Clinical drug–drug interaction studies through CYP3A and P-gp for BAY 2927088 using itraconazole, carbamazepine, and midazolam

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INTRODUCTION

- Sevabertinib (BAY 2927088) is a potent, oral tyrosine kinase inhibitor that has demonstrated manageable safety and encouraging responses in patients with advanced non-small cell lung cancer with human epidermal growth factor receptor 2-activating mutations[1,2]
- *In vitro*, sevabertinib is metabolized primarily by cytochrome P450 3A4 (CYP3A4) and acts as a substrate for efflux transporters such as P-glycoprotein (P-gp)[3]
- *In vitro*, sevabertinib is an inducer of sensitive CYP3A4 substrates but also a potential CYP3A4 inhibitor[3]
- Here, we report the findings of 2 clinical drug–drug interaction studies evaluating the impact of a strong CYP3A4/P-gp inhibitor (itraconazole [ITZ]) and a strong CYP3A4 inducer (carbamazepine [CBZ]) on sevabertinib, as well as the impact of sevabertinib on a sensitive CYP3A4 substrate (midazolam [MDZ])

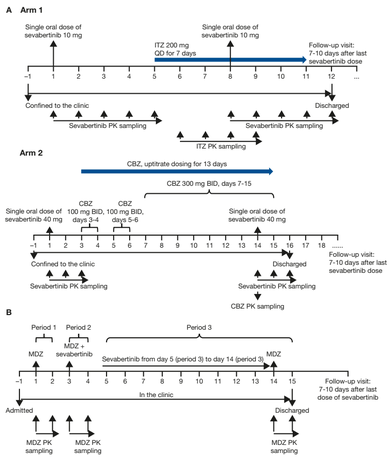
OBJECTIVES

- The primary objectives were to investigate the effect of:
  - ITZ and CBZ on the pharmacokinetics (PK) of sevabertinib
  - Single and multiple doses of sevabertinib on the PK of MDZ
- The secondary objectives were to evaluate the safety and tolerability of sevabertinib when administered alone and co-administered with ITZ, CBZ, or MDZ
- Exploratory objectives included assessing the effect of:
  - ITZ and CBZ on the PK of M1, the major metabolite of sevabertinib
  - Sevabertinib on the PK of 1-hydroxymidazolam (1-OH-MDZ), the major metabolite of MDZ

METHODS

- 2 Phase I, open-label, fixed-sequence, crossover, single-center studies were conducted
- Participants were healthy males or females of non-childbearing potential, aged 18-55 years
- The first 2-arm study investigated the effects of ITZ and CBZ on sevabertinib and M1 (Figure 1A)
  - In arm 1, participants received a single oral dose of sevabertinib 10 mg on days 1 and 8, and ITZ 200 mg once daily (QD) on days 5-11
  - In arm 2, participants received a single oral dose of sevabertinib 40 mg on days 1 and 14, and CBZ 100 mg twice daily (BID) on days 3 and 4, titrated to 200 mg BID on days 5 and 6 and maintained at 300 mg BID (600 mg total daily dose) on days 7-15
  - All participants were included in the safety analysis; 1 participant in arm 1 withdrew from the study and was excluded from PK analyses
- The second single-arm study investigated the impact of sevabertinib on MDZ and 1-OH-MDZ (Figure 1B)
  - In period 1, participants received a single dose of MDZ 1 mg on day 1
  - In period 2, participants received a single dose of MDZ 1 mg co-administered with sevabertinib 20 mg on day 3
  - In period 3, participants received pretreatment with sevabertinib 20 mg BID alone on days 5-14, followed by a single dose of MDZ 1 mg co-administered with sevabertinib 20 mg on day 14
  - All participants were valid for safety and PK analyses
- All treatments were administered within 30 minutes after the start of a light meal
- Plasma drug concentrations were quantified using fully validated liquid chromatography–tandem mass spectrometry methods in accordance with guidelines from the European Medicines Agency, the US Food and Drug Administration, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use,[4–7] and PK parameters were calculated using non-compartmental analysis
- Safety and tolerability were closely monitored throughout the studies
  - Adverse events (AEs) were considered treatment-emergent if they began or worsened from the first study intervention up to 7 days after the last dose, and were reported using MedDRA version 27.0
- The first study was conducted from April 10 to June 12, 2024
- The second study was conducted from April 17 to June 23, 2024

Figure 1. Study schema for the effect of ITZ and CBZ on sevabertinib and M1 (A) and the effect of sevabertinib on MDZ and 1-OH-MDZ (B)



Sparse PK sampling for sevabertinib on days 3-5, 7, 9, and 11-14 are not shown

RESULTS

Effect of ITZ and CBZ on sevabertinib

Participants and demographics

- Overall, 98 participants were enrolled and screened, and 30 participants were eligible for, assigned to, and received ⩾1 study intervention (arm 1 or 2)
  - In arm 1, 1 participant (6.7%) withdrew after the start of the intervention period
  - In arm 2, 1 participant (6.7%) withdrew after the start of the intervention period
- In arm 1, 93.3% of the participants were male, 46.7% were Black or African American, 46.7% were White, 6.7% were Asian, and the participants' mean age was 37.9 years
- In arm 2, 86.7% of the participants were male, 53.3% were Black or African American, 46.7% were White, and the participants' mean age was 39.1 years

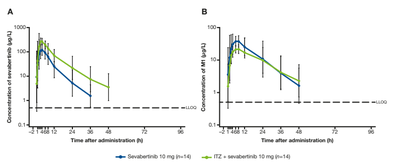
Effect of ITZ on the PK of sevabertinib and M1

- Co-administration with ITZ increased the mean plasma concentrations of sevabertinib considerably, C_{max} by 60%, and area under the curve (AUC) by 125% (Figure 2A and Table 1)
- Co-administration of sevabertinib with ITZ reduced the mean plasma concentrations of M1 considerably, C_{max} by 48%, and AUC by 27% (Figure 2B and Table 1)

Effect of CBZ on the PK of sevabertinib and M1

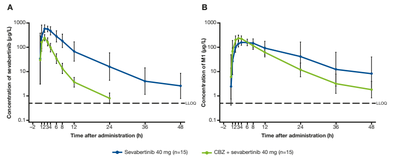
- Pretreatment and co-administration with CBZ reduced the mean plasma concentrations of sevabertinib considerably, C_{max} by 57%, and AUC by 79% (Figure 3A and Table 2)
- Mean plasma concentrations of M1 were considerably higher initially, then lower after 6-8 h of pretreatment with CBZ and co-administration of sevabertinib with CBZ; mean C_{max} was increased by 40%, and mean AUC was reduced by 30% (Figure 3B and Table 2)

Figure 2. Semi-logarithmic plasma concentration–time profiles of sevabertinib alone and when co-administered with ITZ (A) and of M1 following sevabertinib alone and when co-administered with ITZ (B) (geometric mean ± standard deviation)



LLOQ, lower limit of quantification

Figure 3. Semi-logarithmic plasma concentration–time profiles of sevabertinib alone and when pretreated and co-administered with CBZ (A) and of M1 following sevabertinib alone and when pretreated and co-administered with CBZ (B) (geometric mean ± standard deviation)



LLOQ, lower limit of quantification

Safety

- 5 participants (33.3%) in arm 1 and 7 participants (46.7%) in arm 2 had ⩾1 treatment-emergent AE (TEAE), none of which was related to sevabertinib
  - In arm 1, the maximum grade of all TEAEs was 1 or 2
  - In arm 2, 1 patient had a grade 3 TEAE (thrombocytopenia) considered related to CBZ, which led to treatment discontinuation
- No deaths or serious AEs (SAEs) occurred

Effect of sevabertinib on MDZ

Participants and demographics

- Overall, 39 healthy participants were enrolled and screened, 15 of whom were eligible for, assigned to, and received ⩾1 study intervention
  - 4 participants (26.7%) discontinued the intervention period due to a TEAE
- 86.7% of the participants were male, 53.3% were White, 40.0% were Black or African American, 6.7% were Asian, and the participants' mean age was 37.7 years

Effect of sevabertinib on the PK of MDZ and 1-OH-MDZ

- Co-administration with a single dose of sevabertinib increased the mean plasma concentrations of MDZ slightly, C_{max} by 10%, and AUC by 9.8% (Figure 4A and Table 3)
- Pretreatment and co-administration with multiple doses of sevabertinib increased the mean plasma concentrations of MDZ, C_{max} by 79%, and AUC by 95% (Figure 4A and Table 3)
- Pretreatment with sevabertinib and co-administration of sevabertinib with MDZ slightly increased the mean plasma concentrations of 1-OH-MDZ; a single dose of sevabertinib increased C_{max} by 23% and AUC by 13%, and multiple doses of sevabertinib increased C_{max} by 19% and AUC by 17% (Figure 4B and Table 3)

Table 1. Plasma PK parameters of sevabertinib alone and when co-administered with ITZ and of M1 following sevabertinib alone and when co-administered with ITZ

		Sevabertinib			M1		
	N	Sevabertinib alone, geometric mean (% CV)	Sevabertinib with ITZ, geometric mean (% CV)	Ratio of geometric LS mean (2-sided 90% CI)	Sevabertinib alone, geometric mean (% CV)	Sevabertinib with ITZ, geometric mean (% CV)	Ratio of geometric LS mean (2-sided 90% CI)
C_{max}, µg/L	14	190 (24.4)	304 (26.8)	1.60 (1.47, 1.74)	44.1 (25.8)	23.0 (26.5)	0.52 (0.48, 0.56)
AUC, µg•h/L	14	1270 (47.5)	2860 (45.8)	2.25 (2.00, 2.54)	780 (52.7)	566 (52.3)	0.73 (0.67, 0.78)

CI, confidence interval; CV, coefficient of variation; LS, least squares

Table 2. Plasma PK parameters of sevabertinib alone and when pretreated and co-administered with CBZ and of M1 following sevabertinib alone and when pretreated and co-administered with CBZ

		Sevabertinib			M1		
	N	Sevabertinib alone, geometric mean (% CV)	Sevabertinib with CBZ, geometric mean (% CV)	Ratio of geometric LS mean (2-sided 90% CI)	Sevabertinib alone, geometric mean (% CV)	Sevabertinib with CBZ, geometric mean (% CV)	Ratio of geometric LS mean (2-sided 90% CI)
C_{max}, µg/L	15	675 (28.2)	290 (41.7)	0.43 (0.36, 0.51)	172 (27.8)	240 (27.6)	1.40 (1.22, 1.60)
AUC, µg•h/L	15	4250 (56.0)	900 (38.5)	0.21 (0.18, 0.25)	2840 (66.0)	2080 (33.7)	0.70 (0.58, 0.85)

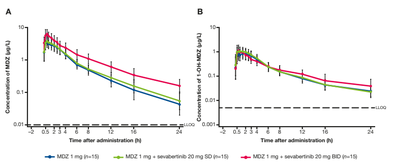
CI, confidence interval; CV, coefficient of variation; LS, least squares

Table 3. Plasma PK parameters of MDZ alone and when co-administered with sevabertinib

	MDZ alone, geometric mean (% CV) *N*=15	MDZ with sevabertinib single dose, geometric mean (% CV) *N*=15	MDZ with sevabertinib multiple doses, geometric mean (% CV) *N*=11	MDZ with sevabertinib single dose/MDZ alone, ratio of geometric LS mean (2-sided 90% CI)	MDZ with sevabertinib multiple doses/ MDZ alone, ratio of geometric LS mean (2-sided 90% CI)
MDZ					
C_{max}, µg/L	3.67 (35.7)	4.05 (27.2)	6.69 (36.9)	1.10 (1.00, 1.22)	1.79 (1.41, 2.26)
AUC, µg•h/L	16.1 (29.5)	17.6 (26.4)	30.6 (28.3)	1.10 (1.00, 1.20)	1.95 (1.65, 2.32)
1-OH-MDZ					
C_{max}, µg/L	1.03 (54.8)	1.27 (38.2)	1.20 (64.0)	1.23 (1.08, 1.40)	1.19 (0.83, 1.70)
AUC, µg•h/L	5.07 (37.0)	5.75 (30.4)	5.69 (43.5)	1.13 (1.07, 1.20)	1.17 (1.00, 1.37)

CI, confidence interval; CV, coefficient of variation; LS, least squares

Figure 4. Semi-logarithmic plasma concentration–time profiles of MDZ alone and when co-administered with sevabertinib (A) and of 1-OH-MDZ following MDZ alone and when co-administered with sevabertinib (B) (geometric mean ± standard deviation)



Safety

- 9 participants (60.0%) had ⩾1 TEAE and ⩾1 TEAE related to sevabertinib
  - There was 1 grade 3 TEAE (diarrhea)
  - 4 participants (26.7%) had grade 2 TEAEs related to sevabertinib (drug eruption) in period 3, which led to treatment discontinuation
- No deaths or SAEs occurred

CONCLUSIONS

- Sevabertinib exposure was increased by the strong CYP3A4 and P-gp inhibitor ITZ and reduced by the strong CYP3A4 and P-gp inducer CBZ
- Sevabertinib pretreatment and co-administration increased MDZ exposure, demonstrating that sevabertinib is a weak CYP3A4 inhibitor
- The TEAEs that occurred during both studies were generally low grade and manageable, and no SAEs occurred

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