ARQ 087 inhibits fibroblast growth factor receptor (FGFR) signaling and rescues aberrant cell proliferation and differentiation in experimental models to craniosynostoses and chondrodysplasias caused by activating mutations in FGFR1, FGFR2 and FGFR3

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INTRODUCTION
Tyrosine kinase inhibitors (TKI) are being developed for therapy of malignancies caused by oncogenic FGFR signaling but little is known about their effect in congenital chondrodysplasias or craniosynostoses associated with activating mutations in FGFR3, FGFR2 and FGFR1. Here we investigated the effects of novel FGFR TKI, ARQ 087, in experimental models to aberrant FGFR3 signaling in cartilage.

CONCLUSIONS
In cultured chondrocytes, ARQ 087 efficiently rescued all major effects of pathological FGFR3 activation, i.e. inhibition of chondrocyte proliferation, loss of extracellular matrix and induction of premature senescence. In ex vivo limb explant cultures, ARQ 087 restored the normal growth plate architecture and obliterated the suppressing FGFR3 effect on chondrocyte hypertrophic differentiation, suggesting that it targets FGFR3 pathway specifically, without interference with pro-growth pathways. This is supported by the lack of ARQ 087’s inhibitory effect on activity of nine FGFR-unrelated receptor tyrosine kinases (AXL, TYRO3, IGF1R, INSR, EGFR, MET, cKIT, TRKA, FLT4). Moreover, ARQ 087 potently inhibited FGFR1 and FGFR2-driven excessive osteogenic differentiation in mouse mesenchymal micromass cultures, and showed activity against activating FGFR1 and FGFR2 mutants associated with various craniosynostoses, such as Pfeiffer, Apert and Beare-Stevenson syndromes, and osteogliophonic dysplasia. Our data warrant further evaluation of ARQ 087 for clinical use in chondrodysplasias and craniosynostoses caused by activating FGFR1-3 mutations.