Effect of food and esomeprazole on the pharmacokinetics of BAY 2927088

PI-065

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INTRODUCTION

- Mutations in human epidermal growth factor receptor 2 (*HER2*) have been reported in approximately 2-4% of patients with non-small cell lung cancer (NSCLC) and are associated with poor patient outcomes[1,2]
- Sevabertinib (BAY 2927088) is an oral tyrosine kinase inhibitor that potently inhibits mutant *HER2* and is being developed for the treatment of adult patients with advanced NSCLC harboring *HER2*-activating mutations[3,4]
- Sevabertinib is a high-permeability compound with low, pH-dependent aqueous solubility[5] that has demonstrated manageable safety[6]
- We performed an open-label, randomized, single-center crossover study to evaluate the effect of food or an acid-reducing agent on the pharmacokinetics (PK) of sevabertinib in healthy participants

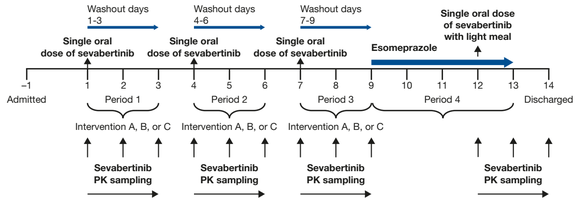
OBJECTIVES

- The primary objectives were to evaluate the effect of:
  - Food on the PK of sevabertinib administered to healthy (1) fasted participants, (2) participants fed a light, low-fat meal, and (3) participants fed a high-fat, high-calorie (HFHC) meal
  - The proton-pump inhibitor esomeprazole on the PK of sevabertinib administered to healthy participants after a light, low-fat meal
- The secondary objective was to assess the safety and tolerability of sevabertinib under fasting or fed conditions, and alone and co-administered with esomeprazole, in healthy participants

METHODS

- Eligible participants were healthy males or females of non-childbearing potential, aged 18-55 years, and with body mass index within the range of 18 to 30 kg/m^2
- Figure 1 shows the study schema. Participants received 4 total single doses of sevabertinib 20 mg and were randomized to 1 of 3 intervention sequences for periods 1-3 during days 1-9 (A-B-C, B-C-A, or C-A-B), with each intervention consisting of a single dose of sevabertinib 20 mg in:
  - A fasted state (A)
  - A fed state: light, low-fat meal (B)
  - A fed state: HFHC meal (C)
- All participants then received 5 total single doses of esomeprazole 40 mg once daily in a fasted state in period 4 from days 9 to 13, and a single dose of sevabertinib 20 mg on day 12 after a light, low-fat meal
- Sevabertinib was administered within 30 minutes after the start of each meal

Figure 1. Study schema



Participants were confined to clinic during days −1 to 14, followed by an ambulant clinic visit 7-10 days after discharge for follow-up

- In all periods, sevabertinib PK sampling was performed before dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours after dosing
- Safety and tolerability were closely monitored throughout the study
  - Treatment-emergent adverse events (TEAEs) were reported using MedDRA version 27.0
- Maximum observed drug concentration (C_{max}) and area under the curve (AUC) of sevabertinib in plasma were calculated using non-compartmental analysis methods and by analysis of variance, assuming log-normally distributed data
  - Analysis for food effect included fixed effects for intervention, intervention sequence, and period and random effect for the participant
  - Analysis for esomeprazole effect included fixed effect for the study intervention and random effect for the participant
- All participants were included in PK and safety analyses
- This study was conducted from March 29 to June 11, 2024

RESULTS

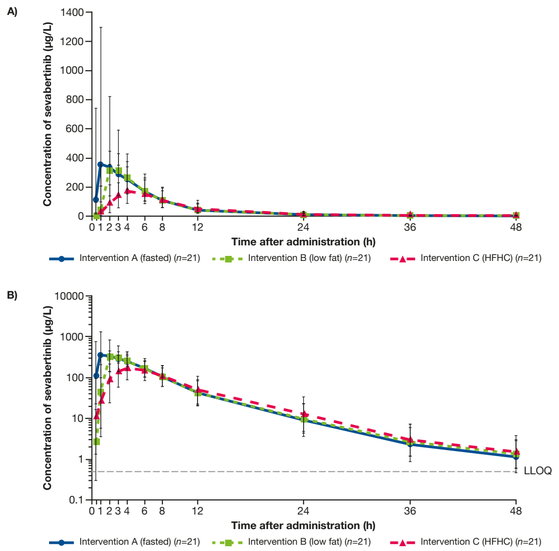
Participants and demographics

- In total, 21 healthy participants were randomized, received intervention, and completed the study
  - Median age was 43.0 years, and 95.2% were male
  - 42.9% of participants were White, 47.6% were Black, 4.8% were Asian, and 4.8% were American Indian or Alaska native
  - 81.0% reported medical history findings, none of which prevented participation in the study

Effect of food

- Median time to reach C_{max} of plasma sevabertinib was 1 h in a fasted state (intervention A); the overall pattern of the concentration–time curves was similar under fasted and fed conditions (interventions B and C) (Figure 2)

Figure 2. Linear (A) and semi-logarithmic (B) plasma concentration–time profiles of sevabertinib after single-dose administration of 20 mg without food (intervention A) and with food (interventions B and C) (geometric mean ± standard deviation)



LLOQ, lower limit of quantification

- Both mean AUC and C_{max} were reduced when sevabertinib was administered under fed conditions (interventions B and C) compared with a fasted state (intervention A), and this effect was greater after HFHC meals (Table 1)
  - With a light, low-fat meal, mean AUC and mean C_{max} decreased by 16% and 28%, respectively, compared with a fasted state
  - With an HFHC meal, mean AUC and mean C_{max} decreased by 28% and 56%, respectively, compared with a fasted state
  - Comparing the effect of an HFHC meal with the effect of a light, low-fat meal, mean AUC and mean C_{max} decreased by 14% and 39%, respectively

Table 1. Effect of food on sevabertinib plasma PK parameters

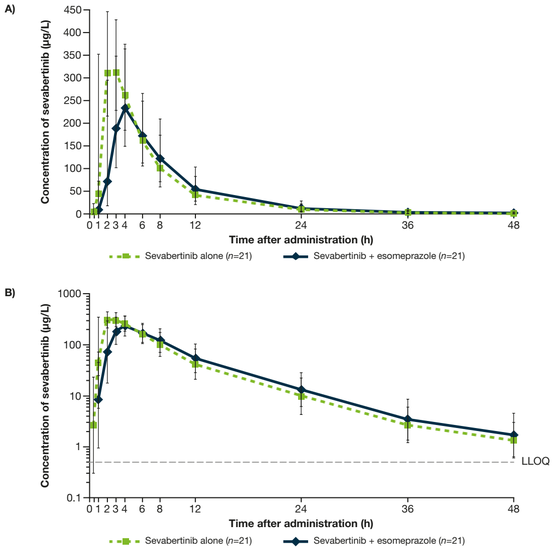
	C_{max}, µg/L	AUC, µg•h/L
n	21	21
Intervention A (fasted), geometric mean (% CV)	490 (62.8)	2680 (56.9)
Intervention B (low fat), geometric mean (% CV)	354 (34.9)	2250 (44.2)
Intervention C (HFHC), geometric mean (% CV)	217 (53.4)	1940 (57.1)
Low fat/fasted, ratio of geometric LS mean (2-sided 90% CI)	0.72 (0.63, 0.83)	0.84 (0.76, 0.92)
HFHC/fasted, ratio of geometric LS mean (2-sided 90% CI)	0.44 (0.39, 0.51)	0.72 (0.66, 0.80)
HFHC/low fat, ratio of geometric LS mean (2-sided 90% CI)	0.61 (0.53, 0.70)	0.86 (0.78, 0.95)

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

Effect of esomeprazole

- Overall, the pattern of the concentration–time curves after sevabertinib administration was similar with or without esomeprazole, although the median time to reach C_{max} was longer and peak plasma levels were lower with esomeprazole co-administration (Figure 3)

Figure 3. Linear (A) and semi-logarithmic (B) plasma concentration–time profiles of sevabertinib after single-dose administration of 20 mg alone (intervention B) and co-administered with esomeprazole (geometric mean ± standard deviation)



LLOQ, lower limit of quantification

- Co-administration of esomeprazole did not affect mean AUC of sevabertinib and decreased mean C_{max} of sevabertinib by 29% compared with sevabertinib alone (Table 2)

Table 2. Effect of esomeprazole on plasma sevabertinib PK parameters

	C_{max}, µg/L	AUC, µg•h/L
n	21	21
Sevabertinib alone,[a] geometric mean (% CV)	354 (34.9)	2250 (44.2)
Sevabertinib with esomeprazole, geometric mean (% CV)	250 (43.7)	2030 (51.3)
Sevabertinib + esomeprazole/sevabertinib alone, ratio of geometric LS mean (2-sided 90% CI)	0.71 (0.61, 0.82)	0.90 (0.79, 1.03)

[a]Intervention B (low fat)

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

Safety

- 9 participants (42.9%) had at least 1 TEAE, none greater than grade 1 in severity
- No sevabertinib-related TEAEs and 1 esomeprazole-related TEAE (headache) were reported
- There were no deaths, serious adverse events, or discontinuations due to TEAEs

CONCLUSIONS

- Sevabertinib exposure was decreased slightly when administered in a fed state, compared with a fasted state, with no clinically relevant difference between meal types (light, low fat *vs* HFHC)
- Sevabertinib exposure was not affected by esomeprazole co-administration, although a slight decrease in peak sevabertinib concentration was observed
- These results support the administration of sevabertinib with food or with acid-reducing agents in clinical trials
- Sevabertinib was safe and well tolerated in healthy participants

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