TYRA-300 promotes bone growth in two mouse models of FGFR3-related skeletal dysplasia

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Background

Achondroplasia (ACH) and hypochondroplasia (HCH), the two most common types of dwarfism, are each caused by gain-of-function alterations in ***FGFR3***[1,2,3].

Infants with ACH can face serious complications related to critical foramen magnum stenosis. Children and adults with ACH may face other challenges including chronic pain, multiple surgeries, and functional limitations[1,4].

The skeletal features and functional limitations seen in HCH are similar to ACH but tend to be milder[3].

FGFR3 is expressed in growth plate chondrocytes and osteoblasts where it negatively regulates endochondral bone growth[2].

Alterations in FGFR3 increase signaling, which impairs chondrogenesis in the growth plate, inhibiting long bone growth. A G380R variant causes ~99% of ACH, and an N540K variant causes ~70–80% of HCH[1,2,3,5,6,7].

TREATMENT

There is currently only one approved treatment option for ACH and no approved options for HCH.

Vosoritide, a C-natriuretic peptide analogue acting exclusively on the MAP kinase pathway, is a daily injection that was approved in ACH to increase annual growth velocity in children with open growth plates.

TYRA-300 is an investigational, oral, highly selective FGFR3 inhibitor[8].

Increased FGFR3 specificity may decrease the risk of toxicities associated with inhibition of FGFR1, 2, and 4. This specificity may provide a more favorable therapeutic window than pan-FGFR inhibitors.

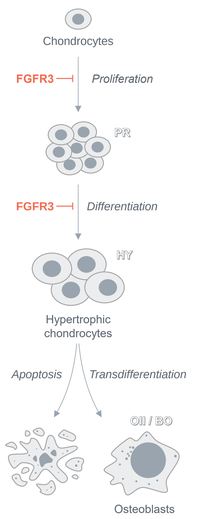
TYRA-300's planned clinical development includes three Phase 2 clinical trials:

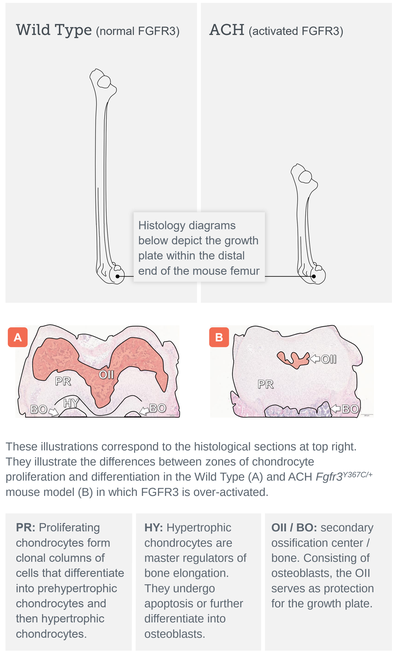
- SURF302[9] for intermediate risk non-muscle invasive bladder cancer,
- BEACH301[10] for pediatric ACH, and
- SURF301[11] for metastatic urothelial cancer, for which TYRA-300 demonstrated initial clinical proof-of-concept results[12].

To assess the potential of TYRA-300 pre-clinically, we evaluated it in an ***Fgfr3***$^{Y367C/+}$ mouse model mimicking ACH[13] and the ***Fgfr3***$^{N534KI/+}$ mouse model of HCH[14,15].

FGFR3 in Bone Growth

FGFR3 plays an inhibitory role in the regulation of chondrocyte proliferation and differentiation.





These illustrations correspond to the histological sections at top right. They illustrate the differences between zones of chondrocyte proliferation and differentiation in the Wild Type (A) and ACH ***Fgfr3***$^{Y367C/+}$ mouse model (B) in which FGFR3 is over-activated.

PR: Proliferating chondrocytes form clonal columns of cells that differentiate into prehypertrophic chondrocytes and then hypertrophic chondrocytes.

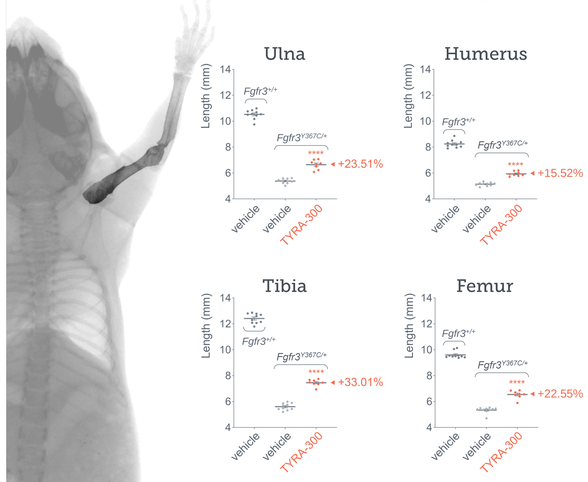
HY: Hypertrophic chondrocytes are master regulators of bone elongation. They undergo apoptosis or further differentiate into osteoblasts.

OII / BO: secondary ossification center / bone. Consisting of osteoblasts, the OII serves as protection for the growth plate.

Results

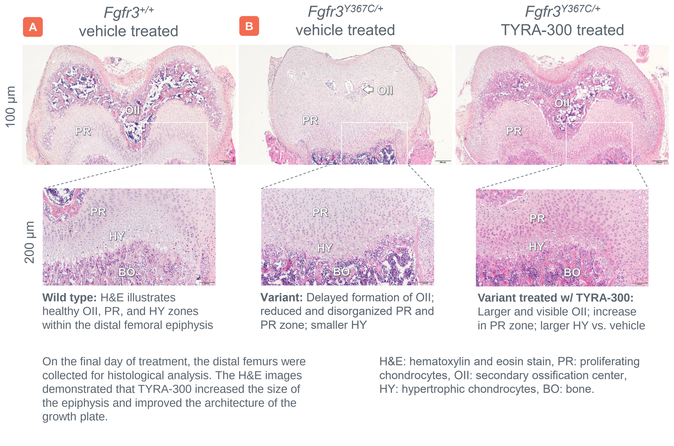
ACHONDROPLASIA

TYRA-300 increased bone growth and improved growth plate architecture in the ***Fgfr3***$^{Y367C/+}$ mouse model



Fgfr3$^{Y367C/+}$ mice were treated with 1.2 mg/kg (SQ) TYRA-300 from day 1 to day 16 after birth, which resulted in statistically significant increases in long bone length.

Kruskal-Wallis test vs. vehicle
**** p < 0.0001



Wild type: H&E illustrates healthy OII, PR, and HY zones within the distal femoral epiphysis

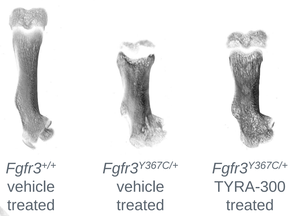
Variant: Delayed formation of OII; reduced and disorganized PR and PR zone; smaller HY

Variant treated w/ TYRA-300: Larger and visible OII; increase in PR zone; larger HY vs. vehicle

On the final day of treatment, the distal femurs were collected for histological analysis. The H&E images demonstrated that TYRA-300 increased the size of the epiphysis and improved the architecture of the growth plate.

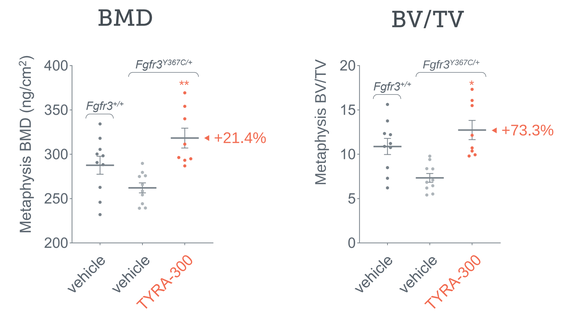
H&E: hematoxylin and eosin stain, PR: proliferating chondrocytes, OII: secondary ossification center, HY: hypertrophic chondrocytes, BO: bone.

TYRA-300 improved bone quality in ***Fgfr3***$^{Y367C/+}$ mice

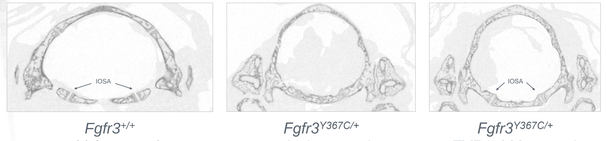


µCT imaging was also performed on the remaining femur, which was used to calculate bone mineral density (BMD) and bone volume to tissue volume (BV/TV) within the metaphysis. TYRA-300 increased BMD and BV/TV, suggesting improved bone quality.

Kruskal-Wallis test vs. vehicle
** p < 0.01
* p < 0.05



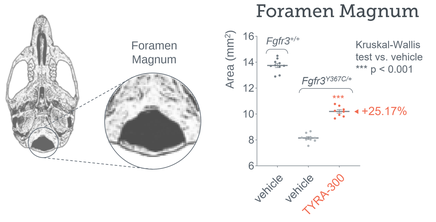
TYRA-300 increased the size of the foramen magnum



On the final day of treatment, skulls were collected for µCT imaging of the foramen magnum (above). ***Fgfr3***$^{Y367C/+}$ mice have premature fusion of the IOSA, while TYRA-300 treatment resulted in partially open IOSA.

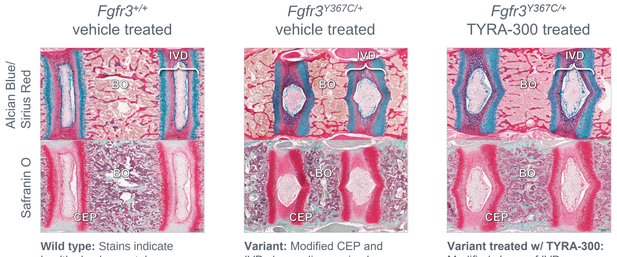
The area of the foramen magnum was quantified from the µCT images, demonstrating that TYRA-300 increased its size (right).

IOSA: interoccipital synchondroses anterior



Kruskal-Wallis test vs. vehicle
*** p < 0.001

TYRA-300 improved the architecture of the lumbar vertebrae



Wild type: Stains indicate healthy lumbar vertebrae; Alcian Blue (blue = glycosaminoglycan), Sirius Red (red = collagen in bone), Safranin O (red = cartilage)

Variant: Modified CEP and IVD shape; disorganized architecture of nucleus pulposus and annulus fibrosus and reduced size of bone trabeculae vs. WT

Variant treated w/ TYRA-300: Modified shape of IVD; architecture of nucleus pulposus, annulus fibrosus, and bone trabeculae is improved relative to vehicle

Histological images of lumbar vertebrae. IVD, intervertebral disc, BO: bone, CEP: cartilage endplate

Foramen magnum stenosis and spinal stenosis are frequent medical complications experienced by those living with ACH[1,4]. Together, these preclinical data indicate that TYRA-300 improved the size and shape of the foramen magnum, increased the lumbar vertebrae length, and improved the shape of the IVDs in ***Fgfr3***$^{Y367C/+}$ mice.

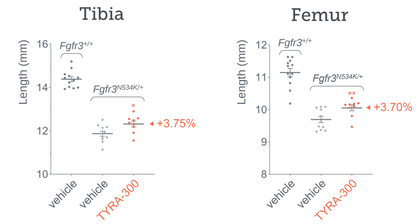
Results

HYPOCHONDROPLASIA

TYRA-300 improved bone growth in ***Fgfr3***$^{N534K/+}$ mouse model

Fgfr3$^{N534K/+}$ mice were treated with 1.8 mg/kg (SQ) TYRA-300 from day 3 to day 24 after birth, which resulted in statistically significant increases in long bone length.

Kruskal-Wallis test vs. vehicle
** p < 0.01
* p < 0.05

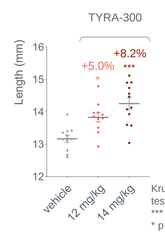


WILD TYPE

Inhibition of wild-type FGFR3 increases bone growth

PRECLINICAL

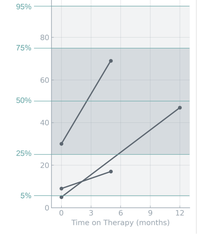
Wild-type mice were treated with increasing doses of TYRA-300 from 4 to 8 weeks of age. Dose-dependent increases in long bone length were observed after treatment.



Kruskal-Wallis test vs. vehicle
*** p < 0.001
* p < 0.05

CLINICAL

Oncology doses of pan-FGFR inhibitors resulted in hyper-typical growth in pediatric cancer patients[16].



HEIGHT PERCENTILES
Pediatric oncology patients with physiologic growth plate signaling treated with Pan-FGFR inhibitors[16]

Next Steps

BEACH301

Ph2 study for children with achondroplasia is open for enrollment

Sentinel Safety Cohort
ACH age 5-10
No run-in

N=	DOSE (mg/kg)
3	0.50
3	0.375
3	0.25
3	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	0.50
6	0.375
6	0.25
6	0.125

months on treatment
Natural Hx (6 mo) 0 6 12

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

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

References

1. Pauli et al., Orphanet J Rare Dis, 2019
2. Ornitz and Legeai-Mallet, Dev Dyn, 2017
3. Bober et al., GeneReviews, 1999
4. Hecht et al., Am J Hum Genet, 1987
5. Rousseau et al., J Med Genet, 1996
6. Bellus et al., Ann N Y Acad Sci, 1996
7. Xue et al., Mol Genet Genomic Med, 2014
8. Hudkins et al., J Med Chem, 2024
9. NCT06995677
10. NCT06842355
11. NCT05544552
12. Tran et al., EORTC-NCI-AACR Symposium, 2024
13. Pannier et al., Biochem Biophys Acta, 2009
14. Loisay et al., JCI Insight, 2023
15. Starrett et al., JCI Insight, 2025
16. Sait et al., Pediatr Blood Cancer, 2023

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