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Effect of itraconazole and rabeprazole on the pharmacokinetics of vimseltinib, an oral inhibitor of the colony-stimulating factor 1 receptor, in healthy participants

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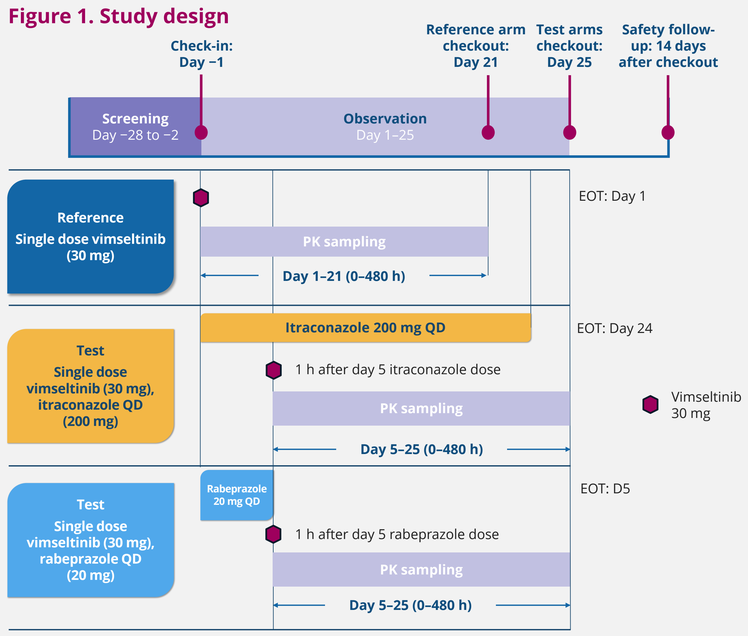
Introduction

- Tenosynovial giant cell tumor (TGCT) is a locally aggressive neoplasm caused by the dysregulation of the colony-stimulating factor 1 (*CSF1*) gene leading to overproduction of CSF1[1,2]
- Vimseltinib is an oral, switch-control tyrosine kinase inhibitor designed to selectively and potently inhibit the CSF1 receptor[3]
  - Vimseltinib was approved in February 2025 by the US Food and Drug Administration (FDA) for the treatment of adult patients with symptomatic TGCT for whom surgical resection will potentially cause worsening functional limitation or severe morbidity[4]
  - In September 2025, vimseltinib was also approved by the European Commission for the treatment of TGCT in a similar patient population[5]
- The US Prescribing Information and European Medicines Agency Summary of Product Characteristics for vimseltinib include guidance for concomitant medication use based on preclinical studies
  - In these studies, vimseltinib was a P-glycoprotein (P-gp) substrate and showed pH-dependent solubility, indicating potential for drug-drug interactions (DDIs) with P-gp inhibitors and acid-reducing agents (ie, proton pump inhibitors [PPIs])
- Consistent with the pivotal MOTION phase 3 trial, vimseltinib 30 mg was the dose tested in this DDI assessment
- Here, we report results from a randomized, open-label, phase 1 study investigating the effects of itraconazole (P-gp inhibitor) and rabeprazole (PPI) on the pharmacokinetics (PK) of vimseltinib in healthy adults

Methods

- Eligible participants were adults aged 18–60 years with a body mass index ≥18.5 and ≤30.4 kg/m^2
- Key exclusion criteria included significant disease or surgical history, recent (≤14 days prior to day 1) prescription medication intake, and pregnancy or breastfeeding for female participants
- Participants were randomized 1:1:1 and received either a single 30-mg dose of vimseltinib alone (reference), vimseltinib with itraconazole (test), or vimseltinib with rabeprazole (test; **Figure 1**)
- Blood samples were collected for PK analysis as scheduled per arm
- Log-transformed PK parameters (maximum concentration [C_{max}], area under the curve [AUC] from first dose to last quantifiable concentration [$AUC_{0-tlast}$], and AUC extrapolated to infinity [AUC_{0-inf}]) for vimseltinib alone (reference) vs with itraconazole (test) or with rabeprazole (test) were analyzed using an analysis of variance model with treatment as a fixed effect
- Geometric mean ratios (GMRs) along with their corresponding 90% confidence intervals, were constructed to determine the effect of itraconazole and rabeprazole on vimseltinib PK
- Safety was monitored throughout the study

Figure 1. Study design



EOT, end of treatment; PK, pharmacokinetics; QD, once daily.

Results

- A total of 89 participants were enrolled in this study
- Baseline characteristics were similar between treatment arms (**Table 1**)

Table 1. Participant demographics and characteristics

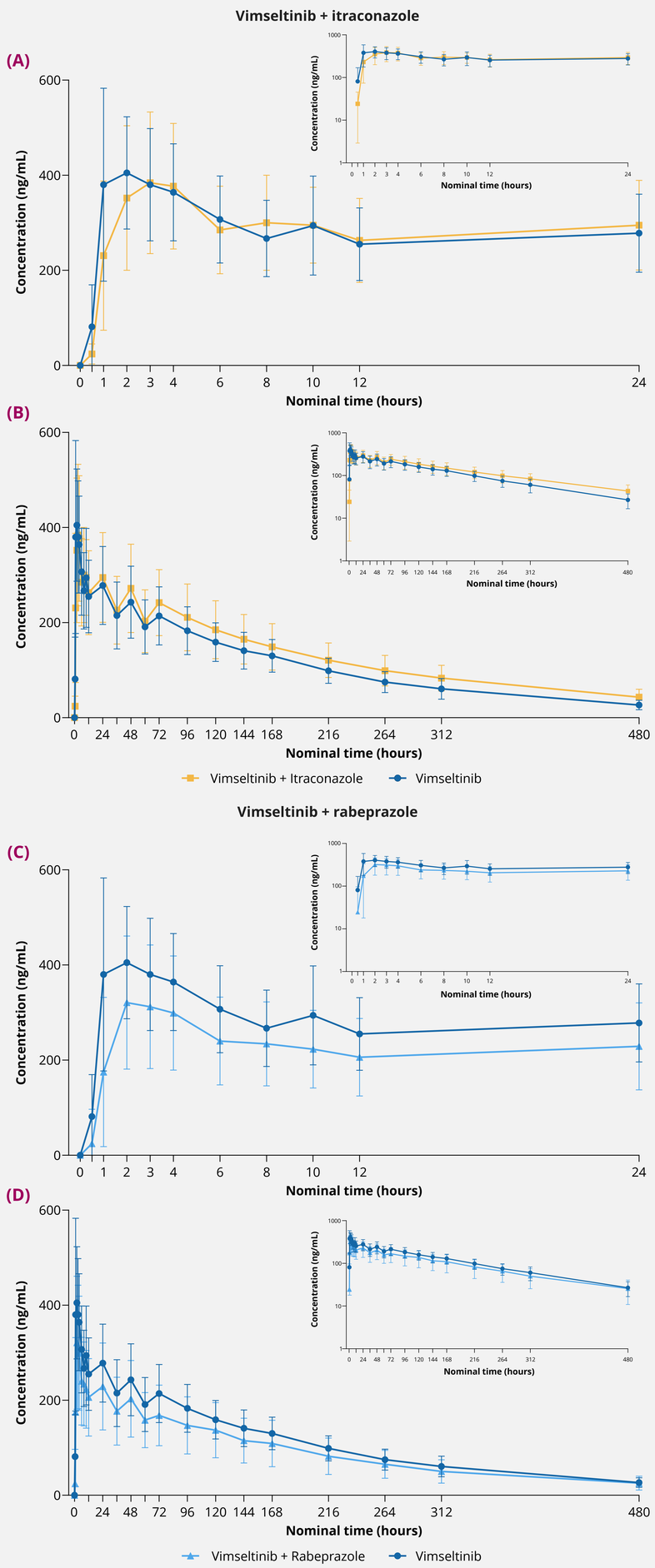
Category	Vimseltinib n = 29	Vimseltinib + itraconazole n = 30	Vimseltinib + rabeprazole n = 30
Age, years, median (range)	35 (18–59)	34 (18–53)	32 (21–59)
Sex, n (%)			
Male	19 (66)	17 (57)	17 (57)
Female	10 (34)	13 (43)	13 (43)
Race, n (%)			
White	18 (62)	17 (57)	15 (50)
Black or African American	8 (28)	10 (33)	13 (43)
Asian	1 (3)	1 (3)	1 (3)
Multiple[a]	1 (3)	1 (3)	1 (3)
Native Hawaiian or Other Pacific Islander	1 (3)	1 (3)	0
Ethnicity, n (%)			
Not Hispanic or Latino	23 (79)	17 (57)	24 (80)
Hispanic or Latino	6 (21)	13 (43)	6 (20)
Female participant of childbearing potential,[b] n (%)	9 (90)	11 (85)	11 (85)
Height, cm, median (range)	173.7 (154.1–194.1)	168.8 (153.0–190.5)	167.8 (151.2–188.1)
Weight, kg, median (range)	72.3 (52.8–110.3)	73.3 (53.2–100.8)	72.1 (54.3–102.0)
BMI, kg/m^2, median (range)	25.8 (19.8–29.8)	26.1 (19.7–30.8)	26.5 (20.3–30.3)

[a]Two participants reported race as Black or African American and White. One participant reported race as Asian and White. [b]Calculated out of all female participants.
BMI, body mass index.

Pharmacokinetics

- The plasma concentration-time profiles of vimseltinib are shown in **Figure 2**

Figure 2. Mean plasma concentration-time profile of vimseltinib over 24 hours (A,C) and 480 hours (B,D) when administered with itraconazole (A,B) or rabeprazole (C,D) on linear and semi-log scales (insets)



All values below the limit of quantification (1.0 ng/mL) were taken as 0 for calculation of summary statistics.
Concentrations collected outside the predefined collection window have been excluded.

- PK parameters for vimseltinib administered alone, with itraconazole, or with rabeprazole are described in **Table 2**
- GMRs for vimseltinib C_{max} were within the bioequivalence range and $AUC_{0-tlast}$ and AUC_{0-inf} were 17% and 22% higher, respectively, when administered with itraconazole (**Table 3, Figure 3A**)
- GMRs for vimseltinib PK parameters were lower and just outside the bioequivalence range when taken with rabeprazole than when alone (**Table 3**, **Figure 3B**)

Table 2. Plasma PK parameters of vimseltinib by treatment

Parameter	n	Vimseltinib	n	Vimseltinib + itraconazole	n	Vimseltinib + rabeprazole
T_{max}, h, median (range)	29	2 (1–4)	30	3 (1–24)	30	3 (0.5–48.23)
C_{max}, ng/mL, mean (CV%)	29	425 (38.1)	30	408 (33.9)	30	313 (61.8)
$AUC_{0-tlast}$, h*ng/mL, mean (CV%)	29	51,200 (27.0)	30	60,100 (30.9)	30	38,600 (52.1)
AUC_{0-inf}, h*ng/mL, mean (CV%)	28	57,200 (26.1)	23	69,900 (30.8)	28	45,100 (50.3)
$t_{1/2}$, h, mean (CV%)	29	142 (29.5)	30	177 (21.7)	30	148 (25.8)

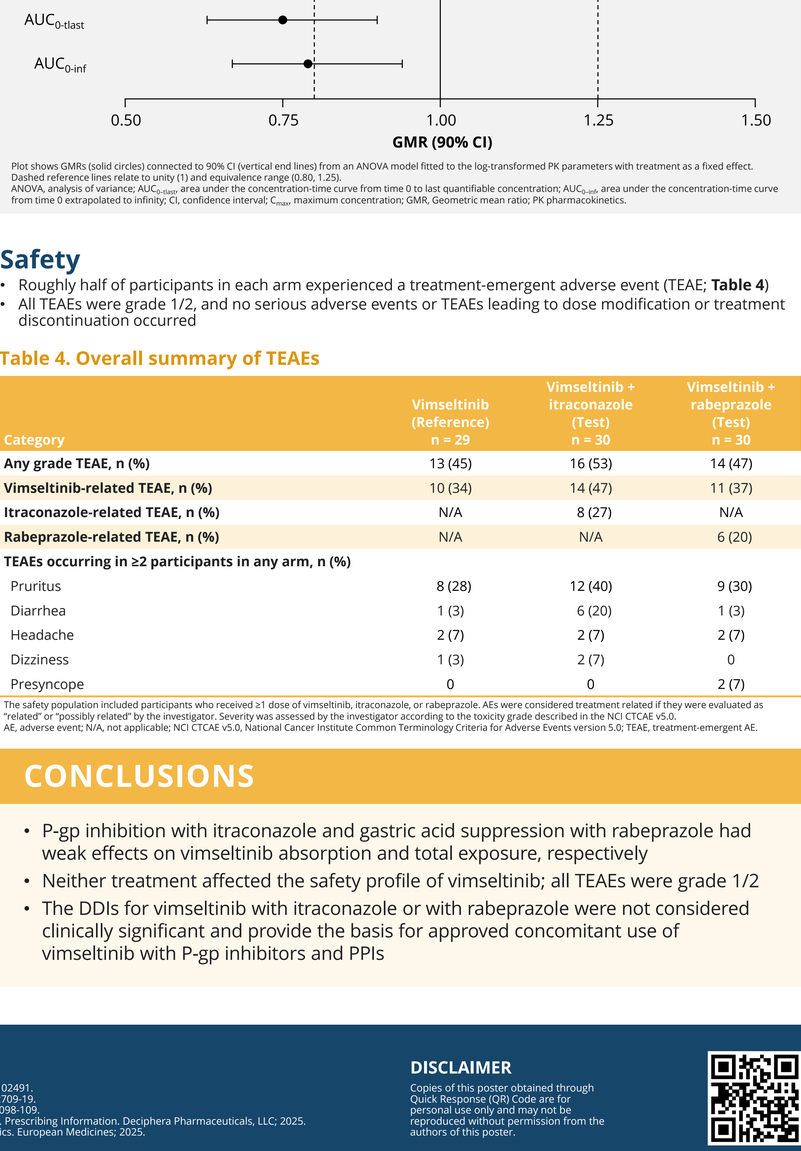
Relevant values are presented as geometric mean (geometric CV%).
AUC_{0-inf}, area under the concentration time-curve from time 0 extrapolated to infinity; $AUC_{0-tlast}$, area under the concentration-time curve from time 0 to last quantifiable concentration; C_{max}, maximum concentration; CV%, coefficient of variation; $t_{1/2}$, terminal elimination half-life; T_{max}, time to reach maximum concentration.

Table 3. Statistical comparison of vimseltinib PK parameters

PK parameter	n (Test)	n (Reference)	Geometric mean (Test)	Geometric mean (Reference)	Ratio (90% CI) Test/reference
Vimseltinib, 1 hour after itraconazole					
C_{max}	30	29	408	425	0.96 (0.83–1.12)
$AUC_{0-tlast}$	30	29	60,100	51,200	1.17 (1.04–1.33)
AUC_{0-inf}	23	28	69,900	57,200	1.22 (1.07–1.39)
Vimseltinib, 1 hour after rabeprazole					
C_{max}	30	29	313	425	0.74 (0.60–0.91)
$AUC_{0-tlast}$	30	29	38,600	51,200	0.75 (0.63–0.90)
AUC_{0-inf}	28	28	45,100	57,200	0.79 (0.67–0.94)

AUC_{0-inf}, area under the concentration time-curve from time 0 extrapolated to infinity; $AUC_{0-tlast}$, area under the concentration-time curve from time 0 to last quantifiable concentration; CI, confidence interval; C_{max}, maximum concentration; PK, pharmacokinetic.

Figure 3. Forest plot summarizing the effect of itraconazole (A) and rabeprazole (B) on vimseltinib PK



Plot shows GMRs (solid circles) connected to 90% CI (vertical end lines) from an ANOVA model fitted to the log-transformed PK parameters with treatment as a fixed effect.
Dashed reference lines relate to unity (1) and equivalence range (0.80, 1.25).
ANOVA, analysis of variance; $AUC_{0-tlast}$, area under the concentration-time curve from time 0 to last quantifiable concentration; AUC_{0-inf}, area under the concentration-time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum concentration; GMR, Geometric mean ratio; PK pharmacokinetics.

Safety

- Roughly half of participants in each arm experienced a treatment-emergent adverse event (TEAE; **Table 4**)
- All TEAEs were grade 1/2, and no serious adverse events or TEAEs leading to dose modification or treatment discontinuation occurred

Table 4. Overall summary of TEAEs

Category	Vimseltinib (Reference) n = 29	Vimseltinib + itraconazole (Test) n = 30	Vimseltinib + rabeprazole (Test) n = 30
Any grade TEAE, n (%)	13 (45)	16 (53)	14 (47)
Vimseltinib-related TEAE, n (%)	10 (34)	14 (47)	11 (37)
Itraconazole-related TEAE, n (%)	N/A	8 (27)	N/A
Rabeprazole-related TEAE, n (%)	N/A	N/A	6 (20)
TEAEs occurring in ≥2 participants in any arm, n (%)			
Pruritus	8 (28)	12 (40)	9 (30)
Diarrhea	1 (3)	6 (20)	1 (3)
Headache	2 (7)	2 (7)	2 (7)
Dizziness	1 (3)	2 (7)	0
Presyncope	0	0	2 (7)

The safety population included participants who received ≥1 dose of vimseltinib, itraconazole, or rabeprazole. AEs were considered treatment related if they were evaluated as "related" or "possibly related" by the investigator. Severity was assessed by the investigator according to the toxicity grade described in the NCI CTCAE v5.0.
AE, adverse event; N/A, not applicable; NCI CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; TEAE, treatment-emergent AE.

CONCLUSIONS

- P-gp inhibition with itraconazole and gastric acid suppression with rabeprazole had weak effects on vimseltinib absorption and total exposure, respectively
- Neither treatment affected the safety profile of vimseltinib; all TEAEs were grade 1/2
- The DDIs for vimseltinib with itraconazole or with rabeprazole were not considered clinically significant and provide the basis for approved concomitant use of vimseltinib with P-gp inhibitors and PPIs

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