Clinical pharmacology of AZD4635 (A2ARi): Integration of PK data from cancer patients (CP) and healthy volunteer (HV) clinical trials to provide dosing recommendations

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Introduction

- AZD4635 is an A2A receptor antagonist currently being tested as monotherapy and in combination with durvalumab in patients with advanced solid cancers[1]
- In the phase 1 trial, safety and pharmacokinetics (PK) of AZD4635 nanosuspension (NS) was assessed as monotherapy or in combination with durvalumab[2,3]
- In the HV study, a single dose of AZD4635 was evaluated to assess relative bioavailability, effect of high fat meal and effect of proton pump inhibitor (PPI) on new capsule formulation (CF). Here we present PK results from both trials to provide dosing and formulation recommendation for ongoing clinical trials

Methods

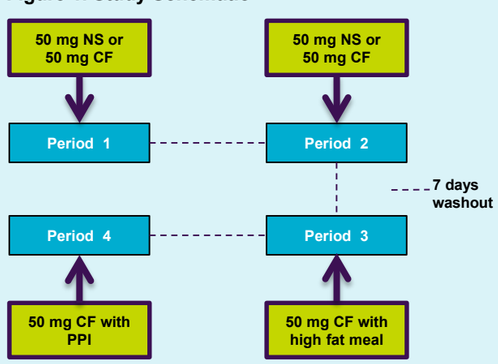
Phase 1 Study in CP:

- An open-label, multicenter study in advanced solid malignancies (NCT02740985)
- AZD4635 was administered as a NS at various dose levels (75mg QD, 100 mg QD & 125 mg BID) as monotherapy or in combination (75 or 100 mg QD) with durvalumab

Clinical Pharmacology Study in HV:

- An open-label, single-dose (50 mg), 2-part crossover clinical pharmacology study was conducted in 20 HV (non-smoking, male) (NCT03710434)

Figure 1. Study Schematic



Methods

- PK parameters including maximum plasma concentration (Cmax) and area under the plasma concentration-time curve from time zero to infinity (AUC) were calculated by non-compartmental analysis methods using Phoenix WinNonlin software (v8.0)
- Formal statistical analyses were performed on the PK parameters to assess relative bioavailability, food effect and impact of pH on AZD4635 PK

Results

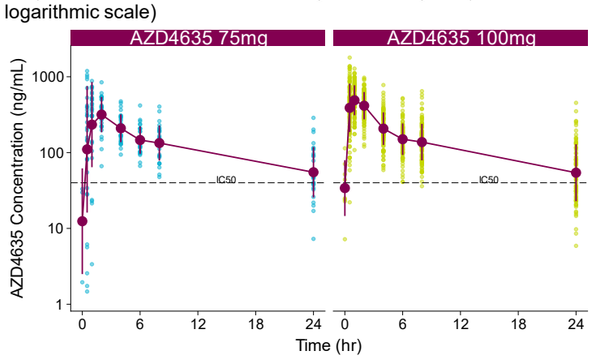
Phase 1 Study in CP:

- AZD4635 exposure at 75 and 100 mg were above the invitro IC_{50} for A2AR inhibition through out the dosing interval (Figure 2)
- AZD4635 NS rapidly appeared in plasma after single or multiple oral administration with median tmax of 1 h and declined in a biphasic manner with a t1/2 of 13.13 h (mean, 100mg QD)

Clinical Pharmacology Study in HV:

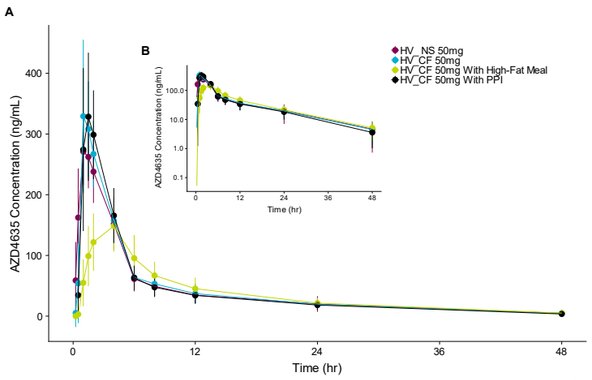
- Peak (Cmax) and overall (AUC) exposure of AZD4635 were approximately 27% and 10% higher, respectively, for CF relative to NS
- High fat meal resulted 12% decrease in AUC and 56% reduction in Cmax (Figure 3 & 4)
- PPI (Lansoprazole) coadministration resulted in similar AUC and Cmax suggesting minimal impact of pH changes

Figure 2. Plasma concentration profile of AZD4635 in CP:
Mean Plasma AZD4635 Concentration vs Time Profiles Following Single Oral Doses of AZD4635 75mg and 100mg NS (semi-logarithmic scale)



Mean ± SD
IC50 @ 1 μM adenosine

Figure 3. Plasma concentration profile of AZD4635 in HV:
A) Mean AZD4635 Concentration vs Time Profiles Following Single Oral Doses of 50 mg AZD4635 NS, CF, CF with high fat meal, CF with PPI (linear scale), B) Semi-logarithmic scale



Mean ± SD

Figure 4. Boxplot of AUC and Cmax of AZD4635 in CP and HV

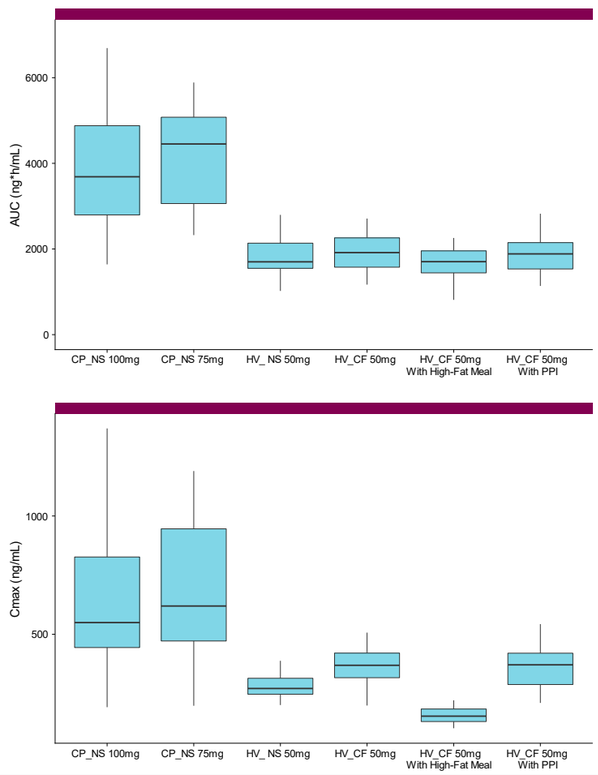


Table 1: Plasma PK parameters of AZD4635

Treatment	Cmax[a] (ng/mL)	AUC[a] (ng.h/mL)	GMR[b] of Cmax	GMR[b] of AUC
HV NS 50mg	281 (17.9)	1890 (29.8)		
HV CF 50mg	355 (28.6)	1920 (27.5)	127.39 (114.77 - 141.41)	109.35 (102.60 - 116.54)
HV CF 50mg With High-Fat Meal	157 (24.0)	1690 (31.8)	44.26 (39.94 - 49.06)	88.03 (82.77 - 93.63)
HV CF 50mg With PPI	351 (26.5)	1870 (27.8)	99 (89.33 - 109.73)	97.66 (91.82 - 103.88)
CP NS 75mg#	594.13 (55.9)	4780.3 (47)		
CP NS 100mg#	580.21 (42.6)	4364.8 (60.4)		

a Geometric mean (CV%)
b Geometric mean ratio (GMR) of test vs reference (90% CI)
CP interim PK data based on DCO of 27 February 2019

Conclusions

- Based on totality of exposure and safety data from ongoing Phase I study in CP at various doses of AZD4635 NS, and data from HV study for both NS and CF, a dose of 75 mg CF has been proposed for further clinical investigations.
- As food can mitigate gastrointestinal toxicities, and there was a lack of significant effect on AUC, the current fasting restrictions have been relaxed to allow patients to receive AZD4635 with or without food.
- No impact of PPI allows for better compliance as the target patient population may also be receiving gastric modifiers (e.g. antacids, H2 antagonists, PPIs).

References

1. Johnström, Peter, et al. "AZD4635 A2A receptor occupancy in cynomolgus monkey using PET and its application to an oncology clinical development program." (2017): 2641-2641.
2. Borodovsky, Alexandra, et al. "Inhibition of A2AR by AZD4635 induces anti-tumor immunity alone and in combination with anti-PD-L1 in preclinical models." (2018): 3751-3751.
3. Bendell, Johanna, et al. "Abstract CT026: Evidence of immune activation in the first-in-human Phase Ia dose escalation study of the adenosine 2a receptor antagonist, AZD4635, in patients with advanced solid tumors." (2019): CT026-CT026.

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