TYRA-300 demonstrates significant increases in bone length and foramen magnum area in a mouse model of FGFR3-related skeletal dysplasia

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BACKGROUND

Achondroplasia (ACH) is the most common human skeletal dysplasia and cause of disproportionate short stature, affecting ~1 in 25,000 births. Infants with ACH can face serious complications related to critical foramen magnum stenosis leading to cervicomedullary compression and requiring surgical intervention[1,2]. A specific mutation in FGFR3, G380R, causes approximately 99% of pediatric ACH[1,3,4,5]. FGFR3 is expressed in growth plate chondrocytes and osteoblasts where it functions to regulate endochondral bone formation[5]. The G380R mutation, as well as other mutations, results in increased FGFR3 activity, which impairs chondrogenesis in the growth plate, disturbing long bone elongation[5].

TREATMENT

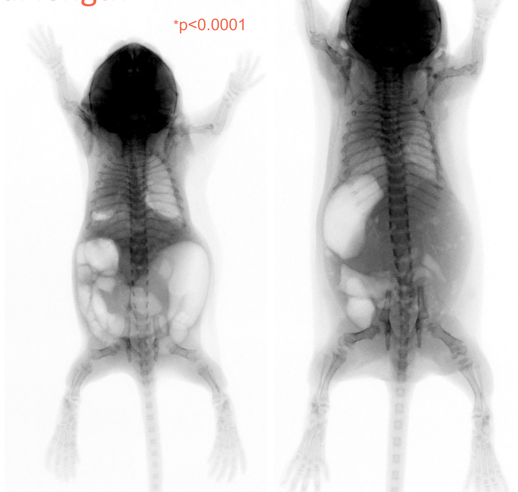
There is currently only one approved treatment option for ACH. Vosoritide, a C-naturetic peptide analogue, acting exclusively on the MAP kinase pathway, was approved in 2021 as a daily injection to increase annual growth velocity in children with open growth plates. To provide an orally bioavailable therapy that acts specifically on the bone development pathway, infigratinib, a pan-FGFR1/2/3 inhibitor, was investigated in an *Fgfr3*$^{Y367C/+}$ mouse model[6,7] and is currently in clinical trials for ACH. TYRA-300 is an oral, highly selective FGFR3 inhibitor currently undergoing a Phase1 clinical trial, SURF301 (Study in Untreated and Resistant FGFR3+ Advanced Solid Tumors), which may provide a favorable therapeutic window with respect to anticipated toxicities compared to pan-FGFR inhibitors based on its specificity profile. To assess the potential of TYRA-300 pre-clinically, we used a mouse model recapitulating most of the hallmarks of ACH. This *Fgfr3*$^{Y367C/+}$ driven mouse model is characterized by a disproportionate short stature and a growth deficit affecting both endochondral and membranous ossification[6,7,8,9,10].

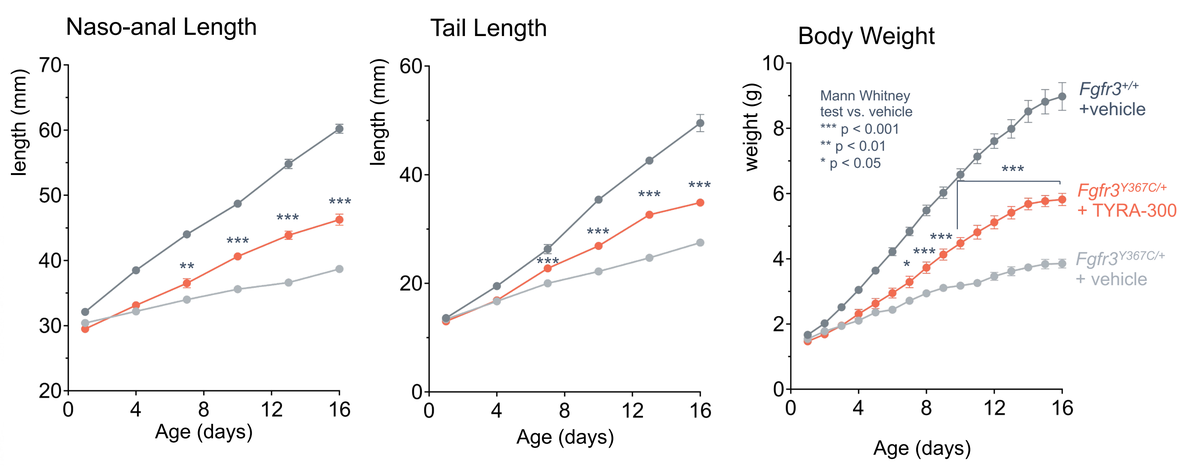
RESULTS

TYRA-300 increased bone growth in the *Fgfr3*$^{Y367C/+}$ mouse model of FGFR3-related skeletal dysplasia

17.9% increase in naso-anal length*

*p<0.0001





Fgfr3$^{Y367C/+}$ mouse[1] increase in length compared to vehicle-treated

	Dose (mg/kg/day)	Femur	Tibia	Humerus	Ulna
TYRA-300[2]	1.2	22.6%*	33.0%*	15.5%*	23.5%*
infigratinib[3]	2.0	20.9%	32.6%	11.9%	22.3%
infigratinib[4]	0.5	10.4%	16.8%	7.3%	11.1%

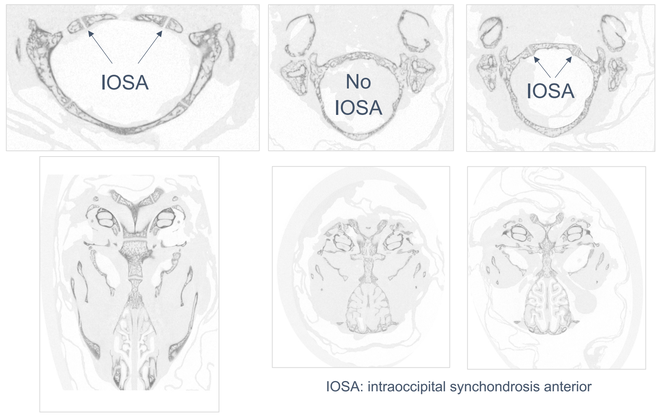
*p<0.0001

Data reflects separate experiments for TYRA-300 and infigratinib;

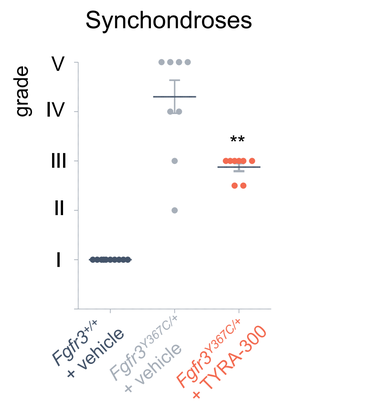
1. Daily subcutaneous injection of TYRA-300 at 1.2 mg/kg/day for 15 days starting at Day 1;
2. n=8 for TYRA-300 and n=10 for vehicle, after excluding three mice from the dataset when molecular analysis showed chimeric incorporation of mutation;
3. Data from Komra-Ebri et al 2016;
4. Demuynck, 2019; 0.167mg/kg human equivalent dose for 0.514mg/kg; 0.667mg/kg human equivalent dose for 2.058mg/kg; infigratinib human recommended phase 2 dose for ACH is 0.25mg/kg

TYRA-300 improved the synchondroses of the foramen magnum

Fgfr3$^{+/+}$ vehicle treated | *Fgfr3*$^{Y367C/+}$ vehicle treated | *Fgfr3*$^{Y367C/+}$ TYRA-300 treated



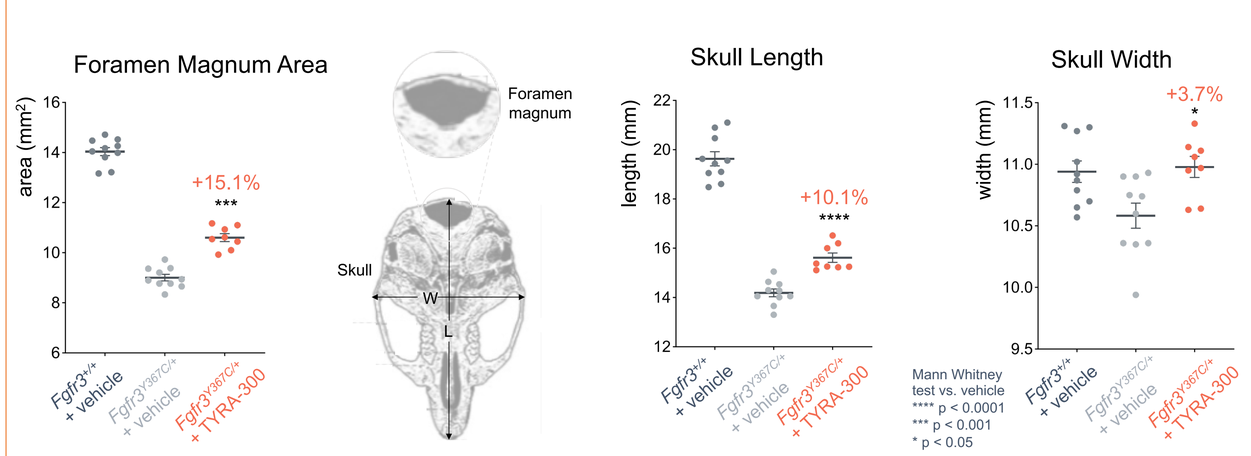
IOSA: intraoccipital synchondrosis anterior



Grades explained

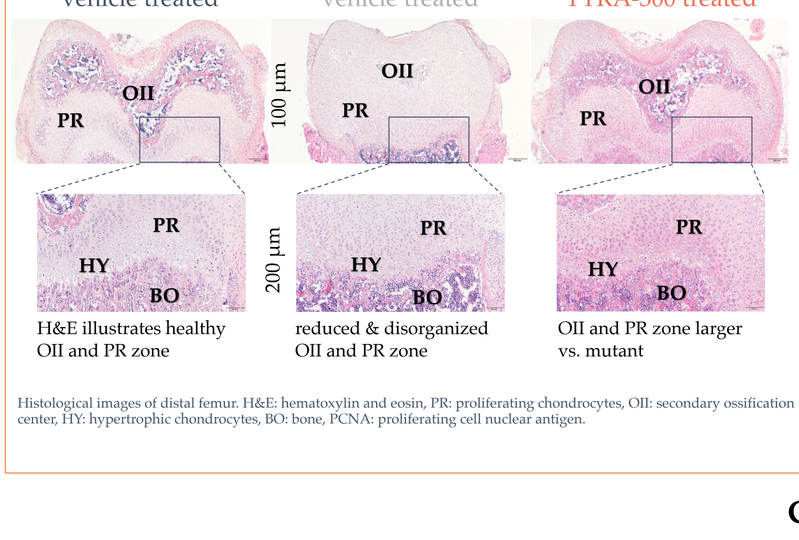
- **I:** borders of synchondroses completely separated;
- **II:** clear separation with some areas of possible bone bridging;
- **III:** bony bridge between the two borders;
- **IV:** completely fused with remnants of margin (cartilage);
- **V:** completely fused synchondroses

TYRA-300 improved the size and shape of the skull and foramen magnum



TYRA-300 increased proliferation and differentiation of chondrocytes within the femur growth plate

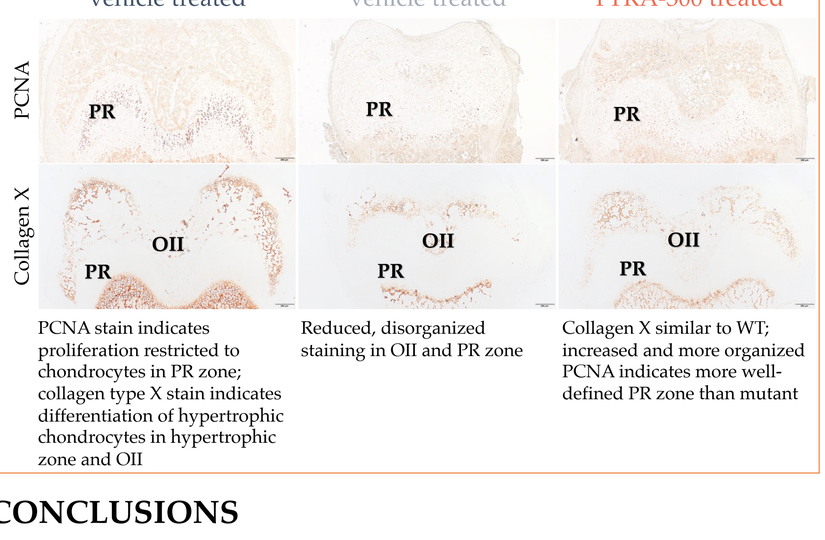
Fgfr3$^{+/+}$ vehicle treated | *Fgfr3*$^{Y367C/+}$ vehicle treated | *Fgfr3*$^{Y367C/+}$ TYRA-300 treated



H&E illustrates healthy OII and PR zone

reduced & disorganized OII and PR zone

OII and PR zone larger vs. mutant



PCNA stain indicates proliferation restricted to chondrocytes in PR zone; collagen type X stain indicates differentiation of hypertrophic chondrocytes in hypertrophic zone and OII

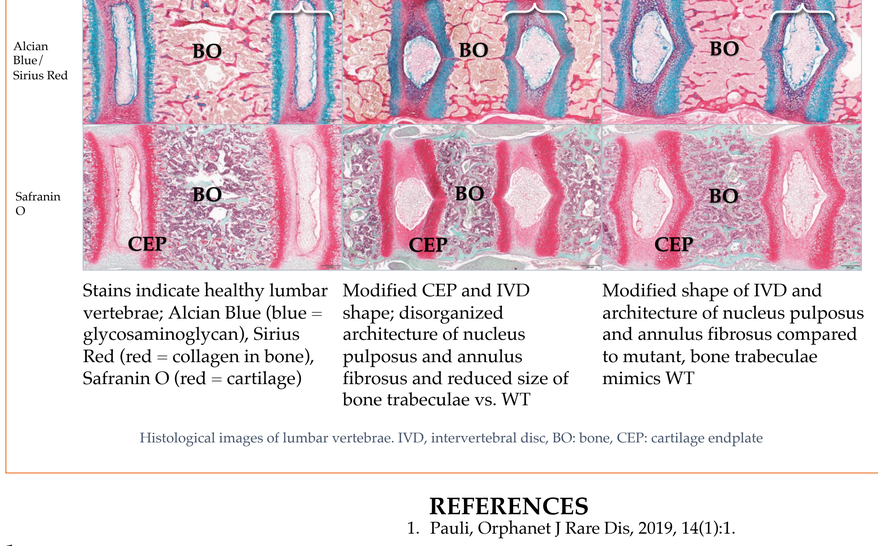
Reduced, disorganized staining in OII and PR zone

Collagen X similar to WT; increased and more organized PCNA indicates more well-defined PR zone than mutant

Histological images of distal femur. H&E: hematoxylin and eosin, PR: proliferating chondrocytes, OII: secondary ossification center, HY: hypertrophic chondrocytes, BO: bone, PCNA: proliferating cell nuclear antigen.

TYRA-300 improved the architecture of the lumbar vertebrae

Fgfr3$^{+/+}$ vehicle treated | *Fgfr3*$^{Y367C/+}$ vehicle treated | *Fgfr3*$^{Y367C/+}$ TYRA-300 treated



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

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

Modified shape of IVD and architecture of nucleus pulposus and annulus fibrosus compared to mutant, bone trabeculae mimics WT

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

CONCLUSIONS

TYRA-300 increased bone length of the appendicular skeleton in the *Fgfr3*$^{Y367C/+}$ mouse model. Improvements in the foramen magnum area and synchondroses were observed with TYRA-300. Histological staining indicated that TYRA-300 restored the architecture of the growth plate by improving proliferation and differentiation of chondrocytes. The length and architecture of the lumbar vertebrae improved after treatment with TYRA-300. The FDA granted TYRA-300 Orphan Drug Designation for the treatment of ACH. Using the data from SURF-301 and additional preclinical data, TYRA expects to submit an IND in 2024 to initiate a Phase 2 clinical study in pediatric achondroplasia.

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