ACCEL Program: Oral Infigratinib for Hypochondroplasia

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MAT-US-INFI-0020

Disclaimers

The safety and efficacy of infigratinib have not been demonstrated and infigratinib has not been approved by any regulatory agency for the use described here.

To the children, families, and advocates, who have been a part of this program:

THANK YOU

Developing new treatment options relies entirely on your guidance, dedication, and effort.

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Who Are BridgeBio Pharma and QED Therapeutics?

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QED is part of the BridgeBio family of companies

BridgeBio is a biotechnology company **dedicated to the development of novel, genetically targeted therapies for rare diseases**

Our mission:

To **discover, create, test** and **deliver** transformative medicines to treat people who live with genetic conditions and cancers with clear genetic drivers

Our purpose:

Providing **hope** through **rigorous science**

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About QED Therapeutics:
We are solely focused on skeletal dysplasias

QED Therapeutics

- Affiliate Company of BridgeBio Pharma Inc
- Founded in January 2018
- Headquarters in San Francisco, CA
- ~80 employees
- **Solely focused** on development of infigratinib for FGFR-driven skeletal dysplasias, e.g. achondroplasia and hypochondroplasia

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What Is Infigratinib?

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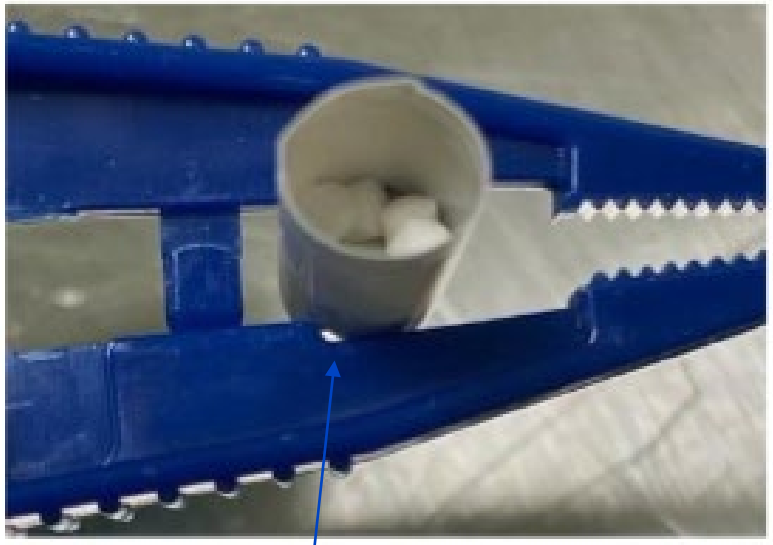
Infigratinib is an investigational medicine that targets FGFR

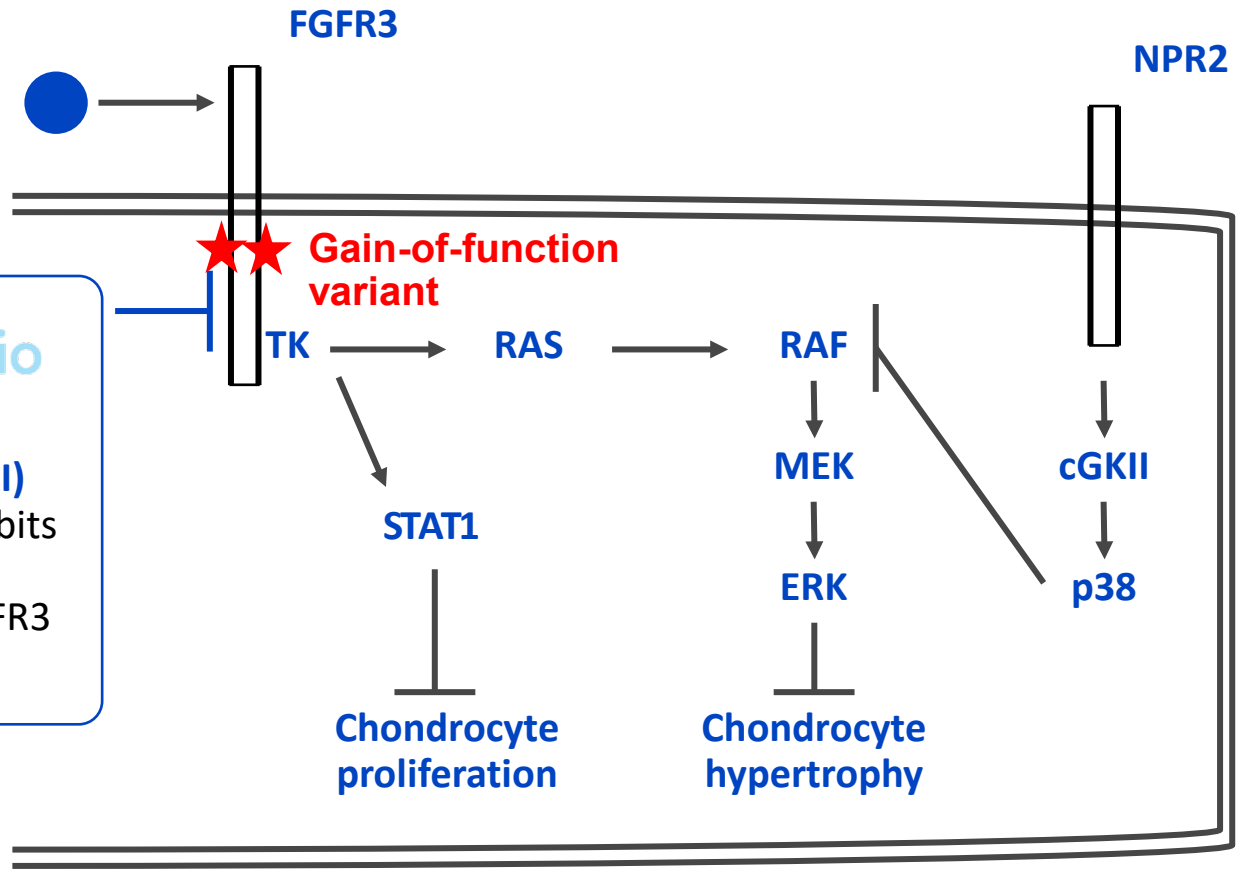
- Infigratinib is designed to decrease FGFR signaling inside a cell.[1]
- Infigratinib is being developed for oral administration as a sprinkle capsule with minitablets (~2mm in diameter) for potential treatment option in achondroplasia and hypochondroplasia with oral administration.
- The different strengths of the sprinkle capsules depend on the number of minitablets encapsulated per capsule.
- The sprinkle capsule strength for each child is based on the weight.
- The capsules can be taken either directly intact or the contents can be sprinkled on soft food



Minitablets inside a sprinkle capsule

SOURCE: 1: Komla-Ebri et al. J Clin Invest. 2016

Let's first look at how infigratinib might work inside human cells in FGFR-3 driven skeletal dysplasias



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Infigratinib (FGFR1-3 TKI)
Directly inhibits the gain-of-function FGFR3 receptor

- Infigratinib is designed to target achondroplasia and hypochondroplasia **directly at the source**: FGFR3 overactivity
- Infigratinib **inhibits both downstream pathways** responsible for the clinical phenotype associated with achondroplasia and hypochondroplasia

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SOURCE: Ornitz DM et al. Developmental Dynamic 2017; Richette Joint Bone Spine 2007; Unger Curr Osteoporos Rep 2017, Hoover-Fong Am J Gen Med 2017

What is the available data to support the initiation of a program for children with hypochondroplasia?

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PROPEL 2 Results: Phase 2 Study for Children With Achondroplasia

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The PROPEL Program in Achondroplasia

PROPEL

Observational Run-in (N ≈ 250)

Participants: Children and adolescents (2.5 to <17 years) with achondroplasia

1° endpoint: AHV

Duration: ≤2 years (≥6 months required for PROPEL interventional studies)

PROPEL2

Phase 2 Open-Label Dose-Escalation and Dose-Expansion (N ≈ 108)

Participants: Children (3–11 years) who complete ≥6 months in PROPEL

1° endpoints: TEAEs, CFB in AHV, and PK parameters

Duration: ≤18 months

PROPEL3

Phase 3 Randomized, Double-Blinded, and Placebo-Controlled (N ≈ 110)

Participants: Children and adolescents (3 to <18 years) who complete ≥6 months in PROPEL and have growth potential

1° endpoint: CFB in AHV

Key 2° endpoints: CFB in height Z-score (on ACH growth charts) and upper to lower body segment ratio.

Other 2° endpoints: Changes in physical functioning, HRQoL, cognitive function, participant and caregiver evaluation of treatment benefit

Duration: 12 months

PROPEL Open Label Extension

Open-label Extension (N ≈ 280)

Participants: Children and adolescents (3 to <18 years) who complete a prior PROPEL study and have growth potential

1° endpoints: TEAEs; changes in height Z-score (on ACH and non-ACH growth charts)

2° endpoints: Changes in upper body to lower body segment ratio; changes in HRQoL, overall body pain, functional abilities, cognitive function, and complications associated with ACH

Duration: 10 years*

ACH, achondroplasia; AHV, annual height velocity; CFB, change from baseline; HRQoL, health-related quality of life; PK, pharmacokinetics; TEAE, treatment-emergent adverse event. *Infigratinib given until final or near-final height reached.

Source: NCT04265651, NCT06164951, NCT05145010

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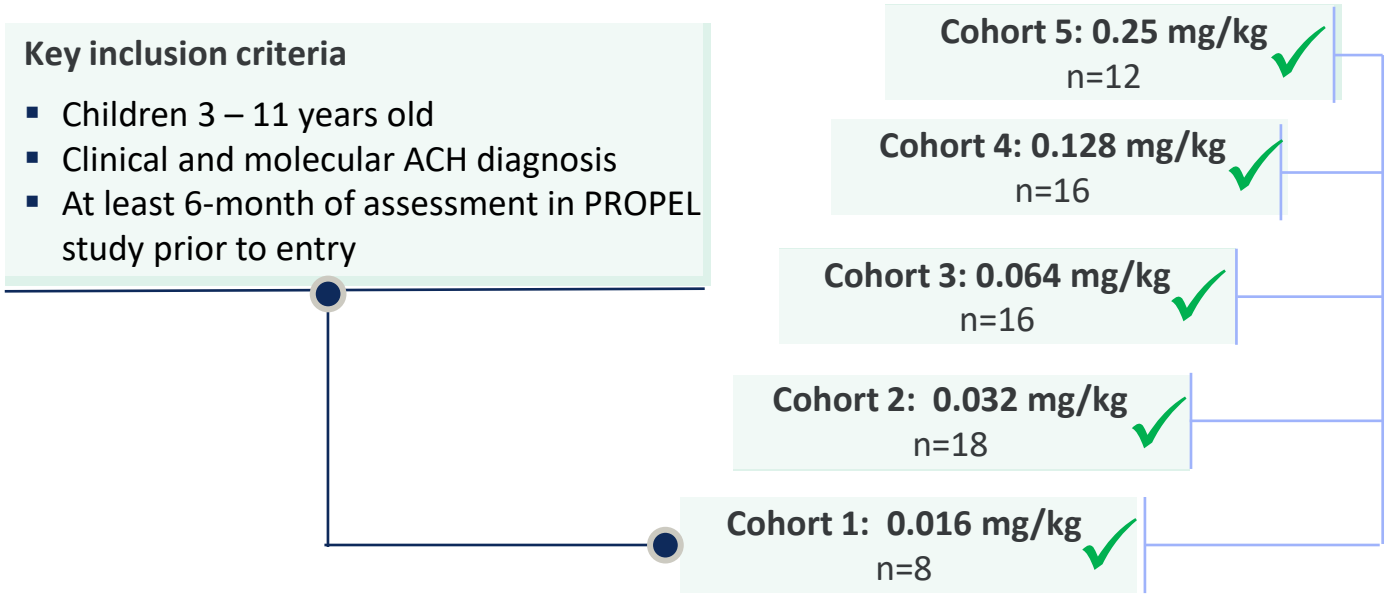
PROPEL2 Clinical Program Design for Achondroplasia

Phase 2 Open-Label Dose-Escalation and Dose-Expansion (N ≈ 108)

Key inclusion criteria

- Children 3 – 11 years old
- Clinical and molecular ACH diagnosis
- At least 6-month of assessment in PROPEL study prior to entry



Primary endpoints

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

Main secondary endpoints

- Change in upper body to lower body segment proportionality
- Patient-reported outcome measures: PedsQoL, QoLISSY, Pain-NRS
- Height-for-age z-score

Note: cohort sizes represent number of children who have completed or are anticipated to complete a month six visit. The planned interim analysis for Cohort 5 was when M6 data for 10 children was available. M6 AHV data is only available from the first 10 with the remaining 2 having six month visits shortly
Source: Savarirayan et al 2022 Ther Adv Musculoskelet Dis

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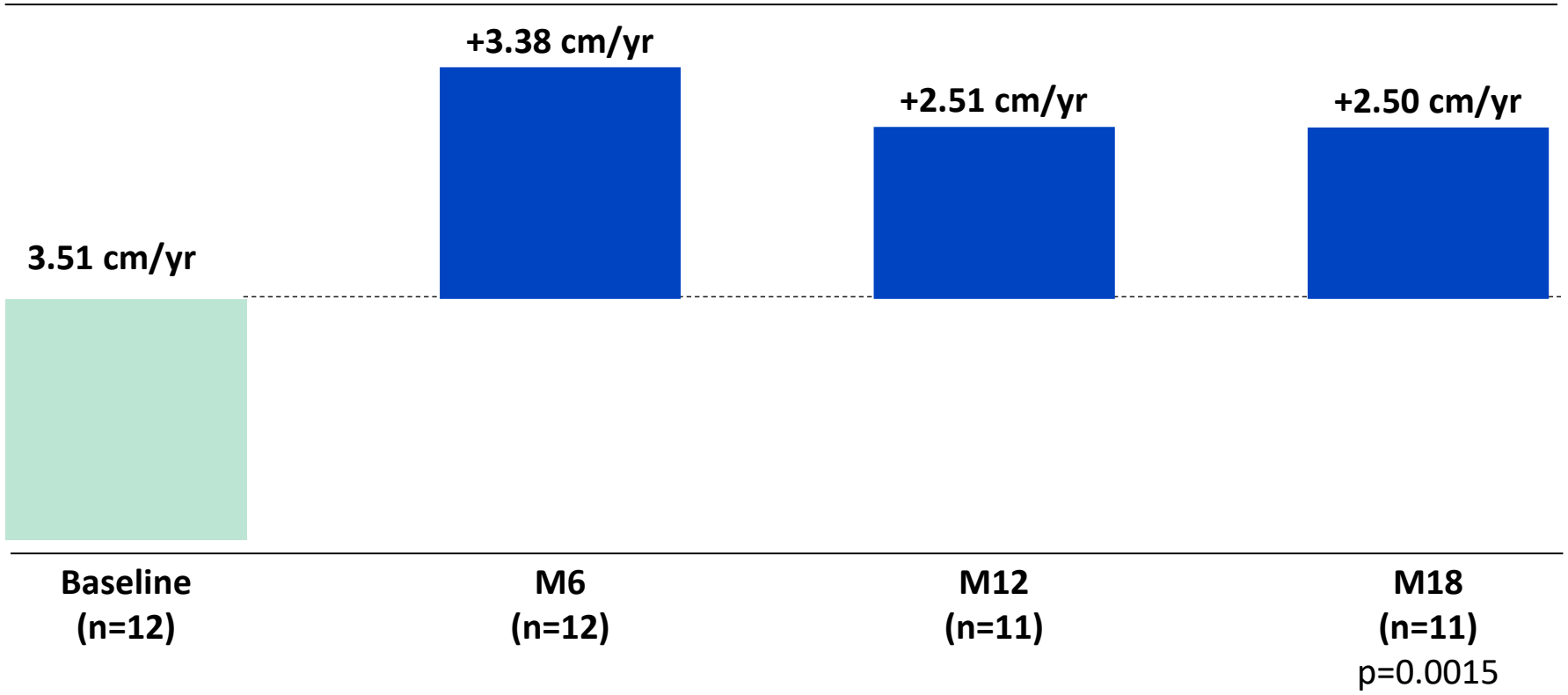
PROPEL 2 Cohort 5: Change From Baseline in AHV (ACH)

Mean change from baseline in annualized height velocity (AHV)



Baseline Demographics	
Female:Male ratio	**7:5**
Mean age at screening (yr) <5 5 - <8 8 - <11 >=11	**7.24** 8% 58% 25% 8%
Baseline AHV (cm/yr) Mean (SD)	**3.51 (1.3)**

The AHV increased from a baseline of ~3.5 cm/year to ~6.0 cm/year oninfigratinib treatment at 18 months.

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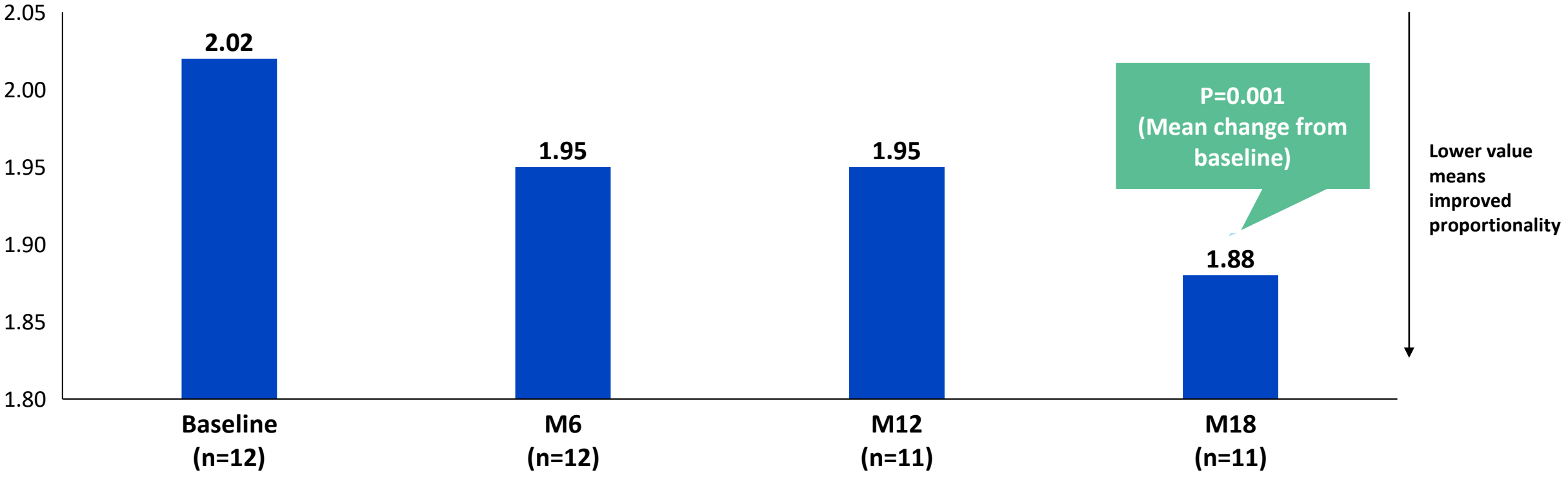
Source: Data on file. NOTE: 1 child dropped out before month 12 assessments as study site closed due to PI departure. This child was a responder at month 6.

PROPEL 2 Cohort 5: Upper/Lower Body Segment Ratio (ACH)

Upper body to lower body segment ratio



Statistically significant improvement in proportionality was observed at 18 months.
For context, the upper/lower body segment ratio of those of average stature is 1.0.

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Source: Data on file. NOTE: 1 child dropped out before month 12 assessments as study site closed due to PI departure. This child was a responder at month 6.

Cohort 5 (0.25 mg/kg) of the PROPEL 2 Trial (ACH): Infigratinib was well-tolerated, with no related AEs

- In Cohort 5 (the highest dose escalation level of 0.25 mg/kg):
  - No serious adverse events (SAEs), no AEs that required treatment discontinuation
  - Most TEAEs were grade 1 in severity and none of the TEAEs were assessed as related to study drug
  - 0 subjects with grade 3 TEAEs
  - 0 hyperphosphatemia events
  - No accelerated progression of the bone age

Infigratinib in PROPEL 2 cohort 5 was well-tolerated with no safety signals identified through month 18

Overview of Rationale for Initiation of Hypochondroplasia Program

- Efficacy and safety profile of infigratinib in achondroplasia are sustained through 18 months in the current data, now with a statistically-significant improvement in proportionality
- PROPEL 3 pivotal study of infigratinib in achondroplasia is enrolling globally
- The clinical data for infigratinib in achondroplasia encouraged us to research infigratinib in hypochondroplasia, a related FGFR3-condition

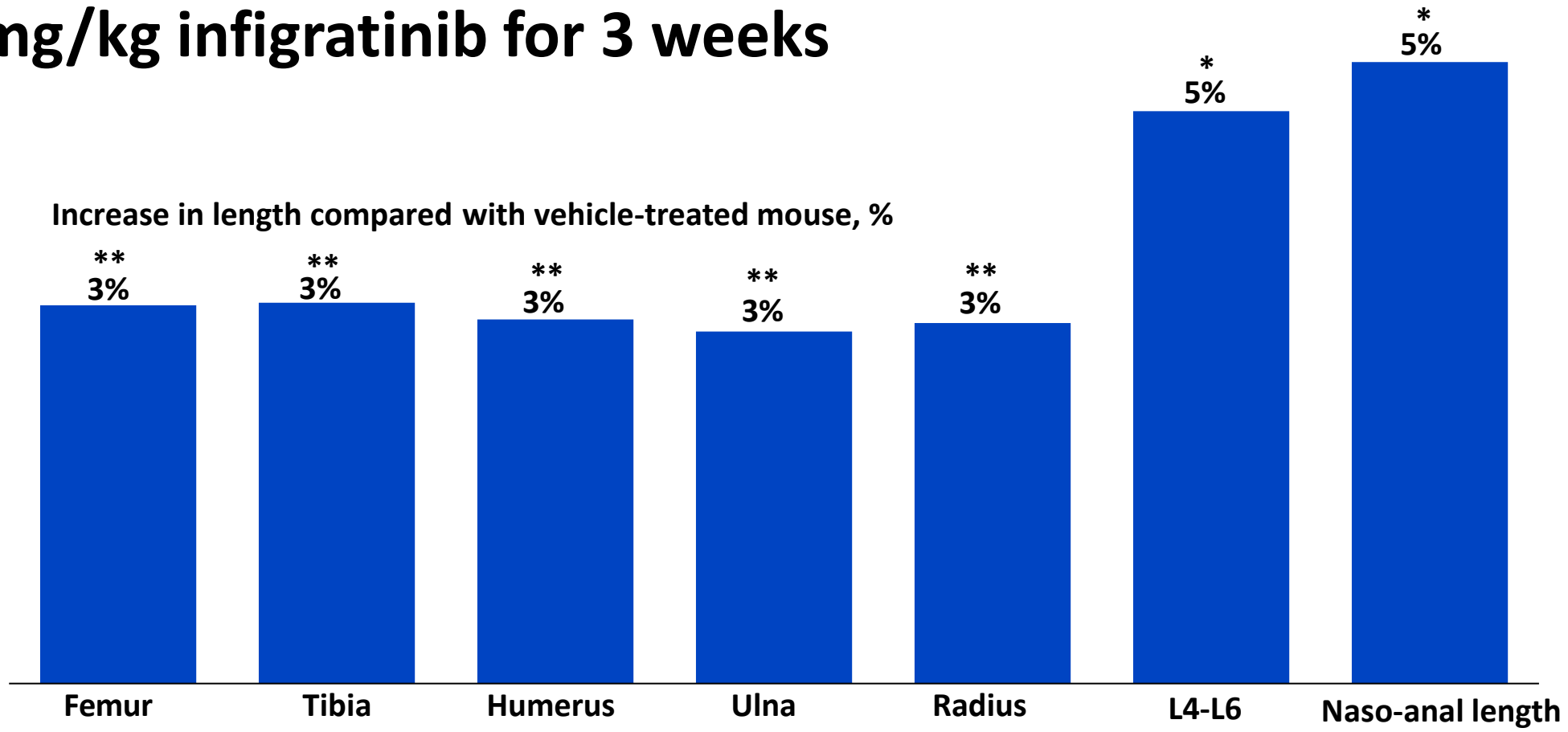
Pre-Clinical Data of Infigratinib in Hypochondroplasia

Hypochondroplasia is an FGFR3-related skeletal dysplasia

- **Autosomal dominant condition**
- **Similar incidence to achondroplasia**
- **Greater genetic heterogeneity in *FGFR3* pathogenic variants (e.g. N540K in addition to others)**
- **Clinical features:**
  - Moderate disproportionate short stature
  - Head circumference larger than average
  - Tibia bowing
- **Potential and reported medical complications:**
  - Delayed motor milestones
  - Reports of epilepsy, temporal lobe abnormalities & other cognitive functions[2,3]

1. Rousseau et al. J Med Genet. 1996;33(9):749-752; 2. Linnankivi et al (2012). Am J Med Genet. 158A:3119–3125; 3. Philpott et al (2013). Pediatr Radiol (2013). 43:1190–1195

Skeletal growth observed in HCH mice treated with daily 1 mg/kg infigratinib for 3 weeks



Moderate, but statistically significant increase in long bones was observed in infigratinib-treated mice

SOURCE: Data on file *p<0.05; **p<0.001, ***p<0.001 NOTE: doses given SC for 21 days (PND3-24)

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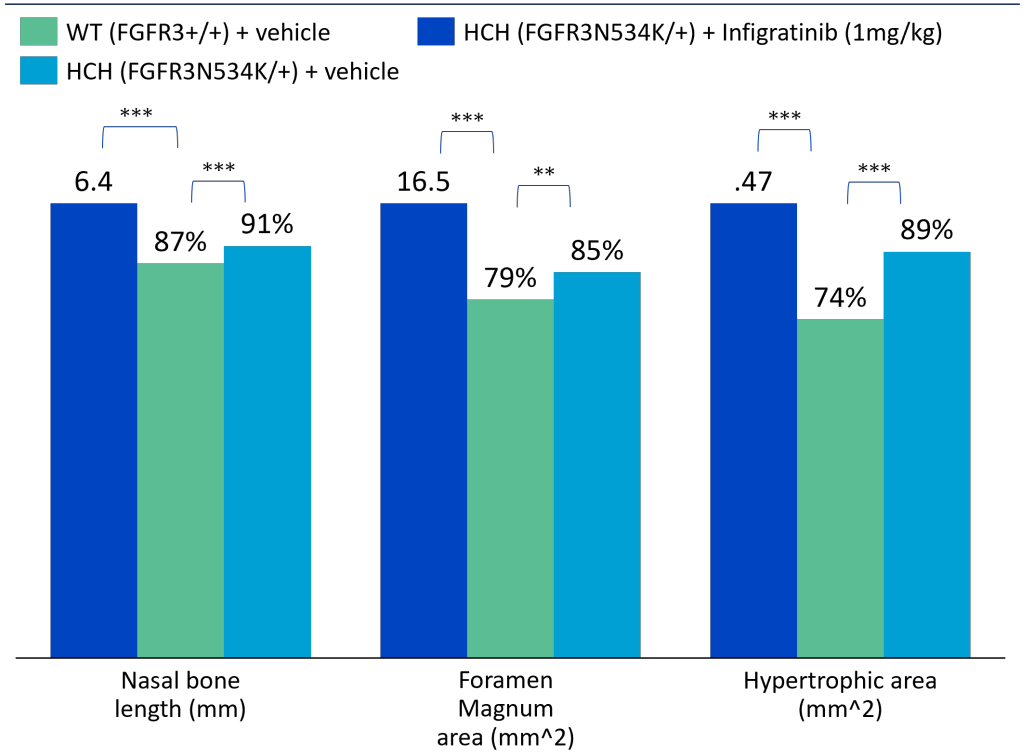
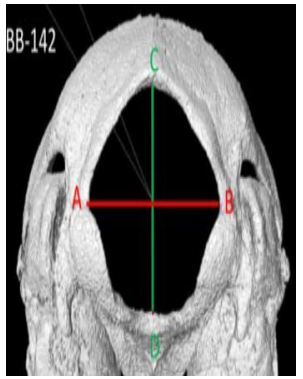
The data included here reflect preclinical (non-human) studies of infigratinib. The findings from these animal studies should not be interpreted as a guarantee of benefit in humans

Skull, foramen magnum, and growth plate histology after infigratinib treatment

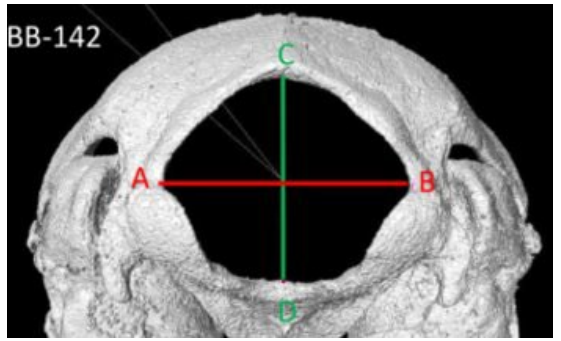
Measurements in WT and mutant mice (mm) and Percentage (%) of WT in treated FGFR3N534K/+ mice



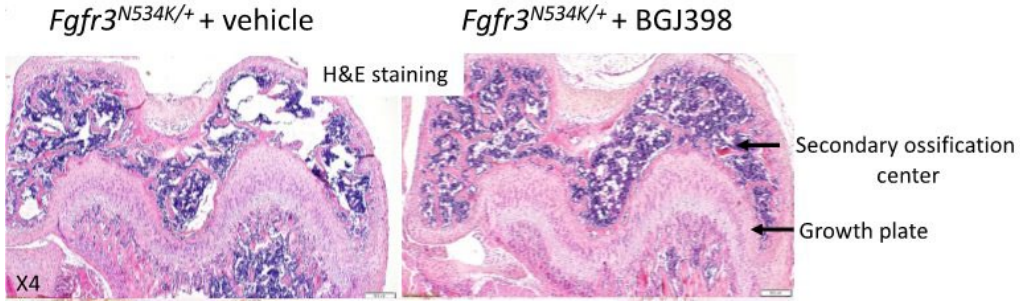
Nasal bone



Foramen magnum



Growth plate hypertrophic chondrocyte region



Statistical significant improvements in nasal bone length, foramen magnum area and growth plate histology observed in infigratinib-treated HCH mice

SOURCE: Data on file *p<0.05; **p<0.001, ***p<0.001 NOTE: doses given SC for 21 days (PND3-24)
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Overview of Pre-Clinical Data of Infigratinib in HCH

- Low-dose treatment with infigratinib in this HCH mouse model improved the clinical hallmarks of human pathology and significantly lengthened the long bones and improved foramen magnum length
- Results suggest that daily infigratinib is able to counteract condition at its source in a mouse model of hypochondroplasia
- Results provide a rationale for further exploring infigratinib for the potential treatment of children with hypochondroplasia

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What Is ACCEL Program?

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The ACCEL clinical program consists of an observational run-in and an interventional study with long-term follow-up

Observational Run-in

Children and adolescents (2.5 to <17 years) with hypochondroplasia (HCH)

Primary objective: Establish baseline height velocity (HV)

Primary endpoints: Annualized height velocity (AHV)

Phase 2/3 Open-Label Phase followed by a Double-Blinded, Randomized, Placebo-Controlled Study (0.25 mg/kg/day)

Phase 2: Open-Label Phase

Children (5 – 11 years with growth potential) with HCH who completed ≥6 months in ACCEL

Primary objectives: Obtain preliminary efficacy, safety and tolerability of infigratinib in HCH

Primary endpoints: Change from baseline in HV and safety endpoints

Pivotal Phase 3: Double-Blinded, Randomized, Placebo-Controlled Phase

Children and adolescents (3 – <18 years with growth potential) with HCH who completed ≥6 months in ACCEL

Primary objectives: Evaluate safety and efficacy of infigratinib in HCH

Primary endpoints: Change from baseline in AHV vs. placebo

Open-Label Extension (planned)

Eligible children and adolescents who completed either portion will be offered treatment with infigratinib until final height/near final height

Primary objectives: Evaluate long term safety, tolerability and efficacy of infigratinib in HCH

The ACCEL trials will also evaluate changes in growth, body proportions and HCH -related complications

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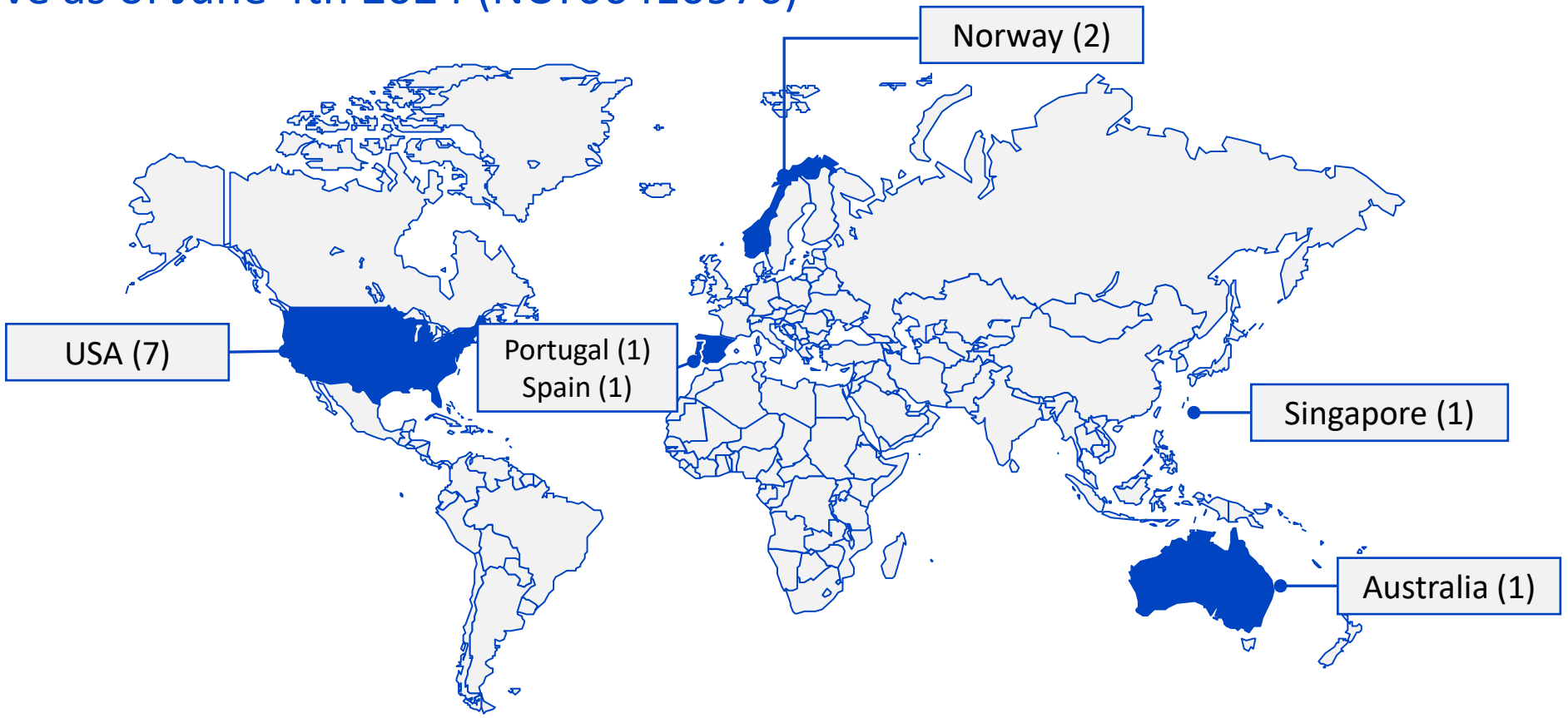
Clinicaltrials.gov listing: NCT06410976 (ACCEL)

ACCEL Site Locations

Effective as of June 4th 2024 (NCT06410976)



Note: This is a subset of the expected sites for ACCEL – please check back at clinicaltrials.gov or email medinfo@qedtx.com

Conclusions

- The clinical data for infigratinib in achondroplasia encouraged us to research infigratinib in hypochondroplasia, a related FGFR3-condition
- Pre-clinical HCH mouse model results informed the clinical development of infigratinib
- Expansion of infigratinib in hypochondroplasia is now initiated, with the ACCEL clinical trial open and first participant enrolled

To the children, families, and advocates, who have been a part of this program:

THANK YOU

Developing new treatment options relies entirely on your guidance, dedication, and effort.

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Thank You!

Contact medinfo@qedtx.com for any questions on the ongoing trials

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