

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 mpk 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 (C_T), expected 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 JNJ493 on Calcium, Phosphate, FGF23, 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

In vitro	SNU-16 proliferation IC ₅₀ (nM)
Human gastric carcinoma	0.37

In vivo SNU-16 xenograft model based analysis results

The analysis of data from different xenograft experiments identified a range of C_T in terms of total plasma concentrations between 9.7 and 89.0 ng/mL, which corresponded to 0.5 and 2.4 ng/mL in terms of free (unbound) plasma concentrations

Results of the clinical phase 1 trial

PK model results Phase 1 dose escalation study:

- A 2-compartment open model with first-order absorption and first-order elimination from the central compartment accommodated the total plasma concentration of all dose levels
- 2 Significant covariates identified:
 - ❖ Fu ~ AGP on Plasma Volume and Plasma Clearance
 - ❖ BSA on Plasma Volume
- PK appeared linear across the tested dose range
- Relatively long terminal plasma half-life (approx. 50-60 hours)

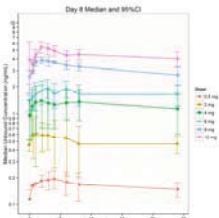


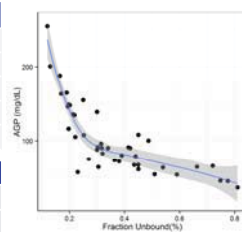
Table 1. Estimated Total JNJ-42756493 PK parameters from NONMEM model

Parameter	Pop Est.	%CV
CL/F (L/h)	0.29	30%
Vplasma (L)	20.2	51%
Q (L/h)	0.47	/
Vperif. (L)	7.38	86%
Ka (1/h)	1.09	30%

Parameter	FU=0.1%	FU=0.8%
CL/F (L/h)	0.12	0.59
Vplasma (L)	11.1	33.4

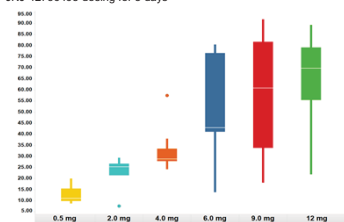
	BSA=1.3	BSA=2.3
Vplasma (L)	14.8	27.5

Fig. 2. Relationship between AGP concentrations and fraction unbound of JNJ-42756493



Plasma phosphate concentrations

Fig. 3 Observed % change from baseline phosphate plasma concentrations after JNJ-42756493 dosing for 8 days



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

$$E = E_0 + \frac{E_{\max} \cdot C_u}{EC_{50} + C_u}$$

E₀ = Baseline value
 E_{max} = Maximal phosphate increase
 EC₅₀ = Unbound Concentration reaching 50% of maximum phosphate increase
 C_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.

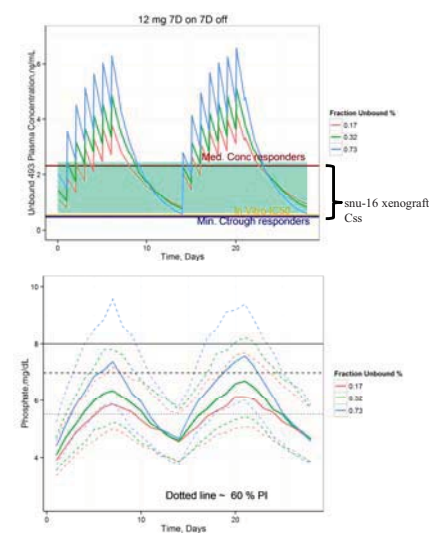
Parameter	Pop Est.	%CV
E ₀ (mg/dL)	3.51	13.0
E _{max} (mg/dL)	7.9	32.4
EC ₅₀ (ng/mL)	1.3	25.0

Conclusions

The modeling exercise allowed to define dosing regimens sustaining JNJ-42756493 plasma concentrations able to provide antitumor activity and, at the same time, maintaining the phosphate concentration <8 mg/dL.

Simulations exercises allowed therefore to predict the outcome of different dosing regimens. A regimen of 7 days on and 7 days off is currently being tested in the phase 1 study and preliminary data indicates that the observed data are aligning with the simulation.

Observed covariates, might give guidance to allow for future dose or dosing regimen adaptation, or be suggestive to more strictly follow phosphate plasma levels in a selection of patients.



References

- [1] Simeoni, M et al. Clinical Cancer Research 2004; 64, 1094-1101.

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