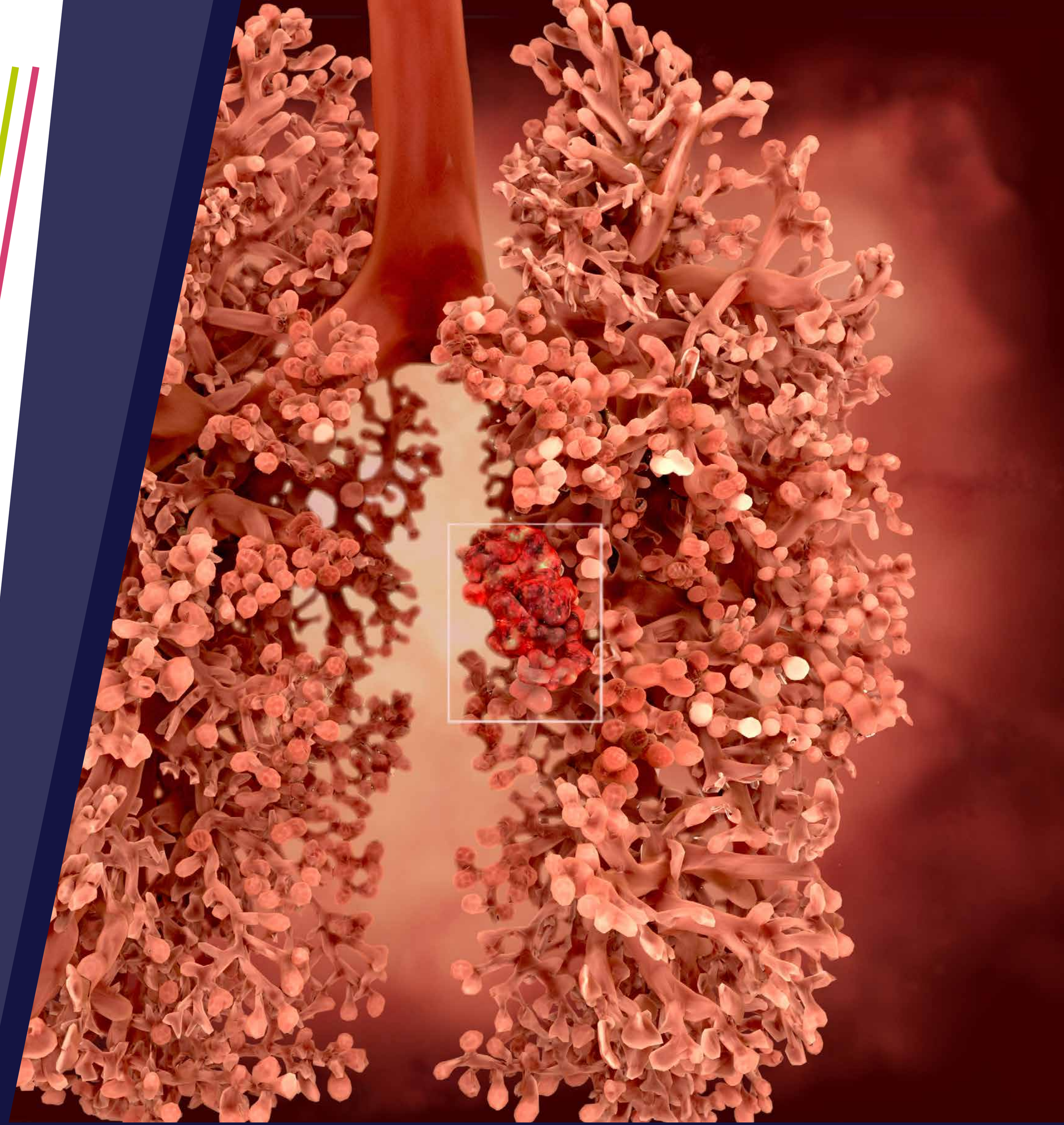
SEVABERTINIB

CLINICAL DRUG–DRUG INTERACTION STUDIES INVESTIGATING THE PHARMACOKINETICS AND SAFETY OF SEVABERTINIB

Alissa Uddin, PharmD[1], on behalf of Barbara J. Brennan, PharmD[1], Michaela Damaske[2], Frank-Thorsten Hafner, PhD[3], Robert Fricke, PhD[2], Isabel Piel, PhD[3], Clemens-Jeremias von Buehler, PhD[3], Michael Niehues, PhD[2,3], Natalia Jungmann, PhD[3], Stefanie Reif, PhD[2], Sue Prendergast, MSc[4], Philip Lienau, PhD[2], Bart Ploeger, PhD[2], Chunlin Chen, MD, PhD[1,a]

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

[a]Affiliation at the time the study was performed



INTRODUCTION

Sevabertinib (BAY 2927088) is an oral tyrosine kinase inhibitor being developed for treatment of adults with advanced NSCLC harboring HER2-activating mutations[1,2]

OBJECTIVE

Primary objectives were to investigate the effect of:

- The CYP3A4/P-gp inhibitor itraconazole and CYP3A4/P-gp inducer carbamazepine on the PK of sevabertinib (NCT06348888)
- Sevabertinib on the PK of the CYP3A4 substrate midazolam (NCT06360211)
- Sevabertinib on P-gp using dabigatran etexilate, and on BCRP using rosuvastatin (NCT06329895)

METHODS

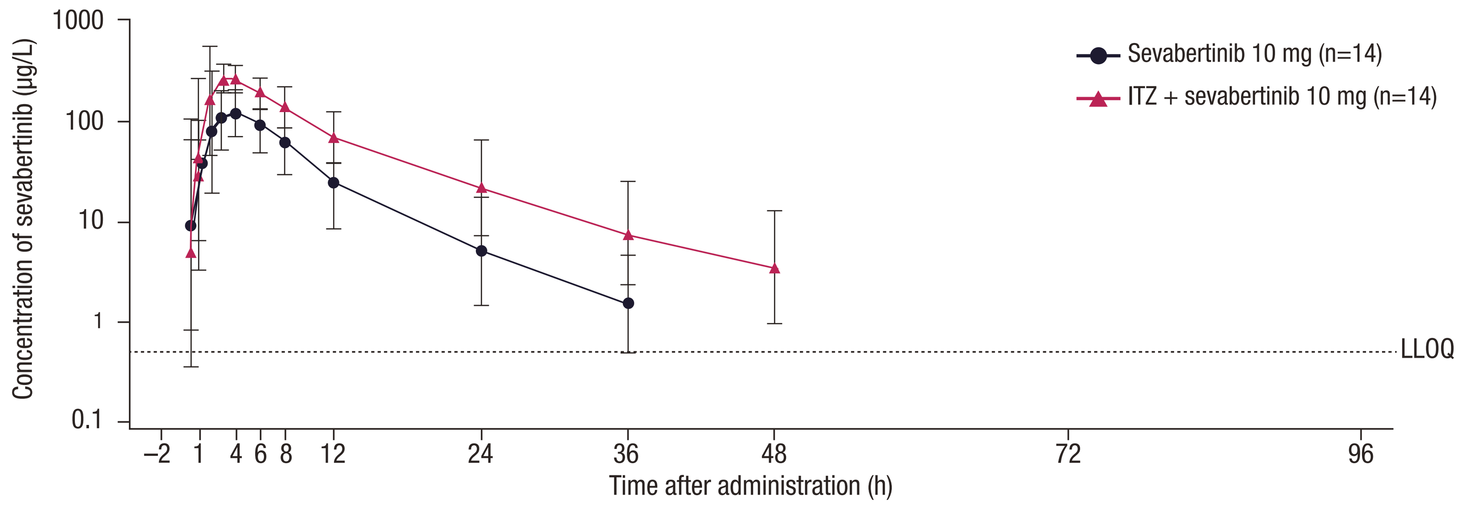
Three Phase I, open-label, fixed sequence, crossover trials were conducted in healthy participants

Dosing schema for the three clinical trials are presented in the online supplement

AUC and C_{max} were assessed, and safety was monitored throughout the studies

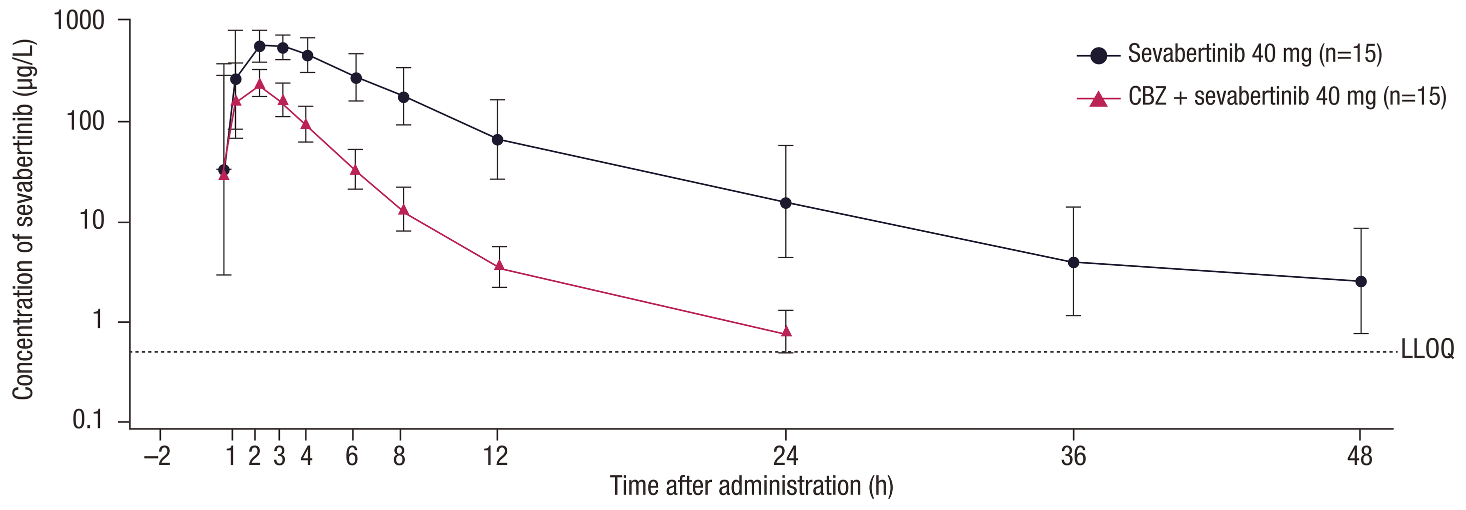
NCT06348888

Co-administration with itraconazole increased mean sevabertinib AUC by 125% and C_{max} by 60%


Concentration of sevabertinib (µg/L)
1000
100
10
1
0.1
–2
1
4
6
8
12
24
36
48
72
96
Time after administration (h)
Sevabertinib 10 mg (n=14)
ITZ + sevabertinib 10 mg (n=14)
LLOQ

AUC, area under the curve; C_{max}, maximum observed plasma drug concentration; h, hours; ITZ, itraconazole; LLOQ, lower limit of quantification.

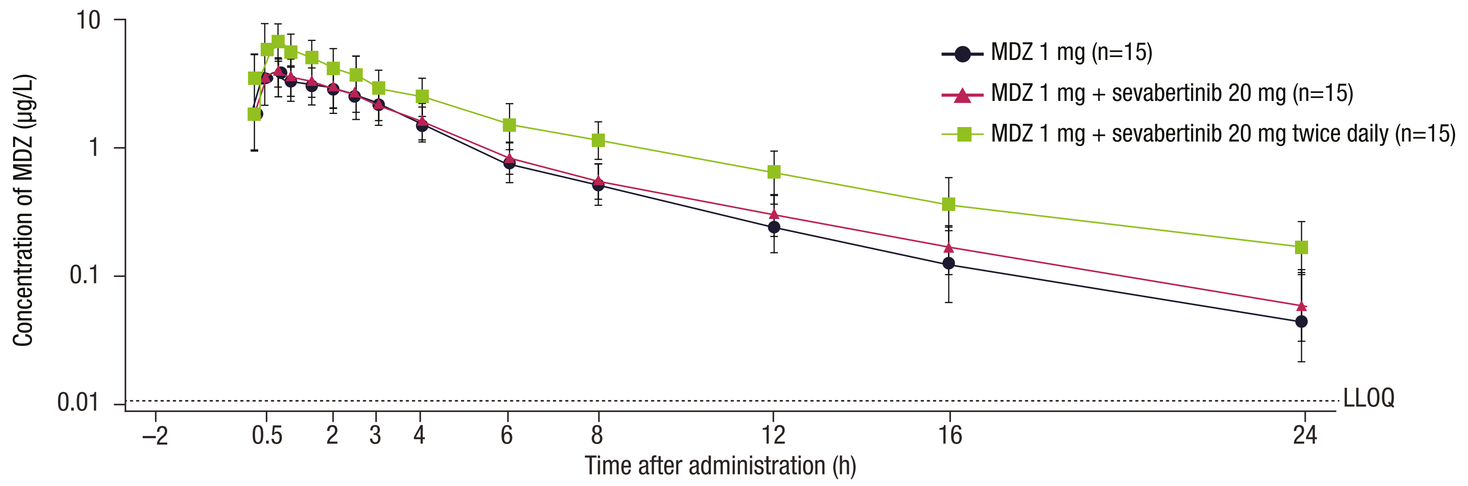
Co-administration with carbamezapine reduced mean sevabertinib AUC by 79% and C_{max} by 57%


Concentration of sevabertinib (µg/L)
1000
100
10
1
0.1
–2
1
2
3
4
6
8
12
24
36
48
Time after administration (h)
Sevabertinib 40 mg (n=15)
CBZ + sevabertinib 40 mg (n=15)
LLOQ

AUC, area under the curve; CBZ, carbamazepine; C_{max}, maximum observed plasma drug concentration; h, hours; LLOQ, lower limit of quantification.

NCT06360211

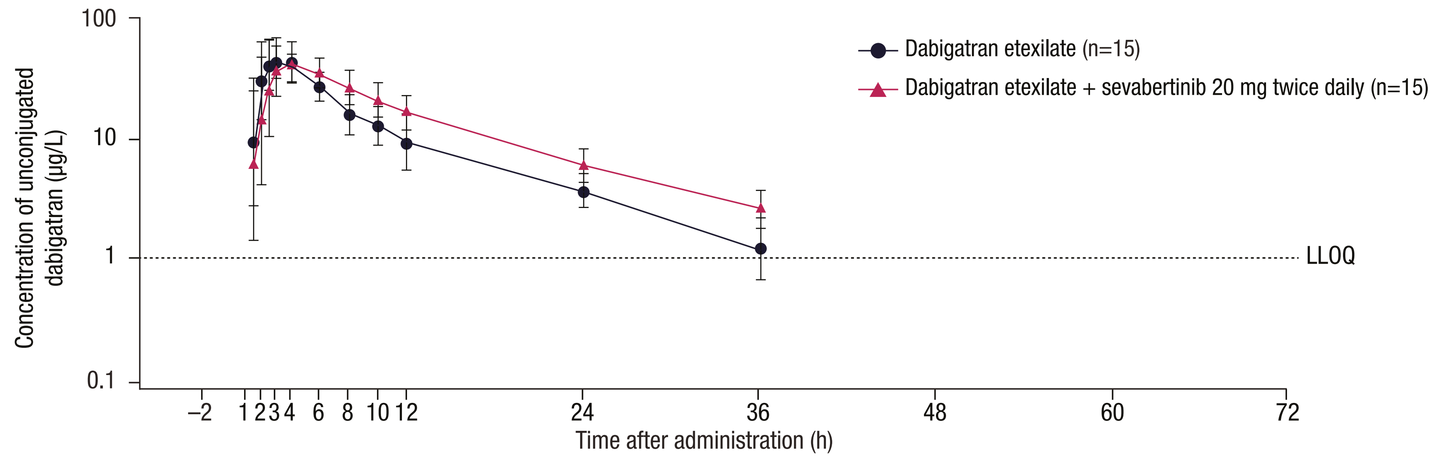
Co-administration with a single dose of sevabertinib increased mean midazolam AUC by 10% and C_{max} by 10%
Pretreatment and co-administration with multiple doses of sevabertinib increased mean midazolam AUC by 95% and C_{max} by 79%


Concentration of MDZ (µg/L)
10
1
0.1
0.01
–2
0.5
2
3
4
6
8
12
16
24
Time after administration (h)
MDZ 1 mg (n=15)
MDZ 1 mg + sevabertinib 20 mg (n=15)
MDZ 1 mg + sevabertinib 20 mg twice daily (n=15)
LLOQ

AUC, area under the curve; C_{max}, maximum observed plasma drug concentration; h, hours; LLOQ, lower limit of quantification; MDZ, midazolam.

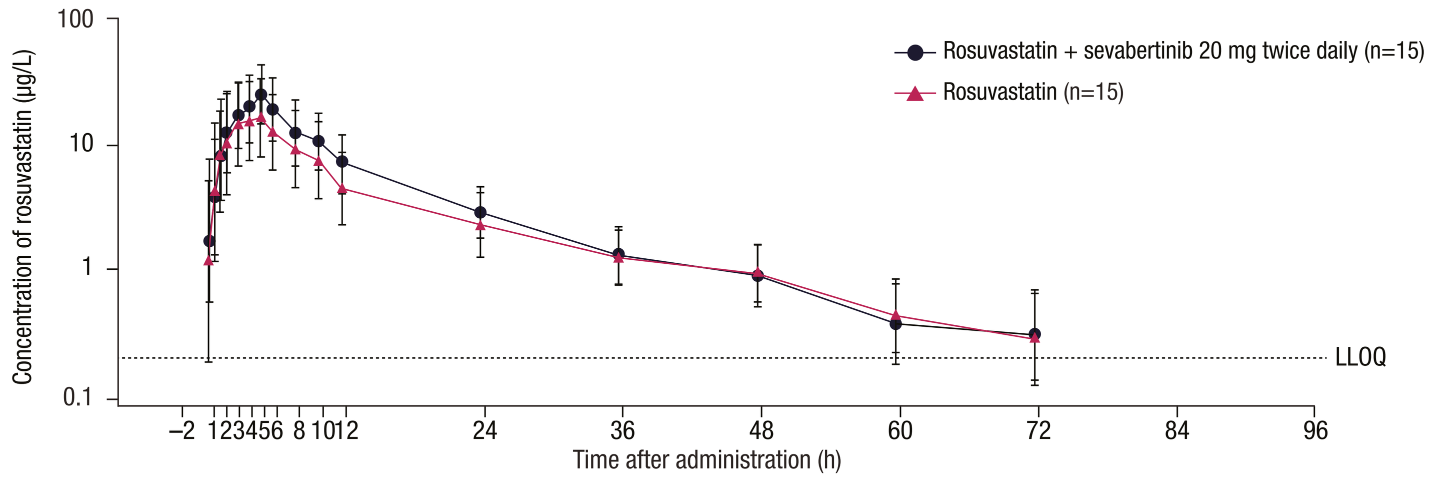
NCT06329895

Co-administration with sevabertinib increased unconjugated dabigatran AUC by 39% and decreased C_{max} by 4%


Concentration of unconjugated dabigatran (µg/L)
100
10
1
0.1
–2
1
2
3
4
6
8
10
12
24
36
48
60
72
Time after administration (h)
Dabigatran etexilate (n=15)
Dabigatran etexilate + sevabertinib 20 mg twice daily (n=15)
LLOQ

AUC, area under the curve; C_{max}, maximum observed plasma drug concentration; h, hours; LLOQ, lower limit of quantification.

Co-administration with sevabertinib increased rosuvastatin AUC by 25% and C_{max} by 37%


Concentration of rosuvastatin (µg/L)
100
10
1
0.1
–2
1
2
3
4
5
6
8
10
12
24
36
48
60
72
84
96
Time after administration (h)
Rosuvastatin + sevabertinib 20 mg twice daily (n=15)
Rosuvastatin (n=15)
LLOQ

AUC, area under the curve; C_{max}, maximum observed plasma drug concentration; h, hours; LLOQ, lower limit of quantification.

CONCLUSIONS

- Sevabertinib exposure was increased by CYP3A4/P-gp inhibition and reduced by CYP3A4/P-gp induction
- Our findings indicate that sevabertinib is a weak inhibitor of CYP3A4, P-gp, and BCRP
- Sevabertinib was well tolerated in all three studies

SCAN ME FOR MORE INFO

References: 1. Siegel F et al. Cancer Res 2023;83(Suppl 7):1098-1099;
2. Siegel F et al. EJC Supplements 2022;174(Suppl 1):S9-S10.

Abbreviations: AUC, area under the curve; BCRP, breast cancer resistant protein; C_{max}, maximum observed plasma drug concentration; CYP3A4, cytochrome P450 3A4; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; P-gp, P-glycoprotein; PK, pharmacokinetics.

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