In vivo observations
- Clinical observations during treatment were performed every 3 days (third limbs movement, posture, and active locomotion) and were performed at the time of scoring.
- X-ray assessments
- Lateral X-ray images were taken of all animals by Faxitron MX20 Cabinet X-ray system (FaxitronXray, IL, USA) following terminal sacrifice.

Mechanism
- Fgfr3N534K/+ mice displayed progressive dwarfism throughout development.
- Biochemical analysis of Fgfr3N534K/+ mice demonstrated increased levels of p-ERK1/2 and p-S6.
- In-vivo ERK1/2 phosphorylation (MAP kinase pathway) in femoral growth plate was reduced by infigratinib.
- Analysis of long bones after necropsy showed an impressive and significant modification of bone length.
- Growth curves (naso-anal length, tail length, and weight) showed the efficacy of treatment after 21 days of injections.
- Results of bone lengths and the age of the mice were modified by treatment.
- Infigratinib impacted the cartilage growth plate, significantly increasing the hypertrophic area and inhibiting the MAP kinase pathway (ERK1/2 phosphorylation) controlling the chondrocyte differentiation.

Discussion
- Infigratinib 1 mg/kg every 3 days did not modify endochondral and membrane ossification processes in the developing mouse.
- Daily infigratinib 1 mg/kg modified the whole skeleton in this mouse model of HCH.
- Growth curves (naso-anal length, tail length, and weight) showed the efficacy of treatment after 21 days of injections.
- Analysis of long bones after necropsy showed a significant and significant modification of bone lengths.
- The age and length of the skull were modified by treatment.
- Infigratinib impacted the cartilage growth plate, significantly increasing the hypertrophic area and inhibiting the MAP kinase pathway (ERK1/2 phosphorylation) controlling the chondrocyte differentiation.

Conclusions
- These results demonstrate that daily infigratinib 1 mg/kg is able to counteract the constitutive activation of FGFR3 resulting from the heterozygous FGFR3 mutation located in the kinase 1 domain of FGFR3.
- Infigratinib treatment improved the growth plate hypertrophic area (collagen type X immunostaining), treatment modified hypertrophic chondrocyte area and decreased the number of hyperphosphorylated chondrocytes compared with untreated chondrocytes.

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References