

Low-dose infigratinib, an oral selective fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, demonstrates activity in preclinical models of FGFR3-related disorders

Elena Muslimova,¹ Benoit Demuynck,² Léa Loisy,² Morgan Paull,¹ Laurence Legeai-Mallet²

¹QED Therapeutics, San Francisco, California, USA; ²Université de Paris Cité, Imagine Institute, Laboratory of Molecular and Physiopathological Bases of Osteochondrodysplasia, INSERM UMR 1163, F-75015, Paris, France

Disclosures

- Elena Muslimova is an employee of QED Therapeutics, affiliate of BridgeBio Pharma, Inc.
- Disclaimer: Infigratinib has not been approved by the FDA or any other regulatory authority for treatment of achondroplasia or hypochondroplasia, as its efficacy and safety have not yet been established

Hypochondroplasia and achondroplasia are common forms of skeletal dysplasias caused by the FGFR-3 gene mutation

Incidence

- Achondroplasia (ACH), an autosomal dominant disorder with an incidence between 1 in 15,000 and 1 in 30,000 live births worldwide^{1,2}
- For hypochondroplasia (HCH), the prevalence is not fully clear, although it is believed to be similar to ACH³

Presentation

- ACH is the most common cause of disproportionate short stature with significant co-morbidities including spinal stenosis, sleep apnea, chronic otitis media with conductive hearing loss, and narrowing of the foramen magnum
- HCH is a mild form of disproportionally short stature characterized by macrocephaly, brachydactyly, mild joint laxity. Complications common to ACH occur less frequently or are not present. Intellectual disability and epilepsy may be more prevalent

Etiology

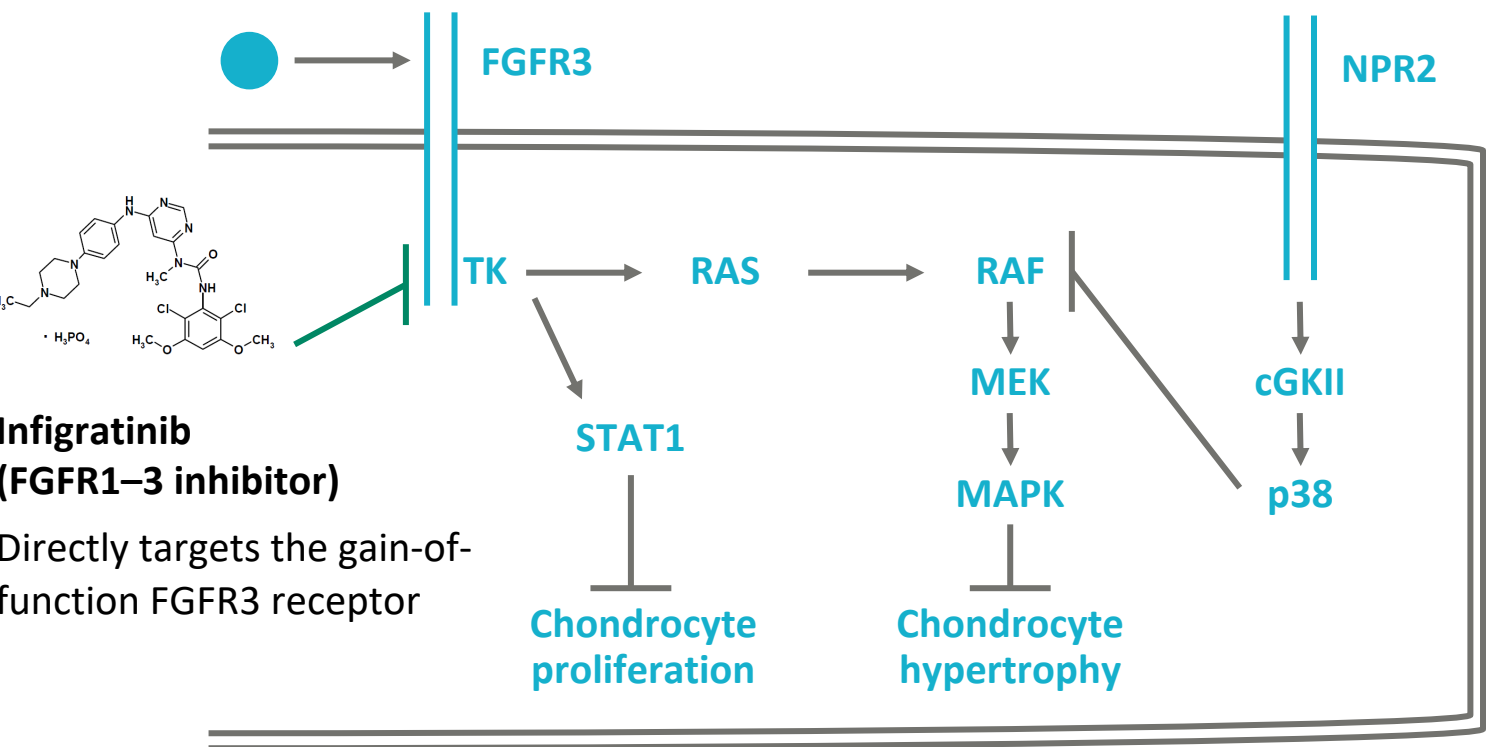
- Approximately 80% of cases of ACH are de-novo gain of function pathogenic variant in the *FGFR3* gene, of which 99% are p.Gly380Arg substitution in the transmembrane domain of *FGFR3*
- 70–80% of cases of HCH are due to pathogenic variants in the intracellular FGFR3-TKI domain, such as the missense mutation p.Asn540Lys³

Therapeutic options

- There is currently one approved treatment option for ACH and none for HCH

Infigratinib directly targets FGFR3 overactivity, the underlying cause of HCH and ACH

Mechanism



SOURCE: Adapted from Ornitz DM, et al.⁴

Infigratinib

- Orally-available, selective, ATP-competitive **FGFR-selective tyrosine kinase inhibitor**
 - Selective for FGFR 1, 2 & 3

Biochemical activity of infigratinib (nM IC ₅₀)	
FGFR1	0.9
FGFR2	1.4
FGFR3	0.9
FGFR4	60
VEGFR2	180

SOURCE: Guagnano D, et al.⁵

ACH (*Fgfr3*^{Y367C/+}) mice were treated daily with infigratinib at different dosing schedules

Mouse model and drug treatment


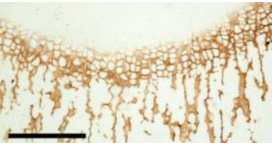
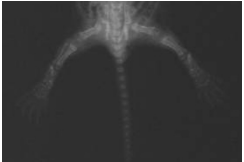
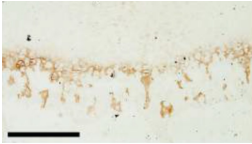
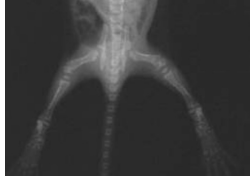
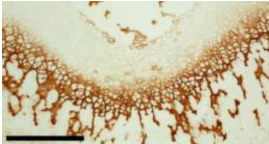
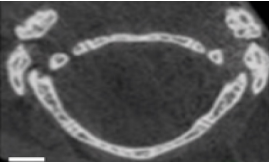

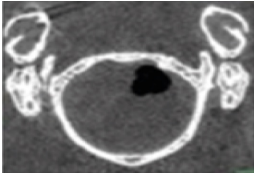
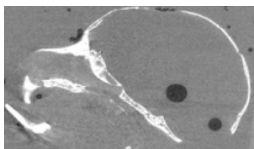
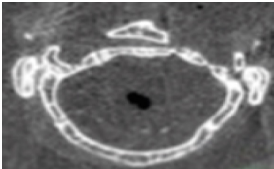
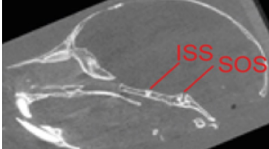
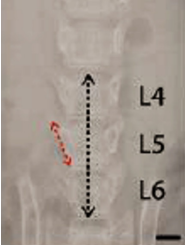
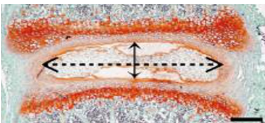
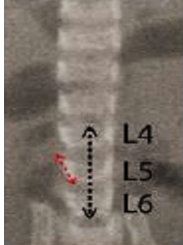
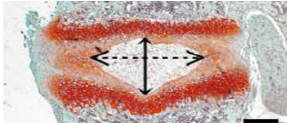
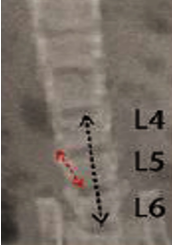
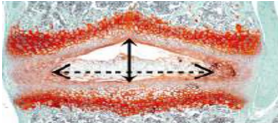
- The *Fgfr3*^{Y367C/+} mice were generated by crossing CMV-Cre mice (C57BL/6J) with mice exhibiting germline transmission of the Y367C mutation corresponding to the human Y373C mutation. The *Fgfr3*^{Y367C/+} mice exhibit all clinical hallmarks of achondroplasia
- Infigratinib was given via subcutaneous administration due to the size and age of the mice, which makes oral gavage impractical
- *Fgfr3*^{Y367C/+} mice were treated once daily at 0.2 mg/kg, 0.5 mg/kg, or 2 mg/kg for 15 days. Treatment started at PND1.

• Observations and assessments

- Clinical observations
- X-ray assessments by Faxitron MX20 Cabinet X-ray system
- Bone length measurements via calipers at necropsy
- Histological and immunohistochemical assessment
- μ CT images of skulls using Skyscan-1172

ACH (Fgfr3^{Y367C/+})

mouse model data 2 mg/day QD

		FGFR3 wild type No treatment	FGFR3 mutant mouse No treatment	FGFR3 mutant mouse Infigratinib treatment	Key results
<p>Mouse model of ACH (Fgfr3^{Y367C/+}) showed a robust long bone response to infigratinib of >20%</p>	<p>X-ray</p> <p>Collagen X immunostaining</p>	 	 	 	<p>21% increase in femur length</p> <p>33% increase in tibia length</p> <p>Impaired differentiation of hypertrophic chondrocytes improved</p>
<p>Infigratinib reduced foramen magnum (FM) defects and increased craniofacial skeleton growth in FGFR3^{Y367C/+} mice</p>	<p>FM area</p> <p>Craniofacial skeleton</p>	 	 	 	<p>17% mean increase in FM area</p> <p>6% mean increase in Anterior-Posterior skull length</p>
<p>The spine of mice treated with infigratinib was longer compared with those without treatment</p>	<p>Vertebral body length</p> <p>Intervertebral disk width</p>	 	 	 	<p>12% mean increase in L4-L6 length</p> <p>73% mean increase in intervertebral disc width</p>

The current study aimed to test infigratinib in a mouse model of HCH (*Fgfr3*^{Asn534Lys/+})

- We hypothesized that the oral, selective FGFR 1–3 tyrosine kinase inhibitor (TKI) infigratinib could improve defective endochondral and membranous ossification and ameliorate the phenotype in a mouse model of HCH (*Fgfr3*^{N534K/+})

Fgfr3^{Asn534Lys/+} mice were treated with infigratinib in intermittent and daily dosing schedules

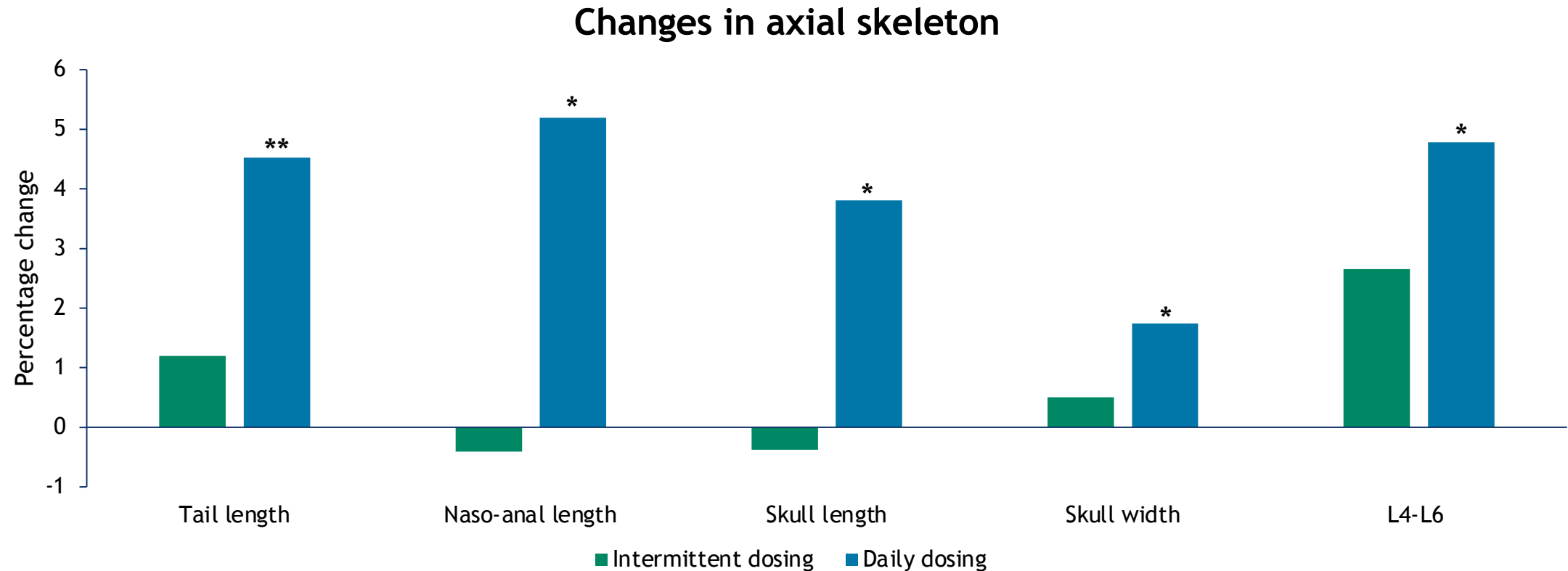
Mouse model and drug treatment

- The *Fgfr*^{N534K/+} mouse model was generated by crossing CMV-Cre mice (C57BL/6J) to mice exhibiting the germline transmission of the *N534K* mutation corresponding to the human *N540K* (HCH) mutation (Loisay et al. in review)
- Infigratinib was given via subcutaneous administration due to the size and age of the mice, which makes oral gavage impractical
- *Fgfr*^{N534K/+} mice were either treated from PND 4 – PND 19 for 15 days (Day 0 = birth) with infigratinib 1 mg/kg sc every 3 days (intermittent dosing), or were treated with infigratinib 1 mg/kg sc qd from PND 3 - PND 24 for 21 days (daily dosing)

Observations and assessments

- Clinical observations
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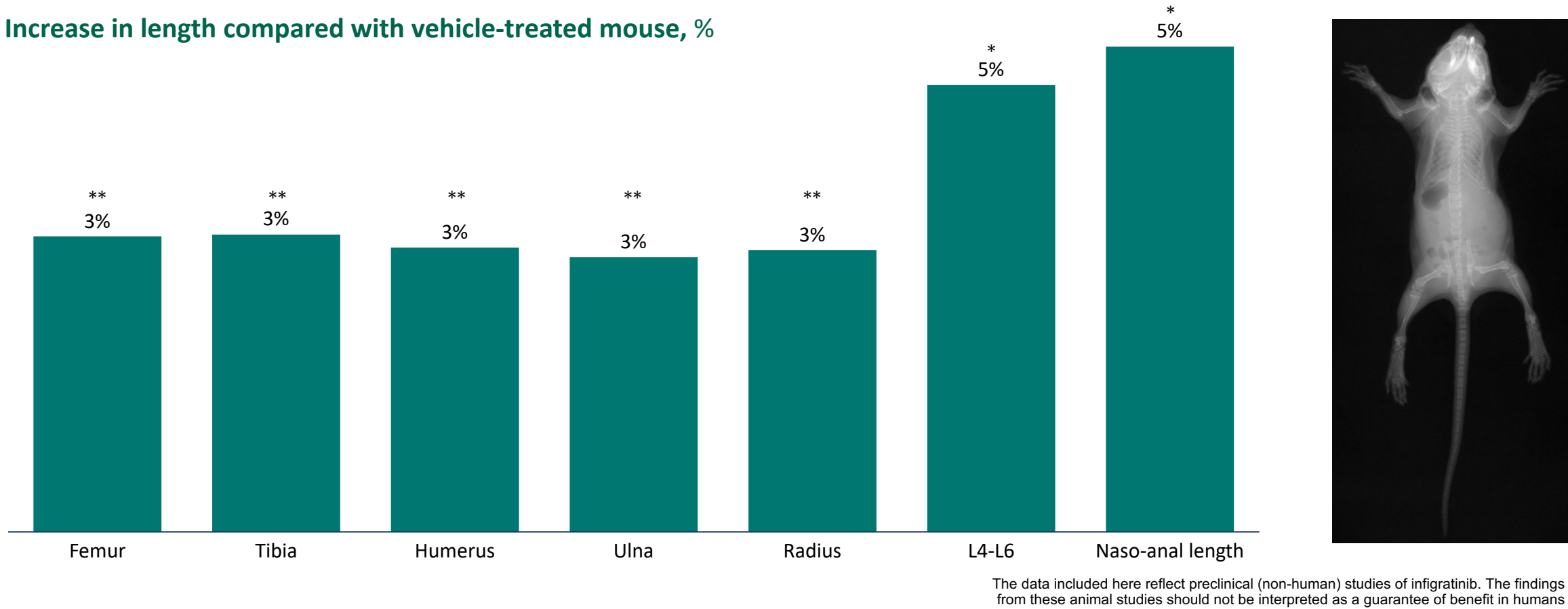
With daily dosing, infigratinib showed statistically significant changes in all measured parameters



Intermittent: infigratinib 1 mg/kg q 3 days; daily: infigratinib 1 mg/kg daily in *Fgfr3*^{N534K/+} mice

*p<0.05; **p<0.01vs vehicle-treated animals

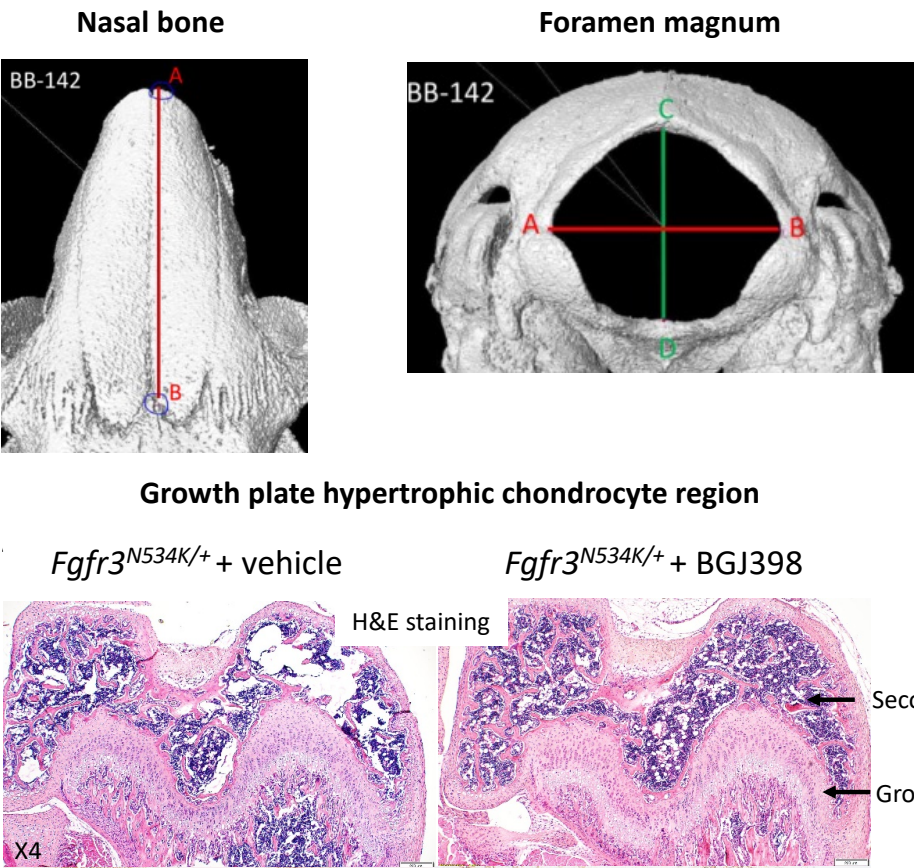
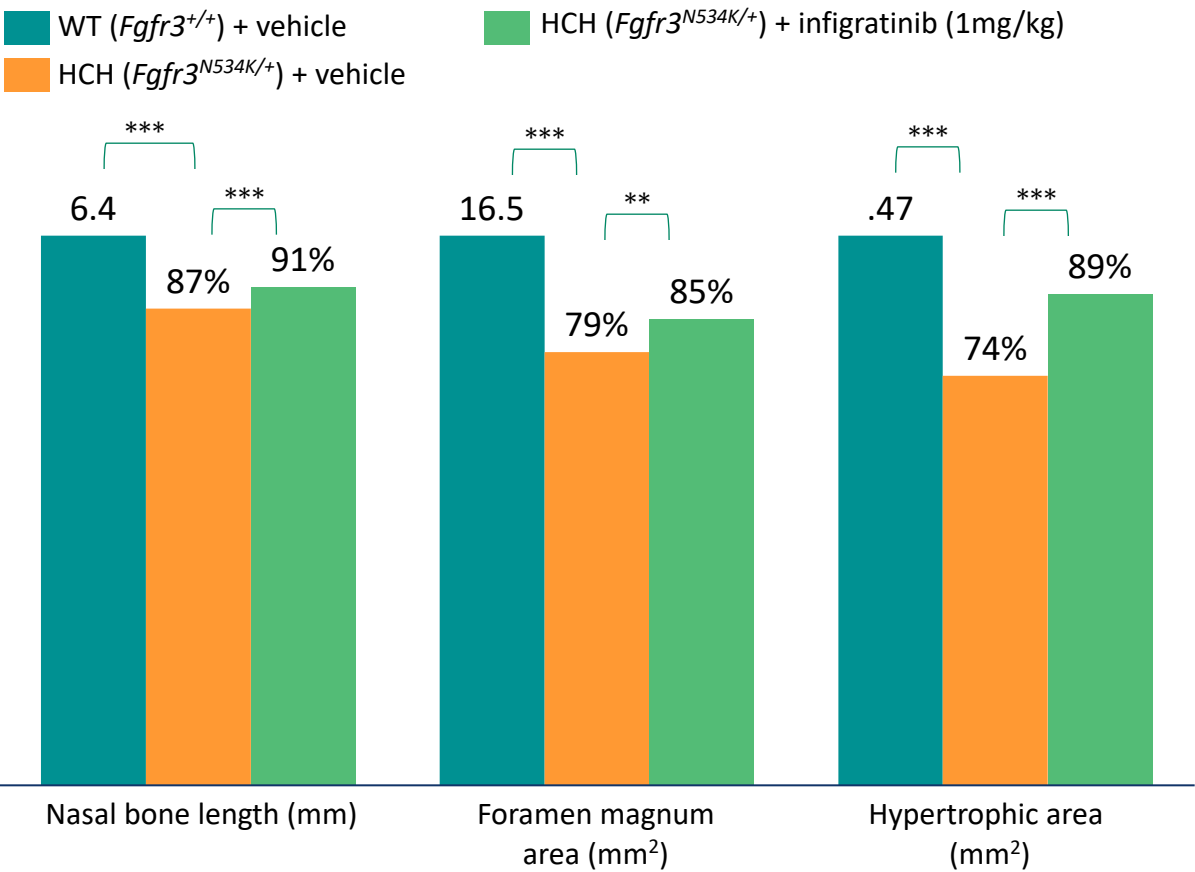
Moderate but statistically significant skeletal growth was seen in HCH mice treated with daily 1 mg/kg infigratinib for 3 weeks



Changes are substantial in context of a milder starting phenotype, especially compared with ACH

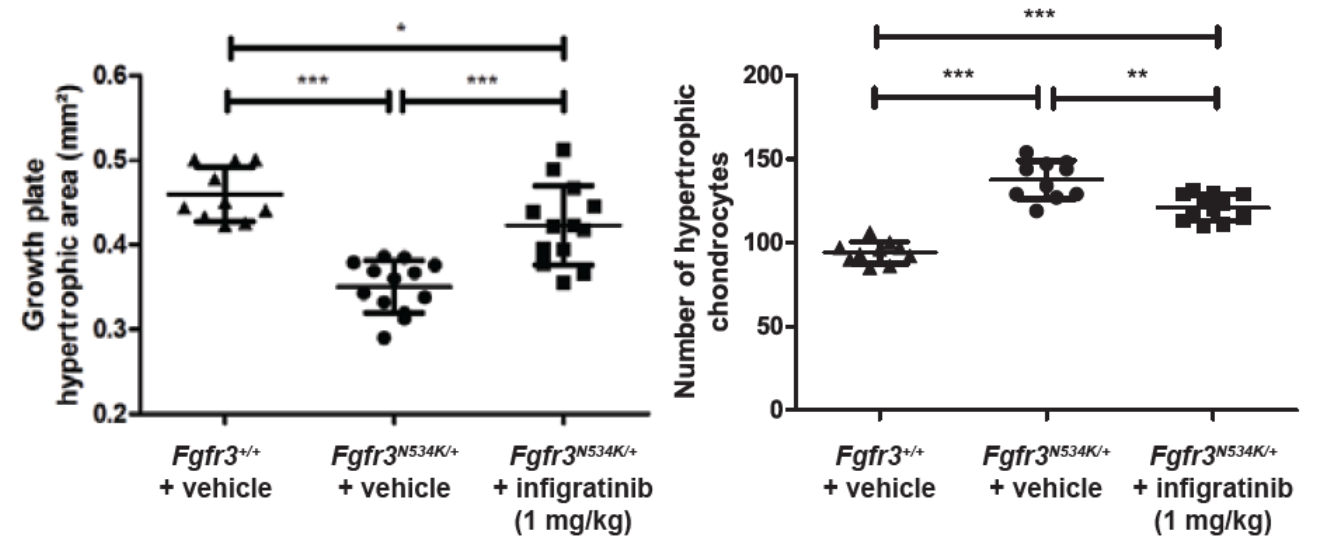
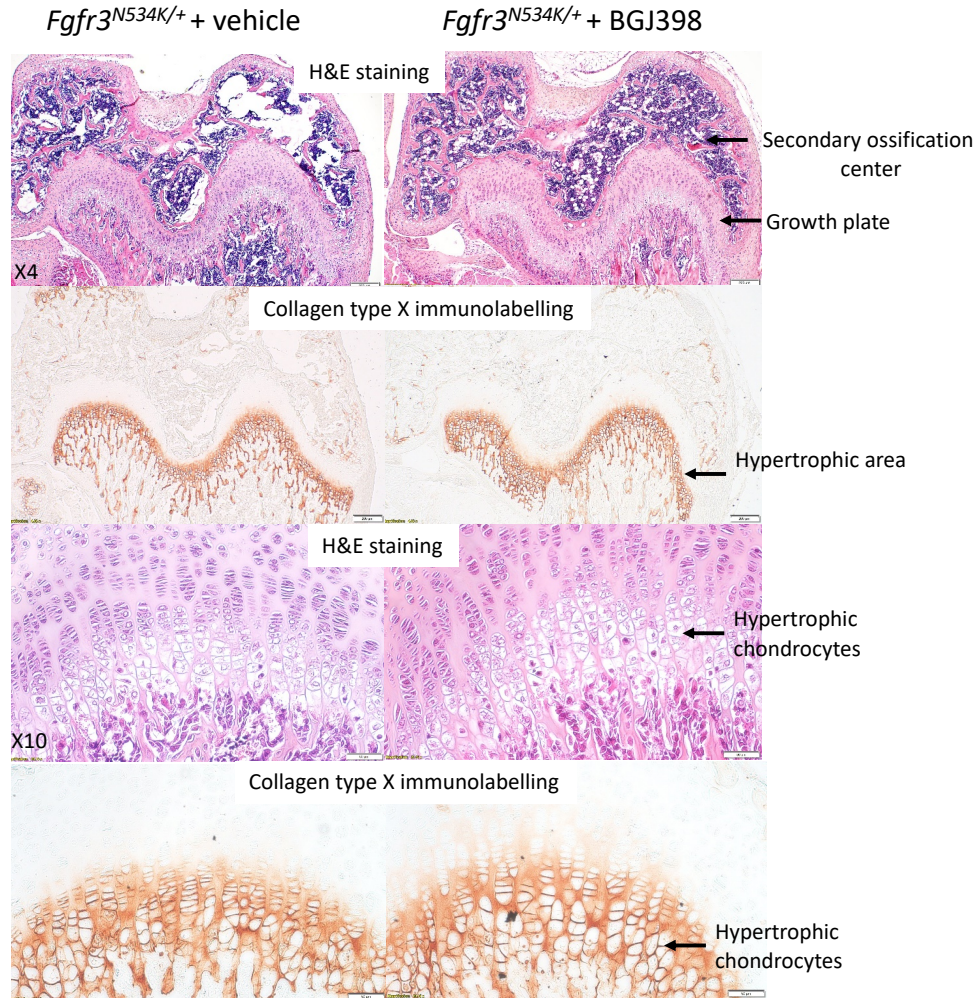
Skull, foramen magnum, and growth plate histology data all paint a consistent picture of improvement after infigratinib treatment

Measurements in WT and mutant mice (mm) and percentage (%) of WT in treated FGFR3^{N534K/+} mice



Infigratinib showed statistically significant changes in all measured parameters and improved the hypertrophic zone area in the growth plate

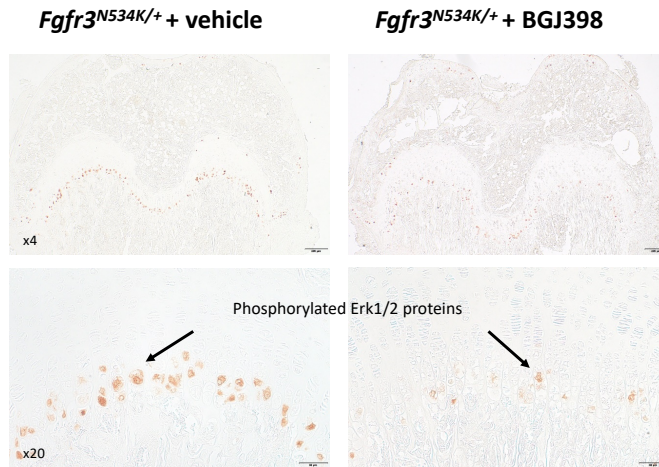
In addition to the effect on bone parameters, daily infigratinib improved cartilage growth plate



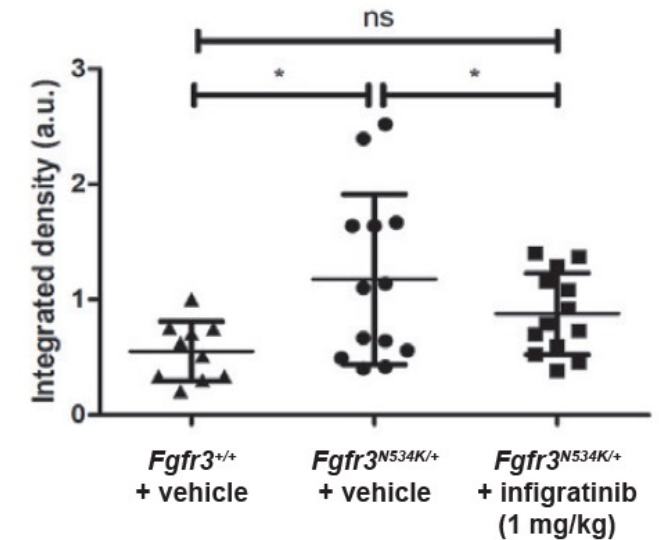
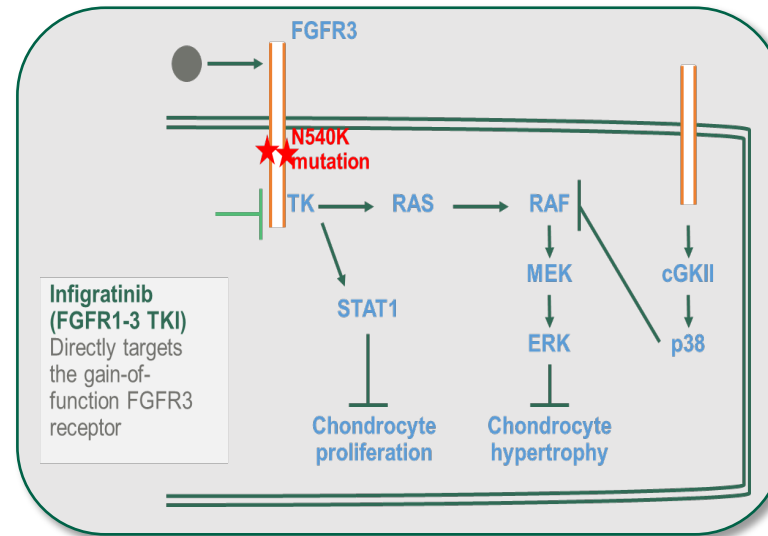
- Infigratinib treatment improved hypertrophic area of the growth plate (collagen type X immunolabelling)
- Treatment modified hypertrophic chondrocyte area and decreased number of hypertrophic chondrocytes compared with untreated mice

Daily infigratinib also impacted MAPK signaling, downstream of FGFR3

ERK1/2 phosphorylation



Dosing: infigratinib 1 mg/kg daily



ERK1/2 phosphorylation (MAP kinase pathway) in femoral growth plate was reduced by infigratinib treatment
The expression of phosphorylated ERK1/2 in treated mice is similar to that seen in the wild-type growth plate

Results support investigating infigratinib as potential therapeutic option in children with HCH

- Low-dose treatment with infigratinib in this HCH mouse model ameliorated the clinical hallmarks of human pathology and significantly lengthened the axial skeleton, the appendicular skeleton, and improved foramen magnum length
- These results demonstrate that daily infigratinib 1 mg/kg is able to counteract the constitutive activation of FGFR3 resulting from the heterozygous *N540K* mutation localized in the kinase domain of FGFR3
- These results, although of a lower magnitude, are in line with those previously reported in a mouse model of ACH (*Fgfr3*^{Y367C/+}), and provide a rationale for targeting FGFR3 with a TKI such as infigratinib for the treatment of children with HCH
- Development of infigratinib in ACH is currently ongoing
- QED has initiated plans to develop infigratinib in HCH

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- And most importantly, thank you to the people and families with ACH, HCH and other conditions who drive our research and the search for treatment options

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THANK YOU!

Contact:

Elena Muslimova, MD, PhD

elena.muslimova@bridgebio.com