TYRA

TYRA-300 Demonstrates Significant Increases in Growth and Bone Length in a Mouse Model of FGFR3-Related Skeletal Dysplasia

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ACH can result in serious clinical complications

ACH is the most common cause of disproportionate short stature

MECHANISM

FGFR3 G380R gain of function mutation accounts for over 99% of ACH[1,2]

FGFR3 inhibits chondrocyte proliferation and differentiation, resulting in decreased longitudinal bone growth[3]

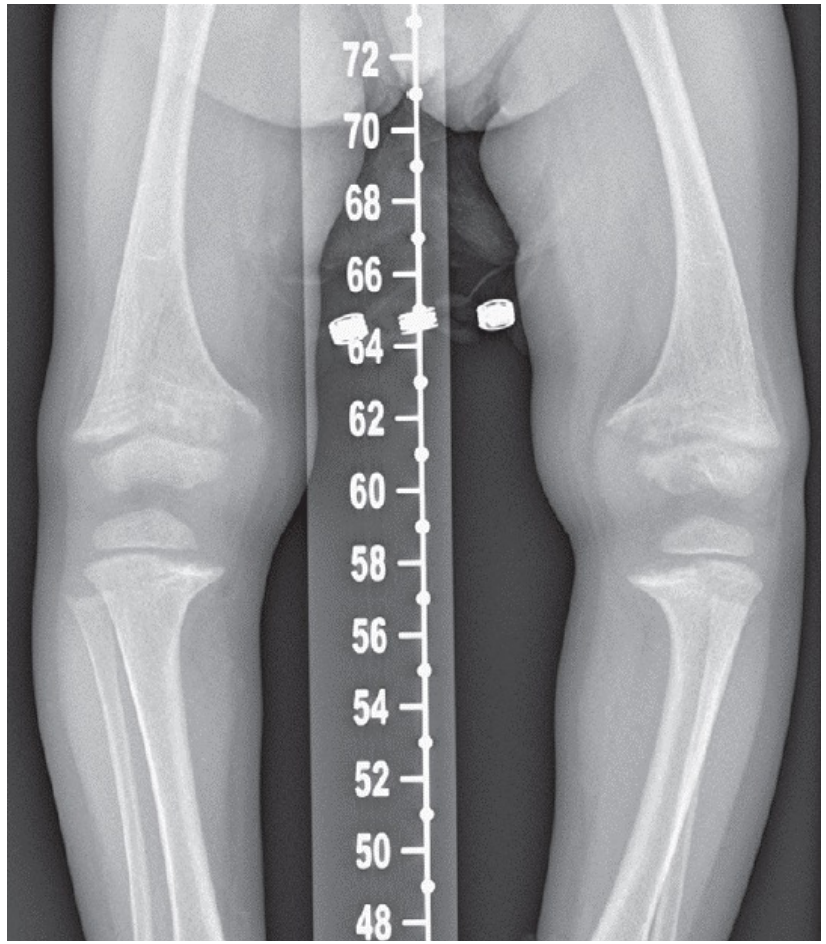
COMPLICATIONS

Infants can face serious complications related to critical foramen magnum stenosis[4,5]

Additionally: ENT, orthopedic and spinal surgeries

1. Bellus et al., 1995; 2. Rousseau et al., 1994; 3. Ornitz and Legeai-Mallet, 2017; 4. Hecht et al., 1987; 5. Pauli et al., 2019

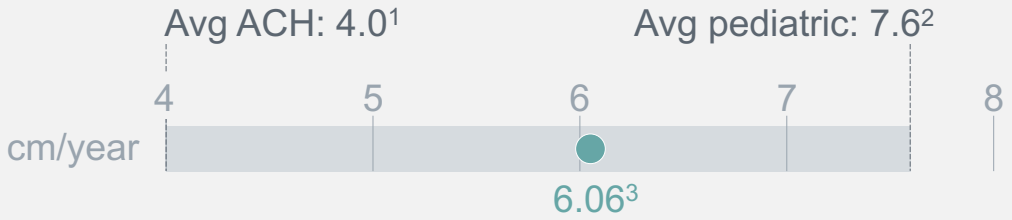
There is a strong need for an oral therapy selective for FGFR3



Vosoritide
(CNP analog)

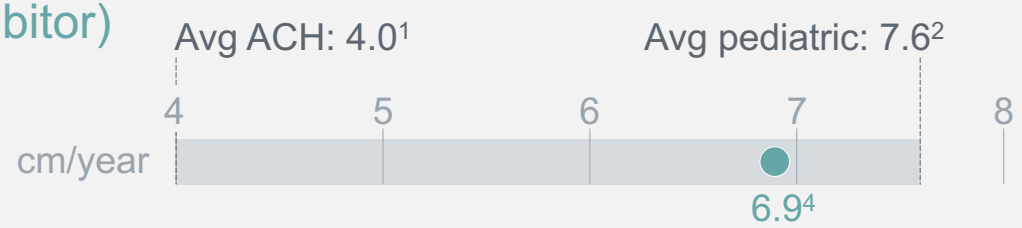
Daily injection,
US FDA-approved

Annual Height Velocity (AHV)



Infigratinib
(Pan-FGFR1/2/3 inhibitor)

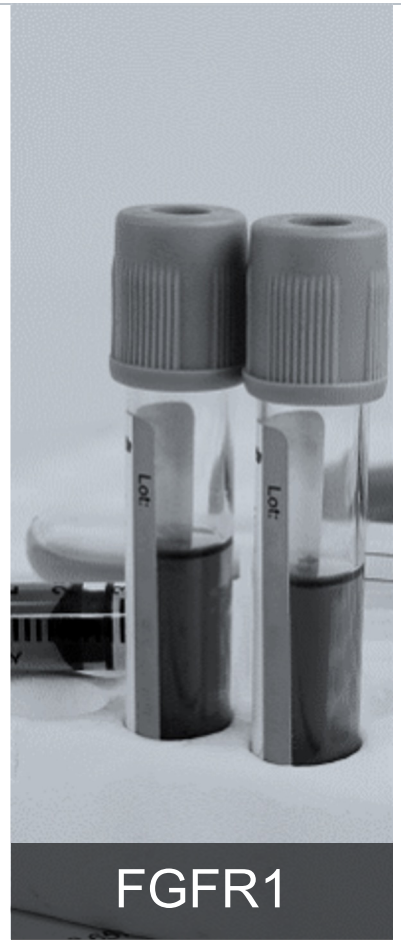
Oral, Phase 2 trial

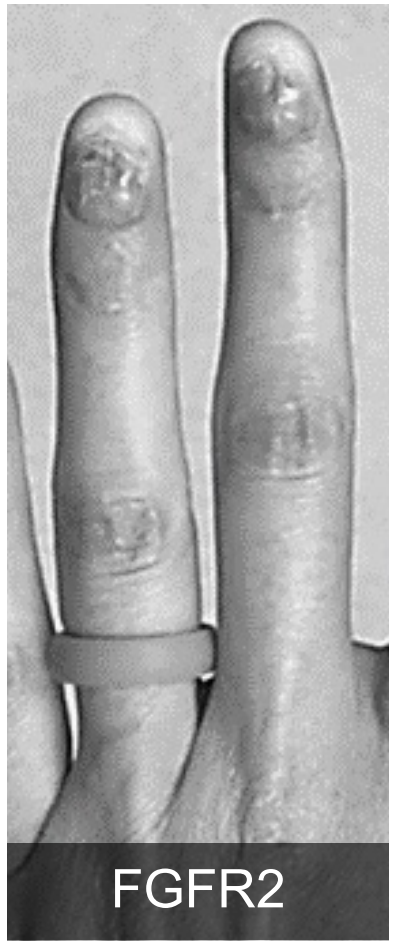


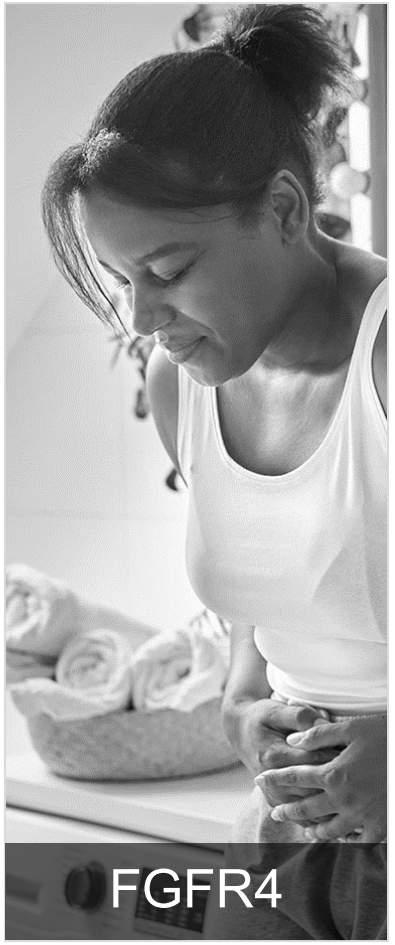
1. Savarirayan, 2021 (5 to 14yrs); 2. Merck Manuals (12mo to 10yrs); 3. Phase 2 Cohort 3 Data, VOXOGO Label, Savarirayan, 2021; 4. Cohort 5 0.250mg/kg daily, Savarirayan, 2023 (ENDO)

Side effects lead to dose reduction or discontinuation in oncology

PAN-FGFR INHIBITOR	% PATIENTS DOSE REDUCTION/ DISCONTINUATION
pemigatinib	23%
futibatinib	63%
erdafitinib	66%
infigratinib	75%



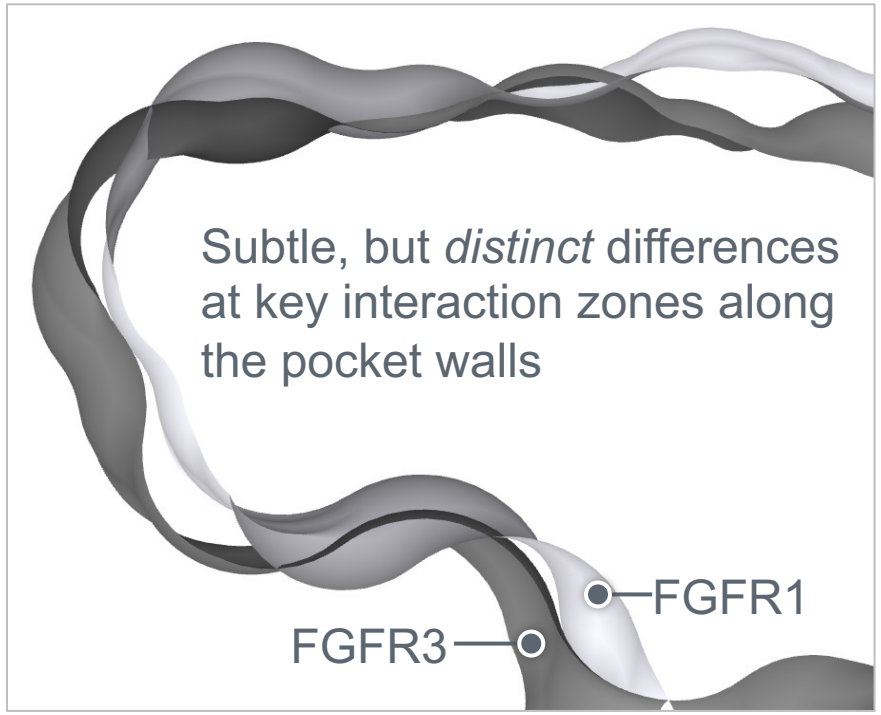




Source: product labels and websites

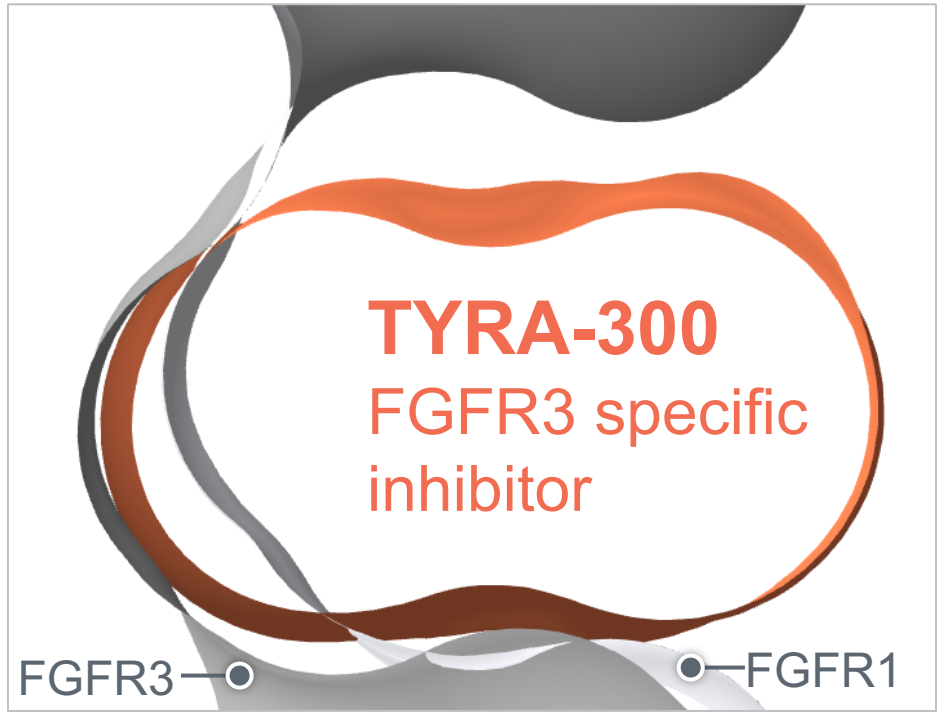
The challenge: FGFR family active sites are nearly identical

FGFR isoform selectivity



MOLECULAR MODEL

dozens of high-resolution crystal structures



CRYSTALLOGRAPHY

3.0Å cross-sections

TYRA-300 is more selective for FGFR3 than pan-FGFR inhibitors

TYRA-300 selectivity vs. approved or late-stage clinical compounds: Ba/F3 Cellular IC_{50} (nM)

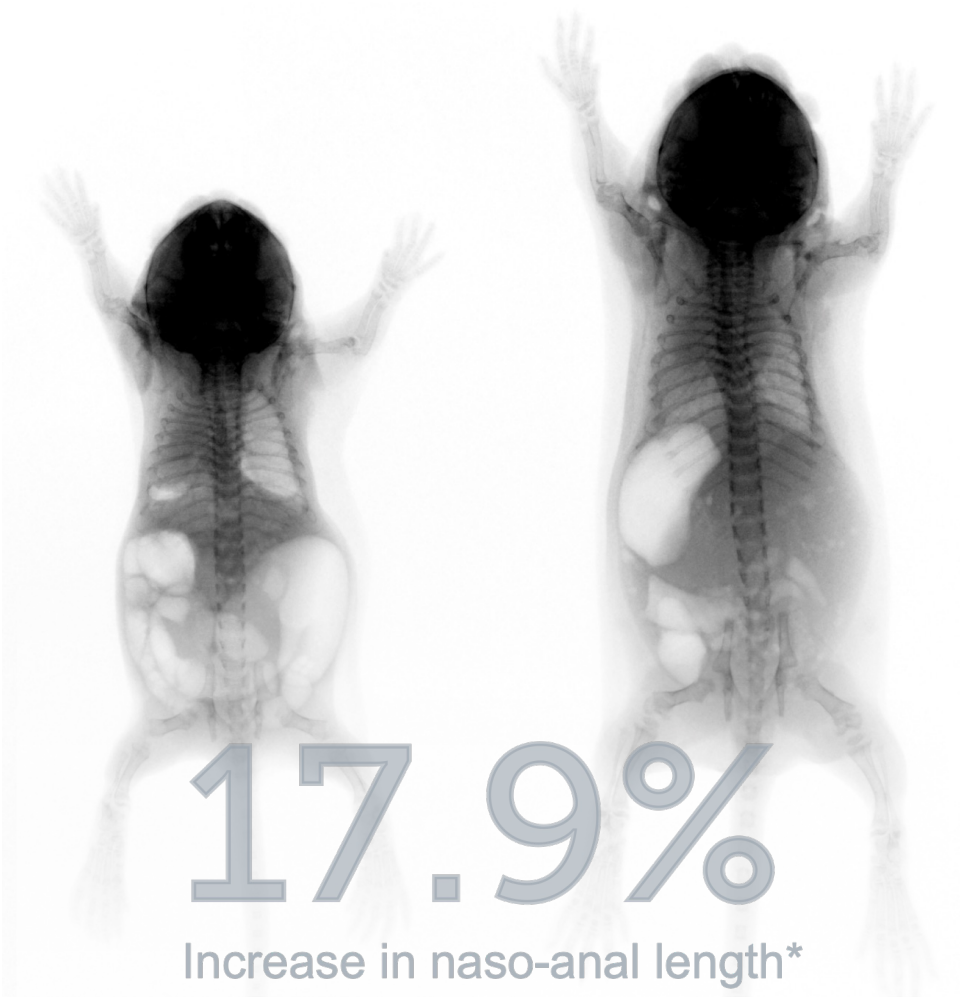
	erdafitinib	futibatinib	pemigatinib	infigratinib	TYRA-300
FGFR1	5.5	3.9	12.3	15.3	113
FGFR2	1.8	1.0	4.3	5.8	34.9
FGFR3	1.3	0.8	5.2	6.9	1.8
FGFR4	17.7	6.1	142	459	98.4

Fold Selectivity for FGFR3

FGFR1	4.2x	4.9x	2.4x	2.2x	63x
FGFR2	1.4x	1.3x	0.8x	0.8x	19x
FGFR4	14x	7.6x	27x	67x	55x

TYRA-300 shows significant isoform selectivity for FGFR3 over other FGFR isoforms

TYRA-300 increased bone growth in the Fgfr3$^{Y367C/+}$ mouse model



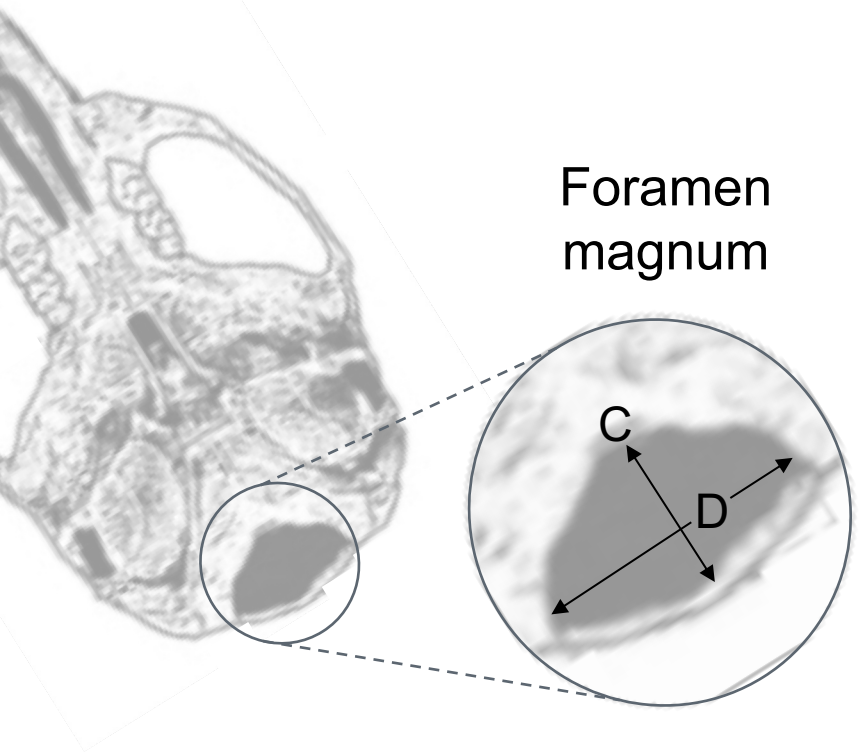
	Dose (mg/kg/day)	Femur	Tibia	L4-L6
TYRA-300	1.2[1]	22.6%*	33.0%*	23.5%*
Infigratinib	2.0[2]	20.9%	32.6%	12.1%
infigratinib	0.5[3]	10.4%	16.8%	N/R

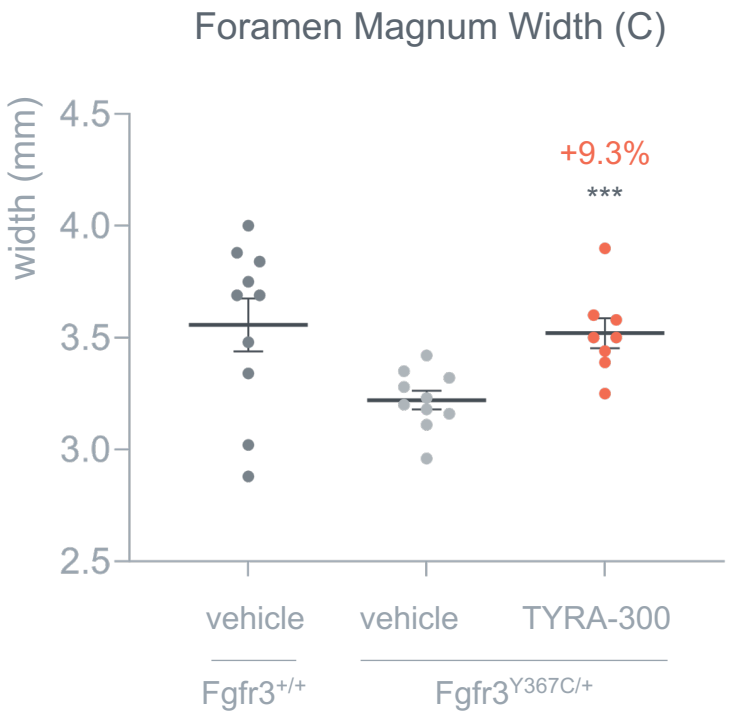
*p<0.0001

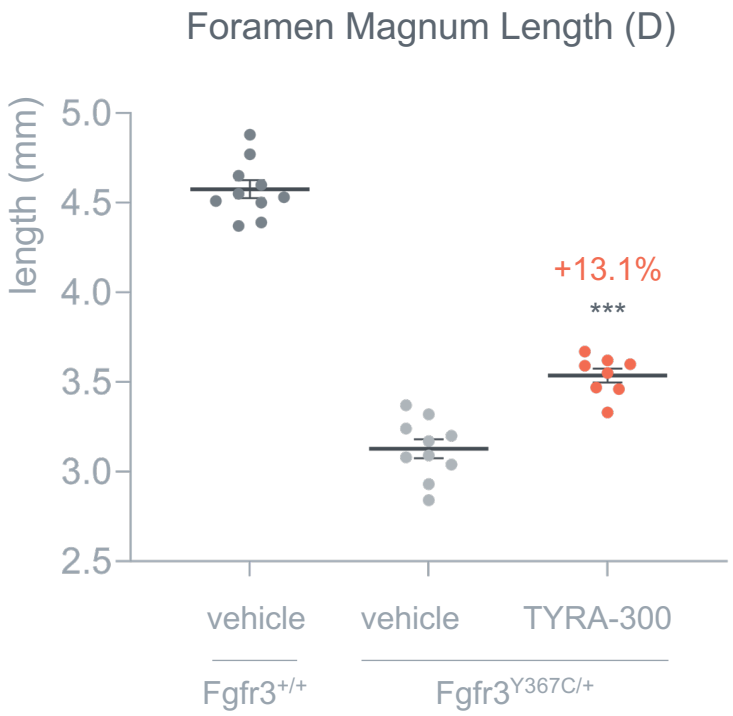
Experiment conducted in the lab of Laurence Legeai-Mallet at Imagine Institute in Paris, France; data reflects separate experiments for TYRA-300 and infigratinib

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

TYRA-300 improved the shape of the foramen magnum



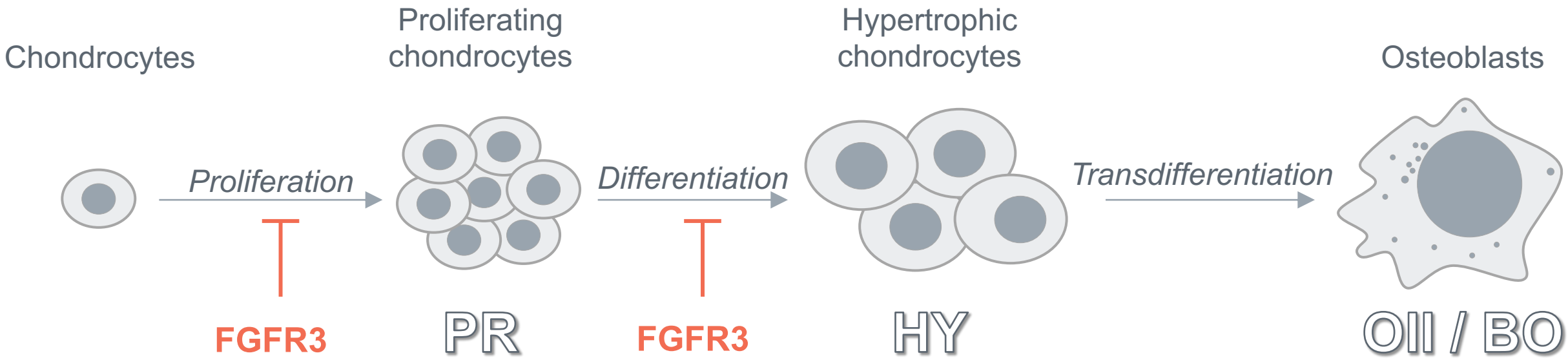




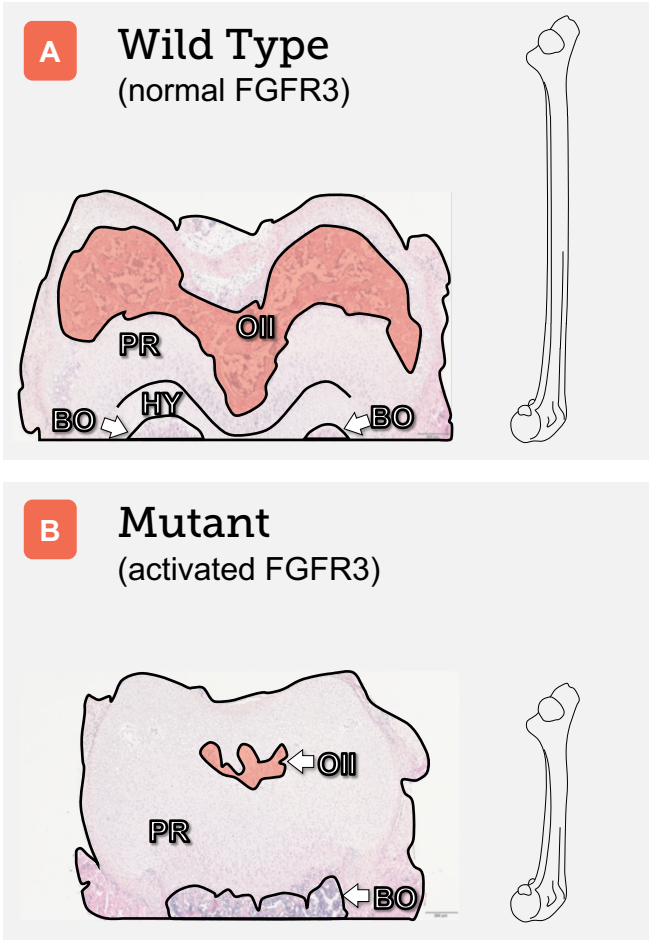
Experiment conducted in the lab of Laurence Legeai-Mallet at Imagine Institute in Paris, France; Daily subcutaneous injection of TYRA-300 at 1.2 mg/kg/day for 15 days starting at Day 1; n=8 for TYRA-300 and n=10 for vehicle, after excluding three mice from dataset when molecular analysis showed chimeric incorporation of mutation.

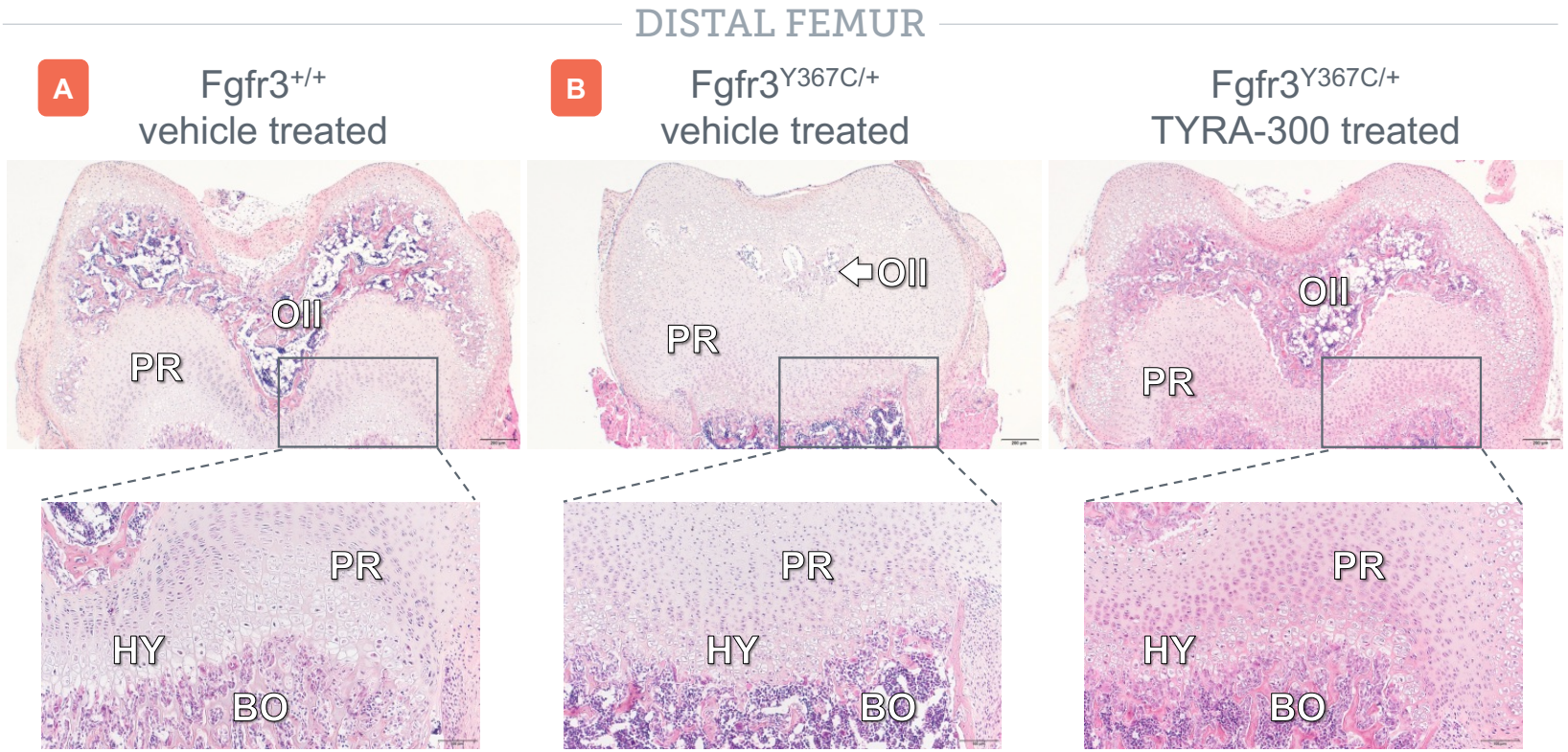
Mann Whitney test vs. vehicle
*** $p < 0.001$

FGFR3 regulates chondrocyte proliferation and differentiation



TYRA-300 restored the architecture of the growth plate





Experiment conducted in the lab of Laurence Legeai-Mallet at Imagine Institute in Paris, France
Hematoxylin and eosin stains of distal femurs. PR: proliferating chondrocytes, OII: secondary ossification center, HY: hypertrophic chondrocytes, BO: bone

Here are our key pre-clinical conclusions about TYRA-300

	TYRA-300
FGFR3 Wild Type	21 nM
FGFR3 G380R	21 nM

1. Demonstrated significant isoform selectivity for FGFR3 over other FGFR isoforms
2. Exhibited equal binding against the FGFR3 G380R mutant and wild-type FGFR3 (NanoBRET™ assay)
3. Increased bone length of the appendicular and axial skeleton in the $Fgfr3^{Y367C/+}$ mouse model
4. Improved the diameter and shape of the skull and foramen magnum
5. Restored growth plate architecture by improving proliferation and differentiation of chondrocytes

Here is an outline of our clinical path

ODD	The US FDA granted TYRA-300 Orphan Drug Designation for the treatment of ACH
IND	TYRA plans to file an IND for TYRA-300 in ACH using data from SURF-301 and additional preclinical data
PH 2	TYRA plans to initiate a Phase 2 study in ACH in 2024

We greatly appreciate our collaborative Parisian partners!

Laurence Legeai-Mallet
Matthias Guillo
Nabil Kaci