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

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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. Given that infigratinib inhibits FGFR1 at certain doses an effect on phosphorus levels was 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/study type 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. Infigratinib was given orally at doses ranging from 0.03 mg/kg to 30 mg/kg. 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.

Results

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–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 lower 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.

References


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Table 1. Studies assessed

<table>
<thead>
<tr>
<th>Species</th>
<th>Early type</th>
<th>Early dose (mg/kg)</th>
<th>Day of PK</th>
<th>Day of PK measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>12 week dosing (oral dose)</td>
<td>1, 3, 10</td>
<td>Day 70</td>
<td>Week 12</td>
</tr>
<tr>
<td>Rat</td>
<td>12 week dosing (oral dose)</td>
<td>1, 3, 10</td>
<td>Week 12</td>
<td>Day 70</td>
</tr>
<tr>
<td>Mouse</td>
<td>1 week peri-dosing (oral dose)</td>
<td>0.005, 0.015, 0.15</td>
<td>Day 10</td>
<td>Day 10</td>
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<tr>
<td>Mouse</td>
<td>2 week peri-dosing (oral dose)</td>
<td>0.005, 0.015, 0.15</td>
<td>Day 10</td>
<td>Day 10</td>
</tr>
<tr>
<td>Mouse</td>
<td>4 week peri-dosing (oral dose)</td>
<td>0.005, 0.015, 0.15</td>
<td>Day 10</td>
<td>Day 10</td>
</tr>
</tbody>
</table>

PK/phosphorus assessments

Both PK and PD 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 differences in phosphorus levels between vehicle control and treated group are indicated with a p-value. Log AUC0–24 vs. total phosphorus was calculated and is displayed in scatter plots.

Linear regression log AUC0–24 vs. phosphorus (% change from control) was calculated and is depicted in scatter plots with linear regression. Equation and goodness of fit (R2 values) are displayed.