Infigratinib Clinical Development Program Update

Ravi Savarirayan

Murdoch Children's Research Institute, Royal Children's Hospital Victoria
University of Melbourne
Parkville, Victoria, Australia

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Disclosures

- Honoraria from QED, BioMarin, Ascendis and Tyra.

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Infigratinib is an investigational agent that is not approved for use by any regulatory authority.

Presentation overview

QED Clinical Development Program Update
Infigratinib & the PROPEL Program for ACH
PROPEL 2 Cohort 5: Data Update
PROPEL 3: Update
Hypochondroplasia: ACCEL Program
Closing and Q&A

ACH: Achondroplasia

Achondroplasia

The PROPEL Program

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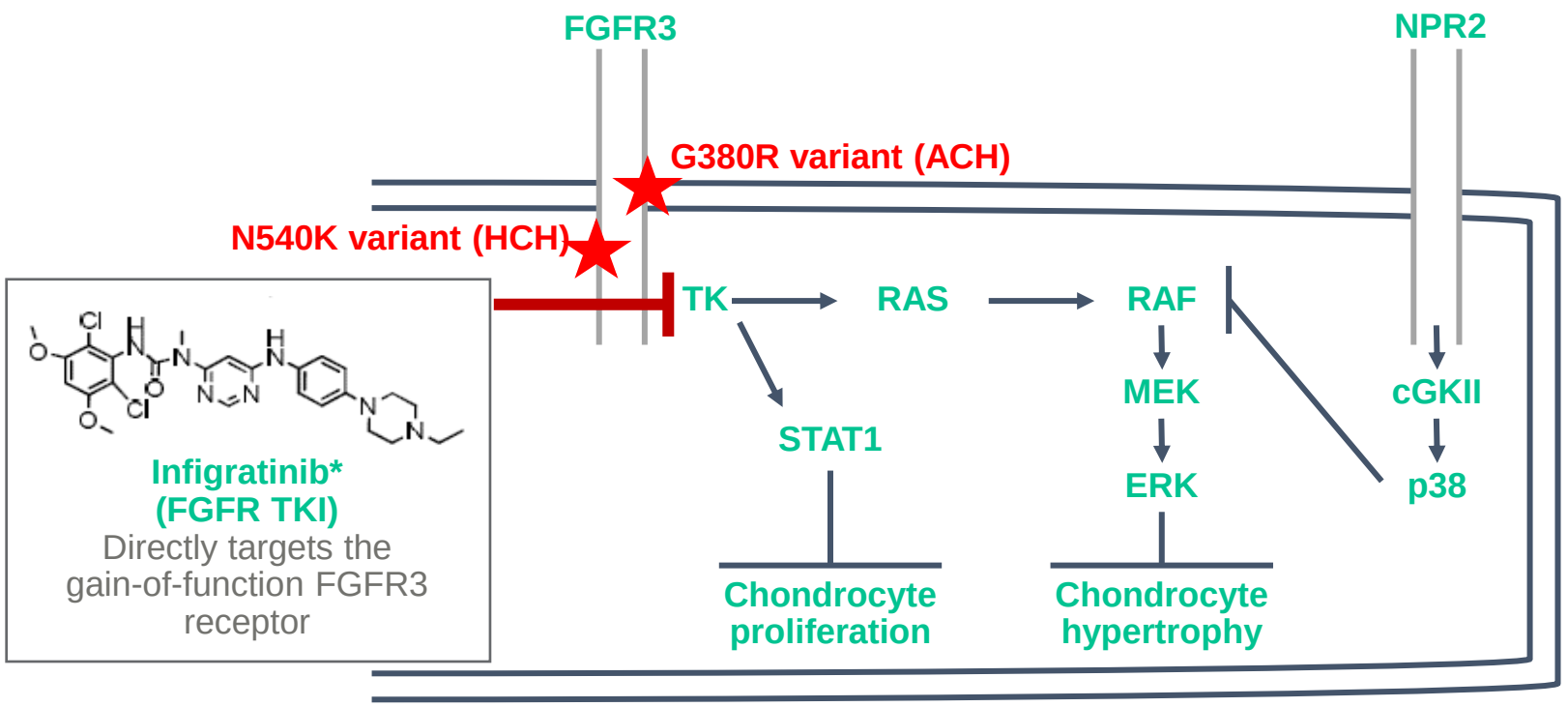
Infigratinib* is an oral FGFR3 inhibitor in development as a treatment option for achondroplasia & hypochondroplasia

Mechanism of action



Infigratinib

- **Oral FGFR1-3 tyrosine kinase inhibitor**
- **Inhibits all pathways** responsible for the clinical phenotype associated with achondroplasia (ACH) & hypochondroplasia (HCH)

Infigratinib directly targets FGFR3 overactivity, the underlying cause of achondroplasia & hypochondroplasia

Ornitz DM. & Legeai-Mallet L. Dev Dyn. 2017; Savarirayan R. et al. Ther Adv Musculoskelet Dis. 2022.

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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.

Clinicaltrials.gov ID: NCT04265651, NCT06164951, NCT05145010

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PROPEL 2: Trial Overview

PROPEL

Phase 0 Observational Run-in (n≈250)

Primary objective
- Collect baseline AHV for children being considered for future interventional studies

Primary endpoint
- AHV

Key inclusion criteria
- Age 2.5 to <17 years at study entry
- Clinical ACH diagnosis

Children are followed for a minimum of 6 months to establish baseline AHV

After the observational period, children may be eligible to roll over into an interventional trial

PROPEL2

Phase 2 Dose Escalation (n~50) and PK Substudy (n~24)

Dose Escalation

Primary objective
- Identify safe therapeutic dose for expansion/pivotal study (n=40)

Primary endpoints
- TEAEs + change from baseline in AHV

Key inclusion criteria
- Age 3–11 years
- Clinical and molecular ACH diagnosis

PK Substudy

Primary objective
- Characterize PK profile of infigratinib and its major metabolites (n=18)

Primary endpoints
- PK parameters of infigratinib and major active metabolites (eg, C_{max}, C_{last}, T_{max}, AUC_{24}, $T_{1/2}$, AUC_{inf}, CL/F, Vz/F, and R_{acc})

Key inclusion criteria
- Age 8–11 years
- Clinical and molecular ACH diagnosis

Ascending dose cohorts, opened after safety review

Phase 2 Dose Expansion (n~20)

Primary objective
- Preliminary evidence of efficacy

Primary endpoint
- Change from baseline in AHV

Key inclusion criteria
- Same as dose escalation

- Children who complete 12 months' treatment in PROPEL 2 may enter PROPEL OLE
- 20 new children for expansion
- 12 months at recommended dose

Infigratinib dose selection
After ≥6 months of treatment in all cohorts

- **Dose level 5 (n=10)** 0.25 mg/kg daily
- **Dose level 4 (n=10)** 0.128 mg/kg daily
- **Dose level 3 (n=10)** 0.064 mg/kg daily
- **Dose level 2 (n=10)** 0.032 mg/kg daily
- **Dose level 1 (n=10)** 0.016 mg/kg daily

PROPEL Open Label Extension

Open-label Extension (n=280)

Primary objective
- Safety and tolerability of long-term daily infigratinib
- Efficacy of long-term daily infigratinib

Primary endpoint
- Change over time in height Z-score in relation to ACH and non-ACH growth charts

Participants
- Rolled over from prior studies (n=230) or infigratinib naïve (n=50)
- Age 3 to <18 years at screening

Methodology
- Study duration: >10 years
- Treatment and participation duration will vary
- Participants continue to receive infigratinib until they reach final or near-final height

AHV = annualized height velocity; PK = pharmacokinetics; TEAE = treatment-emergent adverse event.

Savarirayan R, et al. Ther Adv Musculoskelet Dis 2022.

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PROPEL 2: Safety Summary

Cohort 5 (highest dose escalation level of 0.25 mg/kg/day):

- No serious adverse events (SAEs)
- No adverse events (AEs) that required treatment discontinuation
- Most treatment-emergent adverse events (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 ocular adverse events**
- **0 hyperphosphatemia events**
- No accelerated progression of bone age

Cohorts 1-4:

- No new hyperphosphatemia events or SAEs
  - Only 1 previously reported case of mild hyperphosphatemia in cohort 3, which resolved with dose interruption and did not recur after dose reduction as required per protocol

Data on file

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PROPEL 2: Safety Profile

Common AEs across all cohorts

AEs occurring in ≥10% of study participants	Total (%) N = 72
Nasopharyngitis	29 (40.3%)
COVID-19	24 (33.3%)
Headache	24 (33.3%)
Vomiting	22 (30.6%)
Pain in extremity	20 (27.8%)
Ear infection	19 (26.4%)
Pyrexia	18 (25.0%)
Abdominal pain	11 (15.3%)
Cough	11 (15.3%)
Diarrhea	11 (15.3%)
Rhinitis	11 (15.3%)
Viral infection	11 (15.3%)
Upper respiratory tract infection	10 (13.9%)
Abdominal pain upper	8 (11.1%)
Ear pain	8 (11.1%)
Nausea	8 (11.1%)
Oropharyngeal pain	8 (11.1%)
Otitis media	8 (11.1%)

Data on file

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PROPEL 2: Cohort 5 Baseline Characteristics

Female : Male ratio	7 : 5
Mean age at screening (years) <5 5 – <8 8 – <11 ≥11	7.24 8% 58% 25% 8%
Baseline AHV (cm/year) Mean (SD)	3.51 (1.3)

Data on file

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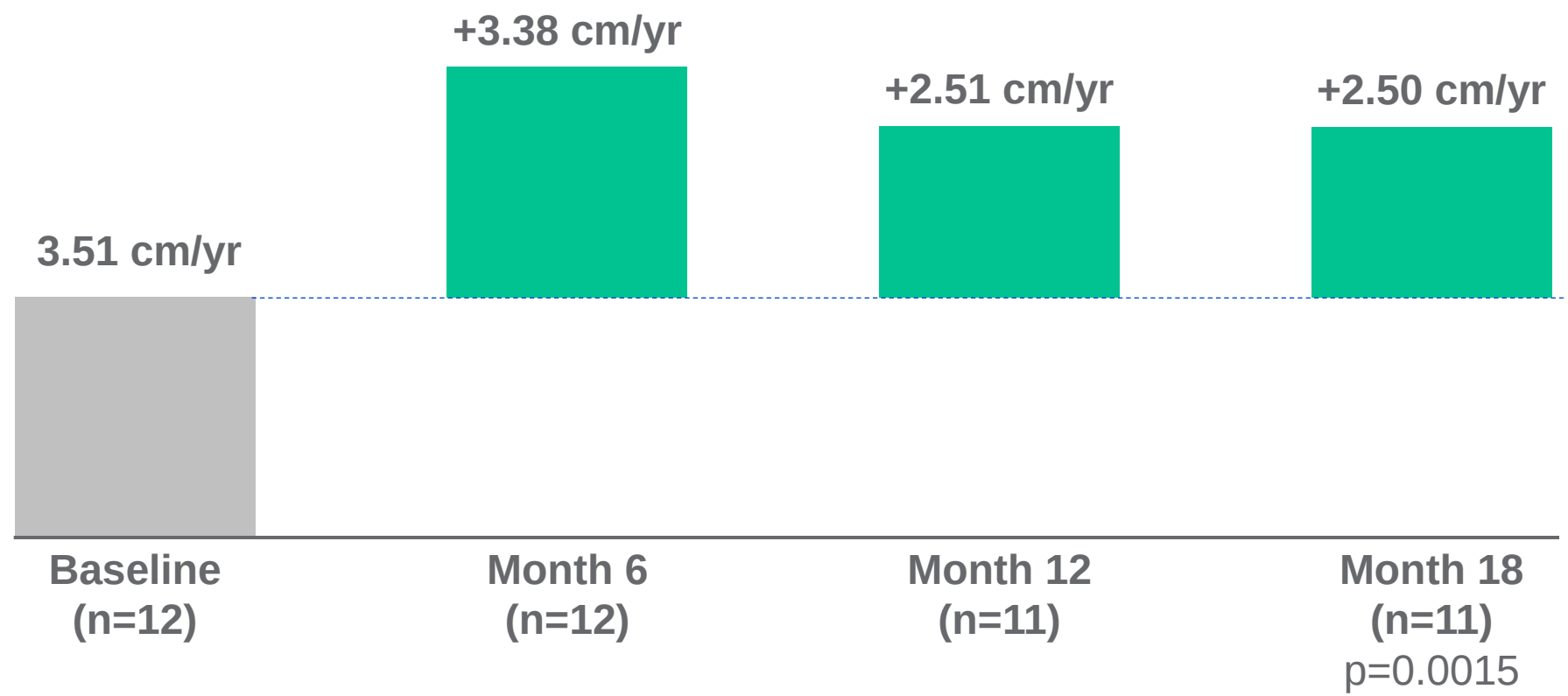
PROPEL 2: Cohort 5 Efficacy Results

Mean change from baseline in annualized height velocity (AHV)



Change from baseline in AHV over time demonstrates durability of treatment effect

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.

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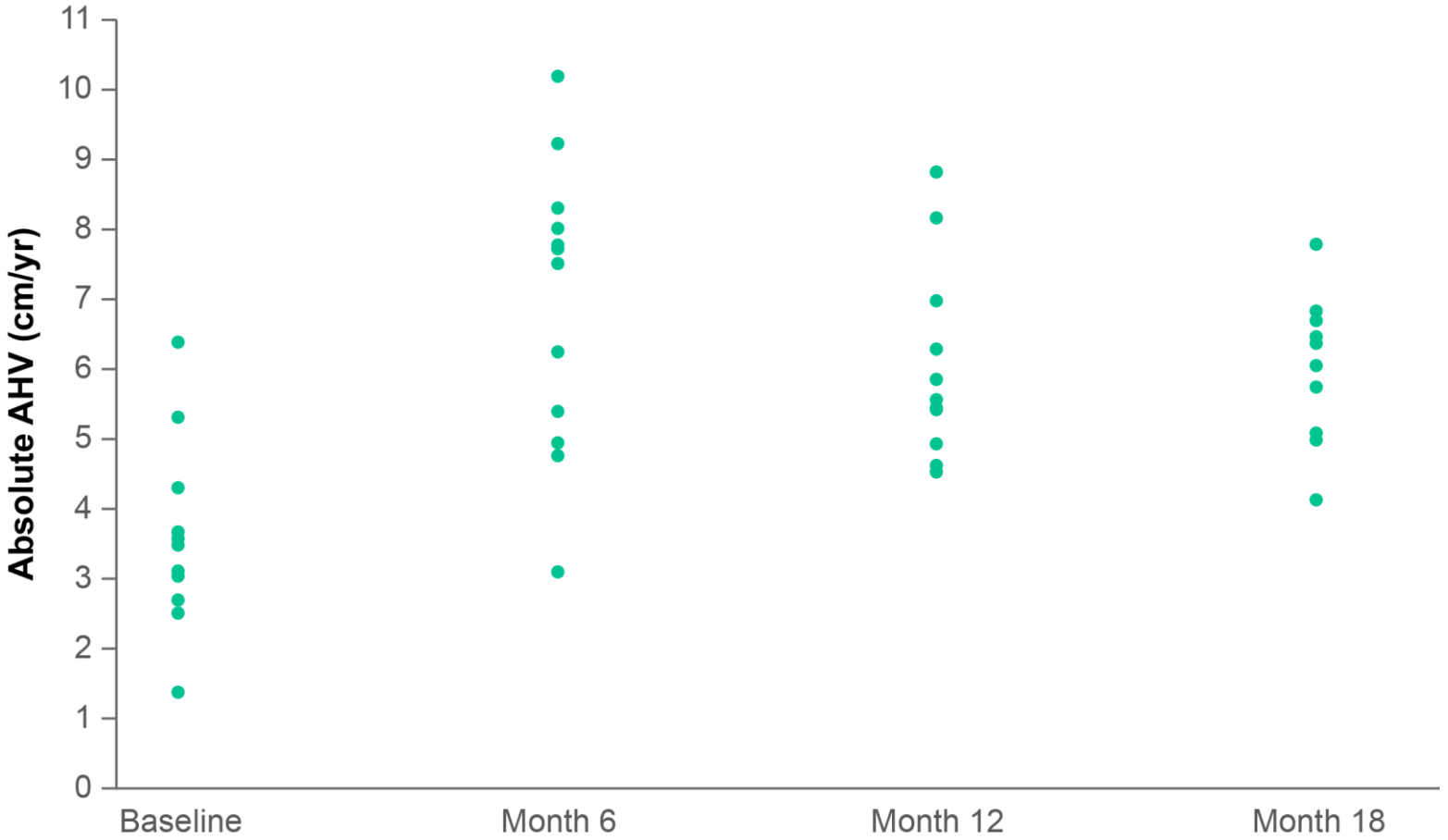
PROPEL 2: Cohort 5 Efficacy Results

Absolute AHV individual values (cm/yr)



91% of participants had an increase in AHV from Baseline to Month 18

73% of participants had an increase of greater than 25% in AHV from Baseline to Month 18

Data on file
AHV: Annualized height velocity

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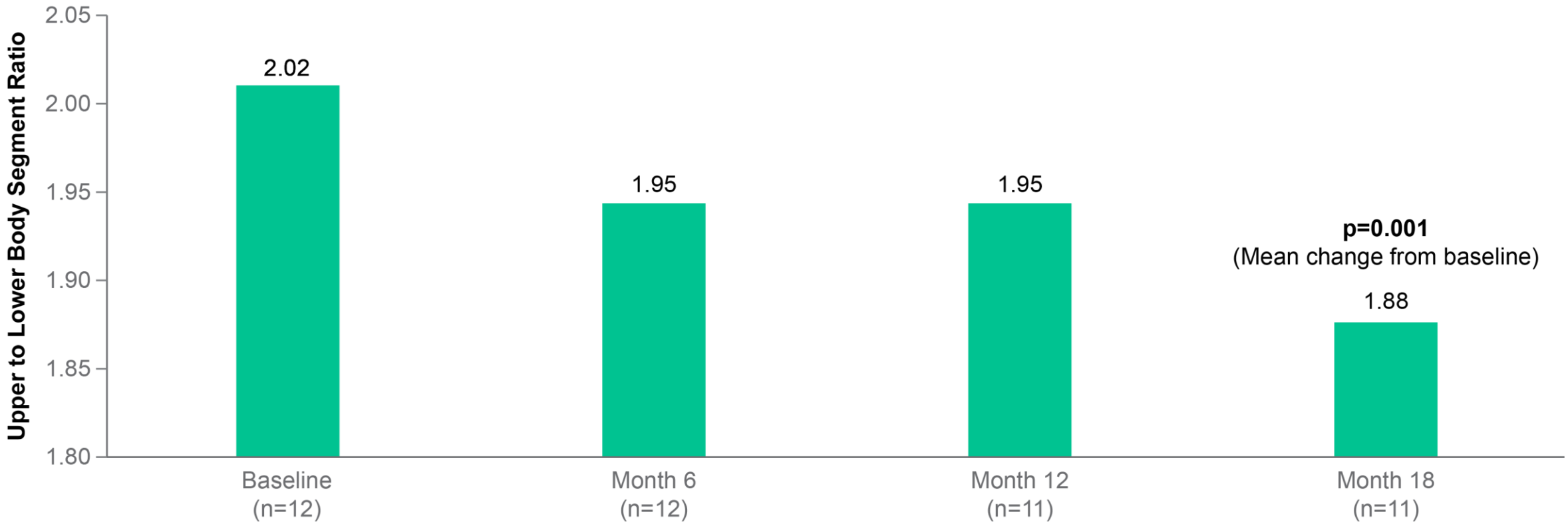
PROPEL 2: Cohort 5 Efficacy

Upper to lower body segment ratio



Infigratinib* showed continued improvement in upper to lower body segment ratio

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. Infigratinib is an investigational agent that is not approved for use by any regulatory authority.

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PROPEL 3: Last patient in expected by end of 2024

PROPEL: Observational run-in → **PROPEL3: Ph3 randomized, double-blinded pivotal trial (n=~110)** → **PROPEL OLE: Open-label extension**

Observational

Children are followed for a minimum of 6 months

2:1

- **0.25 mg/kg/day Infigratinib***
- **Placebo**

52-week duration

0.25 mg/kg/day Infigratinib*

Followed on treatment until final adult height is reached

Key inclusion criteria

- Children 3 – <18 years old with open growth plates

Primary endpoint:

- Change from baseline in annualized height velocity (AHV) at week 52 compared to placebo

Key secondary endpoints:

- Change from baseline in height z-score
- Change from baseline in upper body:lower body segment ratio

Other secondary endpoints:

- Change in physical functioning; HRQoL; cognitive function, participant and caregiver evaluation of treatment benefit (qualitative interview)

Clinicaltrials.gov ID: NCT06164951

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Hypochondroplasia

The ACCEL Program

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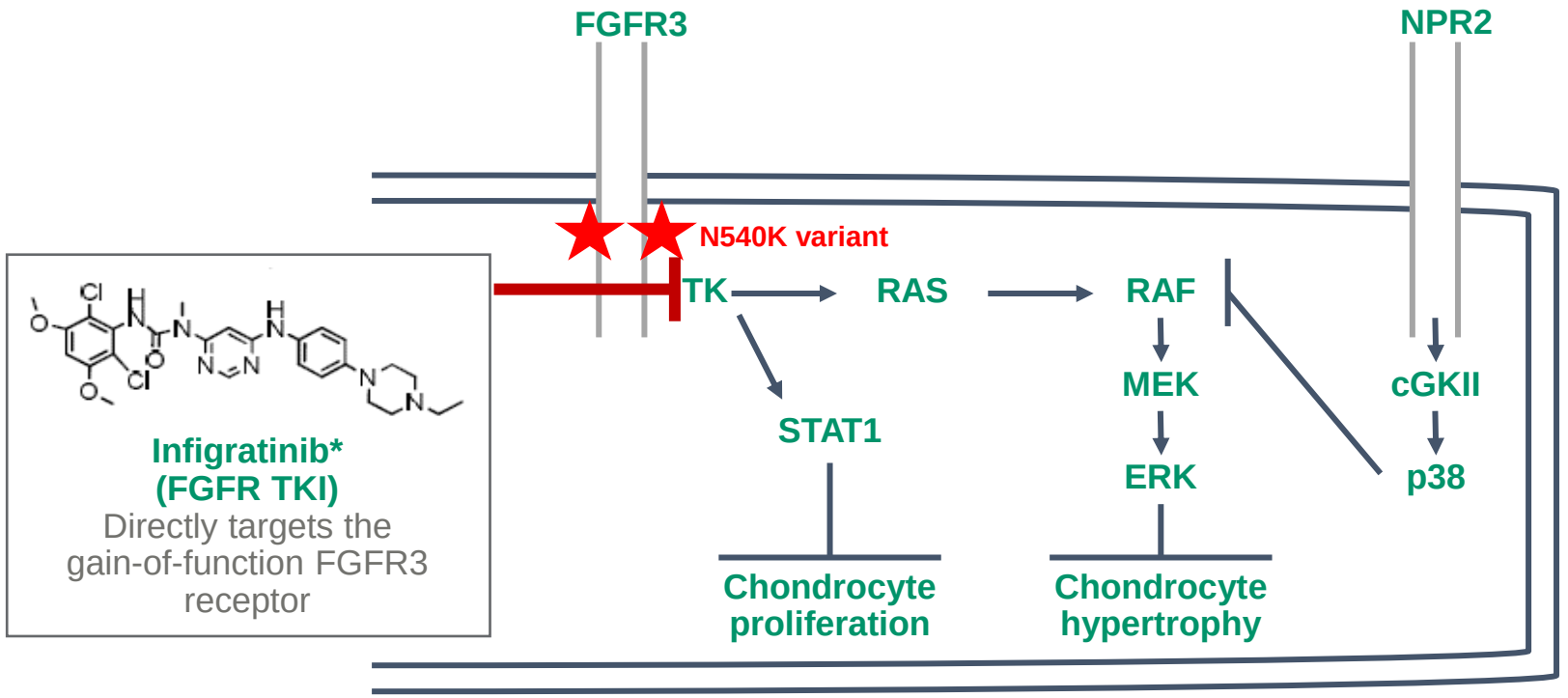
Hypochondroplasia is an FGFR3-related skeletal dysplasia with a need for treatment options



- Disproportionate short stature genetic condition due to heterogeneous FGFR3 pathogenic variants (primarily N540K)[1]
- Similar incidence to achondroplasia[1]
- Medical complications may include epilepsy, temporal lobe abnormalities and cognitive difficulties[1-3]
- To date, no targeted treatments available

Infigratinib* directly targets the underlying cause of hypochondroplasia, FGFR3 overactivity

1. Bober MB et al. 2020 https://www.ncbi.nlm.nih.gov/books/NBK1477/;
2. Linnankivi T et al. Am J Med Genet A. 2012; 3. Philpott CM et al. Pediatr Radiol. 2013.

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The ACCEL Program in Hypochondroplasia

ACCEL

Observational Run-in

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

Primary objective: Baseline height velocity (HV)

Primary endpoint: Annualized height velocity (AHV)

ACCEL 2/3

Phase 2/3 Open-Label Phase followed by a Double-Blinded, Randomized, Placebo-Controlled Study

Phase 2: Open-Label Phase

Children (5 – 11 yr with growth potential) completed ≥6 months in ACCEL

Primary objectives: Preliminary efficacy and safety

Primary endpoint: Change from baseline in AHV and safety endpoints

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

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

Primary objectives: Efficacy and safety of infigratinib

Primary endpoint: Change from baseline in AHV vs. PBO at 52 wks

ACCEL OLE

Open-Label Extension (planned)

Eligible children and adolescents who completed either phase 2/3 can enroll and receive infigratinib* until final height/near final height

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

The ACCEL Program will also evaluate changes in other indicators of growth, body proportions, and HCH-related complications

Clinicaltrials.gov ID: NCT06410976, HCH; hypochondroplasia, pbo; placebo

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Summary

- In the **PROPEL 2 study**, the **selected dose of 0.25mg/kg/day of oral infigratinib* was considered safe and well-tolerated**
- Infigratinib* demonstrated a **durable increase from baseline in AHV for up to 18 months** with a **statistically significant improvement in upper to lower body segment ratio**
- **PROPEL 3 pivotal study** of infigratinib* in achondroplasia is enrolling, on track for **last patient in by end of 2024**
- Expansion of the development of **infigratinib* to hypochondroplasia is initiated**, with the ACCEL clinical trial open and **first participants enrolled**

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

Thank you

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