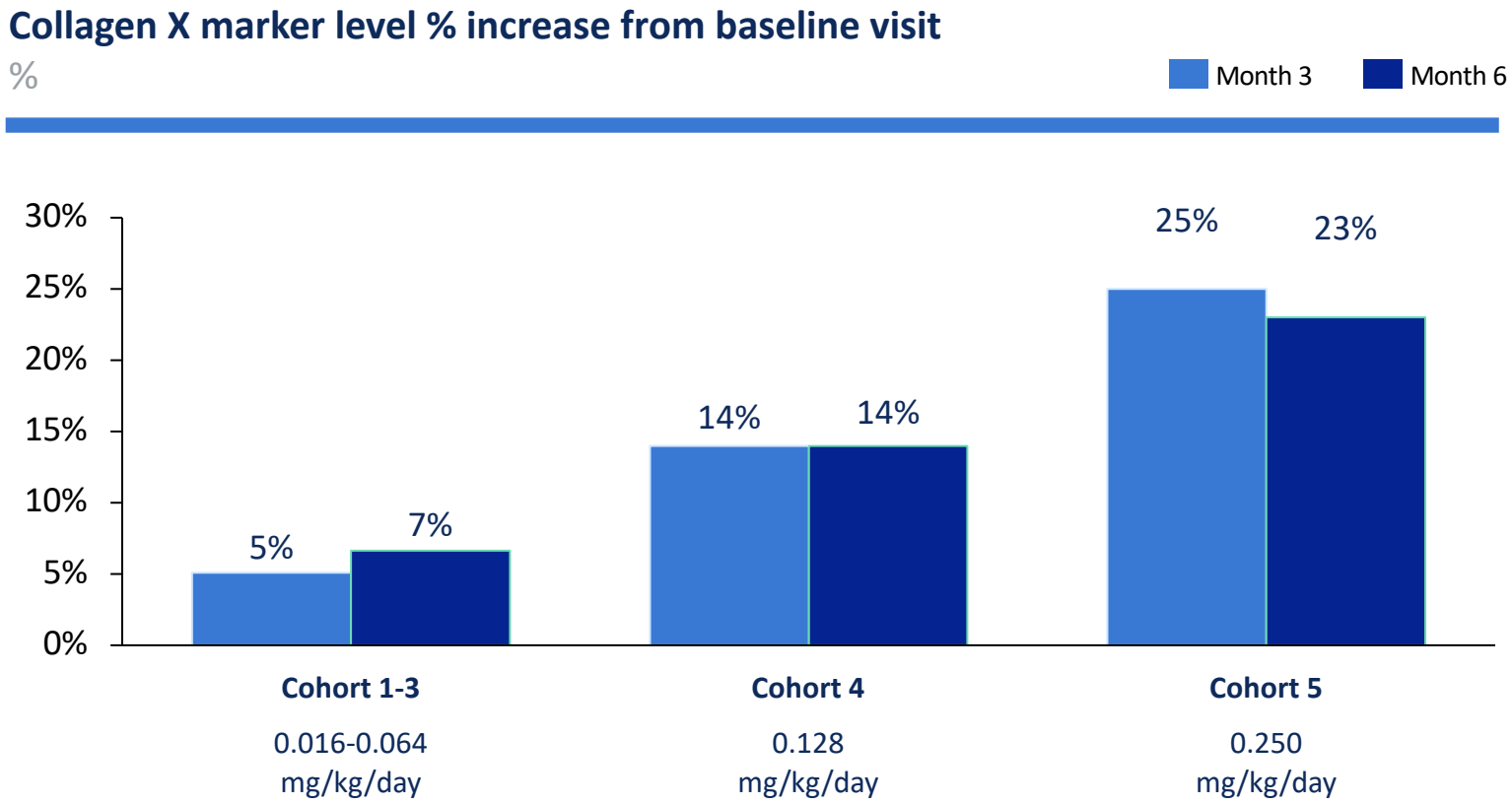
Mean upper to lower body segment ratio



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.

Collagen X Marker (CXM), an independent, real-time biomarker of bone growth, showed a dose-responsive increase



- Collagen X is synthesized and deposited in the hypertrophic zones of active growth plates
- Upon endochondral ossification, collagen X is degraded and the NC1 domain, the marker designated as CXM, is released into the circulation in proportion to overall growth plate activity
- Circulating CXM levels correlates well with growth velocity in real time

The increase in CXM further supports the clinical response

Source: Data on file; Coghlan et al 2017; Linsenmayer et al 1988

Summary

- Treatment with oral infigratinib has been **well tolerated**, with no SAE, or TEAE that led to treatment discontinuation
- At cohort 5 dose level, (0.25mg/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 to BL, with a change of **+3.38cm/year**
- This increase in growth was translated in an increase in z-score of +0.29 standard deviation scores compared to ACH growth charts and +0.25 standard deviation scores compared to average height growth charts
- Changes in linear growth are supported by increase in CXM, supporting a true biologic effect

Source: Data on file.

Conclusions

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

THANK YOU

SCAN ME