2.6.5.12.3 CYP の阻害（in vitro）

Test Article: lenvatinib mesilate

Inhibition of CYPs In Vitro **Study Number: E[redacted]023** **Location in CTD: 5.3.2.2.4**

Study System	in vitro
Test System	Human liver microsomes in the presence of an NADPH-generating system
Method	Incubation of lenvatinib with human liver microsomes for 5 to 60 minutes at 37 °C
Assay/Analyte	HPLC/Metabolites formed by CYP mediated metabolism
Concentration	100 µmol/L as lenvatinib mesilate

CYP Isoforms	**Substrate (concentration)**	**Metabolic Reaction**	**Inhibition (%)**	**K_i (µmol/L)**
CYP1A2	7-Ethoxyresorufin (0.5 µmol/L)	*O*-Deethylation	37.3±2.0	NT
CYP2A6	Coumarin (2 µmol/L)	7-Hydroxylation	2.4±2.4	NT
CYP2B6	7-Benzyloxyresorufin (1.5 µmol/L)	*O*-Debenzylation	21.4±2.4	NT
CYP2C9	Tolbutamide (400 µmol/L)	4-Methylhydroxylation	42.2±1.9	NT
CYP2C19	S(+)-Mephenytoin (50 µmol/L)	4′-Hydroxylation	24.2±4.5	NT
CYP2D6	Bufuralol (30 µmol/L)	1′-Hydroxylation	21.7±0.0	NT
CYP2E1	Chlorzoxazone (50 µmol/L)	6-Hydroxylation	–0.5±0.5	NT
CYP3A	Nifedipine (6 µmol/L)	Oxidation	24.5±0.5	NT
	Midazolam (5 µmol/L)	1′-Hydroxylation	56.6±0.9	106.4[a], 57.0[b]

The concentration of lenvatinib was expressed in terms of the mesilate salt. The inhibition (%) in the presence of lenvatinib mesilate is shown as mean ± SEM of 3 samples. The K_i and K_i' were estimated using data sets of the mean value of 2 samples. Inhibition (%) and the inhibition constant were calculated using the equation in 5.3.2.2.4.
CYP = cytochrome P450, K_i = inhibition constant at competitive inhibition, K_i' = inhibition constant at uncompetitive inhibition, NT = not tested, NADPH = reduced form of nicotinamide adenine dinucleotide phosphate.
a: K_i (at competitive inhibition).
b: K_i' (at uncompetitive inhibition).
Additional Information: Lenvatinib showed weak inhibitory effects on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A, and virtually no inhibitory effects on CYP2A6 and CYP2E1 in human liver microsomes. The type of inhibition by lenvatinib on midazolam 1′-hydroxylation was mixed type (competitive and uncompetitive).

2.6.5.12.3 CYP の阻害（in vitro）（続き）

Test Article: lenvatinib mesilate

Inhibition of CYPs In Vitro **Study Number: PK-Test-0072** **Location in CTD: 5.3.2.2.5**

Study System	in vitro
Test System	Human liver microsomes in the presence of an NADPH-generating system
Method	Incubation of lenvatinib with human liver microsomes (final concentration: 0.1 mg/mL) for 5 minutes at 37 °C
Assay / Analyte	LC-MS/MS / Metabolites formed by CYP mediated metabolism
Concentration	0, 3, 10, 30, and 100 µmol/L as lenvatinib mesilate

CYP Isoforms	Substrate (concentration)	Metabolic Reaction	Lenvatinib (µmol/L)	Inhibition (%)	IC_{50} (µmol/L)
CYP2C8	Paclitaxel (8 µmol/L)	6α-Hydroxylation	0	NA	10.1
			3	5.1	
			10	49.8	
			30	85.7	
			100	>88.8	
CYP3A	Testosterone (50 µmol/L)	6β-Hydroxylation	0	NA	>100
			3	4.3	
			10	17.1	
			30	38.2	
			100	49.3	

The concentration of lenvatinib was expressed in terms of the mesilate salt. The inhibition (%) was shown as mean of 3 samples. Inhibition (%) and IC_{50} were calculated using the equation in 5.3.2.2.5.

CYP = cytochrome P450, IC_{50} = half-maximal inhibitory concentration, K_i = inhibition constant at competitive inhibition, K_i' = inhibition constant at uncompetitive inhibition, NA = not applicable, NADPH = reduced form of nicotinamide adenine dinucleotide phosphate.

Additional Information: Lenvatinib weakly inhibited CYP2C8 but did not inhibit CYP3A in human liver microsomes when paclitaxel and testosterone were used as the respective probe substrates. Lenvatinib appeared to be a mixed type (competitive and uncompetitive) CYP2C8 inhibitor with inhibition constants (K_i and K_i') of 10.9 and 56.6 µmol/L, respectively.

2.6.5.12.4 CYP の阻害（時間依存性）

Test Article: lenvatinib mesilate

Inhibition of CYP3A In Vitro (Time- and concentration-dependency)　Study Number: PK-Test-0040　Location in CTD: 5.3.2.2.6

Study System	in vitro	
Test System	Human liver microsomes in the presence of an NADPH-generating system	
Method	Lenvatinib was pre-incubated with human liver microsomes at 37 °C for 30-minutes prior to addition of midazolam	
Assay/Analyte	HPLC/1′-hydroxymidazolam	
Concentration	0, and 3 to 100 µmol/L as lenvatinib mesilate in pre-incubation assays	
Concentration of Lenvatinib Mesilate in Pre-Incubation Assays	**Decrease in Inhibition Activity (%) After a 30-Minute Pre-Incubation**	**Substrate and Metabolic Reaction**
0 µmol/L	0.0	Midazolam 1′-hydroxylation
3 µmol/L	4.4	
10 µmol/L	10.7	
30 µmol/L	35.7	
50 µmol/L	47.4	
70 µmol/L	49.9	
100 µmol/L	48.1	
Troleandomycin (5 µmol/L, as a positive control inhibitor)	48.0[a]	

The concentration of lenvatinib was expressed in terms of the mesilate salt. Each value represents the mean of 3 determinations. Decrease in inhibition activity (%) was calculated by equation in 5.3.2.2.6.

CYP = cytochrome P450, K_I = half-maximal inhibitory concentration of k_{inact}, k_{inact} = maximal inactivation rate constant, NADPH = reduced form of nicotinamide adenine dinucleotide phosphate.

a: The inhibition of CYP3A after a 10-minute pre-incubation study.

Additional Information: Time-dependent inhibition of CYP3A (midazolam 1′-hydroxylation) by lenvatinib was observed. The kinetic parameters (k_{inact} and K_I) of lenvatinib on midazolam 1′-hydroxylation were estimated to be 0.0835 min^{-1} and 72.266 µmol/L, respectively.

2.6.5.12.4 CYP の阻害（時間依存性）（続き）

Test Article: lenvatinib mesilate

Inhibition of CYPs In Vitro (Time-dependency) **Study Number: PK-Test-0079** **Location in CTD: 5.3.2.2.7**

Study System	in vitro		
Test System	Human liver microsomes in the presence of a NADPH-generating system		
Method	Lenvatinib was pre-incubated with human liver microsomes at 37 °C for 30-minutes prior to addition of the appropriate CYP substrate		
Assay	LC-MS/MS		
Analyte	Metabolites formed by CYPs mediated metabolism		
Concentration	0 and 50 µmol/L as lenvatinib mesilate in pre-incubation assays		
CYP Isoforms (Substrate)	**Decrease in Inhibition Activity (%) (50 µmol/L Lenvatinib Mesilate, 30-Minute Pre-Incubation)**	**Positive Control Inhibitor, Concentration in Pre-Incubation Assay**	**Comparative Decrease in Inhibition Activity (%) (Positive Control)**
CYP1A2 (Phenacetin)	–1.3	Furafylline, 3 µmol/L	60.8
CYP2A6 (Coumarin)	–1.6	8-Methoxypsoralen, 0.3 µmol/L	48.5
CYP2B6 (Bupropion)	20.4	Ticlopidine, 0.3 µmol/L	25.5
CYP2C8 (Paclitaxel)	–9.8	Gemfibrozil 1-*O*-β-glucuronide, 10 µmol/L	40.2
CYP2C9 (Tolbutamide)	3.5	Tienilic acid, 10 µmol/L	21.5
CYP2C19 (*S*(+)-Mephenytoin)	–1.3	Ticlopidine, 3 µmol/L	38.4
CYP2D6 (Bufuralol)	–2.2	Paroxetine, 3 µmol/L	48.4
CYP2E1 (Chlorzoxazone)	7.4	Sodium *N*,*N*-diethyldithiocarbamate, 5 µmol/L	27.6

The concentration of lenvatinib was expressed in terms of the mesilate salt. Each value represents the mean of 3 determinations. Decrease in inhibition activity (%) was calculated using the equation in 5.3.2.2.7.

CYP = cytochrome P450, NADPH = reduced form of nicotinamide adenine dinucleotide phosphate.

Additional Information: Lenvatinib did not show time-dependent inhibitory effects on CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. Lenvatinib showed a weak time-dependent inhibition of CYP2B6, but this time-dependent inhibition was not detected at concentrations less than or equal to 10 µmol/L.

2.6.5.12.5 UGT の阻害（in vitro）

Test Article: lenvatinib mesilate

Inhibition of UGTs In Vitro **Study Number: XT[redacted]5084** **Location in CTD: 5.3.2.2.9**

Study System	in vitro			
Test System	Human liver microsomes			
Method	Incubation for 5 minutes at 37 °C			
Assay	LC-MS/MS			
Analyte	Metabolites formed by UGT mediated metabolism			
Concentration	0, 0.03, 0.1, 0.3, 1, 3, 10, and 30 µmol/L as lenvatinib mesilate			
UGT Isoforms	**Substrate (concentration)**	**Enzyme Reaction**	**IC_{50} (µmol/L)**	**Inhibition (%)[a] at 30 µmol/L**
UGT1A1	17β-Estradiol (9 µmol/L)	3-Glucuronidation	10.6	68.2
UGT1A4	Trifluoperazine (12 µmol/L)	Glucuronidation	14.0	60.3
UGT1A6	1-Naphthol (1 µmol/L)	Glucuronidation	>30.0	11.4
UGT1A9	Propofol (20 µmol/L)	Glucuronidation	>30.0	31.9
UGT2B7	Morphine (400 µmol/L)	3-Glucuronidation	>30.0	11.5

The concentration of lenvatinib was expressed in terms of the mesilate salt. To calculate IC_{50} values, average data obtained from duplicate samples for each test article concentration were used.

IC_{50} = half-maximal inhibitory concentration, UGT = uridine 5′-diphospho-glucuronosyltransferase.

a: Inhibition (%) = 100% − percent solvent control.

Additional Information: Lenvatinib inhibited UGT1A1 and UGT1A4 with IC_{50} values of 10.6 and 14.0 µmol/L, respectively. Lenvatinib weakly inhibited UGT1A9, with 31.9% inhibition observed at 30 µmol/L; however, the IC_{50} value for this enzyme was greater than 30.0 µmol/L. There was little or no evidence of inhibition of UGT1A6 and UGT2B7 by lenvatinib.

2.6.5.13 薬物動態試験：排泄
2.6.5.13.1 ラット（単回，放射能）

Test Article: [^{14}C]lenvatinib mesilate

Rats **Study Number:** AE-4150-G **Location in CTD:** 4.2.2.2.5

Strain/Gender/Number of Animals	Sprague Dawley/Male/3		
Feeding Condition	Fasted[a]		
Vehicle / Formulation	3% 0.1 mol/L HCl in water / Solution		
Method of Administration / Dose	Oral / 3 mg/kg		
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (CP-3028)		
Analyte/Assay	Radioactivity/LSC		
Time (h)	**Excretion of Radioactivity (% of dose)**		
	Urine	**Feces**	**Total**
0 – 6	5.0±0.4	NA	NA
0 – 12	7.9±0.4	NA	NA
0 – 24	10.5±0.6	82.3±1.2	92.8±0.8
0 – 48	11.4±0.8	86.2±0.7	97.7±0.2
0 – 72	11.7±0.8	86.6±0.7	98.4±0.2
0 – 96	11.9±0.8	86.7±0.7	98.7±0.2
0 – 120	12.0±0.8	86.9±0.7	98.9±0.2
0 – 144	12.1±0.8	87.0±0.7	99.1±0.2
0 – 168	12.2±0.9	87.2±0.6	99.4±0.2
Carcass (168 h)			1.7±0.3

Dose was expressed in terms of the mesilate salt. Values represent the mean ±SEM of 3 animals. For measurement of background radioactivity in urine and feces, control excreta was collected from some of the extra animals. The detection limit of radioactivity in LSC was defined as twice the background radioactivity.
HCl = hydrochloric acid, NA = not applicable.
a: The animals were fasted from about 17:00 on the day before administration, and feeding was resumed after sample collection at 4 hours after dosing. Water was given freely.
Additional Information: This study also investigated the blood level of radioactivity (Section 2.6.5.3.2.2), the distribution of radioactivity in organs and tissues (Section 2.6.5.5.1), and the biliary excretion of radioactivity (Section 2.6.5.14.1).

2.6.5.13.2 サル（単回，放射能）

Monkeys

Study Number	**AE-4151-G**			**AE-6917-G**		
Location in CTD	**4.2.2.2.6**			**4.2.2.2.7**		
Test Article	**[^{14}C]lenvatinib mesilate**			**[^{14}C]CB-lenvatinib mesilate**		
Strain	Cynomolgus			Cynomolgus		
Gender/Number of Animals	Male/3			Male/3		
Feeding Condition	Fasted[a]			Fasted[a]		
Vehicle / Formulation	3% 0.1 mol/L HCl in water / Solution			3% 0.1 mol/L HCl in water / Solution		
Method of Administration / Dose	Oral / 3 mg/kg			Oral / 3 mg/kg		
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (CP-3028)			[^{14}C] / [redacted] MBq/mg (CP-3896)		
Analyte/Assay	Radioactivity/LSC			Radioactivity/LSC		
Time (h)	**Excretion of Radioactivity (% of dose)**			**Excretion of Radioactivity (% of dose)**		
	Urine	**Feces**	**Total**	**Urine**	**Feces**	**Total**
0 – 6	2.8±1.0	NA	NA	NA	NA	NA
0 – 12	6.1±1.7	NA	NA	NA	NA	NA
0 – 24	9.5±1.9	14.6±7.1	24.1±9.0	69.2±3.3	7.0±0.2	76.2±3.2
0 – 48	12.9±1.0	52.0±17.0	64.9±17.3	76.3±1.6	11.7±0.6	88.1±1.1
0 – 72	15.2±1.2	64.3±10.7	79.5±10.1	78.2±1.3	12.8±1.0	90.9±0.4
0 – 96	16.1±1.5	68.5±8.2	84.6±7.1	78.9±1.4	13.3±1.1	92.2±0.4
0 – 120	16.6±1.6	70.4±6.9	87.0±5.5	79.3±1.3	13.5±1.2	92.8±0.4
0 – 144	16.9±1.7	71.4±6.3	88.3±4.8	79.7±1.3	13.6±1.2	93.3±0.3
0 – 168	17.2±1.7	72.8±5.2	90.0±3.6	79.9±1.3	13.6±1.2	93.5±0.2
Residual	**Residual Radioactivity (% of dose)**			**Residual Radioactivity (% of dose)**		
Gastric contents (168 h)	0.0±0.0			NA		
Small intestine contents (168 h)	0.0±0.0			NA		
Large intestine contents (168 h)	0.7±0.5			NA		
Cage washing (168 h)	1.1±0.3			1.5±0.2		

Dose was expressed as that of the mesilate form. Values represent the mean ±SEM of 3 animals. For measurement of background radioactivity in urine and feces, control excreta was collected from some of the animals before administration. The detection limit of radioactivity in LSC was defined as twice the background radioactivity.
CB = chlorobenzene, HCl = hydrochloric acid, NA = not applicable.
a: The animals were fasted from about 17:00 on the day before administration (4.2.2.2.6) or fasted for at least 16 hours until administration (4.2.2.2.7), and the feeding was resumed after sample collection at 4 hours after administration. Water was given freely.
Additional Information: This study also investigated the blood, plasma, and red blood cells levels of radioactivity (Section 2.6.5.3.4.2 and 2.6.5.3.4.3) and the distribution of radioactivity in organs and tissues (Section 2.6.5.5.2).

2.6.5.14 薬物動態試験：排泄：胆汁中
2.6.5.14.1 ラット胆汁排泄（放射能）

Test Article: [^{14}C]lenvatinib mesilate

Rats **Study Number:** AE-4150-G **Location in CTD:** 4.2.2.2.5

Strain/Gender/Number of Animals	Sprague Dawley/Male/3		
Feeding Condition	Fasted[a]		
Vehicle / Formulation	3% 0.1 mol/L HCl in water / Solution		
Method of Administration / Dose	Oral / 3 mg/kg		
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (CP-3028)		
Analyte/Assay	Radioactivity/LSC		
Time (h)	**Excretion of Radioactivity (% of dose)**		
	Bile	**Urine**	**Feces**
0 – 2	9.1±2.4	NA	NA
0 – 4	18.8±4.4	NA	NA
0 – 6	25.9±5.4	NA	NA
0 – 8	30.4±5.6	NA	NA
0 – 12	35.4±5.5	NA	NA
0 – 24	40.4±5.0	15.8±1.4	22.3±4.9
0 – 48	41.6±4.9	18.1±1.1	27.2±5.4
Residual	**Residual Radioactivity (% of dose)**		
Gastrointestinal contents (48 h)	4.7±2.8		
Carcass (48 h)	5.6±0.5		

Dose was expressed in terms of the mesilate salt. Values represent the mean ±SEM of 3 animals. Bile-duct cannulated rats were used in the study. For measurement of background radioactivity in bile, control bile was collected from some of the extra animals. The detection limit of radioactivity in LSC was defined as twice the background radioactivity.

HCl = hydrochloric acid, NA = not applicable.

a: The animals were fasted from about 17:00 on the day before administration, and feeding was resumed after sample collection at 4 hours after dosing. Water was given freely.

Additional Information: This study also investigated the blood level of radioactivity (Section 2.6.5.3.2.2), the distribution of radioactivity in organs and tissues (Section 2.6.5.5.1), and the excretion of radioactivity in urine and feces (Section 2.6.5.13.1).

2.6.5.15 薬物動態試験：薬物相互作用

非臨床における in vivo 薬物間相互作用試験については，該当なし。

In vitro 薬物間相互作用を査定する試験として，CYP 誘導，CYP 阻害，UGT 誘導，UGT 阻害，及び P-gp 誘導については，2.6.5.12 項又は 2.7.2.2.1 項に示し，トランスポーター（P-gp 及び BCRP 含む）に対する基質性及び阻害活性については，2.6.5.16 項又は 2.7.2.2.1 項に示した。レンバチニブと CYP3A 基質又は CYP2C8 基質との薬物間相互作用のモデリングシミュレーションについては，2.6.5.16 項に示した。アルデヒドオキシダーゼ活性に対する阻害能については 2.6.5.16 項に示した。

2.6.5.16 薬物動態試験：その他

2.6.5.16.1 P-gp：輸送活性及び阻害活性

Test Article: [^{14}C]lenvatinib mesilate

Transport by P-gp **Study Number: GE-0556-G** **Location in CTD: 5.3.2.3.2**

Study System	in vitro
Test System	Cultured monolayers of LLC-PK1 cells and human P-gp expressing LLC-PK1 cells
Method	Incubation of [^{14}C]lenvatinib mesilate with cell monolayers for 1, 2, and 4 hours at 37 °C
Assay/Analyte/Concentration	LSC/Radioactivity/1, 3, and 10 µmol/L as [^{14}C]lenvatinib mesilate
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (CFQ40380)

Compound (concentration)	**Control Cells (LLC-PK1)**			**P-gp Expressing LLC-PK1 Cells**		
	Permeation Clearance[a] (µL/well/h)		**Permeation Clearance Ratio[b]**	**Permeation Clearance[a] (µL/well/h)**		**Permeation Clearance Ratio[b]**
	Apical to Basal	**Basal to Apical**		**Apical to Basal**	**Basal to Apical**	
[^{14}C]Lenvatinib (1 µmol/L)	15.20±0.68	19.40±1.14	1.28	4.486±0.732	48.94±2.21	10.91
[^{14}C]Lenvatinib (3 µmol/L)	15.90±0.28	20.85±0.57	1.31	4.724±0.304	48.10±0.29	10.18
[^{14}C]Lenvatinib (10 µmol/L)	16.49±0.29	21.98±1.36	1.33	5.521±0.503	43.88±2.36	7.95
[^{3}H]Digoxin (1 µmol/L, as a positive control)	1.412±0.039	2.433±0.186	1.72	0.9900±0.0576	12.09±0.36	12.21

The concentration of [^{14}C]lenvatinib was expressed in terms of the mesilate salt. Each permeation clearance represents the mean ±SD of 3 samples.
dpm = disintegrations per minute, P-gp = P-glycoprotein.
a: Permeation clearance was calculated as the slope of the regression line between the cleared volume and incubation time passing through the origin.
Cleared volume (µL/well) = Permeated amount (dpm/well) / Initial concentration (dpm/µL).
b: Permeation clearance ratio = Basal to apical permeation clearance (µL/well/h) / Apical to basal permeation clearance (µL/well/h).
Additional Information: The cleared volumes of [^{14}C]mannitol, a paracellular diffusion marker, were almost constant for all experiments. [^{3}H]Digoxin, the typical P-gp substrate, was clearly transported in P-gp expressing LLC-PK1 cells. Lenvatinib was shown to be a substrate of P-gp.

2.6.5.16.1 P-gp：輸送活性及び阻害活性（続き）

Test Article: lenvatinib mesilate

Inhibition of P-gp **Study Number: GE-0556-G** **Location in CTD: 5.3.2.3.2**

Study System	in vitro
Test System	Cultured monolayers of LLC-PK1 cells and human P-gp expressing LLC-PK1 cells
Method	Incubation in cell monolayers for 2 hours at 37 °C
Assay	LSC
Analyte	^{3}H radioactivity of [^{3}H]digoxin
Concentration	1, 3, and 10 µmol/L as lenvatinib mesilate

Compound (concentration)	**Control Cells (LLC-PK1)**			**P-gp Expressing LLC-PK1 Cells**			**Percent of Control[c]**
	Cleared Volume[a] (µL/well)		**Cleared Volume Ratio[b]**	**Cleared Volume[a] (µL/well)**		**Cleared Volume Ratio[b]**	
	Apical to Basal	**Basal to Apical**		**Apical to Basal**	**Basal to Apical**		
[^{3}H]Digoxin (1 µmol/L, control)	2.765±0.297	3.630±0.636	1.31	1.640±0.105	23.77±1.89	14.49	100.00
[^{3}H]Digoxin (1 µmol/L) + Lenvatinib (1 µmol/L)	2.926±0.072	3.644±0.115	1.25	1.756±0.226	23.79±0.63	13.55	93.03
[^{3}H]Digoxin (1 µmol/L) + Lenvatinib (3 µmol/L)	2.689±0.317	3.179±0.403	1.18	1.591±0.216	21.11±1.19	13.27	90.96
[^{3}H]Digoxin (1 µmol/L) + Lenvatinib (10 µmol/L)	2.992±0.052	3.358±0.176	1.12	1.889±0.264	21.20±0.47	11.22	75.76
[^{3}H]Digoxin (1 µmol/L) + Verapamil (30 µmol/L)	4.116±0.208	4.021±0.135	0.98	6.522±0.234	10.54±0.44	1.62	NC

The concentration of lenvatinib was expressed in terms of the mesilate salt. Each cleared volume represents the mean ±SD of 3 samples. Incubation time was 2 hours.
dpm = disintegrations per minute, IC_{50} = half-maximal inhibitory concentration, NC = not calculated, P-gp = P-glycoprotein.
a: Cleared volume (µL/well) = Permeated amount (dpm/well) / Initial concentration (dpm/µL).
b: Cleared volume ratio = Basal to apical cleared volume (µL/well) / Apical to basal cleared volume (µL/well).
c: Percent of control = (cleared volume ratio in the presence of inhibitors – 1) / (cleared volume ratio in the absence of inhibitors – 1) × 100.
Additional Information: The cleared volumes of [^{14}C]mannitol, a paracellular diffusion marker, were almost constant for all experiments. Verapamil, a P-gp inhibitor, clearly inhibited [^{3}H]digoxin transport in P-gp expressing LLC-PK1 cells. Lenvatinib showed concentration dependent inhibition of [^{3}H]digoxin transport in the P-gp expressing cells with IC_{50} value of 30.28 µmol/L (extrapolated value), indicating that lenvatinib is a weak inhibitor for P-gp.

2.6.5.16.2 OAT1，OAT3，OCT2，OATP1B1 及び OATP1B3：輸送活性及び阻害活性

Test Article: [^{14}C]lenvatinib mesilate

Transport by OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 **Study Number: GE-0791-G** **Location in CTD: 5.3.2.3.3**

Study System/Test System	in vitro/Cell culture system of S2 cells and human OAT1, OAT3, or OCT2 expressing S2 cells in vitro/Cell culture system of HEK293 cell and human OATP1B1 or OATP1B3 expressing HEK293 cells
Method	Incubation of [^{14}C]lenvatinib with cell cultures for designated times at 37 °C
Assay/Analyte / Concentration	LSC/Radioactivity / 1 µmol/L as [^{14}C]lenvatinib mesilate
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (CP-3765)

Compound (concentration)	**Cell Type**	**Uptake (µL/mg protein)**			
		1 min	**2 min**	**5 min**	**15 min**
[^{14}C]Lenvatinib (1 µmol/L)	S2, control of OATs and OCT2	76.1±2.9	76.5±9.0	106±11	98.5±6.6
	S2, OAT1 expressed	71.0±4.9	75.8±4.3	107±3	NT
	S2, OAT3 expressed	102±4	105±8	109±6	NT
	S2, OCT2 expressed	NT	79.1±3.3	107±9	94.6±8.9
	HEK293, control of OATP1B1	44.6±5.2	67.2±2.5	63.4±7.8	NT
	HEK293, OATP1B1 expressed	62.9±2.6	64.5±2.3	80.6±4.2	NT
	HEK293, control of OATP1B3	47.0±3.8	64.5±6.3	54.8±3.1	NT
	HEK293, OATP1B3 expressed	57.1±2.5	65.4±3.0	85.8±2.3	NT

Typical Substrate (concentration)	**Cell Type**	**Uptake (µL/mg protein)**	
		2 min	**5 min**
[^{3}H]*p*-Aminohippuric acid (1 µmol/L)	S2, control of OAT1	0.408±0.055	NT
	S2, OAT1 expressed	18.9±1.2	NT
[^{3}H]Estrone sulfate (0.05 µmol/L)	S2, control of OAT3	2.35±0.08	NT
	S2, OAT3 expressed	20.5±1.1	NT
[^{14}C]Metformin (10 µmol/L)	S2, control of OCT2	NT	1.32±0.13
	S2, OCT2 expressed	NT	19.2±0.5
[^{3}H]β-Estradiol 17-(β-D-glucuronide) (0.05 µmol/L)	HEK293, control of OATP1B1	0.426±0.102	NT
	HEK293, OATP1B1 expressed	6.41±0.83	NT
	HEK293, control of OATP1B3	0.411±0.066	NT
	HEK293, OATP1B3 expressed	19.9±0.2	NT

The concentration of [^{14}C]lenvatinib was expressed in terms of the mesilate salt. Each value represents the mean ±SD of 3 samples. The uptake was calculated using the equation in 5.3.2.3.3.

NT = not tested, OAT = organic anion transporter, OATP = organic anion transporting polypeptide, OCT = organic cation transporter.

Additional Information: The uptake results for typical substrates indicated that all assay systems were appropriate to evaluate the involvement of OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 in the transport of lenvatinib. Lenvatinib was not a substrate for OAT1, OAT3, OCT2, OATP1B1, and OATP1B3.

2.6.5.16.2 OAT1，OAT3，OCT2，OATP1B1 及び OATP1B3：輸送活性及び阻害活性（続き）

Test Article: lenvatinib mesilate

Inhibition of OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 **Study Number: GE-0791-G** **Location in CTD: 5.3.2.3.3**

Study System	in vitro
Test System	Cell culture system of S2 cells and human OAT1, OAT3, or OCT2 expressing S2 cells Cell culture system of HEK293 cells and human OATP1B1 or OATP1B3 expressing HEK293 cells
Method	Incubation of lenvatinib with cell cultures for designated times at 37 °C
Assay/Analyte	LSC/Radioactivity of transporter specific radiolabeled substrates
Concentration	0, 0.1, 0.3, 1, 3, 10, and 30 µmol/L as lenvatinib mesilate

Substrate (concentration, incubation time)	**Cell System**	**Lenvatinib Mesylate Concentration (µmol/L)**							**IC_{50} (µmol/L)**	**Typical Inhibitor Uptake[a] (µL/mg protein)**
		0	**0.1**	**0.3**	**1**	**3**	**10**	**30**		
		Uptake (µL/mg protein)								
[^{3}H]*p*-Aminohippuric acid (1 µmol/L, 2 min)	Control	0.861	0.752	0.983	0.776	1.01	0.830	0.681	NA	0.624
	OAT1	13.4	14.5	11.9	11.4	10.2	6.40	2.83	7.36	1.46
[^{3}H]Estrone sulfate (0.05 µmol/L, 2 min)	Control	1.45	1.87	1.66	1.92	2.01	2.02	2.29	NA	1.98
	OAT3	18.2	17.5	16.2	15.6	12.1	6.80	4.06	4.11	2.87
[^{14}C]Metformin (10 µmol/L, 5 min)	Control	0.775	0.918	0.815	0.660	0.861	0.758	0.702	NA	0.553
	OCT2	12.8	11.6	11.1	10.8	11.0	6.01	5.13	10.8	1.28
[^{3}H]β-Estradiol 17-(β-D-glucuronide) (0.05 µmol/L, 2 min)	Control	0.418	0.379	0.411	0.339	0.464	0.356	0.327	NA	0.353
	OATP1B1	12.4	11.1	8.22	9.71	8.56	6.05	3.96	7.29	1.14

Substrate (concentration, incubation time)	**Cell System**	**Lenvatinib Mesylate Concentration (µmol/L)**							**IC_{50} (µmol/L)**	**Typical Inhibitor Uptake[a] (µL/mg protein)**
		0	**0.1**	**0.3**	**1**	**3**	**10**	**30**		
		Uptake (µL/mg protein)								
[^{3}H]β-Estradiol 17-(β-D-glucuronide) (0.05 µmol/L, 2 min)	Control	0.632	0.733	0.467	0.667	0.561	0.723	0.651	NA	0.538
	OATP1B3	19.5	20.2	21.8	21.9	25.0	19.6	16.3	>30	2.33

The concentration of lenvatinib was expressed in terms of the mesilate salt. Each value represents the mean of 3 samples. The uptake was calculated using the equation in 5.3.2.3.3.

IC_{50} = half-maximal inhibitory concentration, NA = not applicable, OAT = organic anion transporter, OATP = organic anion transporting polypeptide, OCT = organic cation transporter.

a: Typical inhibitors used are probenecid (100 µmol/L) for OAT1 and OAT3, quinidine (300 µmol/L) for OCT2, and rifampicin (10 µmol/L) for OATB1B1 and OATB1B3.

Additional Information: The uptake results of positive control inhibitors indicated that all assay systems were appropriate to evaluate the inhibition of OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 by lenvatinib. Lenvatinib showed inhibitory effects on OAT1, OAT3, OCT2, and OATP1B1 with the IC_{50} values of 7.36, 4.11, 10.8, and 7.29 µmol/L, respectively, and minimal or no inhibitory effect on OATP1B3 (IC_{50} >30 µmol/L).

2.6.5.16.3 BCRP：輸送活性及び阻害活性

Test Article: [^{14}C]lenvatinib mesilate

Transport by BCRP **Study Number: GE-0791-G** **Location in CTD: 5.3.2.3.3**

Study System	in vitro
Test System	Cultured monolayers of LLC-PK1 cells and human BCRP expressing LLC-PK1 cells
Method	Incubation of [^{14}C]lenvatinib with cell monolayers for 0.5, 1, and 2 hours at 37 °C
Assay/Analyte	LSC/Radioactivity
Concentration	1 µmol/L as [^{14}C]lenvatinib mesilate
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (CP-3765)

Compound (concentration)	**Typical Inhibitor (concentration)**	**Control Cells (LLC-PK1)**			**BCRP Expressing LLC-PK1 Cells**		
		Papp (× 10^{-6} cm/s)		**Efflux Ratio[a]**	**Papp (× 10^{-6} cm/s)**		**Efflux Ratio[a]**
		Apical to Basal	**Basal to Apical**		**Apical to Basal**	**Basal to Apical**	
[^{14}C]Lenvatinib (1 µmol/L)	–	39.7±1.2	57.2±2.1	1.4	10.6±0.4	88.9±3.1	8.4
	Ko143 (1 µmol/L)	38.4±1.0	55.4±2.8	1.4	36.5±1.3	47.5±1.6	1.3
[^{3}H]Prazosin (0.01 µmol/L, positive control)[b]	–	41.3±2.7	46.6±2.5	1.1	6.19±0.37	85.3±5.5	13.8
	Ko143 (1 µmol/L)	43.2±1.6	47.4±1.6	1.1	38.6±0.9	46.5±2.3	1.2

The concentration of [^{14}C]lenvatinib was expressed in terms of the mesilate salt. Each Papp value represents the mean ±SD of 3 samples. Papp was calculated using the equation in 5.3.2.3.3.

BCRP = breast cancer resistance protein, Papp = apparent permeability coefficient,

– = not added.

a: Efflux ratio = mean Papp from basal to apical / mean Papp from apical to basal.

b: Incubation time was 1 hour.

Additional Information: The permeation assay of [^{14}C]mannitol (1 µmol/L, marker for membrane integrity) indicated that the BCRP expressing cells and control cells used in the experiment formed highly developed tight junctions. The efflux ratio of [^{3}H]prazosin, a typical substrate of BCRP, in the BCRP expressing cells was 12.5-fold greater than that in the control cells, and declined to 1.2 in the presence of Ko143, a typical inhibitor, indicating that test system was appropriate to evaluate the involvement of BCRP in the membrane permeation. The efflux ratio of [^{14}C]lenvatinib in the BCRP expressing cells was 6-fold higher than that in the control cells, and declined to 1.3 in the presence of Ko143. These results suggest that lenvatinib is a substrate of BCRP.

2.6.5.16.3 BCRP：輸送活性及び阻害活性（続き）

Test Article: lenvatinib mesilate

Inhibition of BCRP **Study Number: GE-0791-G** **Location in CTD: 5.3.2.3.3**

Study System	in vitro
Test System	Cultured monolayers of LLC-PK1 cells and human BCRP expressing LLC-PK1 cells
Method	Incubation in cell monolayers for 1 hour at 37 °C
Assay/Analyte	LSC/^{3}H radioactivity of [^{3}H]prazosin
Concentration	0, 0.1, 0.3, 1, 3, 10, and 30 µmol/L as lenvatinib mesilate

Compound (concentration)	**Control Cells (LLC-PK1)**			**BCRP Expressing LLC-PK1 Cells**			**Percent of Control**
	Papp (× 10^{-6} cm/sec)		**Efflux Ratio**	**Papp (× 10^{-6} cm/sec)**		**Efflux Ratio**	
	Apical to Basal	**Basal to Apical**		**Apical to Basal**	**Basal to Apical**		
[^{3}H]Prazosin (0.01 µmol/L, control)	47.4±2.2	40.4±1.3	0.9	7.34±0.37	81.5±1.3	11.1	100.0
[^{3}H]Prazosin (0.01 µmol/L) + Lenvatinib (0.1 µmol/L)	47.1±2.0	42.7±0.9	0.9	7.38±0.32	83.8±3.0	11.4	102.9
[^{3}H]Prazosin (0.01 µmol/L) + Lenvatinib (0.3 µmol/L)	48.7±6.0	46.4±1.7	1.0	7.33±0.48	82.5±2.4	11.3	101.0
[^{3}H]Prazosin (0.01 µmol/L) + Lenvatinib (1 µmol/L)	46.7±0.8	44.7±1.4	1.0	8.26±0.64	85.1±3.1	10.3	91.2
[^{3}H]Prazosin (0.01 µmol/L) + Lenvatinib (3 µmol/L)	46.6±1.1	44.4±0.6	1.0	7.86±0.85	84.9±4.6	10.8	96.1
[^{3}H]Prazosin (0.01 µmol/L) + Lenvatinib (10 µmol/L)	45.3±0.9	42.3±0.3	0.9	10.7±0.6	85.5±0.9	8.0	69.6
[^{3}H]Prazosin (0.01 µmol/L) + Lenvatinib (30 µmol/L)	40.8±1.9	37.1±1.0	0.9	10.5±0.7	76.6±5.0	7.3	62.7
[^{3}H]Prazosin (0.01 µmol/L) + Ko143 (1 µmol/L)	39.4±3.1	39.1±0.6	1.0	33.4±0.7	39.1±0.5	1.2	2.0

The concentration of lenvatinib was expressed as mesilate form. Each Papp value represents the mean ±SD of 3 samples. Papp was calculated by equation in 5.3.2.3.3. Efflux ratio = mean Papp from basal to apical / mean Papp from apical to basal. The percent of control was calculated using the efflux ratio.

BCRP = breast cancer resistance protein, IC_{50} = half-maximal inhibitory concentration, Papp = apparent permeability coefficient.

Additional Information: The permeation assay of [^{14}C]mannitol (1 µmol/L, marker for membrane integrity) indicated that the BCRP expressing cells and control cells used in the experiment formed highly developed tight junctions. The percent of control of [^{3}H]prazosin in the BCRP expressing cells declined from 100% (in the absence of Ko143, a typical inhibitor) to 2.0% in the presence of Ko143 (1 µmol/L), indicating that this test system was appropriate to evaluate the inhibitory effects on the [^{3}H]prazosin transport mediated by BCRP. Lenvatinib slightly inhibited BCRP-mediated transport of [^{3}H]prazosin in a concentration-dependent manner, and the transport of [^{3}H]prazosin decreased to 62.7% of control at the highest lenvatinib concentration tested (30 µmol/L). Lenvatinib had weak inhibitory potency on BCRP-mediated transport of [^{3}H]prazosin (IC_{50} >30 µmol/L).

2.6.5.16.4 OCT1 及び BSEP：輸送活性及び阻害活性

Test Article: [^{14}C]lenvatinib mesilate

Transport by OCT1 and BSEP **Study Number:** GE-0942-G **Location in CTD:** 5.3.2.3.4

Study System	in vitro
Test System	Cell culture system of HEK293 cells and human OCT1 expressing HEK293 cells Inside-out membrane vesicles and human BSEP expressing vesicles
Method	Incubation of [^{14}C]lenvatinib in test system for designated times at 37 °C
Assay/Analyte	LSC/Radioactivity
Concentration	1 and 10 µmol/L as [^{14}C]lenvatinib mesilate for the OCT1 assay and BSEP assay, respectively
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (CP-3765)

Compound or Typical Substrates (concentration)	**Assay Type**	**Uptake (µL/mg protein)**			
		2 min	**5 min**	**10 min**	**15 min**
[^{14}C]Lenvatinib (1 µmol/L)	Control HEK293 cells	47.2±2.9	55.2±3.0	NT	60.3±3.4
	OCT1 expressed HEK293 cells	41.8±4.8	54.2±3.0	NT	60.6±4.7
[^{14}C]Tetraethylammonium (5 µmol/L)	Control HEK293 cells	NT	NT	NT	1.83±0.10
	OCT1 expressed HEK293 cells	NT	NT	NT	91.2±3.7
[^{14}C]Lenvatinib (10 µmol/L)	Control vesicles	27.7±15.6	39.8±13.1	38.2±11.6	NT
	BSEP expressed vesicles	59.4±21.0	26.6±9.9	36.0±16.6	NT
[^{3}H]Taurocholic acid (2 µmol/L)	Control vesicles	NT	11.7±0.7	NT	NT
	BSEP expressed vesicles	NT	168±7	NT	NT

The concentration of [^{14}C]lenvatinib was expressed in terms of the mesilate salt. Each value represents the mean ±SD of 3 samples. The uptake was calculated using the equation in 5.3.2.3.4.

BSEP = bile salt export pump, NT = not tested, OCT = organic cation transporter.

Additional Information: The uptake results of typical substrates indicated that all assay systems were appropriate to evaluate the involvement of OCT1 and BSEP in the transport of lenvatinib. Lenvatinib is not likely to be a substrate for OCT1 and BSEP.

2.3.5.16.4 OCT1 及び BSEP：輸送活性及び阻害活性（続き）

Test Article: lenvatinib mesilate

Inhibition of OCT1 and BSEP **Study Number: GE-0942-G** **Location in CTD: 5.3.2.3.4**

Study System	in vitro
Test System	Cell culture system of HEK293 cells and human OCT1 expressing HEK293cells Inside-out membrane vesicles and human BSEP expressing vesicles
Method	Incubation of lenvatinib in the test systems for the designated times at 37 °C
Assay/Analyte	LSC/Radioactivity of transporter specific radiolabeled substrates
Concentration	OCT1 assay: 0, 0.1, 0.3, 1, 3, 10, and 30 µmol/L as lenvatinib mesilate BSEP assay: 0, 0.1, 0.3, 1, 3, 10, and 25 µmol/L as lenvatinib mesilate

Substrate (concentration, incubation time)	**Assay Type**	**Lenvatinib Mesilate Concentration (µmol/L)**								**IC_{50} (µmol/L)**	**Typical Inhibitor Uptake[a] (µL/mg protein)**
		0	**0.1**	**0.3**	**1**	**3**	**10**	**25**	**30**		
		Uptake (µL/mg protein)									
[^{14}C]Tetraethylammonium (5 µmol/L, 15 min)	Control	1.95	1.97	1.89	1.82	1.45	0.976	NT	0.599	NA	0.557
	OCT1	90.8	100	97.8	91.0	78.7	56.0	NT	23.4	14.9	8.29
[^{3}H]Taurocholic acid (2 µmol/L, 5 min)	Control	10.5	11.0	12.0	12.8	10.0	10.8	11.6	NT	NA	11.5
	BSEP	211	189	208	193	176	131	83.6	NT	14.2	57.9

The concentration of lenvatinib was expressed in terms of the mesilate salt. Each value represents the mean of 3 samples. The uptake was calculated using the equation in 5.3.2.3.4.

BSEP = bile salt export pump, IC_{50} = half-maximal inhibitory concentration, NA = not applicable, NT = not tested, OCT = organic cation transporter.

a: Typical inhibitors used are quinidine (100 µmol/L) for OCT1 and cyclosporin A (10 µmol/L) for BSEP.

Additional Information: The uptake results of positive control inhibitors indicated that this assay system was appropriate to evaluate the inhibition of OCT1 and BSEP by lenvatinib. Lenvatinib inhibited OCT1 and BSEP with the IC_{50} values of 14.9 and 14.2 µmol/L, respectively.

2.6.5.16.5 CYP 以外の酵素による代謝の見積もり

Test Article: lenvatinib mesilate

Estimation of Non-CYP Enzyme **Study Number: DMPKT20[redacted]-015** **Location in CTD: 5.3.2.2.12**

Study System	in vitro
Test System	Liver 9000×g supernatant (S9) of rats, dogs, monkeys, and human
Method	Incubation of lenvatinib or its metabolites for 2 hours at 37 °C with or without NADPH
Assay / Analyte	LC-MS/MS / Metabolites derived from lenvatinib
Concentration	0.01 mmol/L (as lenvatinib mesilate)

Test Compound	**Metabolites Observed**	**Molecular Ion (*m/z*)**	**Liver S9**							
			Rat		**Dog**		**Monkey**		**Human**	
			NADPH (–)	**NADPH (+)**	**NADPH (–)**	**NADPH (+)**	**NADPH (–)**	**NADPH (+)**	**NADPH (–)**	**NADPH (+)**
Lenvatinib	M3′	443	N	N	N	N	Y	Y	Y	Y
	M2′	429	N	N	N	N	N	Y	N	Y
M2	M2′	429	NT	NT	NT	NT	Y	Y	Y	Y
M3	M2′	429	NT	NT	NT	NT	N	N	N	N
M3′	M2′	429	NT	NT	NT	NT	N	N	N	N

The concentration of lenvatinib was expressed in terms of the mesilate salt. M2, M3, M2′ and M3′ in this study correspond to serial metabolite Nos. me114, me107, me118, and me115, respectively. Final protein concentration of S9 was 2 mg/mL.

m/z = mass-to-charge ratio of protonated ion, N = not detected by mass spectrometry, NADPH = reduced form of nicotinamide adenine dinucleotide phosphate, NADPH (–) = without NADPH, NADPH (+) = with NADPH, NT = not tested, S9 = 9000×g supernatant of homogenate (subcellular fraction containing microsomes and cytosol), Y = detected by mass spectrometry.

Additional Information: Human recombinant aldehyde oxidase generated M3′ from lenvatinib and M2′ from M2.

2.6.5.16.6 アルデヒドオキシダーゼ活性に対する阻害能

Test Article: lenvatinib mesilate and its metabolites

Inhibition Effects on Aldehyde Oxidase **Study Number: DMPKT20[redacted]-004** **Location in CTD: 5.3.2.2.10**

Study System	in vitro						
Test System	Pooled human liver cytosol						
Method	Incubation of lenvatinib or its metabolites in test system for designated times at 37 °C						
Assay / Analyte	LC-MS/MS / Phthalazone						
Test Compound	**Remaining Activity (% of Control)**						
Concentration (μmol/L)	**Lenvatinib**	**M1**	**M2**	**M3**	**M2´**	**M3´**	**M5**
100	63.8	91.5	34.0	30.0	109.5	NT	82.1
50	NT	NT	35.4	36.6	NT	95.0	NT
20	NT	NT	43.6	61.9	NT	NT	NT
10	84.9	101.8	51.7	71.7	100.5	98.1	101.8
5	NT	NT	62.1	80.7	NT	NT	NT
2	NT	NT	76.6	90.5	NT	NT	NT
1	NT	NT	84.5	96.0	NT	NT	NT
IC_{50} (μmol/L)	>100	>100	11.57	30.78	>100	>50	>100

The concentration of lenvatinib was expressed in terms of the mesilate salt. M1, M2, M3, M2´, M3´, and M5 in this study correspond to serial metabolite Nos. me88, me114, me107, me118, me115, and me37, respectively. Human liver cytosol protein concentration was 0.1 mg/mL. The inhibition of human aldehyde oxidase by lenvatinib was evaluated by determining the metabolism of phthalazine to phthalazone. Phthalazine concentration was 10 μmol/L. Remaining activity percent was calculated as a percent of control by 3 samples. Remaining activity percent and IC_{50} were calculated using the equations in 5.3.2.2.10.

IC_{50} = half-maximal inhibitory concentration, K_m = concentration indicating half of the V_{max}, NT = not tested, V_{max} = maximum velocity of enzyme reaction.

Additional Information: Michaelis-Menten type of enzyme kinetics on aldehyde oxidase using human liver cytosol (0.1 mg/mL) was observed. The K_m and V_{max} were estimated to be 24.29 μmol/L and 4.798 nmol/min/mg protein of human liver cytosol, respectively. In this study, IC_{50} value of raloxifene (positive control of aldehyde oxidase inhibitor) was 0.003475 μmol/L.

2.6.5.16.7 Simcyp による薬物間相互作用シミュレーション

Test Article: lenvatinib mesilate

Simcyp® Simulation **Study Number: DMPKA20[redacted]-156** **Location in CTD: 4.2.2.6.1**

Study System	Simulation of lenvatinib as a perpetrator of drug-drug interactions					
Test System	Assessing the potential risk of drug-drug interaction between lenvatinib and the CYP3A substrate midazolam or the CYP2C8 substrate repaglinide					
Method	Human physiologically-based pharmacokinetic model using Simcyp® (version 13.1)					
Dose (mg)	24 and 32					
Drug	**Lenvatinib Dose (mg)**	**AUC_R Geometric Mean**	**95% Confidence Interval**	**AUC_R Median**	**AUC_R Maximum**	**AUC_R Minimum**
Midazolam (2 mg)	24	1.24	1.10 to 1.49	1.21	1.72	1.07
	32	1.28	1.12 to 1.60	1.25	1.90	1.08
Repaglinide (0.25 mg)	24	1.005	1.002 to 1.010	1.005	1.014	1.001
	32	1.007	1.003 to 1.014	1.006	1.019	1.002

AUC_R = area under the concentration-time curve ratio of midazolam or repaglinide in the absence and presence of lenvatinib.

Additional Information: Overall, the physiologically-based pharmacokinetic model developed for lenvatinib using Simcyp produced concentration-time results in a good agreement with those observed in clinical trials. The results of the simulations suggested that there is no significant drug-drug interaction risk between lenvatinib and midazolam or repaglinide at the clinical dose of 24 mg of lenvatinib.