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 Savarirayan1, Josep Maria De Bergua2, Paul Arundel3, Jean Pierre Salles4, Vrinda Saraff5, Borja Delgado6, Antonio Leiva-Gea6, Helen McDevitt7, Marc Nicolino8, Massimiliano Rossi8, Maria Salcedo9, Valerie Cormier-Daire10, Mars Skae11, Peter Kannu12, Michael B. Bober13, John Phillips III14, Howard Saal15, Paul Harmatz16, Christine Burren17, Toby Candler17, Terry Cho18, Elena Muslimova18, Richard Weng18, Supriya Raj1, Julie Hoover-Fong19, Melita Irving20, Daniela Rogoff18

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


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

**Mechanism of action**

Infigratinib (FGFR1–3 TKI) directly targets the gain-of-function FGFR3 receptor.

**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

**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

<table>
<thead>
<tr>
<th>Cohort</th>
<th>0.016-0.064 mg/kg/day</th>
<th>+0.22 P=0.02</th>
<th>0.128 mg/kg/day</th>
<th>+1.52 P=0.02</th>
<th>0.250 mg/kg/day</th>
<th>+3.38 P=0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohorts 1-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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)**: 3.52 (1.3)
- **Month 6 AHV (cm/year)**: 6.9 (2.06)
  - Mean (SD)
  - Median: 7.58

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

P values: 6-month AHV vs BL AHV
Month 6 changes in height z-score and body proportions compared with baseline levels

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

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Mean (SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1-3</td>
<td>0.016–0.064 mg/kg/day</td>
<td>+0.03</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>0.128 mg/kg/day</td>
<td>+0.11</td>
</tr>
<tr>
<td>Cohort 5</td>
<td>0.250 mg/kg/day</td>
<td>+0.29</td>
</tr>
</tbody>
</table>

P=0.005
P=0.0003

Mean upper to lower body segment ratio

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Mean upper to lower body segment ratio</th>
<th>P values 6-month z-score vs baseline z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1-3</td>
<td>1.98</td>
<td></td>
</tr>
<tr>
<td>Cohort 4</td>
<td>2.12</td>
<td></td>
</tr>
<tr>
<td>Cohort 5</td>
<td>2.06</td>
<td></td>
</tr>
</tbody>
</table>

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

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 **+3.38 cm/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