Food & Formulation effect of a Novel Src Homology region 2 domain−containing protein tyrosine phosphatase 2 (SHP2) allosteric inhibitor in combination with pembrolizumab

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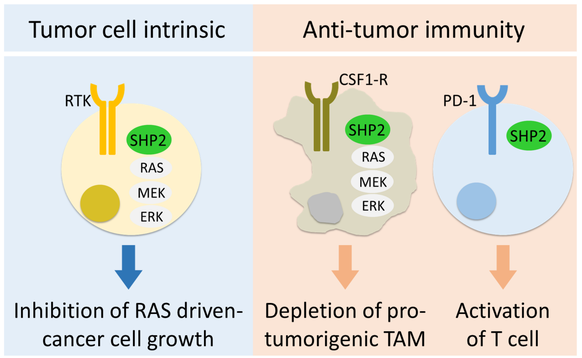
INTRODUCTION

- SAR442720 (SAR'720) is an orally bioavailable, potent, and selective Src homology region 2-containing protein tyrosine phosphatase 2 (SHP2) allosteric inhibitor that is being developed for participants with tumors harboring certain activating mutations or other genetic aberrations in the RAS mitogen-activated protein kinase (MAPK) pathway, including upstream mutations in receptor tyrosine kinases (RTKs). SHP2 also plays a vital role in promoting antitumor immunity and enhancing T cells cytotoxic function.
- Based on available data, a PBPK model was developed to assess food effect, and the preliminary results indicated no food effect. To further validate this finding, a food effect study was conducted.
- SAR'720 was being developed as a monotherapy as well as in combination with other oncology assets. In TCD16210 study part-4, the primary objective was to evaluate the effect of food on the pharmacokinetics (PK) of SAR'720 tablet and to assess the relative bioavailability of SAR'720 tablet formulation (test) compared to the SAR'720 capsule formulation (reference) when dosed in combination with pembrolizumab in participants with advanced solid tumors.

Figure 1: SAR442720 Drives Anti-Tumor Benefit via Both Cell-Intrinsic and Immune System Mechanisms[1]



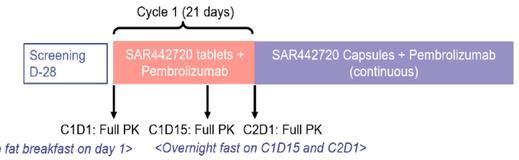
METHODS

- **Study Design:** 15 participants were enrolled in this part (Part 4) of the study in which SAR'720 was administered orally at the previously determined RP2D in combination with pembrolizumab. The first treatment cycle was for 21 days in which participants were administered SAR'720 tablet formulation (test) and starting from C2D1, SAR'720 capsule formulation (reference) until the end of treatment (Figure 2). SAR'720 was administered orally 200 mg D1D2 and pembrolizumab was administered as IV infusion over 30 mins at 200 mg Q3W.
- **Sample size consideration:** Patients who completed all of cycle 1 and C2D1 with meal information, full PK, and no dose reduction/ missed doses on C1D1, C1D15 and C2D1 were considered evaluable. Such 9 evaluable subjects were needed to provide maximum of 20% imprecision for the geometric mean ratio of PK parameters between formulation and fasting status, with 90% assurance and assuming a within subject variability of 20% for the steady-state AUC.

METHODS (CONT'D)

- **Sample Scheme:** Intensive PK samples were collected for SAR'720 starting at predose, 0.5, 1, 2, 4, 8 and 24 hours post dose at C1D1 and C1D15 for food effect assessment; and C2D1 for formulation assessment. Sparse PK samples were collected for pembrolizumab.
- **Bioanalytical Methods:** A validated LC MS/MS assay (LLOQ 1.00 ng/mL) and validated ELISA assay (LLOQ 30.0 ng/mL) was used to assay SAR'720 in plasma and pembrolizumab in serum, respectively from the participants.
- **Pharmacokinetic (PK) analysis**: SAR'720 PK parameters were calculated by Non-compartmental Analysis using Phoenix version 8.3.
- **Statistical Analysis:** Food effect was assessed using a linear mixed effects model with fed state taken as a fixed effect (fed versus fasting) and patient as random variable. Formulation effect was assessed using a linear mixed effects model with formulation as a fixed effect (tablet versus capsule) and patient as random variable.

Figure 2: Study Design



Abbreviations: C= cycle, D = day, PK = pharmacokinetics

RESULTS

- Considering the study design and repeat administration to the same subjects, measurable SAR'720 concentrations were observed in the predose PK samples at Cycle 1 Day 15 (C1D15) and Cycle 2 Day 1 (C2D1).
- Since the predose concentrations for C1D15 and C2D1 were >5% of C_{max}, adjusted concentrations were used to evaluate food and formulation effect.
- Adjusting concentrations using λz was not feasible because λz could not be estimated accurately, therefore an alternative approach was utilized where predose concentrations were subtracted over the entire profiles for C1D15 and C2D1.
- PK parameters were then recalculated using adjusted concentrations to evaluate food and formulation effect.

Food Effect

- The observed data demonstrated that presence of food slightly delayed the absorption (T_{max} from 2.02 hours in fasted state to 3.75 hours in fed state) and slightly reduced the C_{max} (from 828 ng/mL in fasted state to 637 ng/mL in fed state; Table 1). This delay decreased the rate and the extent of SAR'720 absorption leading to a fed/fasted geometric mean ratio (90% CI) of 0.7782 (0.6837 to 0.8857) for C_{max} and 0.8996 (0.6933 to 1.1673) for AUC_{last}, respectively (Table 2).

RESULTS (CONT'D)

Figure 3: Mean (±SD) SAR442720 plasma concentration-time profile on C1D1 and C1D15 (fed versus fasted)

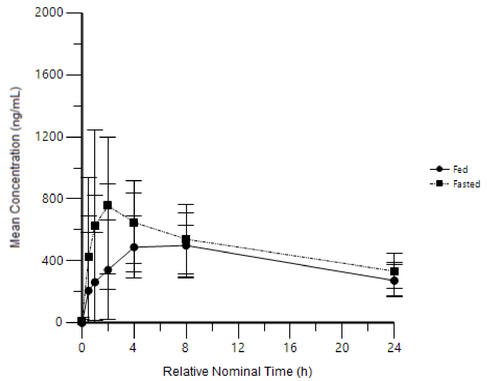


Table 1. Pharmacokinetic parameters for SAR442720 - Food effect

Cycle	Day	Formulation/ Meal	Statistics	AUC_{last} (h*ng/mL)	C_{max} (ng/mL)	T_{max}[a] (h)
1	1	Tablets/ Fed	N	9	9	9
			Mean ± SD	9410 ± 3310	637 ± 220	3.75 [1.08-24]
			(Geo. Mean) [CV%]	(8830) [35]	(599) [34]	
1	15	Tablets/ Fasted	N	9	9	9
			Mean ± SD	10800 ± 4290	828 ± 310	2.02 [0.9-7.58]
			(Geo. Mean) [CV%]	(9810) [40]	(770) [37]	

C_{max}: maximum concentration observed; AUC_{last}: area under curve from zero to the last timepoint
T_{max}: time to reach maximum concentration; CV: coefficient of variation; SD: standard deviation;
[a] Median (Min – Max) values

Table 2. Point estimates of treatment rations with 90% confidence intervals – Food effect

Comparison	Parameter	Point estimate	90% CI
Fed vs. Fasted	C_{max}	0.7782	(0.6837 to 0.8857)
	AUC_{last}	0.8996	(0.6933 to 1.1673)

C_{max}: maximum concentration observed; AUC_{last}: area under curve from zero to the last timepoint;
CI: confidence interval.

Formulation effect

- The tablet formulation demonstrated slightly faster absorption (T_{max}) 2.02 hours when compared with capsule formulation, which was 3.6 hours and slightly increased C_{max} to 828 ng/mL from 658 ng/mL for capsules (Table 3). Therefore, the change of the oral formulation of SAR'720 under fasted conditions, from capsules (reference) to tablets (test) resulted in a slight increase in the absorption, which is translated to a more marked effect on C_{max} than on AUC_{last}: tablet/capsule geometric mean ratio (90% CI) was 1.3136 (1.0742 to 1.6062) for C_{max} and 1.0766 (0.8154 to 1.4213) for AUC_{last}

Figure 4: Mean (±SD) SAR442720 plasma concentration-time profiles on C1D15 and C2D1 (Tablets versus capsules)

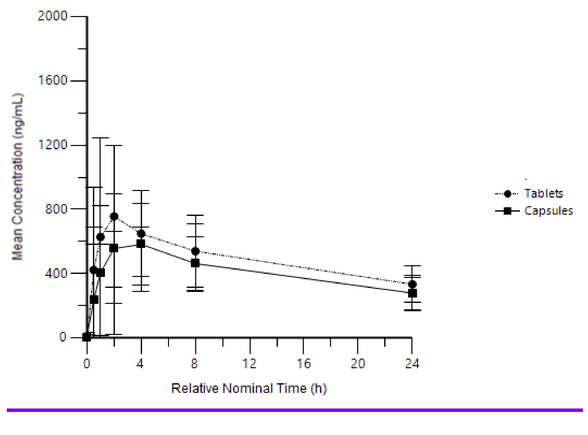


Table 3. Pharmacokinetic parameters for SAR442720 – Formulation effect

Cycle	Day	Formulation/ Meal	Statistics	AUC_{last} (h*ng/mL)	C_{max} (ng/mL)	T_{max}[a] (h)
1	15	Tablets/ Fasted	N	9	9	9
			Mean ± SD	10800 ± 4290	828 ± 310	2.02 [0.9-7.58]
			(Geo. Mean) [CV%]	(9810) [40]	(770) [37]	
2	1	Capsules/ Fasted	N	9	9	9
			Mean ± SD	9800 ± 3970	658 ± 326	3.6 [0.93-24]
			(Geo.Mean) [CV%]	(9120) [41]	(586) [50]	

C_{max}: maximum concentration observed; AUC_{last}: area under curve from zero to the last timepoint
T_{max}: time to reach maximum concentration; CV: coefficient of variation; SD: standard deviation;
[a] Median (Min – Max) values

Table 4. Point estimates of treatment rations with 90% confidence intervals – Formulation effect

Comparison	Parameter	Point estimate	90% CI
Tablets vs. Capsules	C_{max}	1.3136	(1.0742 to 1.6062)
	AUC_{last}	1.0766	(0.8154 to 1.4213)

C_{max}: maximum concentration observed; AUC_{last}: area under curve from zero to the last timepoint;
CI: confidence interval.

CONCLUSIONS

- **Considering the extent of observed food effect, it can be concluded that the presence of food had a negligible effect on SAR442720 exposure, therefore it can be administered with or without food.**
- **Similarly, from a formulation bridging perspective, the observed changes in SAR442720 exposure with tablet instead of capsule administration is not considered clinically meaningful. Therefore, SAR442720 can be dosed as tablets or capsules for future studies.**

DISCLOSURES:

KJ, DS, YZ, and OY are employees of Sanofi and hold stock in the company. SM and GA were employees of Sanofi during the conduct of this study and may have held stock or stock options. ZW and XW are employees of Revolution Medicines and hold stock in the company.

REFERENCES:

1.Cancer Research. 2020 Jul 1;80(13):2889-2902

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