Low-dose infigratinib treatment does not lead to changes in phosphorus in preclinical animal studies

Maribel Reyes, PhD;[1] Uma Sinha, PhD;[2] Gary Li, PhD,[1] David Martin, PhD[1]

[1]QED Therapeutics Inc., San Francisco, CA, USA; [2]BridgeBio Pharma, Palo Alto, CA, USA

#5120

Background

- Infigratinib (BGJ398) is a selective adenosine triphosphate (ATP) competitive fibroblast growth factor receptor (FGFR) 1–3 tyrosine kinase inhibitor.
- Low-dose infigratinib is under evaluation for the treatment of achondroplasia, the most common form of disproportionate short stature.
- Low doses of infigratinib have been shown to be effective in improving skeletal abnormalities in a mouse model of achondroplasia.[1,2]
- Given that infigratinib inhibits FGFR1 at certain doses an effect on phosphorous would be expected, but the dose at which this occurs is unknown.
- We sought to understand the relationship between low doses of infigratinib and changes in phosphorus in preclinical animal models.

Methods

- Changes in phosphorus were tested at multiple doses in three different species (mouse, rat, and dog) across five different studies (Table 1).
- Animal species/strains were as follows:
  - **Mouse:** C57BL/6 strain.
  - **Rat:** Wistar Hannover [Crl:WI(Han)].
  - **Dog:** Beagle.
- All animals were treated in accordance with standard guidelines for the care of laboratory animals.[3–6]
- Infigratinib was given orally at doses ranging from 0.03 mg/kg to 30 mg/kg.

Table 1. Studies assessed

Species	Study type	Doses tested (mg/kg)	Day of PK	Day of PD measurement
Dog	13-week toxicology (oral dose)	1, 3, 10	Day 78	Week 12
Rat	13-week toxicology (oral dose)	1, 3, 10	Week 12	Week 12
Rat	8-week juvenile toxicology (oral dose)	0.03, 0.1, 0.3, 1	Day 62	Day 62
Mouse	28-day transgenic mouse toxicology	1, 3, 10, 20, 30	Day 28	Day 29
Mouse	Bridging oral and SC dosing (only oral data used)	0.5, 1, 2, 3, 5	Day 10	Day 10

Note: date from juvenile rat analyzed is from Day 62 ("adult" rats).
Juvenile toxicology and mouse studies used a group of animals for PD and satellite animals for PK.
Therefore, the average PD for subgroups was calculated for PK/PD analysis.

PK/phosphorus assessments

- Both PK and PD (i.e., phosphorus) data were available in all species.
- Measurement days ranged from day 10 to week 12, although PK/PD measurements occurred within 1 day of each other.
- Dose vs. total phosphorus was calculated and is displayed in box plots. One-way multiple comparison ANOVA was conducted for each dose level within each species. Significant difference in phosphorus levels between vehicle control and treated group are indicated with a p-value.
- Log $AUC_{0\text{–}24}$ vs. total phosphorus was calculated and is displayed in scatter plots.
- Log $AUC_{0\text{–}24}$ vs. phosphorus (% change from control) was calculated and is displayed in scatter plots.
- Linear regression log $AUC_{0\text{–}24}$ vs. phosphorus (% change from control) was calculated and is displayed in scatter plots with linear regression. Equation and goodness of fit (R2 values) are displayed.

Figure 1. Dog (week 12)

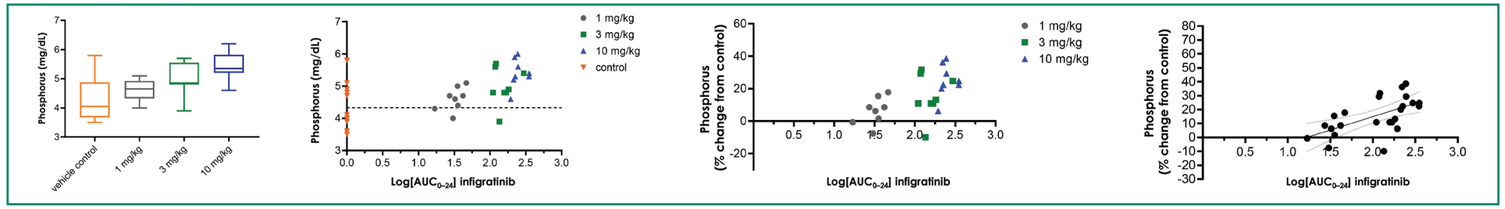


Figure 2. Rat (week 12)

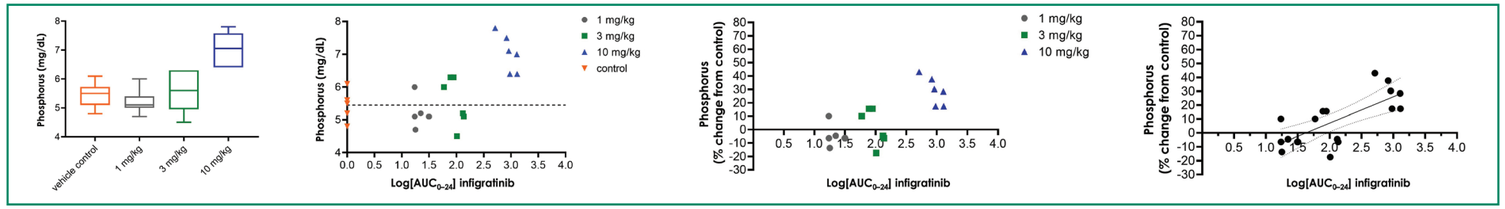


Figure 3. Juvenile rat (day 62)

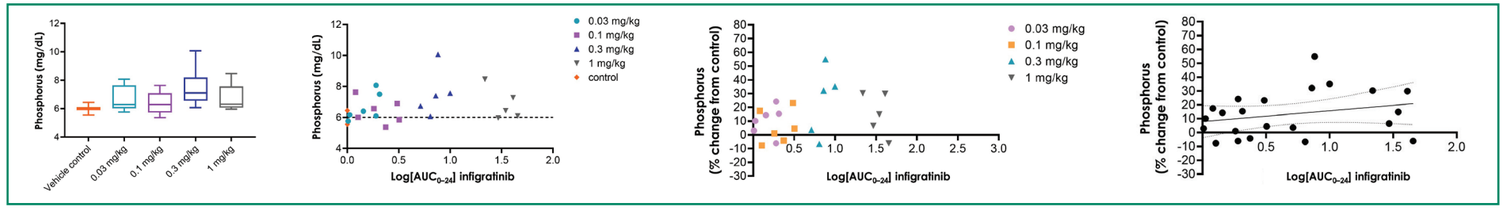


Figure 4. Transgenic mouse (day 29)

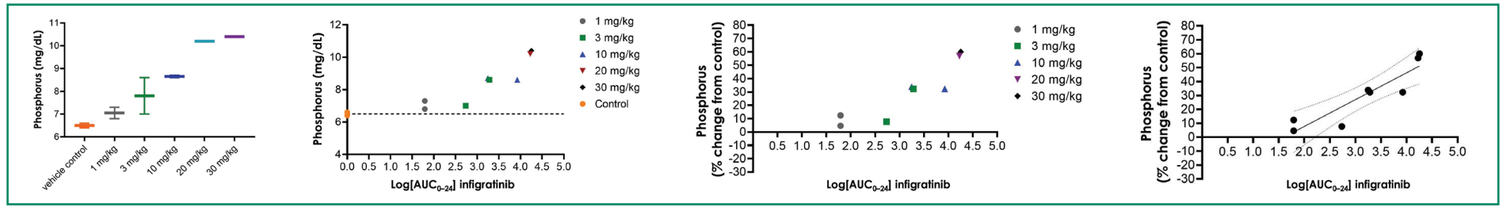
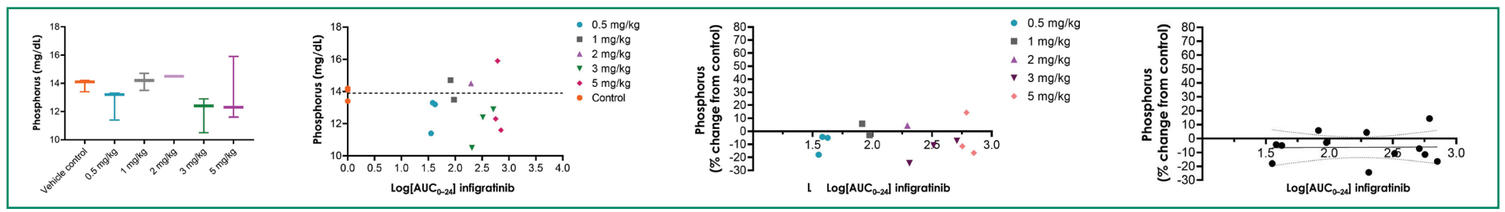


Figure 5. Mouse (day 10)



Results

- Exposure–phosphorus relationships were consistent across species (dog, rat, mouse).
- A dose–phosphorus and exposure ($AUC_{0\text{–}24}$)–phosphorus relationship was observed at doses of infigratinib ≥10 mg/kg across transgenic mouse, rat and dog studies.
- No significant dose–phosphorus relationship was observed in rats and mice treated with doses of infigratinib ranging from 0.03 mg/kg to 5 mg/kg.
- At low doses, the exposure ($AUC_{0\text{–}24}$)-phosphorus relationship showed a shallow slope with linear regression analysis in rats and mice. One outlier was observed.

Conclusions

- These findings from five studies in three different species indicate that the exposure-phosphorus relationship is consistent.
- Importantly, no relationship was observed between dose and phosphorus levels in rats and mice treated with infigratinib at or below 5 mg/kg (human equivalent dose of 0.41 mg/kg based on mouse to human conversion), which is higher than the doses expected to be tested in studies planned with achondroplasia.
- Despite hyperphosphatemia being one of the earlier on-target toxicities expected with infigratinib, this study suggests that low doses of infigratinib (shown previously to improve skeletal abnormalities in an achondroplasia mouse model) do not seem to result in meaningful changes in phosphorus.
- Infigratinib is being evaluated in global clinical studies in children with achondroplasia in 2020. The planned dose of infigratinib to be tested in achondroplasia will be 0.016 mg/kg.

References

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