Prenatal treatment with dabogratinib increases both long bones and size of the foramen magnum and delays premature fusion of synchondroses in a mouse model mimicking achondroplasia

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INTRODUCTION

Achondroplasia

Achondroplasia (ACH) is the most common form of heritable skeletal dysplasia, affecting approximately 250,000 people worldwide.[1,2]

ACH is caused by a gain of function variant in the FGFR3 gene, most commonly G380R in >99% of cases.[1-4]

Aberrant FGFR3 signaling inhibits chondrocyte proliferation and differentiation, resulting in impaired endochondral ossification and abnormal skeletal development.[2,3]

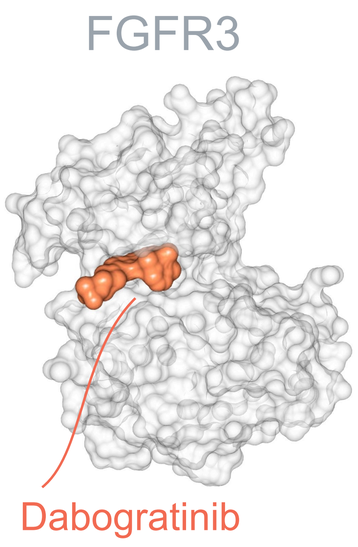
Individuals with ACH can experience lifelong morbidity, with early complications including foramen magnum stenosis, recurrent otitis media, sleep-disordered breathing, and ongoing impact across childhood and adulthood.[1,3,5,6]

Critical foramen magnum stenosis requires surgical decompression in 20% of infants with ACH and in severe cases can result in sudden death.[7,8]

Prenatal MRIs have detected foramen magnum stenosis *in utero* in several case reports.[9]

Approved CNP analogs indirectly modulate the FGFR3 pathway,[2,10,11] while pan-FGFR inhibition has demonstrated encouraging safety and efficacy, supporting direct FGFR inhibition.[12]

There is an unmet medical need for non-surgical therapies to address foramen magnum stenosis in infants.



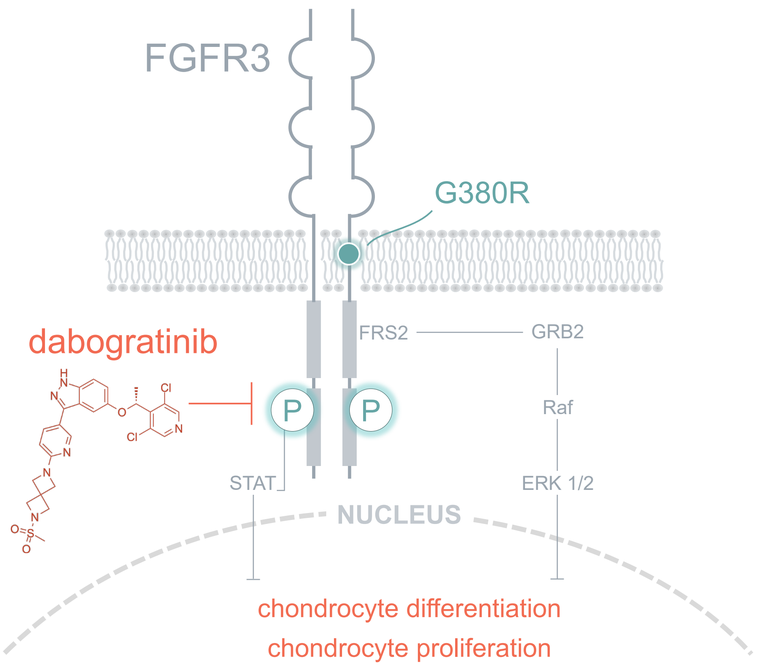
Dabogratinib

Dabogratinib is an oral, highly selective FGFR3 inhibitor designed to directly target the underlying driver of ACH while minimizing off-target effects.[13]

By avoiding toxicities associated with inhibition of FGFR1, FGFR2, and FGFR4, dabogratinib may provide greater efficacy with a larger therapeutic window than non-isoform selective FGFR inhibitors.[14]

Dabogratinib was previously evaluated in the *Fgfr3*$^{Y367C/+}$ mouse model mimicking the phenotype of ACH[15], in which postnatal treatment from birth resulted in significant increases in long bone lengths and cranial growth.[16]

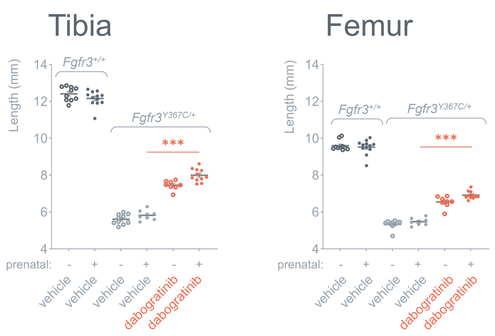
Dabogratinib is currently being evaluated in a Phase 2 trial in children ages 3-10 with ACH, BEACH301 (NCT06842355).

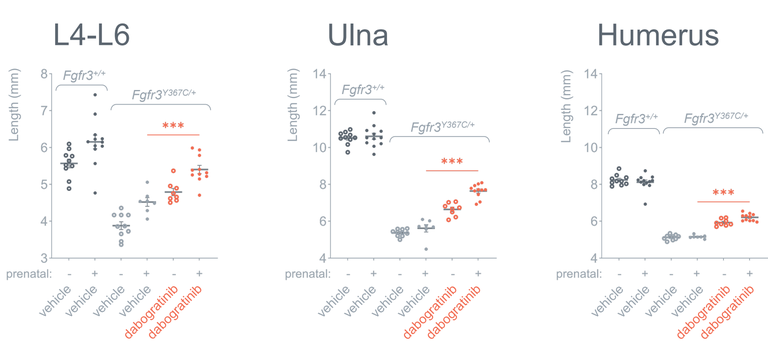


Prenatal treatment increased long bone length

On the final day of treatment, long bones and L4-L6 lumbar vertebrae were measured by caliper. All lengths increased significantly.

Mann-Whitney U test vs. vehicle
*** p < 0.001



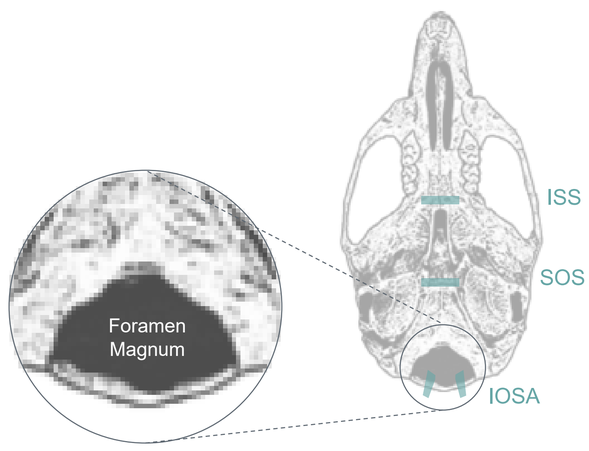


RESULTS

Prenatal plus postnatal treatment with dabogratinib increased the size of the foramen magnum

In the current study, pregnant mice were treated with 2.7 mg/kg SC dabogratinib from embryonic day 14.5 (E14.5) through birth, then neonatal *Fgfr3*$^{Y367C/+}$ mice were treated with either vehicle or 1.2 mg/kg SC dabogratinib from 1 day after birth for 15 days (right).

On the final day of treatment, skulls were collected for µCT imaging of the foramen magnum (bottom left). The area of the foramen magnum was quantified from the µCT images (bottom right).



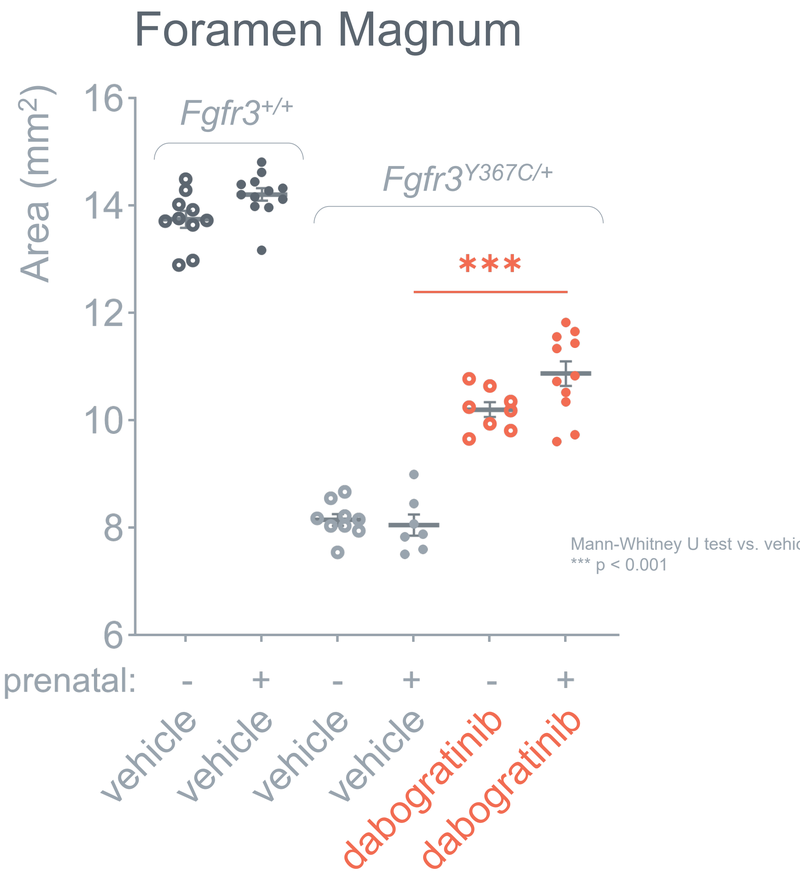
Fgfr3$^{Y367C/+}$ mice treated with vehicle have premature fusion of the IOSA, while postnatal dabogratinib treatment resulted in partially open IOSA (left) and increased the area of the foramen magnum by 25.2% (below).[16]

Prenatal plus postnatal treatment with dabogratinib further delayed the premature fusion of the synchondroses, resulting in open IOSA (left) and a 35.1% increase in the area of the foramen magnum (below).

IOSA: intraoccipital synchondroses anterior

ISS: intersphenoidal synchondrosis

SOS: spheno-occipital synchondrosis



Prenatal plus postnatal treatment delayed the premature fusion of synchondroses

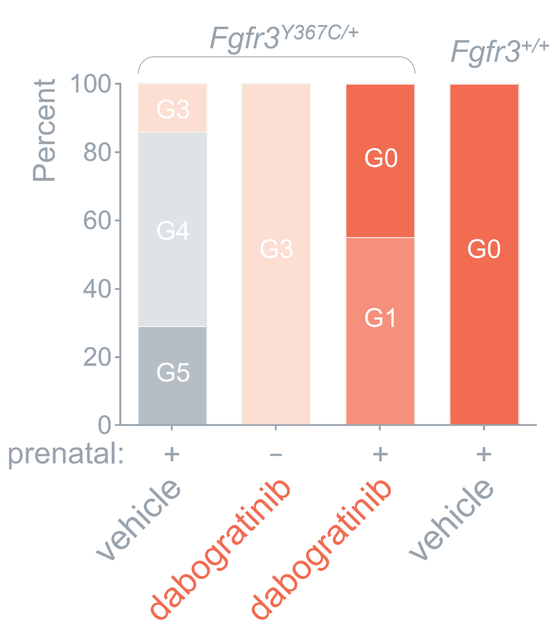
The level of fusion of the IOSA, SOS and ISS were graded using the µCT images. 0 denotes an open and 5 denotes a closed synchondrosis.

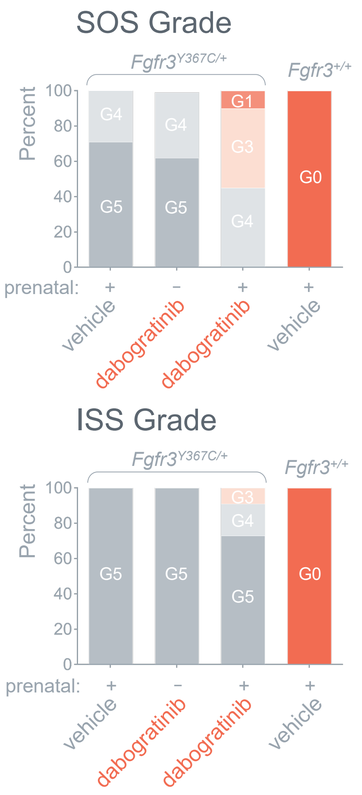
Fusion Grades

5	Complete (100%)
4	Near-complete (75-100%)
3	Advanced (50-75%)
2	Partial (25-50%)
1	Early-stage (0-25%)
0	None (open synchondroses) (0%)

Fgfr3$^{Y367C/+}$ mice have premature fusion of the IOSA which was delayed with dabogratinib treatment. Prenatal plus postnatal treatment had a greater effect than postnatal treatment alone.

As with the IOSA, both the SOS and ISS were prematurely fused at P16 in *Fgfr3*$^{Y367C/+}$ mice. Postnatal treatment did not significantly affect premature fusion of the SOS and ISS, while prenatal plus postnatal treatment had a partial effect on delaying the premature fusion of the SOS and ISS.





CLINICAL TRIAL

BEACH/301

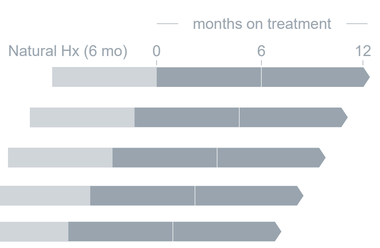
Sentinel Safety Cohort
ACH age 5-10
No run-in
Anticipate n=~25 total enrollment

	DOSE (mg/kg)
	0.625
✓	0.50
✓	0.375
✓	0.25
✓	0.125

**Dose decisions based on 6 participants. Additional participants may be assigned at discretion of Sponsor.

Cohorts 1 and 2*

N=**	DOSE (mg/kg)
6	0.625
6	0.50
6	0.375
6	0.25
6	0.125



*Cohort 1 (6-mo run-in)
Treatment naïve;
ACH age 3-10

*Cohort 2 (6-mo run-in)
Received prior growth-accelerating therapy; ACH age 3-10

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