Clinical drug–drug interaction studies investigating the effect of BAY 2927088 on P-gp and BCRP using dabigatran etexilate and rosuvastatin

PII-022

Chunlin Chen,[1] Michaela Damaske,[2] Frank-Thorsten Hafner,[3] Robert Fricke,[2] Stefanie Reif,[2] Sue Prendergast,[4] Philip Lienau,[2] Bart Ploeger,[2] Barbara J. Brennan[1]

[1]Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA; [2]Bayer AG, Berlin, Germany; [3]Bayer AG, Wuppertal, Germany; [4]Bayer plc, Reading, UK

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 harboring *HER2*-activating mutations[1,2]
- *In vitro*, sevabertinib has shown evidence of inhibiting the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)[3]
  - Potential drug–drug interactions due to inhibition of intestinal and systemic P-gp and BCRP at the clinically relevant sevabertinib dose of 20 mg twice daily may be expected
- Here, we report the findings of clinical drug–drug interaction studies investigating the effects of multiple doses of sevabertinib on the pharmacokinetics (PK) of the P-gp substrate dabigatran etexilate and the BCRP substrate rosuvastatin in healthy volunteers

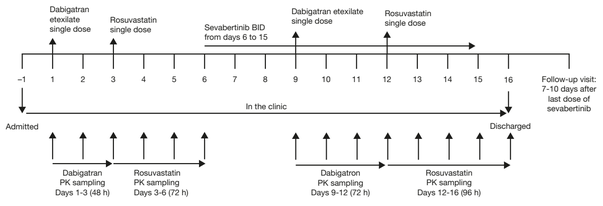
OBJECTIVES

- The primary objective was to evaluate the effects of sevabertinib on the PK of unconjugated dabigatran or rosuvastatin
- The secondary objective was to assess the safety and tolerability of sevabertinib when administered alone and with dabigatran or rosuvastatin
- Exploratory objectives included evaluating the effects of sevabertinib on the PK of coproporphyrins I and III, endogenous biomarkers for organic anion-transporting polypeptides 1B1 and 1B3

METHODS

- This was a Phase I, open-label, non-randomized, fixed-sequence, crossover, single-center trial (Figure 1)
  - 2 doses of dabigatran 75 mg and 2 doses of rosuvastatin 10 mg were administered to each participant, alone or in combination with sevabertinib
  - Sevabertinib 20 mg twice daily was administered in a fed state over 10 days, resulting in a total dose of 400 mg for each participant who completed the intervention period
  - Serial plasma samples were collected throughout the intervention period for dabigatran and rosuvastatin PK analyses
- Participants were healthy males or females of non-childbearing potential, aged 18-55 years
- All 15 participants who received at least 1 treatment were included in the safety analysis set and the analyses of dabigatran PK and coproporphyrin PK. 1 participant withdrew early from the study and was excluded from the PK analysis of rosuvastatin
- Plasma concentrations of sevabertinib, dabigatran, rosuvastatin, and coproporphyrins I and III 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[5-8]
- Plasma PK parameters were calculated using non-compartmental analysis
- The ratios of geometric least squares means and 2-sided 90% confidence intervals were determined assuming log-normally distributed data and by analysis of variance, including intervention and participant effects
- Safety and tolerability were closely monitored throughout the study
  - Adverse events were considered treatment-emergent (TEAE) if they had started or worsened after the first administration of study intervention (dabigatran) up to the follow-up visit, and were reported using MedDRA version 27.0
- The study was conducted from March 25 to June 10, 2024

Figure 1. Study schema



Sparse PK sampling for sevabertinib on days 7-12 and blood sampling for coproporphyrin I and III on days 3, 4, 12, and 13 are not shown

RESULTS

Participants and demographics

- Of 43 participants who were enrolled and screened, 15 were eligible and then assigned to and received ⩾1 study intervention
  - All participants were male (100%), with a mean age of 31.5 years, and 60% were White. Although current smokers were not allowed, 80% reported a history of smoking
  - 14 participants (93.3%) completed the intervention period and 1 participant (6.7%) withdrew after the start of the intervention period

PK of dabigatran

- When co-administered with sevabertinib, mean plasma concentrations of unconjugated dabigatran were slightly higher (Figure 2)
- Co-administration with sevabertinib decreased the maximum observed drug concentration (C_{max}) of unconjugated dabigatran by less than 5% and increased the area under the curve (AUC) by 39% (Table 1)

PK of rosuvastatin

- Mean plasma concentrations of rosuvastatin were slightly higher up to 24 h after dosing when co-administered with sevabertinib, and comparable with or without sevabertinib after 24 h (Figure 3)
- Co-administration with sevabertinib increased the C_{max} of rosuvastatin by 37% and the AUC by 25% (Table 2)

PK of coproporphyrins I and III

- The C_{max} and AUC (from 0 to 24 h) of coproporphyrin I were nearly unchanged when rosuvastatin was co-administered with sevabertinib
- For coproporphyrin III, almost all concentrations were below the lower limit of quantification

Safety

- All 15 participants (100%) reported gastrointestinal TEAEs during sevabertinib treatment, alone or in combination with dabigatran or rosuvastatin
  - The most common gastrointestinal TEAE was diarrhea (93.3%)
  - Other frequent TEAEs were skin and subcutaneous tissue disorders (86.7%), respiratory, thoracic, and mediastinal disorders (53.3%), and eye disorders (33.3%)

Table 1. Plasma PK parameters of unconjugated dabigatran alone and when co-administered with sevabertinib

	N	Unconjugated dabigatran alone, geometric mean (% CV)	Unconjugated dabigatran with sevabertinib, geometric mean (% CV)	Ratio of geometric LS mean (2-sided 90% CI)
C_{max}, µg/L	15	47.0 (29.4)	45.3 (35.8)	0.96 (0.88, 1.06)
AUC, µg•h/L	15	375 (30.5)	522 (30.7)	1.39 (1.29, 1.50)

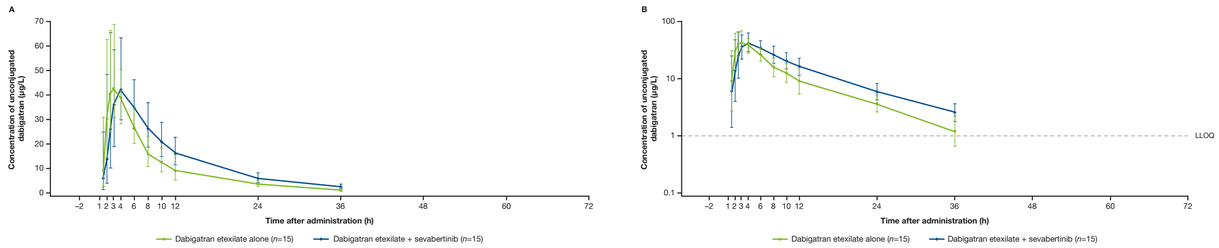
CI, confidence interval; CV, coefficient of variation; LS, least squares

Table 2. Plasma PK parameters of rosuvastatin alone and when co-administered with sevabertinib

	N	Rosuvastatin alone, geometric mean (% CV)	Rosuvastatin with sevabertinib, geometric mean (% CV)	Ratio of geometric LS mean (2-sided 90% CI)
C_{max}, µg/L	14	1.90 (76.0)	2.60 (58.7)	1.37 (1.14, 1.63)
AUC, µg•h/L	14	22.3 (65.5)	27.9 (54.5)	1.25 (1.13, 1.39)

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

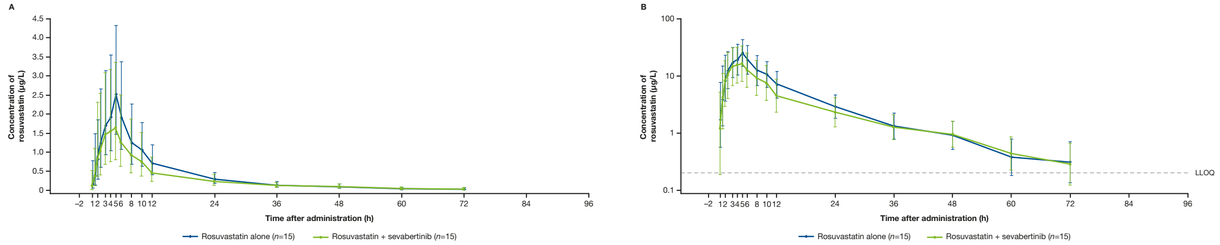
Figure 2. Linear (A) and semi-logarithmic (B) plasma concentration–time profiles of unconjugated dabigatran alone and when co-administered with sevabertinib (geometric mean ± standard deviation)



Blood sampling for dabigatran PK was up to 48 h after dosing on day 1 and up to 72 h after dosing on day 9

LLOQ, lower limit of quantification

Figure 3. Linear (A) and semi-logarithmic (B) plasma concentration–time profiles of rosuvastatin alone and when co-administered with sevabertinib (geometric mean ± standard deviation)



Blood sampling for rosuvastatin PK was up to 72 h after dosing on day 1 and up to 96 h after dosing on day 12

LLOQ, lower limit of quantification

- 4 participants (26.7%) experienced dabigatran-related TEAEs and 2 participants (13.3%) experienced rosuvastatin-related TEAEs
- No TEAEs were of severe intensity, and there were no deaths, serious adverse events, or discontinuations due to TEAEs

CONCLUSIONS

- Pretreatment and co-administration with sevabertinib slightly increased the exposure of unconjugated dabigatran and rosuvastatin, indicating weak inhibition of P-gp and BCRP, respectively
- Sevabertinib resulted in no change to coproporphyrin I exposure, supporting no inhibition of organic anion-transporting polypeptides 1B1 and 1B3
- Sevabertinib was safe and well tolerated; the most common TEAEs were consistent with the safety profile of sevabertinib and manageable

References

1. Girard N et al. *J Clin Oncol* 2024; 42 (Suppl 17): LBA8598
2. Loong HHF et al. *Ann Oncol* 2023; 34 (Suppl 2): S761-S762
3. Bayer data on file
4. EMA. 2011. Available at: https://www.ema.europa.eu/en/documents/other/overview-comments-received-guideline-validation-bioanalytical-methods-emeachmpewp1922172009_en.pdf
5. US FDA. 2018. Available at: https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf
6. ICH. 2022. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m10-bioanalytical-method-validation-step-5_en.pdf
7. EMA. 2012. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-laboratories-perform-analysis-or-evaluation-clinical-trial-samples_en.pdf

Acknowledgments

This study was supported by Bayer AG. Caudex, an IPG Health Company, provided medical writing and editorial assistance in the development of this poster, funded by Bayer AG

Scan this QR code to download an electronic version of this poster

Presented at the American Society for Clinical Pharmacology and Therapeutics Annual Meeting, May 28-31, 2025, Washington, DC, USA

Presenting author: Barbara J. Brennan