Modelling and simulation approach to optimize the pharmacological activity during a Phase 1 study of JNJ-42756493, a selective and potent FGFR 1, 2, 3 and 4 inhibitor.

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Introduction
JNJ-42756493 is a potent and selective pan-fibroblast growth factor receptor (FGFR 1, 2, 3 and 4) oral inhibitor, which is currently under development for patients with cancer with FGFR aberrations.

Non-clinical data obtained in vitro (FGFR pathway inhibition) and in vivo (antitumor activity in xenograft models) were used to anticipate the plasma concentrations of the compound expected to provide therapeutic benefit using a translational pharmacokinetic-pharmacodynamic (PK-PD) approach. JNJ-42756493 was known to be avidly bound to Alpha 1-acid glycoprotein (AGP), so that appropriate corrections for the different binding of the compound to AGP in different species, including humans, had to be applied.

These data were evaluated together with the outcome of a phase 1 dose-escalation trial, including the assessment of clinical antitumor activity, pharmacological response, safety/tolerability and pharmacokinetics, in a translational PK-PD approach. This exercise had the aim to simulate the potential outcome of different dosing regimens to be proposed for phase 2 trials.

Methods

In vitro experiments
- Drug IC50 was determined using a SNU-16 cell proliferation assay.

In vivo preclinical experiments
- Antitumor experiments were performed in mice and rats xenografted with SNU-16 tumor cells. PK was assessed in ancillary groups of animals at dose levels from 6.25 to 20 mg/kg given once or twice daily; antitumor activity was evaluated in SNU-16 xenografted animals. Simeoni model [1] was used to establish the threshold concentration for tumor eradication (Ct). limit to be related to antitumor response in human subjects.

Clinical phase I trial
- JNJ-42756493 was tested in a Phase 1 dose-escalation trial. Doses from 0.5 to 12 mg were given once daily to patients affected by different solid tumors.
- PK, safety and tolerability (including serum calcium and phosphate) and antitumor activity were assessed after single and repeated daily dose administration.
- Non-linear mixed effect (NONMEM) PK models were used to describe the PK during the trial. At each dose level, observed and model-predicted plasma concentrations were compared to the levels expected to be of clinical relevance based on non-clinical in vitro and in vivo experiments.
- Dose linearity was closely monitored given nonlinear PK observed in animals and the AGP variability observed in patients.
- Graphical analysis was performed to assess the effects of JNJ-493 on Calcium, Phosphate, FGFR23, Parathyroid Hormone and Vitamin-D biomarkers.
- The relationship between plasma concentration and the phosphate elevation was described using a PK-PD model.

Results

In vitro Activity of JNJ-42756493

Table 1. Estimated Trial: JNJ-42756493 PK parameters from NONMEM model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pop Est</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/h)</td>
<td>0.29</td>
<td>30%</td>
</tr>
<tr>
<td>Vplasma (L)</td>
<td>20.2</td>
<td>51%</td>
</tr>
<tr>
<td>Q (L/h)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Vperf. (L)</td>
<td>7.38</td>
<td>86%</td>
</tr>
<tr>
<td>Ka (h)</td>
<td>1.09</td>
<td>30%</td>
</tr>
<tr>
<td>V/F</td>
<td>8.48</td>
<td></td>
</tr>
<tr>
<td>Vplasma (L)</td>
<td>11.1</td>
<td>33.4</td>
</tr>
<tr>
<td>F0</td>
<td>0.12</td>
<td>0.59</td>
</tr>
<tr>
<td>Vplasma (L)</td>
<td>14.9</td>
<td>27.5</td>
</tr>
</tbody>
</table>

Plasma phosphate concentrations

The relationship between Unbound JNJ-42756493 and phosphate concentrations was described using an Emax model:

\[ E = E_0 + \frac{E_{\text{max}} \times C_{\text{U}}}{EC_{\text{50}} + C_{\text{U}}} \]

- \( E_0 \) = Baseline value
- \( E_{\text{max}} \) = Maximal phosphate increase
- \( EC_{\text{50}} \) = Unbound Concentration reaching 50% of maximal phosphate increase
- C_{\text{U}} = Unbound plasma concentration

Baseline phosphate plasma concentrations, unbound fraction ~AGP blood levels and BSA can be considered as influential covariates on increase of the plasma phosphate concentrations.

References


Acknowledgments

The authors acknowledge the valuable contribution of all people involved in the generation of the results. This work is the result of a cross-functional collaboration involving many people from Janssen R&D Oncology Toxicology, Model Based Drug Development, Clinical Pharmacology, and Compound Development.

Based on the raw content, the document discusses the development of JNJ-42756493, a potent and selective pan-fibroblast growth factor receptor (FGFR) inhibitor, including preclinical and clinical data, with a focus on pharmacokinetic and pharmacodynamic models to optimize its therapeutic benefits. The study involved Phase 1 dose-escalation trials in humans and xenograft models to evaluate antitumor activity, safety, and tolerability. The results include in vitro and in vivo experiments, with emphasis on the relationship between plasma concentration and calcium levels, using an Emax model to describe the relationship. The document also mentions the involvement of multiple Janssen teams and collaborators from different institutions in the research and development process.