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ORIGINAL ARTICLE

# Pharmacokinetics of sunitinib malate in subjects with hepatic impairment

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**Abstract** This study evaluated the effect of hepatic impairment on the pharmacokinetics of sunitinib and its active metabolite, SU12662. This open-label study enrolled subjects with normal hepatic function ($n = 8$), mild (Child–Pugh [CP]-A; $n = 8$), or moderate (CP-B; $n = 8$) hepatic impairment. Subjects received sunitinib 50 mg as a single oral dose. Mild or moderate hepatic impairment did not significantly alter sunitinib, SU12662, or total drug (TD) systemic exposure. In subjects with normal hepatic function, mild, or moderate hepatic impairment, respectively, TD $AUC_{0-\infty}$ was 1,938, 2,002, and 1,999 ng h/ml, TD $AUC_{0-last}$ was 1,913, 1,956, and 1,958 ng h/ml, and TD $C_{max}$ was 26.0, 27.3, and 26.7 ng/ml. There were no other notable pharmacokinetic differences and sunitinib was well tolerated. The pharmacokinetic findings of this study do not indicate a need to adjust the currently approved starting dose of sunitinib (50 mg daily on Schedule 4/2) for cancer patients with mild to moderate liver impairment.

**Keywords** Pharmacokinetics and pharmacodynamics · Angiogenesis inhibitors: hepatic impairment

Laurie Sherman, Bob Ryan, and Melvin Toh are no longer Pfizer employees.

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## Introduction

Sunitinib malate (SU11248; SUTENT®) is an oral, multitargeted tyrosine kinase inhibitor with antiangiogenic and antitumor activities. Sunitinib selectively inhibits class III and V split-kinase domain receptor tyrosine kinases, including platelet-derived growth factor receptors (PDGFR-α and PDGFR-β), vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, and VEGFR-3), stem cell factor receptor (KIT), and Fms-like tyrosine kinase-3 receptor (FLT3); sunitinib also inhibits the glial cell-line derived neurotrophic factor receptor (rearranged during transfection; RET) [1–6]. In biochemical and cellular assays, the primary active metabolite of sunitinib (SU12662) demonstrated similar potency to the parent compound in terms of inhibition of the activity of these receptor tyrosine kinases [6].

Sunitinib has received regulatory approval from the United States Food and Drug Administration (FDA)—and marketing authorization from the European Commission—for the treatment of patients with gastrointestinal stromal tumor (GIST) after progression on or intolerance to imatinib mesylate and advanced renal cell carcinoma (RCC). The current recommended dose is sunitinib 50 mg daily administered in repeated cycles of 4 weeks on treatment, followed by 2 weeks off treatment (Schedule 4/2) [6]. The compound

has also shown efficacy in a variety of other tumor types and is currently being evaluated in phase II and III studies in patients with neuroendocrine tumors [7], metastatic breast cancer [8], and non-small cell lung cancer [9, 10].

Following oral administration, maximum plasma concentrations of sunitinib are generally observed between 6 and 12 h post-dose [6]. Food has no effect on the bioavailability of the compound [11], and both area under the plasma concentration–time curve and maximum plasma concentration increase dose-proportionately with sunitinib 25–100 mg [6].

Sunitinib is metabolized mainly by cytochrome P450 3A4 (CYP3A4) to form the active metabolite, SU12662; SU12662 is also metabolized by CYP3A4 [6, 12]. SU12662 comprises 23–37% of the total exposure [20]. Sunitinib and SU12662 are the major drug-related compounds that have been identified in plasma, urine, and feces (representing 91.5, 86.4 and 73.8% of radioactivity in pooled samples, respectively); minor metabolites have been identified in urine and feces, but are generally not found in plasma [6, 12]. In a mass balance study, 61% of the administered sunitinib dose was eliminated in feces, with renal elimination accounting for 16% [6, 12].

SU12662 has a similar receptor tyrosine kinase inhibitory profile to sunitinib in preclinical assays, as well as comparable human plasma protein binding (sunitinib is $\simeq$95% protein bound to albumin in vitro; SU12662 is $\simeq$90% bound), with no concentration dependence in the range of 100–4,000 ng/ml [13]. The combination of sunitinib plus SU12662 therefore represents a clinically relevant measure of the total active drug in plasma [6].

Following a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and SU12662 are approximately 40–60 and 80–110 h, respectively [6]. With repeated daily administration, sunitinib accumulates three to fourfold, while SU12662 accumulates seven to tenfold; steady-state concentrations of sunitinib and the primary metabolite are achieved within 10–14 days [6]. No significant changes in the pharmacokinetics of sunitinib or SU12662 have been observed with repeated administration, nor have differences in pharmacokinetics been seen between healthy volunteers and patients with solid tumors [6].

In a population pharmacokinetic analysis, no relationship was observed between liver enzyme levels (evaluated using baseline alanine aminotransferase [ALT] values [0–35 U/l, $n = 175$; 36–69 U/l, $n = 23$; 70–140 U/l, $n = 6$; >140 U/l, $n = 1$]) and sunitinib or SU12662 pharmacokinetics [14]. The objective of the present study was to evaluate the pharmacokinetics of sunitinib and SU12662 in subjects with mild and moderate hepatic impairment following a single dose of sunitinib. The aim was to provide sunitinib starting dose recommendations for patients with hepatic impairment. The safety and tolerability of sunitinib in subjects with mild and moderate hepatic impairment were also assessed.

## Methods

### Study design

This was an open-label, parallel-group study performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and applicable local regulatory requirements and laws. The Institutional Review Board for each study center (Southern Institutional Review Board, Miami, FL, USA and INTEGREVIEW, Austin, TX, USA) approved the protocol and other relevant documents before the study started, and all participants gave written informed consent.

### Subjects

Participants were male or female subjects with normal hepatic function ($n = 8$), or mild ($n = 8$) or moderate ($n = 8$) hepatic impairment. Hepatic impairment was graded using the Child–Pugh (CP) classification [15, 16]. The protocol specified that subjects with normal hepatic function were recruited after subjects with mild (CP class A [CP-A; score 5–6) and moderate (CP class B [CP-B]; score 7–9) hepatic impairment had completed the study. Four of the subjects with normal hepatic function were matched—with respect to age ($\pm$5 years), weight ($\pm$10 kg), and gender—to four subjects in each of the CP-A and CP-B groups (those with the lowest [$n = 1$], highest [$n = 1$], and median [$n = 2$] weights in each group).

Subjects with normal hepatic function were required to be healthy as defined by having no clinically relevant abnormalities identified by a detailed medical history and full physical examination. Exclusion criteria included a history of regular alcohol consumption (>7 and >14 drinks/week for women and men, respectively), and the use of prescription or non-prescription drugs (except acetaminophen $\leq$1 g/day), vitamins, and dietary supplements during the study period.

Subjects with hepatic impairment were required to have stable hepatic dysfunction resulting from cirrhosis (not secondary to other diseases) and normal renal function (creatinine clearance >80 ml/min). Any other clinically significant diseases (e.g., those that contra-indicated the use of the study drug or may have affected the pharmacokinetics of sunitinib) or laboratory abnormalities, the use of prescription or non-prescription drugs that inhibited or induced CYP3A4, and the use of dietary supplements during the study period were exclusion criteria for subjects with hepatic impairment.

In addition, female subjects of child-bearing potential were required to use an acceptable method of non-hormonal contraception, and all subjects were required to abstain from alcohol, caffeine- (including chocolate), xanthine-, and grapefruit-containing products, and strenuous exercise during the study.

### Sunitinib administration

Subjects with hepatic impairment were admitted to the clinical research unit 2 days prior to dosing (day 1). Subjects with normal hepatic function were admitted the day before dosing (day 0). On day 1, following a 10-h fast, subjects received a single 50-mg oral dose of sunitinib. Subjects fasted for 4 h after dosing. All subjects remained in the clinical research unit until day 7.

A single 50-mg dose was deemed adequate since the approved daily dose of sunitinib is 50 mg on Schedule 4/2 (4 weeks on treatment followed by 2 weeks off treatment) and no significant pharmacokinetic changes have been observed with repeated versus single administration of sunitinib/SU12662 [6]. This single dose was expected to be safe and tolerable in subjects with hepatic impairment, as a previous study showed that single higher doses of 150- and 175-mg loading doses of sunitinib were well tolerated in patients with advanced solid tumors [17].

### Evaluation of sunitinib and SU12662 pharmacokinetics

Blood samples (4 ml) for sunitinib and SU12662 assays were collected before and 1, 2, 4, 6, 8, 12, and 16 h after the dose of sunitinib on day 1. Samples were also collected on days 2–7 (24, 36, 48, 72, 96, 120, and 144 h after dosing). On days 9, 11, 13, 15, 17, and 21, subjects returned to the clinical research unit for additional pharmacokinetic blood sample collections. Separate blood samples (10 ml) were also collected before and 6 h after dosing on day 1 to measure the unbound fraction of sunitinib and SU12662.

All pharmacokinetic blood samples were collected into tubes containing potassium ethylenediaminetetraacetic acid ($K_2$EDTA) and kept out of direct sunlight. Within 1 h of collection, samples were centrifuged ($\sim$1,700$g$ at 4°C for about 10 min) and the harvested plasma was stored at approximately −20°C until assay. Blood samples for the measurement of unbound concentrations were collected in phosphate-buffered saline.

Plasma samples for analysis of bound plus unbound concentrations, as well as solely unbound concentrations, were analyzed for sunitinib and SU12662 using a validated method (liquid chromatography with tandem mass spectrometric detection [LC/MS/MS]) as previously described [11]. The lower limit of quantification (LOQ) for both sunitinib and SU12662 was 0.1 ng/ml in human plasma and 0.01 ng/ml in phosphate-buffered saline. For plasma samples, assay accuracy—expressed as bias of quality control (QC) samples—ranged from −0.2 to 0.3% and from 6.3% to 8.9% for sunitinib and SU12662, respectively; assay reproducibility—expressed as coefficient of variation (CV) of QC samples—ranged from 2.8 to 11.8% and from 4.3 to 13.9% for sunitinib and SU12662, respectively. For phosphate-buffered saline, assay accuracy—expressed as bias of QC samples—ranged from −1.3 to 0.7% and −7.6 to 6% for sunitinib and SU12662, respectively; the inter-run CV% could not be calculated as all phosphate-buffered saline samples were analyzed in a single batch.

### Pharmacokinetic endpoints

Pharmacokinetic parameters were estimated by non-compartmental methods using validated software (WinNonlin® Version 4.1.8; Pharsight® Corp., Mountain View, CA, USA). The primary pharmacokinetic endpoints were sunitinib area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty}$), area under the plasma concentration–time curve from zero to time of last measurable concentration ($AUC_{0-last}$), and maximum observed plasma concentration ($C_{max}$). Secondary pharmacokinetic endpoints were sunitinib time to first occurrence of $C_{max}$ ($T_{max}$), terminal phase plasma half-life ($t_{½}$), apparent oral clearance (CL/F), apparent volume of distribution (Vz/F), fraction of drug unbound in plasma (FU), unbound $AUC_{0-\infty}$ ($AUC_{0-\infty,u}$), unbound $AUC_{0-last}$ ($AUC_{0-last,u}$), and unbound $C_{max}$ ($C_{max,u}$). The unbound pharmacokinetic parameters were calculated for each subject by multiplying the relevant PK value by each subject's FU (for example, $AUC_{0-\infty,u} = AUC_{0-\infty} \times FU$).

The pharmacokinetic endpoints for SU12662 were $AUC_{0-\infty}$, $AUC_{0-last}$, $C_{max}$, $T_{max}$, $t_{1/2}$, FU, $AUC_{0-\infty,u}$, $AUC_{0-last,u}$, and $C_{max,u}$. For total drug (sunitinib + SU12662), $AUC_{0-\infty}$, $AUC_{0-last}$, $C_{max}$, and $T_{max}$ were calculated.

### Statistical methods

Sample size ($n = 8$ subjects per group) was based on recommendations from the FDA Guidance for Industry [18].

All pharmacokinetic parameters (except $T_{max}$) were log-transformed and then compared between the group of subjects with normal hepatic function and each group of subjects with hepatic impairment using analysis of variance (ANOVA). Point estimates and 90% confidence intervals (CIs) for the differences between these groups were constructed and then back-transformed to give estimates for ratio comparisons (i.e., moderate hepatic impairment/normal and mild hepatic

impairment/normal). $T_{max}$ was analyzed using a non-parametric method (Wilcoxon rank sum test); the estimates of median differences between the groups were calculated, together with the corresponding ranges.

### Safety evaluation

To ensure the wellbeing of all enrolled subjects, safety was assessed throughout the study. This included physical examinations, 12-lead electrocardiograms (ECGs), measurement of vital signs, and clinical laboratory tests, and reporting of all observed or volunteered adverse events. All adverse events were graded for severity (mild, moderate or severe) and possible relationship to the investigational product by the clinical investigator.

## Results

### Subject characteristics

Twenty-four subjects (16 men, 8 women; 48–78 years of age) were enrolled in and completed the study (first subject visit: September 9, 2005; last subject visit: March 14, 2006); their demographics and baseline characteristics are summarized in Table 1. Within the normal and mildly hepatic impaired groups, the mean ages of subjects were similar. In the moderately hepatic impaired group, one female subject was 78 years old, whereas the mean age of the seven male subjects was 55 years. Mean subject weights were similar in the normal and mildly hepatic impaired groups but higher in the moderately hepatic impaired group; mean body mass indices (BMIs) were higher in both of the hepatic impaired groups than in the normal group.

As required by the protocol, eight of the subjects had normal hepatic function, eight had mild hepatic impairment, and eight had moderate hepatic impairment. All subjects with mild and moderate impairment presented with hepatic cirrhosis. Ascites was noted in all subjects with moderate hepatic impairment; two subjects with mild hepatic impairment had a history of ascites. Baseline laboratory assessments for these 16 subjects revealed abnormalities commonly associated with hepatic impairment (e.g., elevated liver enzymes; data not shown). Serum albumin concentrations (mean and range) at baseline for sunitinib and SU12662 were similar between groups (Table 1).

### Pharmacokinetic parameters

Measurable sunitinib and SU12662 concentrations were achieved within 1 h after dosing in most subjects and remained quantifiable at all following timepoints until at

**Table 1** Demographics and baseline characteristics of study subjects

| Characteristic | Normal function | | | Mild impairment | | | Moderate impairment | | |
|---|---|---|---|---|---|---|---|---|---|
| | Men ($n = 5$) | Women ($n = 3$) | Total ($n = 8$) | Men ($n = 4$) | Women ($n = 4$) | Total ($n = 8$) | Men ($n = 7$) | Women ($n = 1$) | Total ($n = 8$) |
| Age (years) | | | | | | | | | |
| Mean | 58.2 | 56.0 | 57.4 | 59.8 | 59.0 | 59.4 | 54.9 | 78.0 | 57.8 |
| Range | 54–70 | 53–58 | 53–70 | 54–65 | 50–73 | 50–73 | 48–59 | 78–78 | 48–78 |
| Race (*n*) | | | | | | | | | |
| White | 4 | 3 | 7 | 4 | 4 | 8 | 5 | 1 | 6 |
| Black | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 |
| Asian | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Weight (kg) | | | | | | | | | |
| Mean | 84.2 | 69.7 | 78.8 | 85.8 | 72.5 | 79.1 | 87.1 | 83.5 | 86.6 |
| Range | 52.0–109.0 | 55.0–78.0 | 52.0–109.0 | 72.6–98.9 | 51.7–84.8 | 51.7–98.9 | 51.7–112.9 | 83.5–83.5 | 51.7–112.9 |
| BMI ($kg/m^2$) | | | | | | | | | |
| Mean | 27.6 | 25.0 | 26.6 | 30.4 | 28.1 | 29.3 | 28.9 | 34.8 | 29.6 |
| Range | 20.0–36.0 | 21.0–28.0 | 20.0–36.0 | 28.3–32.2 | 18.4–34.2 | 18.4–34.2 | 19.6–35.7 | 34.8–34.8 | 19.6–35.7 |
| Height (cm) | | | | | | | | | |
| Mean | 174.6 | 167.3 | 171.9 | 167.6 | 161.3 | 164.5 | 172.7 | 154.9 | 170.5 |
| Range | 163.0–187.0 | 164.0–172.0 | 163.0–187.0 | 157.5–177.8 | 157.5–167.6 | 157.5–177.8 | 162.6–182.9 | 154.9–154.9 | 154.9–182.9 |
| Serum albumin (g/dl) | | | | | | | | | |
| Mean | NC | NC | 4.15 | NC | NC | 4.34 | NC | NC | 4.04 |
| Range | NC | NC | 3.7–4.5 | NC | NC | 3.8–4.7 | NC | NC | 3.6–4.5 |

*BMI* body mass index, *NC* not calculated

least days 15 and 17, respectively, in all subjects except one. This subject (with normal hepatic function) had sunitinib and SU12662 concentrations that were either very low or below the LOQ for the entire pharmacokinetic sampling period; this was likely the result of an episode of emesis soon after dosing that was reported as an adverse event. Available data for this subject were excluded from the pharmacokinetic summary statistics.

Peak sunitinib and SU12662 concentrations were achieved approximately 6–10 h after dosing (median time to first occurrence of $C_{max}$ [$T_{max}$]) and were followed by a bi-exponential decline. Plasma concentration–time profiles for sunitinib, SU12662, and total drug (sunitinib + SU12662) in the different subject groups during the 96-h period after administration of sunitinib are shown in Fig. 1.

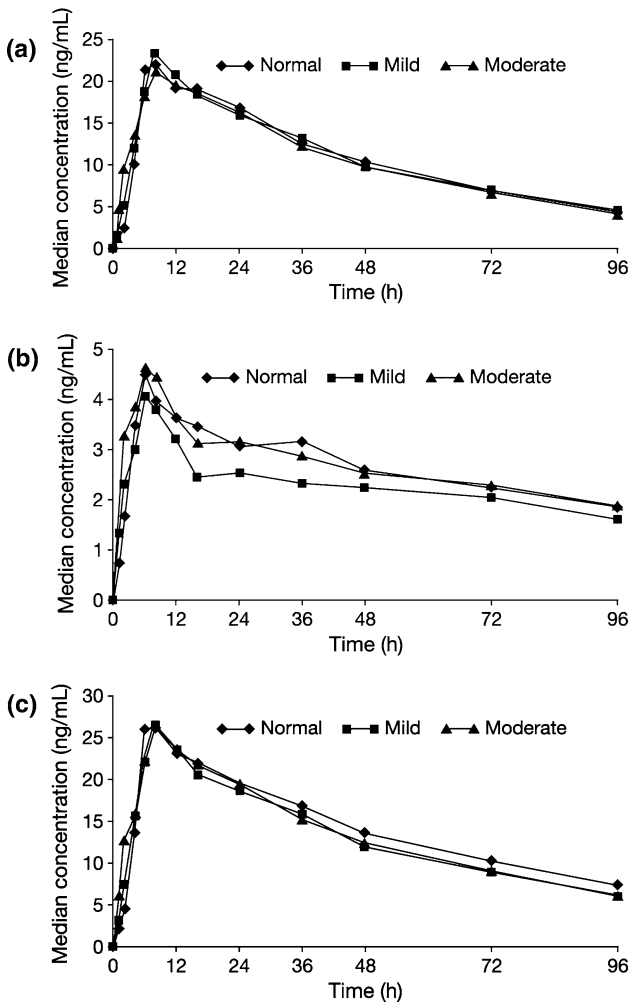


**Fig. 1** Median sunitinib (**a**), SU12662 (**b**), and total drug (sunitinib + SU12662) (**c**) plasma concentration versus time following oral administration of a single 50-mg dose of sunitinib in normal subjects ($n = 7$), and subjects with mild ($n = 8$) or moderate ($n = 8$) hepatic impairment

The pharmacokinetics of sunitinib, SU12662, and total drug were similar in subjects with mild or moderate hepatic impairment as compared to subjects with normal liver function (Table 2). Pairwise comparisons demonstrated that systemic exposure ($AUC_{0-\infty}$, $AUC_{0-last}$, and $C_{max}$) of sunitinib, SU12662, and total drug was not significantly changed in subjects with mild or moderate hepatic impairment compared to normal subjects: the point estimates of the geometric mean ratios all fell within the no-effect boundaries of 80–125% (Table 3). $AUC_{0-\infty}$, $AUC_{0-last}$, and $C_{max}$ were variable in all subjects: inter-subject CVs on measures of systemic exposure ranged from 12.8 to 40.3% for sunitinib and from 25.4 to 54.2% for SU12662. Median $T_{max}$ values for sunitinib were not significantly different in subjects with mild or moderate impairment compared to normal subjects (Table 3); median $T_{max}$ values for SU12662 were similar, although the range was wide in subjects with hepatic impairment (Table 2). Mean $t_{1/2}$ for sunitinib was longer in subjects with hepatic impairment (79.2–79.5 h) compared with normal subjects (63.8 h; Table 2), although the point estimates of the geometric mean ratios fell within the 80–125% range (Table 3). Sunitinib CL/F was not significantly different in subjects with hepatic impairment compared to normal subjects (Table 2).

The percentages of unbound sunitinib and SU12662 were slightly smaller in the subjects with hepatic impairment compared with the normal group (Table 2). Unbound sunitinib exposure ($AUC_{0-\infty,u}$, $AUC_{0-last,u}$, and $C_{max,u}$) was not significantly changed in subjects with mild and moderate hepatic impairment (Table 3). For SU12662, the unbound pharmacokinetic parameters were similar in subjects with hepatic impairment and normal subjects, apart from $AUC_{0-\infty,u}$ and $AUC_{0-last,u}$, which appeared to be slightly lower in the group with mild impairment (Tables 2 and 3). However, significant differences between the 3 groups in unbound pharmacokinetic parameters could not be concluded as all samples were assessed in a single run and the potential for variability in the protein-binding assay could not be quantified.

The SU12662/sunitinib ratios for $AUC_{0-\infty}$ and $C_{max}$ (and for $AUC_{0-\infty,u}$ and $C_{max,u}$) were similar in subjects with mild or moderate hepatic impairment compared with normal subjects (Table 2), indicating minimal impact of mild or moderate hepatic impairment on sunitinib metabolism.

## Safety

During the course of the study, there were no serious or unexpected adverse events. Furthermore, there were no discontinuations (temporary or permanent) from study treatment due to adverse events.

**Table 2** Pharmacokinetic parameters for sunitinib, SU12662, and total drug (sunitinib + SU12662) in plasma

| Parameter | Geometric mean (95% CI) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Normal function ($n = 7$)[a] | | | | Mild impairment ($n = 8$) | | | | Moderate impairment ($n = 8$) | | | |
| | Sunitinib | SU12662 | Total drug[b] | SU12662/ sunitinib[c] | Sunitinib | SU12662 | Total drug[b] | SU12662/ sunitinib[c] | Sunitinib | SU12662 | Total drug[b] | SU12662/ sunitinib[c] |
| Bound + unbound | | | | | | | | | | | | |
| $AUC_{0-\infty}$ (ng h/ml) | 1,369 (1,243, 1,508) | 559 (518, 604) | 1,938 (1,784, 2,104) | 0.41 | 1,514 (1,369, 1,675) | 492 (460, 526) | 2,002 (1,828, 2,192) | 0.32 | 1,477 (1,431, 1,525) | 505 (461, 553) | 1,999 (1,941, 2,059) | 0.34 |
| $AUC_{0-last}$ (ng h/ml) | 1,355 (1,229, 1,494) | 531 (490, 575) | 1,913 (1,760, 2,078) | | 1,485 (1,345, 1,639) | 456 (429, 486) | 1,956 (1,794, 2,133) | | 1,455 (1,408, 1,503) | 475 (432, 522) | 1,958 (1,897, 2,022) | |
| $C_{max}$ (ng/ml) | 21.9 (19.9, 24.0) | 4.35 (3.99, 4.74) | 26.0 (23.8, 28.5) | 0.20 | 23.3 (22.2, 24.4) | 4.35 (3.99, 4.74) | 27.3 (26.0, 28.7) | 0.18 | 22.7 (21.4, 24.0) | 4.28 (3.69, 4.97) | 26.7 (25.0, 28.6) | 0.19 |
| $T_{max}$ (h)[d] | 8.07 (6.00, 16.0) | 6.08 (6.00, 12.0) | 6.10 (6.00, 12.0) | | 8.00 (4.00, 12.0) | 6.00 (4.00, 48.0) | 8.00 (4.00, 12.0) | | 10.0 (1.00, 16.0) | 6.00 (1.00, 36.0) | 8.00 (1.00, 16.0) | |
| $t_{1/2}$ (h) | 63.8 (61.7, 65.9) | 111 (107, 115) | NC | | 79.5 (75.3, 83.9) | 122 (114, 130) | NC | | 79.2 (73.9, 84.9) | 113 (107, 118) | NC | |
| CL/F (l/h) | 36.5 (33.2, 40.2) | NC | NC | | 33.0 (29.9, 36.5) | NC | NC | | 33.8 (32.8, 34.9) | NC | NC | |
| Unbound | | | | | | | | | | | | |
| FU (%) | 9.82 (9.55, 10.1) | 16.0 (15.5, 16.6) | NC | | 8.00 (7.65, 8.37) | 13.5 (13.0, 14.1) | NC | | 8.98 (8.79, 9.17) | 15.6 (15.4, 15.7) | NC | |
| $AUC_{0-\infty u}$ (ng h/ml) | 135 (124, 146) | 89.7 (82.8, 97.2) | NC | 0.67 | 121 (112, 132) | 66.6 (62.6, 70.9) | NC | 0.55 | 133 (128, 137) | 78.6 (72.1, 85.7) | NC | 0.59 |
| $AUC_{0-last,u}$ (ng h/ml) | 133 (123, 144) | 85.1 (78.4, 92.3) | NC | | 119 (110, 129) | 61.8 (58.2, 65.6) | NC | | 131 (126, 135) | 73.9 (67.5, 81.0) | NC | |
| $C_{max,u}$ (ng/ml) | 2.15 (1.98, 2.33) | 0.697 (0.637, 0.763) | NC | 0.32 | 1.87 (1.77, 1.97) | 0.588 (0.535, 0.648) | NC | 0.32 | 2.04 (1.94, 2.14) | 0.667 (0.576, 0.772) | NC | 0.35 |

*CI* confidence interval, *FU* fraction of drug unbound in plasma, *LOQ* limit of quantification, *NC* not calculated

[a] Data for one normal subject were excluded due to sunitinib and SU12662 concentrations that were below the LOQ for the entire sampling period

[b] As sunitinib and SU12662 have different FU, only bound + unbound pharmacokinetic parameters are presented for total drug

[c] Ratio of SU12662/sunitinib exposure

[d] Median (minimum, maximum) is presented for $T_{max}$ instead of geometric mean (95% CI)

The overall incidence of all-causality adverse events was low: six subjects in the normal group reported 16 adverse events, two in the mildly impaired group reported three adverse events, and none of the subjects in the moderately impaired group reported any adverse events. All adverse events were graded as mild or moderate in severity. The most frequently reported adverse events were gastrointestinal disorders, all of which were reported by subjects with normal hepatic function. Four subjects in the normal group and two subjects in the mildly impaired group experienced treatment-related adverse events (in the normal group, these included diarrhea, nausea, vomiting, chest discomfort, paresthesia, pruritus, and rash; in the mildly impaired group, they included hypoglycemia, dizziness, and anxiety), all of which resolved by the end of the study.

## Discussion

The pharmacokinetics of sunitinib and its primary active metabolite, SU12662, following a single 50-mg oral dose were similar in subjects with mild or moderate hepatic impairment compared with subjects with normal liver function. Additionally, no notable differences were noted between groups in baseline albumin or FU.

The results demonstrated that mild or moderate hepatic impairment, defined using the CP classification, did not significantly alter sunitinib systemic exposure ($AUC_{0-\infty}$, $AUC_{0-last}$, and $C_{max}$) after a single dose. Upon examination of the median plasma concentration–time profiles and the mean pharmacokinetic parameters for sunitinib exposure, substantial overlap in the curves and values was revealed. Statistical analysis (ANOVA) of $AUC_{0-\infty}$, $AUC_{0-last}$, and

**Table 3** Results of statistical comparisons of plasma pharmacokinetic parameters between study groups for sunitinib, SU12662, and total drug (sunitinib + SU12662)

| Parameter | Geometric least squares mean ratio (90% CI) | | | | | |
|---|---|---|---|---|---|---|
| | Sunitinib | | SU12662 | | Total drug[a] | |
| | Mild/normal | Moderate/normal | Mild/normal | Moderate/normal | Mild/normal | Moderate/normal |
| Bound + unbound | | | | | | |
| $AUC_{0-\infty}$ (ng h/ml) | 1.11 (0.84, 1.47) | 1.08 (0.81, 1.43) | 0.88 (0.67, 1.16) | 0.90 (0.69, 1.19) | 1.03 (0.80, 1.33) | 1.03 (0.80, 1.32) |
| $AUC_{0-last}$ (ng h/ml) | 1.10 (0.83, 1.45) | 1.07 (0.81, 1.42) | 0.86 (0.65, 1.14) | 0.90 (0.68, 1.18) | 1.02 (0.80, 1.31) | 1.02 (0.80, 1.31) |
| $C_{max}$ (ng/ml) | 1.06 (0.85, 1.34) | 1.04 (0.82, 1.30) | 1.00 (0.67, 1.48) | 0.99 (0.66, 1.46) | 1.05 (0.83, 1.33) | 1.03 (0.81, 1.30) |
| $T_{max}$ (h)[b] | 0.35 (0.73) | −0.23 (0.82) | 2.16 (0.03) | 0.70 (0.48) | −0.29 (0.77) | −0.52 (0.60) |
| $t_{1/2}$ (h) | 1.25 (1.03, 1.51) | 1.24 (1.02, 1.51) | 1.10 (0.92, 1.31) | 1.02 (0.85, 1.21) | NA | NA |
| CL/F (l/h) | 0.90 (0.68, 1.20) | 0.93 (0.70, 1.23) | NA | NA | NA | NA |
| Unbound | | | | | | |
| FU (%) | 0.82 (0.73, 0.92) | 0.91 (0.81, 1.03) | 0.84 (0.76, 0.94) | 0.97 (0.87, 1.09) | NA | NA |
| $AUC_{0-\infty,u}$ (ng h/ml) | 0.90 (0.71, 1.14) | 0.99 (0.78, 1.25) | 0.74 (0.57, 0.97) | 0.88 (0.67, 1.14) | NA | NA |
| $AUC_{0-last,u}$ (ng h/ml) | 0.89 (0.71, 1.13) | 0.98 (0.78, 1.24) | 0.73 (0.55, 0.95) | 0.87 (0.66, 1.14) | NA | NA |
| $C_{max,u}$ (ng/ml) | 0.87 (0.71, 1.07) | 0.95 (0.77, 1.17) | 0.84 (0.56, 1.26) | 0.96 (0.64, 1.43) | NA | NA |

*CI* confidence interval, *FU* fraction of drug unbound in plasma, *NA* not applicable (comparison could not be performed as these parameters were not calculated)

[a] As sunitinib and SU12662 have different FU, only bound + unbound pharmacokinetic parameters are presented for total drug

[b] Wilcoxon *Z*-score (*P*-value) is presented for $T_{max}$ instead of geometric least squares mean ratio (90% CI)

$C_{max}$ confirmed that mild or moderate hepatic impairment did not significantly affect the pharmacokinetics of sunitinib, and this was further supported by there being no statistical differences between the normal and hepatic impaired groups for $T_{max}$ and CL/F. Evaluation of point estimates of the geometric mean ratios for sunitinib $AUC_{0-\infty}$, $AUC_{0-last}$, and $C_{max}$ found that all values fell within the no-effect boundaries of 80–125%, although the CIs were wide.

The half-life of sunitinib while consistent with previous reports [11, 14, 19] was longer in both groups with hepatic impairment compared with the normal group (mild: 79.5 h; moderate: 79.2 h; normal: 63.8 h). However, point estimates of the geometric mean ratio for the half-life of sunitinib fell within the 80–125% range. Although the 90% CI was 102–151%, small patient numbers and the wide %CV may not warrant strict application of the FDA guidance [18] and thus these data are unlikely to indicate clinically significant differences. It is possible that the longer half-life of sunitinib in subjects with hepatic impairment may be explained by a larger volume of distribution in these subjects, resulting from an increase in extracellular fluid (e.g., ascites, peripheral edema), as has been reported [20–22]. When medical histories were taken and clinical examinations performed in this study, ascites were noted in all subjects with moderate hepatic impairment; one subject with mild hepatic impairment had peripheral edema and two subjects with mild hepatic impairment had a history of ascites. In this study, subjects with mild and moderate hepatic impairment had higher BMIs compared with normal subjects; this could also result in larger volumes of distribution for extensively distributed lipophilic drugs, such as sunitinib. Notwithstanding this increase in sunitinib half-life, as the CL/F and exposure of sunitinib were not significantly different between normal and impaired groups, no difference in the accumulation of sunitinib is expected between groups with multiple dosing.

Perhaps unsurprisingly, in light of the lack of effect of mild or moderate hepatic impairment on the pharmacokinetics of sunitinib, the pharmacokinetic parameters for SU12662 and those for the total drug (sunitinib + SU12662) were similar across the groups. Overall, there were no clinically important differences between subjects with mild or moderate hepatic impairment and healthy controls, for both sunitinib and the active metabolite.

Protein binding of sunitinib was similar between groups, although slightly less in the normal group compared with the groups with hepatic impairment. Significant differences between the groups could not be concluded as the variability in the protein-binding assay could not be quantified.

A single 50-mg dose of sunitinib was well tolerated by all study subjects. No subject experienced a serious or unexpected adverse event and no subject discontinued because of an adverse event. The overall incidence of all-causality adverse events was low, with all events being classed as mild or moderate in severity and all resolving by the end of the study. The most frequently reported adverse

events were gastrointestinal disorders, all of which were reported by subjects with normal hepatic function.

In interpreting the results of this study, it should be noted that subjects enrolled had hepatic impairment due to liver cirrhosis, rather than due to liver metastases or hepatocellular carcinoma (HCC) as may often be the case for patients receiving sunitinib in a treatment setting or clinical trial. However, the use of the CP classification in this study was intended to provide a clinically relevant measure of hepatic impairment regardless of its etiology, as this draws upon multiple parameters to give an overall score. To date, no differences in sunitinib pharmacokinetics have been observed between healthy volunteers and cancer patients [6, 14]. Including healthy subjects in this trial is therefore a rational approach and one that provides important comparator data. The use of molecularly targeted drugs in non-cancer patients must be carefully monitored given that the safety profile of the drug is not measured against clinical benefit. Repeat administration was not explored as part of this study, but multiple-dose pharmacokinetics of sunitinib have previously been found to be predictable from single-dose data [6, 14]. Indeed, in a phase II study of sunitinib in patients with advanced HCC [23], dose-adjusted pharmacokinetics in patients with CP Class A and B were comparable to data obtained from other clinical studies [24, 25], after repeated daily administration of 37.5 or 50 mg sunitinib. Nevertheless, the increased incidence of adverse events observed in the Faivre et al. [23] trial underscores the need to take into account the disease setting and other comorbidities in the treatment of patients with hepatic impairment including those with advanced HCC.

Overall, the pharmacokinetic findings of this study do not indicate a need to adjust the currently approved starting dose of sunitinib (50 mg daily on Schedule 4/2 [6]) for cancer patients with mild to moderate liver impairment. Subsequent dose modifications should be based on each patient's ability to tolerate treatment

In conclusion, this hepatic impairment study—which was designed based on recommendations in the FDA Guidance for Industry [18]—provides valuable information following a single, relevant (50 mg) dose of the oncology drug, sunitinib, in subjects without cancer. The pharmacokinetics of sunitinib and SU12662 were similar in subjects with mild or moderate hepatic impairment compared with subjects with normal liver function,

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**Conflict of interest statement** The following authors have disclosures: C. L. Bello, M. Garrett, and J. Smeraglia are Pfizer employees. L. Sherman, B. Ryan, and M. Toh are former Pfizer employees. C. L. Bello, M. Garrett, M. Toh and L. Sherman own Pfizer shares.

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