ELECTRONIC SUPPLEMENTARY MATERIAL

Phase I Study of BI 853520, an Inhibitor of Focal Adhesion Kinase, in Patients with Advanced or Metastatic Nonhematologic Malignancies

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1 Methods

1.1 Patients

Patients aged ≥18 years with a confirmed diagnosis of advanced, measurable or evaluable, non-resectable and/or metastatic non-hematologic malignancy, that was progressive within 6 months prior to study entry as demonstrated by serial imaging and refractory to standard therapy, or for which no effective standard treatment was available, were eligible for enrollment. Patients had to have: life expectancy ≥3 months; Eastern Cooperative Oncology Group performance status of 0 or 1; adequate hematologic, renal, and hepatic function (defined as an absolute neutrophil count ≥1500/mm^3, platelet count ≥100,000/mm^3, serum creatinine ≤1.5 x institutional upper limit of normal [ULN], total bilirubin ≤1.5 x institutional ULN, aspartate amino transferase and/or alanine amino transferase ≤3 x institutional ULN [≤5 x ULN if related to liver metastases]); and available tumor material (archived tissue or fresh biopsy) for determination of E-cadherin expression. Patients also had to be recovered from the reversible toxicities (excluding alopecia) of prior anti-cancer treatment or prior surgery (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] grade <2).

To be eligible for inclusion in the expansion phase of the study, patients had to have measurable progressive disease within the 6 months prior to study entry according to RECIST version 1.1 (23), a diagnosis of one of the following:

- Metastatic pancreatic adenocarcinoma, with no more than two prior regimens for metastatic disease.
- Platinum-resistant ovarian carcinoma, with no more than five prior lines of systemic treatment for metastatic disease.
- Metastatic esophageal carcinoma (of adenocarcinoma or squamous cell histology), with no more than two prior lines of systemic treatment for metastatic disease.
- Metastatic soft tissue sarcoma, with no more than two prior lines of systemic treatment for metastatic disease.

Patients were required to have documented loss of E-cadherin expression in a baseline tumor/metastasis tissue sample as determined by immunohistochemistry. Following a protocol amendment, E-cadherin loss was subsequently not required; however, the determination of E-cadherin status on archived or fresh tumor tissue remained mandatory for exploratory purposes.

Patients were excluded if they met any of the following criteria: serious concomitant non-oncologic disease/illness; known active infectious disease including HIV or active hepatitis C; active/symptomatic brain metastases (patients with a history of treated brain metastases had to have a stable or normal brain magnetic resonance imaging scan at screening with no radiation or surgery for brain metastases within the previous 4 weeks); second malignancy (not cured, or within the previous 5 years) except for adequately resected cervix carcinoma in situ and resected non-melanomatous skin cancers (including basal cell carcinoma and squamous cell cancer); grade-3–4 congestive heart failure, myocardial infarction within 6 months prior to study entry, or symptomatic coronary artery disease; chronic diarrhea or other gastrointestinal disorder that could have interfered with absorption of the study drug; or treatment with cytotoxic anti-cancer therapies or investigational drugs within 4 weeks of the first dose of study drug (or shorter duration for patients treated with non-cytotoxic drugs, with the agreement of the principal investigator and sponsor).

1.2 Study Design and Treatment

Patients received oral BI 853520 in a continuous once-daily (QD) dosing schedule in 28-day cycles. BI 853520 was administered as a film-coated tablet formulation in the morning, 1 hour before breakfast, with at least 200 mL of water. Patients received repeated cycles of BI 853520 treatment provided that treatment was tolerable and their disease did not progress.

In the dose-escalation phase, sequential cohorts of three to six patients received escalating doses of BI 853520 in a standard 3+3 design to establish the maximum tolerated dose (MTD). The starting dose for human clinical testing was 10 mg QD based on pre-clinical toxicology data with BI 853520 in rats and dogs (Boehringer Ingelheim; data on file).

Dose escalation proceeded according to the occurrence of dose-limiting toxicities (DLTs) in cycle 1.

The following drug-related adverse events (AEs) were considered DLT:

- CTCAE grade-3 or -4 non-hematologic toxicity (except inadequately treated nausea, vomiting, or diarrhea).

- Persistent (≥7 days) CTCAE grade-2 nausea and/or vomiting (despite adequate treatment) which might have caused an interruption of drug intake during these days.
- Any interruption of drug intake for ≥7 days due to an AE.
- Any AE which prevented a patient from starting cycle 2 within 14 days of completion of cycle 1.
- CTCAE grade-4 neutropenia lasting ≥7 days (if this occurred, a control hematology test was to be performed at least twice weekly until improvement to a lower grade) and/or complicated by infection.
- CTCAE grade-4 thrombocytopenia (if this occurred, a control hematology test was performed at least twice weekly until improvement to a lower grade), thrombocytopenic bleeding, or any thrombocytopenia requiring platelet transfusion.
- CTCAE grade-3 febrile neutropenia (absolute neutrophil count <1000/mm^3 and fever ≥38.5°C).

1.3 Rules for BI 853520 Dose Escalation During the Dose-Escalation Phase

In case of drug-related AEs of CTCAE grade ≥2 (but no DLT):

- Number of patients with drug-related AEs of CTCAE grade ≥2 at a given dose level:
  - 0 out of 3 – start with the next dose cohort (dose doubling).
  - ≥1 out of 3 – start with the next dose cohort (escalate maximum 50%).

In case of DLT:

- Number of patients with DLT at a given dose level:
  - 1 out of 3 – enter three more patients at this dose level. If none of these additional patients experience a DLT, proceed to the next higher dose level (escalate no more than 35%). If one or more of these additional patients experience a DLT, the dose escalation is to be stopped. Up to three additional patients must be entered at the lower dose level if only three patients have been treated previously at that dose level.
  - ≥2 out of 3 – dose escalation is to be stopped. Up to three additional patients must be entered at the lower dose level if only three patients had been treated previously at that dose level.

– <2 out of 6 (at the highest dose level below the maximum administered dose). This is defined as the MTD. At least six patients evaluable for the safety endpoint must be entered at this dose level before it may be confirmed as the MTD.

Following determination of the MTD, additional patients were enrolled in an expansion cohort for further evaluation of BI 853520 at the MTD.

Treatment was temporarily discontinued for patients experiencing AEs and/or DLT. Patients with DLT or other selected events were allowed to continue treatment only after recovery from the event to grade ≤1 within 14 days, and only with a reduced dose of BI 853520. The reduced dose was valid for all subsequent treatment cycles in the individual patient. Dose reduction was allowed twice for an individual patient during the course of the trial; however, dose reduction below the starting dose was not permitted. Treatment was permanently discontinued for patients who experienced a third episode of DLT/AEs requiring dose reduction, and/or for patients in whom DLT/AEs did not recover sufficiently (i.e., to grade ≤1 within 14 days). Patients who did not complete the first treatment course for reasons other than DLT were excluded from the analysis of the primary endpoint.

1.4 Pharmacokinetics

For plasma pharmacokinetic analyses, blood samples were acquired during cycle 1 on day 1 (prior to dosing, then 30 minutes, 1, 2, 3, 4, 6, 8, 10, 24, and 48 hours post-dosing), days 3, 8, 15, and 22 (prior to dosing), and day 28 (prior to dosing, then 30 minutes, 1, 2, 3, 4, 6, 8, and 10 hours post-dosing) and during cycle 2 onwards on days 1 (24-hour value of steady-state profile) and 15 (prior to dosing). Urine samples were acquired, where possible, at the same time intervals as for blood samples during cycle 1 on days 1–3 and day 28, and on cycle 2, day 1.

Plasma and urine concentrations of BI 853520 were measured by validated assays based on liquid chromatography coupled to tandem mass spectrometry. The lower limit of detection for the assay was 1 nmol/L for plasma and 10 nmol/L for urine. Pharmacokinetic parameters were estimated by non-compartmental analysis using WinNonlin® version 6.3 (Pharsight Corp., Mountain View, California) and outputs were generated using SAS® version 9.2.

1.5 Analysis of Focal Adhesion Kinase Target Engagement

Fresh tumor biopsies were obtained at screening (baseline; pre-treatment sample) and at the end of cycle 1 (post-treatment sample) for all patients included in the expansion cohort. Tumor samples were frozen immediately over liquid nitrogen and stored at –80°C until transfer to Targos Molecular Pathology GmbH (Kassel, Germany) for analysis. Levels of phosphorylated focal adhesion kinase (FAK) and total FAK in tumor biopsies were determined using a FAK [pY397] ELISA kit (Invitrogen).

1.6 Evaluation of E-cadherin

Tumor biopsy from primary or metastatic material was obtained from all patients at screening. In cases where no access to fresh tumor material was possible, archived formalin fixed paraffin embedded biopsies were used. Freshly obtained biopsy material was immediately fixed in formalin, and embedded in paraffin before transfer to Targos GmbH for analysis. The expression of E-cadherin was assessed by immunohistochemistry. For refined assessment of clinical samples, the H-score was adopted. All tumors with scores of 100 or below were rated as E-cadherin low/negative, and an H-score of 100 was defined as the preliminary cut-off value for the exploratory analysis.

2 Results

2.1 Kidney Biopsy

Two patients underwent a kidney biopsy to understand the mechanism of proteinuria. In a patient treated in the dose-escalation phase at a 300 mg dose and who developed grade-3 proteinuria, the biopsy revealed clear obliteration of podocytes with dysjunction from the underlying glomerular basement membrane. In the biopsy of another patient treated at the 200 mg dose, findings were consistent with minimal disease change with 1 of 19 glomeruli globally sclerosed, mild-to-moderate interstitial fibrosis and moderate arteriolar hyalinosis. The biopsy showed glomeruli with mild thickening of the glomerular basement membrane, no segmental scars or immune complex deposition, and moderate to marked foot process effacement.

Table 1 Baseline demographics for dose-escalation phase (treated set)

	Dose cohort						
Characteristic	10 mg	25 mg	50 mg	100 mg	200 mg	300 mg	Total
Patients, *n*	3	3	3	6	11	7	33
Median age, years (range)	60 (55–69)	62 (59–63)	56 (55–72)	59.5 (57–65)	55 (33–68)	70 (46–82)	60 (33–82)
Gender, *n* (%)							
Male	3 (100)	1 (33)	3 (100)	2 (33)	3 (27)	2 (29)	14 (42)
Female	0	2 (67)	0	4 (67)	8 (73)	5 (71)	19 (58)
Ethnicity, *n* (%)							
Caucasian	3 (100)	3 (100)	3 (100)	5 (83)	9 (82)	6 (86)	29 (88)
ECOG PS, *n* (%)							
0	0	0	0	1 (17)	1 (9)	1 (14)	3 (9)
1	3 (100)	3 (100)	3 (100)	5 (83)	10 (91)	6 (86)	30 (91)

Tumor classification, *n* (%)							
Colorectal	1 (33)	1 (33)	2 (67)	1 (17)	2 (18)	3 (43)	10 (30)
Sarcoma of soft tissue & bone	0	1 (33)	0	1 (17)	2 (18)	0	4 (12)
Liver & biliary tree	1 (33)	0	0	1 (17)	0	1 (14)	3 (9)
Esophagus	0	0	0	1 (17)	1 (9)	0	2 (6)
Mesothelial cancers	0	0	1 (33)	0	0	1 (14)	2 (6)
Non-small cell lung cancer	0	0	0	1 (17)	1 (9)	0	2 (6)
Nervous system	0	0	0	0	1 (9)	0	1 (3)
Breast	0	0	0	0	1 (9)	0	1 (3)
Endocrine	1 (33)	0	0	0	0	0	1 (3)
Gastrointestinal tract	0	0	0	0	0	1 (14)	1 (3)

Ovary & fallopian tube	0	0	0	1 (17)	0	0	1 (3)
Pancreas	0	1 (33)	0	0	0	0	1 (3)
Small intestine	0	0	0	0	0	1 (14)	1 (3)
Other	0	0	0	0	3 (27)	0	3 (9)

ECOG PS, Eastern Cooperative Oncology Group performance status

Table 2 Geometric mean (and gCV%) pharmacokinetic parameters of BI 853520 after single oral administration of 10 to 300 mg BI 853520 tablets in cycle 1 (day 1) – PKS

BI 853520 dose	QD (mg)	10	25	50	100	200	300
Patients, *n*		3	3	3	6	73	7
C_{max}	nmol/L	44.8 (183)	200 (32.2)	312 (28.0)	1320 (45.9)	1830 (52.0)	4540 (27.8)
$C_{max,norm}$	[nmol/L]/mg	4.48 (183)	8.01 (32.2)	6.24 (28.0)	13.2 (45.9)	9.14 (52.0)	15.1 (27.8)
AUC_{0-24}	nmol·h/L	330 (182)	2180 (16.3)	2860 (15.8)	13,100 (61.1)	20,400 (52.9)	51,200 (21.2)
$AUC_{0-\infty}$	nmol·h/L	527 (206)	3920 (9.87)	5320 (5.47)	23,000 (74.6)	33,400 (56.6)[a]	86,200 (23.3)
$AUC_{0-\infty,norm}$	[nmol·h/L]/mg	52.7 (206)	157 (9.87)	106 (5.47)	230 (74.6)	167 (56.6)[a]	287 (23.3)
t_{max}*	h	1.07 (1.00–4.05)	2.00 (2.00–2.65)	1.00 (0.667–2.00)	2.01 (1.00–4.00)	2.98 (0.983–8.00)	2.02 (1.23–4.03)
$t_{½}$	h	18.8 (46.8)	21.2 (27.7)	25.2 (17.4)	22.2 (13.1)	19.0 (19.0)[a]	19.4 (13.6)
MRT_{po}	h	24.0 (51.6)	30.1 (15.2)	32.5 (22.5)	29.3 (17.4)	26.2 (19.7)[a]	26.9 (17.2)
CL/F	mL/min	537 (206)	180 (9.87)	266 (5.47)	123 (74.6)	169 (56.6)[a]	98.6 (23.3)

V_z/F	L	873 (150)	331 (36.9)	581 (19.7)	236 (61.0)	279 (53.8)[a]	166 (24.0)
fe_{0-24}	%	2.04 (135)	3.06 (74.4)	3.98 (77.0)	6.23 (98.1)	6.01 (105)[b]	6.48 (30.0)[c]
fe_{0-48}	%	2.49 (141)	6.15 (6.29–6.01)[†]	5.26 (63.1)	8.45 (67.2)	9.08 (35.1)[d]	8.61 (47.0)[e]
CL_{R0-24}	mL/min	17.5 (55.1)	9.91 (86.4)	19.7 (66.8)	13.4 (147)	16.5 (142)[b]	10.8 (35.5)[c]

AUC, area under the plasma concentration–time curve; CL/F, apparent clearance of the analyte in plasma following extravascular administration; CL_{R0-24}, renal clearance of analyte within the time interval 0 to 24 hours; C_{max}, maximum plasma concentration; fe_{0-24}, fraction of analyte excreted in urine within the time interval 0 to 24 hours in % of dose; fe_{0-48}, fraction of analyte excreted in urine within the time interval 0 to 48 hours in % of dose; gCV, geometric coefficient of variation; MRT_{po}, mean residence time of the analyte in the body after administration; PKS, pharmacokinetic set; QD, once-daily; $t_{1/2}$, terminal half-life; t_{max}, time of maximum plasma concentration; V_z/F, apparent volume of distribution during the terminal phase λz following an extravascular administration

*Median and range

[†]Individual values

[a] *N* = 72

[b] *N* = 68

[c] *N* = 6

[d] *N* = 52

[e] *N* = 5

Table 3 Geometric mean (and gCV%) pharmacokinetic parameters of BI 853520 after repeated oral administrations of 10 to 300 mg BI 853520 tablets in cycle 1 (day 28) – PKS

BI 853520 dose	QD (mg)	10	25	50	100	200	300
Patients, *n*		2†	4	3	8	24	2†
$C_{max,ss}$	nmol/L	59.2 (35.2–99.6)	405 (73.6)	430 (27.5)	1430 (53.4)	2580 (60.2)	5060 (4570–5610)
$C_{max,ss,norm}$	[nmol/L]/mg	5.92 (3.52–9.96)	16.2 (73.6)	8.61 (27.5)	14.3 (53.4)	12.9 (60.2)	16.9 (15.2–18.7)
$AUC_{\tau,ss}$	nmol·h/L	816 (494–1350)	5100 (109)	4890 (2.24)	16,300 (50.2)	35,400 (65.9)	79,600 (69,600–91,000)
$AUC_{\tau,ss,norm}$	[nmol·h/L]/mg	81.6 (4.94–135)	204 (109)	97.8 (2.24)	163 (50.2)	177 (65.9)	265 (232–303)
$t_{max,ss}$*	h	3.51 (3.00–4.02)	2.48 (0.517–4.17)	1.00 (1.00–2.00)	2.01 (1.00–2.88)	2.52 (1.00–4.12)	2.50 (2.00–3.00)
$t_{½,ss}$	h	25.8 (19.3–34.5)	27.9 (32.2)[a]	21.5 (38.5)	18.9 (22.9)	20.4 (28.0)[b]	21.6 (18.8–24.9)
$MRT_{po,ss}$	h	36.4 (28.7–46.2)	38.4 (22.5)[a]	27.9 (35.7)	25.4 (21.7)	28.8 (26.1)[b]	31.9 (27.6–36.9)
$CL/F_{,ss}$	mL/min	347 (210–	139	290	174	160	107 (93.3–

		573)	(109)	(2.24)	(50.2)	(65.9)	122)
$V_z/F_{,ss}$	L	776 (628–959)	520 (33.1)[a]	538 (40.0)	284 (57.4)	290 (75.6)[b]	200 (198–201)
$R_{A,AUC}$		1.48 (1.08–2.04)	1.51 (27.2)[a]	1.71 (17.2)	2.01 (19.3)[a]	2.01 (35.0)[b]	1.45 (1.23–1.71)
$R_{A,Cmax}$		0.944 (1.63–0.547)	1.46 (18.3)[a]	1.38 (24.4)	1.56 (25.0)[a]	1.73 (33.8)[b]	1.22 (0.799–1.86)

$AUC_{\tau,ss}$, area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ; CL/F_{ss}, apparent clearance of the analyte in plasma following extravascular administration; $C_{max,ss}$, maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ; gCV, geometric coefficient of variation; $MRT_{po,ss}$, mean residence time of the analyte in the body at steady state after administration; $_{norm}$, dose normalised; PKS, pharmacokinetic set; QD, once-daily; $R_{A,AUC,}$ accumulation ratio based on area under the concentration-time curve of the analyte in plasma; $R_{A,Cmax}$, accumulation ratio based on maximum measured concentration of the analyte in plasma; $t_{1/2,ss}$, terminal half-life of the analyte in plasma at steady state; $t_{max,ss}$, time from last dosing to maximum concentration of the analyte in plasma at steady state; V_z/F_{ss}, apparent volume of distribution during the terminal phase λz at steady state following extravascular administration

*Median and range

†Geometric mean and individual values

[a] *N* = 3

[b] *N* = 23

Table 4 Geometric mean (and gCV%) PK parameters of BI 853520 and unbound BI 853520 after single oral administration of 10 to 300 mg BI 853520 tablets in cycle 1 (day 1) – PKS

BI 853520 dose	QD (mg)	10	25	50	100	200	300
Patients, *n*		3	3	3	6	73	7
BI 853520							
C_{max}	nmol/L	44.8 (183)	200 (32.2)	312 (28.0)	1320 (45.9)	1830 (52.0)	4540 (27.8)
$C_{max,norm}$	[nmol/L]/mg	4.48	8.01	6.24	13.2	9.14	15.1
AUC_{0-24}	nmol·h/L	330 (182)	2180 (16.3)	2860 (15.8)	13,100 (61.1)	20,400 (52.9)	51,200 (21.2)
$AUC_{0-\infty}$	nmol·h/L	527 (206)	3920 (9.87)	5320 (5.47)	23,000 (74.6)	33,400 (56.6)[a]	86,200 (23.3)
$AUC_{0-\infty, norm}$	[nmol·h/L]/mg	52.7	157	106	230	167[a]	287
CL/F	mL/min	537 (206)	180 (9.87)	266 (5.47)	123 (74.6)	169 (56.6)[a]	98.6 (23.3)
V_z/F	L	873 (150)	331 (36.9)	581 (19.7)	236 (61.0)	279 (53.8)[a]	166 (24.0)
$CL_{R,0-24}$	mL/min	17.5 (55.1)	9.91 (86.4)	19.7 (66.8)	13.4 (147)	16.5 (142)[b]	10.8 (35.5)[c]

Unbound BI 853520							
C_{max}	nmol/L	1.93 (77.2)	6.96 (26.9)	14.0 (26.1)	44.9 (16.4)	71.2 (36.4)[d]	154 (28.9)
$C_{max,norm}$	[nmol/L]/mg	0.193	0.278	0.279	0.449	0.356[d]	0.515
AUC_{0-24}	nmol·h/L	14.2 (71.7)	75.9 (34.0)	128 (11.5)	449 (19.9)	784 (34.0)[d]	1740 (31.1)
$AUC_{0-\infty}$	nmol·h/L	22.7 (87.4)	136 (27.2)	238 (6.14)	787 (29.6)	1300 (37.7)[e]	2930 (38.2)
$AUC_{0-\infty, norm}$	[nmol·h/L]/mg	2.27	5.45	4.77	7.87	6.49[e]	9.78
CL/F	mL/min	12,500 (87.4)	5190 (27.2)	5940 (6.14)	3600 (29.6)	4360 (37.7)[e]	2900 (38.2)
V_z/F	L	20,300 (56.1)	9520 (57.6)	13,000 (12.9)	6900 (19.0)	7330 (35.0)[e]	4870 (32.2)
$CL_{R,0-24}$	mL/min	24.4 (51.5)	17.1 (93.9)	26.4 (62.1)	23.6 (102)	25.3 (131)[f]	19.6 (21.1)[c]

AUC_{0-24}, area under the concentration time curve of the analyte in plasma over the time interval from 0 to 24 hours; $AUC_{0-\infty}$, area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity; CL/F, apparent clearance of the analyte in plasma following extravascular administration; $CL_{R,0-24,}$ renal clearance of analyte within the time interval from 0 to 24 hours; C_{max}, maximum measured concentration of the analyte in plasma; gCV, geometric coefficient of variation; $_{norm}$, dose normalised; PKS, pharmacokinetic set; V_z/F_{ss}, apparent volume of distribution during the terminal phase λz following an extravascular administration

[a] *N* = 72

[b] *N* = 68

[c] *N* = 6

[d] $N = 67$

[e] $N = 66$

[f] $N = 64$

Table 5 Geometric mean (and gCV%) PK parameters of BI 853520 and unbound BI 853520 after repeated oral administrations of 10 to 300 mg BI 853520 tablets in cycle 1 (day 28) – PKS

BI 853520 dose	QD (mg)	10	25	50	100	200	300
Patients, *n*		2*	4	3	8	24	2*
BI 853520							
$C_{max,ss}$	nmol/L	59.2 (35.2, 99.6)	405 (73.6)	430 (27.5)	1430 (53.4)	2580 (60.2)	5060 (4570–5610)
$C_{max,ss,norm}$	[nmol/L]/mg	5.92 (3.52, 9.96)	16.2 (73.6)	8.61 (27.5)	14.3 (53.4)	12.9 (60.2)	16.9 (15.2–18.7)
$AUC_{\tau,ss}$	nmol·h/L	816 (494, 1350)	5100 (109)	4890 (2.24)	16,300 (50.2)	35,400 (65.9)	79,600 (69,600–91,000)
$AUC_{\tau,ss,norm}$	[nmol·h/L]/mg	81.6 (4.94, 135)	204 (109)	97.8 (2.24)	163 (50.2)	177 (65.9)	265 (232–303)
$CL/_{F,ss}$	mL/min	347 (210–573)	139 (109)	290 (2.24)	174 (50.2)	160 (65.9)	107 (93.3–122)
$V_Z/F_{,ss}$	L	776 (628–959)	520 (33.1)[a]	538 (40.0)	284 (57.4)	290 (75.6)[c]	200 (198–201)
$CL_{R,0\text{-}24,ss}$	mL/min	– (15.7)	17.5 (41.7)	22.1 (20.0–24.4)*	25.1 (42.9)[b]	20.0 (62.4)[d]	– (10.4)

Unbound BI 853520							
$C_{max,ss}$	nmol/L	2.16 (1.77–2.63)	15.0 (87.7)	20.8 (23.9)	64.0 (25.5)	104 (35.8)[e]	188 (157–226)
$C_{max,ss,norm}$	[nmol/L]/mg	0.216 (0.177–0.263)	0.598	0.415	0.640	0.519[e]	0.627 (0.523–0.752)
$AUC_{\tau,ss}$	nmol·h/L	29.7 (24.8–35.6)	188 (125)	236 (9.31)	729 (28.6)	1410 (41.7)[e]	2960 (2390–3660)
$AUC_{\tau,ss,norm}$	[nmol·h/L]/mg	2.97 (2.48–3.56)	7.54	4.72	7.29	7.07[e]	9.85 (7.96–12.2)
$CL/_{F,ss}$	mL/min	9530 (11,400–7950)	3760 (125)	6000 (9.31)	3880 (28.6)	4010 (41.7)[e]	2870 (3560–2320)
$V_z/F_{,ss}$	L	21,300 (19,100–23,800)	14,700 (49.9)[a]	11,200 (47.8)	6350 (39.5)	7220 (47.2)[f]	5380 (5780–5010)
$CLR_{,0\text{-}24,ss}$	mL/min	– (35.6)	28.4 (50.8)	26.5 (24.8–28.3)*	31.5 (24.9)[b]	29.4 (43.2)[g]	– (18.2)

$AUC_{\tau,ss}$, area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ; CL/F_{ss}, apparent clearance of the analyte in plasma following extravascular administration; $CLR_{,0\text{-}24,ss}$, renal clearance of the analyte in plasma from the time point 0 to 24 hours at steady state; $C_{max,ss}$, maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ; gCV, geometric coefficient of variation; $_{norm}$, dose normalised; PKS, pharmacokinetic set; V_z/F_{ss}, apparent volume of distribution during the terminal phase λz at steady state following extravascular administration

*Geometric mean and individual values

[a] *N* = 3

[b] *N* = 7

[c] *N* = 23

[d] *N* = 19

[e] *N* = 22

[f] *N* = 21

[g] *N* = 17