

# Dose Finding of Lenvatinib in Subjects With Advanced Hepatocellular Carcinoma Based on Population Pharmacokinetic and Exposure–Response Analyses

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## Abstract

Hepatocellular carcinoma (HCC) accounts for up to 90% of primary liver cancer occurrences worldwide. Lenvatinib, a multikinase inhibitor, was approved in radioiodine-refractory differentiated thyroid cancer. In this phase 2 study (study 202), we aimed to identify the lenvatinib optimal dose for subjects with advanced HCC Child-Pugh class A. Pooled data from phase 1 studies in healthy adults and in subjects with mixed tumor types, and from study 202 in subjects with HCC, were analyzed using a population pharmacokinetic approach. The relationship between treatment-emergent adverse events leading to withdrawal or dose reduction during cycle 1 and lenvatinib exposure was explored by logistic regression analysis. A receiver operating characteristics analysis was used to investigate the best cutoff values of lenvatinib exposure and body weight to identify a high-risk group for early dose modification. The final pharmacokinetic model included body-weight effects on apparent clearance and volume. The relationship between the lenvatinib area under the plasma concentration–time curve (AUC) at steady state and body weight demonstrated an increase in AUC as body weight decreased in subjects with HCC. An exposure–response relationship was observed, with higher lenvatinib AUC and lower body weight resulting in earlier drug withdrawal or dose reduction. The best cutoff values for body weight and lenvatinib AUC were 57.8 kg and 2430 ng·h/mL, respectively, to predict the group at high risk for early drug withdrawal or dose reduction. We therefore recommend 12-mg and 8-mg starting doses for subjects  $\geq 60$  kg and  $< 60$  kg, respectively, in subjects with HCC Child-Pugh class A.

## Keywords

lenvatinib, pharmacokinetics, hepatocellular carcinoma, HCC, dose finding

Liver cancer is the second most common cause of cancer-related deaths in the world and is estimated to have been responsible for approximately 745 000 deaths in 2012.<sup>1</sup> Hepatocellular carcinoma (HCC) is the most common type of liver cancer and accounts for up to 90% of primary liver cancer occurrences worldwide.<sup>2</sup> The majority of patients ( $\geq 70\%$ ) are diagnosed with unresectable disease (locally advanced or metastatic) and have poor survival prospects.<sup>3</sup> Up to 90% of patients with HCC have concurrent liver disease such as hepatitis, cirrhosis, or hepatic dysfunction.<sup>4</sup>

Systemic treatment options for HCC are limited; to date, only the tyrosine kinase inhibitor sorafenib has been approved for the systemic treatment of unresectable locally advanced or metastatic HCC after having demonstrated a modest survival benefit in a phase 2 trial and a phase 3 trial.<sup>4,5</sup> A number of other molecularly targeted therapies (eg, linifanib, brivanib, sunitinib, and erlotinib in combination with sorafenib) have been tested in phase 3 studies, but none has demonstrated any additional antitumor activity or survival benefit over sorafenib.<sup>4,6–9</sup>

Lenvatinib is an oral multikinase inhibitor that selectively inhibits the kinase activities of vascular

endothelial growth factor receptors 1 to 3, in addition to other proangiogenic and oncogenic pathways, including fibroblast growth factor receptors 1 to 4, platelet-derived growth factor receptor- $\alpha$ , and RET and KIT proto-oncogenes.<sup>10–12</sup> Lenvatinib was approved as a single agent for the treatment of radioiodine-refractory differentiated thyroid cancer based on the results of a phase 3 randomized trial<sup>13</sup> and in combination with everolimus for the treatment of advanced renal cell carcinoma following 1 prior antiangiogenic therapy based on a phase 2 study.<sup>14</sup>

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The 24-mg once-daily (QD) dose of single-agent lenvatinib was determined by exploring the maximum tolerated dose, safety, tolerability, pharmacokinetic (PK) and pharmacodynamic properties, biomarkers, and antitumor efficacy of lenvatinib at a range of dose levels throughout a global phase 1 program in subjects with solid tumors with 3 different dosing schedules.<sup>15–18</sup> Single-agent lenvatinib had manageable toxicities and demonstrated antitumor activity in each of these phase 1 studies.<sup>15–17</sup>

In vitro and in vivo studies have demonstrated that lenvatinib is metabolized mainly in liver.<sup>19,20</sup> In human liver microsomes, cytochrome P450 (CYP) 3A4 was the predominant CYP isoform involved in the CYP-mediated metabolism of lenvatinib (Eisai data on file). A study of the PK properties of lenvatinib in subjects with either normal hepatic function or mild, moderate, or severe hepatic impairment found that a reduced dose was required in those subjects with severe hepatic disease.<sup>21</sup> Because of the high incidence of toxicities with concurrent liver disease in subjects with HCC, evaluation of the starting dose is recommended for these subjects.<sup>3</sup>

Therefore, a multicenter, open-label, phase 1/2 study of lenvatinib (study 202; 8 to 16 mg/day in 4-week cycles)<sup>22</sup> was undertaken in this population to identify a specific lenvatinib dose appropriate for subjects with HCC. This study consisted of a phase 1 dose-escalation study and a phase 2 expansion study. The maximum tolerated dose identified in the phase 1 part of the study was 12 mg QD in 4-week cycles on a continuous schedule in subjects with Child-Pugh class A.<sup>22</sup> This recommended phase 2 dose was half of the approved dose for subjects with radioiodine-refractory differentiated thyroid cancer. Consequently, the phase 2 expansion study was conducted with lenvatinib 12 mg QD in subjects with HCC Child-Pugh class A. Promising antitumor activity was reported in this study, with a median time to progression of 7.4 months and an objective response rate of 37% based on independent radiologic review per modified Response Evaluation Criteria in Solid Tumors.<sup>23</sup> Determination of the maximum tolerated dose was based on the assumption that the greatest efficacy is achieved with the highest tolerated dose.<sup>24</sup>

A number of other molecularly targeted drugs have been tested in phase 1 and 2 studies for the purpose of identifying an optimal dose of treatment in subjects with HCC<sup>25–30</sup> but have failed their primary endpoints in phase 3 trials. One of the reasons speculated for the failure of these phase 3 studies was the high incidence of toxicity.<sup>4</sup> The maximum tolerated dose as the recommended therapeutic dose is, therefore, sometimes not optimal for targeted oncology drugs in particular.<sup>24</sup> A fine balance between maintaining efficacy and

reducing toxicity is especially necessary in subjects with HCC.<sup>4</sup>

Although the phase 2 expansion study in HCC showed promising antitumor activity and toxicities could be managed with dose modification, approximately 74% of subjects with HCC treated with lenvatinib 12 mg QD required dose reduction to 8 mg.<sup>23</sup> Low body weight and high lenvatinib exposure were reported as possible risk factors for early dose modification as determined by exploratory analyses in this phase 2 expansion study.

Thus, a population PK analysis using pooled data from study 202 and several phase 1 studies was performed, and the exposure–response relationship of safety and efficacy in subjects from study 202 with advanced HCC was analyzed with an aim to identify a more optimal lenvatinib dose for subjects with HCC Child-Pugh class A.

## Methods

This study was conducted with the approval of each Institutional Review Board and in accordance with local laws, the Declaration of Helsinki, and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent. The analyses of this study consisted of a population PK analysis for lenvatinib and exposure–response relationships for safety and efficacy variables. To assess the effect of covariates and assist in the population PK model development, PK data from 8 phase 1 studies in healthy adults and 4 phase 1 studies (NCT00121719, NCT00121680, NCT00280397, NCT01268293) in subjects with mixed tumor types were included in the PK data set along with the PK data from subjects with HCC in study 202 (NCT00946153).

### PK Data Set

The final pooled lenvatinib PK data set included 8761 observations from a total of 452 subjects. Eight phase 1 clinical pharmacology studies contributed 5077 lenvatinib plasma concentrations from 232 subjects. Four phase 1 dose-finding studies contributed 3188 lenvatinib plasma concentrations from 155 subjects with solid tumors. For study 202, 496 lenvatinib plasma concentrations from 65 subjects with HCC were available for population PK analysis. A summary of the demographics and covariates included in the population PK analysis is presented in Table 1.

### PK Model for Lenvatinib

A population PK model for lenvatinib was previously developed using pooled data from 15 clinical studies, including 8 phase 1 studies in healthy subjects, 4 phase 1 studies in subjects with solid tumors, 2 phase 2 studies in subjects with thyroid cancer, and 1 phase 3

**Table 1.** Summary of Baseline Demographics and Categorical Covariates Included in the Population Pharmacokinetic Analysis of Lenvatinib (N = 452)

Covariate (Unit)	Mean (SD)	Median	Range (Min-Max)
Age (years)	48.7 (16.7)	50.0	18.0-85.0
Weight (kg)	75.8 (17.7)	75.1	42.7-147.0
Albumin (g/L)	39.7 (5.4)	40.0	24.0-52.0
Alkaline phosphatase (IU/L)	160.4 (168.8)	81.5	19.0-1133.0
Alanine aminotransferase (IU/L)	29.1 (36.9)	21.0	5.0-660.0
Aspartate aminotransferase (IU/L)	33.8 (49.0)	22.0	8.0-930.0
Bilirubin ( $\mu\text{mol/L}$ )	11.7 (8.5)	10.3	2.0-101.1
Creatinine clearance (mL/min)	103.9 (36.3)	103.6	17.0-268.0
Sex		Female: 162 Male: 290	
Race or ethnicity		White: 253 Black: 66 Japanese: 90 Other Asian: 4 Hispanic: 6 Other: 33	
ECOG performance status		0: 91 1: 61 2: 2 Missing: 298	
Tumor type		HCC: 65 Other tumor: 155 Healthy subjects: 232	
Concomitant CYP3A4 inducers		No: 436 Yes: 16	
Concomitant CYP3A inhibitors		No: 418 Yes: 34	

HCC, hepatocellular carcinoma; CYP, cytochrome P450; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

study in subjects with thyroid cancer.<sup>31</sup> Lenvatinib PK was best described by a 3-compartment model with simultaneous first- and 0-order absorption and linear elimination from the central compartment parameterized for apparent plasma clearance of drug after extravascular administration (CL/F), apparent volume of the central compartment (V1/F), apparent volume of peripheral compartments (V2/F and V3/F), inter-compartmental clearance between V2 and V3 (Q2/F and Q3/F), absorption rate constant ( $K_a$ ), and duration of 0-order absorption (D1). A combined additive and proportional error for time after dose  $\leq 2$  hours and separate proportional error for phase I clinical pharmacology studies and studies of subjects with cancer was used for estimation of residual variability. In the current analysis, this PK model was the starting point for PK model development. The first-order conditional estimation with interaction was used. The final population PK model for lenvatinib was validated using the bootstrap resampling technique.<sup>32</sup> Bootstrap estimates were used to compute confidence intervals (CIs) for all model parameters, including those for the covariate estimates. Five hundred bootstrap replicates were performed. The

PK models were developed in NONMEM version 7.2 interfaced with PDx-Pop version 5.0.

#### Covariate PK Model Development

The effect of each of the following covariates was investigated on the PK of lenvatinib: demographics (weight, sex, race, and age), renal function (creatinine clearance), liver function test (alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, bilirubin, and albumin), and Eastern Cooperative Oncology Group (ECOG) performance status. Differences in the PK parameters of lenvatinib in subjects with HCC versus subjects with other tumor types were also tested.

To examine drug-drug interactions, coadministration of cytochrome P450 3A (CYP3A) inhibitors and inducers was tested in the covariate PK model. Covariates identified as being important were first assessed in the base PK model by univariate addition and ranked in descending order according to the change in objective function value. Variables were then tested by stepwise addition to the model. Covariates were included in the model at a significance level of 1%. When no further significant covariates could be included at the 1% significance level, a backward deletion was carried out at the 0.1% significance level at which the relative influence of each covariate on the model was reevaluated by deleting it from the full model on an individual basis.

Continuous covariates were centered at the median of the observed values and included in the model as follows in the case of body-weight effect on clearance:

$$CL_i = [TVCL \cdot (WGT_i/WGT_{\text{median}})^{\theta_{WGTCL}}] \exp \eta_{i\_CL}$$

where:  $CL_i$  = the value of the PK parameter in the  $i$ -th individual, here for the clearance;  $TVCL$  = the typical population value of the PK parameter;  $\theta_{WGTCL}$  = effect of the covariate (here the weight) on the PK parameter;  $WGT_i$  = covariate value of the  $i$ -th subject;  $WGT_{\text{median}}$  = median study population covariate value; and  $\eta_{i\_CL}$  = random interindividual variable, which is an independent and normally distributed statistical error with a mean 0 and variance  $\omega_{CL}^2$ .

Categorical covariates were tested and incorporated in the model as index variables and included in the model as follows in the case of sex effect on clearance:

$$CL_i = TVCL \cdot (\theta_{\text{SEXCL}})^{\text{SEX}_i} \exp \eta_{i\_CL}$$

where:  $CL_i$  = the value of the PK parameter in the  $i$ -th individual, here for the clearance;  $\text{SEX}_i$  = covariate value of the  $i$ -th subject;  $TVCL$  = the typical population value of the PK parameter corresponding to one of the categories, here for the clearance in male for  $\text{SEX}_i = 0$ ;  $\theta_{\text{SEXCL}}$  = effect of the covariate (here

female clearance compared to male clearance); and  $\eta_{i\_CL}$  = random interindividual variable, which is an independent and normally distributed statistical error with a mean 0 and variance  $\omega^2_{CL}$ .

Individual Bayes post hoc PK parameter estimates generated from the base model as well as their difference from the corresponding population value were plotted vs the covariates to identify potential relationships. Covariates selected were based on physiological and clinical plausibility, and only when a graphical relationship was apparent was the effect of the covariate examined formally.

Coadministration of CYP3A4 inducers was defined as the inducer being given for at least 10 days on or prior to the day of PK assessment. If inducer was stopped within 7 days prior to the day of PK assessment, this was also treated as coadministration. Coadministration of CYP3A inhibitors was defined if inhibitor was given on the day of PK assessment. CYP3A inhibitors and inducers were selected from strong and moderate inhibitors and inducers suggested by the Food and Drug Administration.<sup>33</sup>

#### Lenvatinib Exposure

The final population PK model was used to derive individual PK parameters and lenvatinib exposure in subjects from study 202. These data were then incorporated into the PK/pharmacodynamic data sets. Area under the plasma concentration–time curve at steady state (AUC<sub>ss</sub>), based on the starting dose, was derived as follows, where individual clearance is the model-predicted individual apparent clearance:

$$AUC \left( \text{ng} \cdot \frac{\text{h}}{\text{mL}} \right) = \frac{\text{Starting Dose (mg)} \times 1000}{\text{Individual Clearance} \left( \frac{\text{L}}{\text{h}} \right)}$$

For exposure–response relationship analyses of safety, minimum drug concentration at steady state was also tested as an exposure parameter. The minimum drug concentration at steady state was derived using the trough concentration at cycle 1 day 15 from individually predicted concentration–time profiles.

#### Exposure–Response Relationship Analysis

Time to treatment-emergent adverse event (TEAE) leading to study drug withdrawal or dose reduction was explored for relationships with lenvatinib AUC and body weight using the Kaplan-Meier method. The relationship between the occurrence of TEAEs leading to study drug withdrawal or dose reduction during cycle 1 and lenvatinib exposure was analyzed by logistic regression analysis. The exposure parameters, AUC based on starting dose and minimum drug concentration at steady state, were tested. Several models of lenvatinib effect were evaluated including as a constant

effect, linear model, log-linear model, or saturable effect model. The effect of each of the following covariates on the exposure–response relationship was investigated: demographics (sex, body weight, and age), liver function markers (international normalized ratio, bilirubin, and albumin), baseline platelet count, ECOG performance status, Child-Pugh class, factor of carcinogenesis (hepatitis B virus or hepatitis C virus vs others), portal vein involvement, previous systemic chemotherapy, prior antihypertensive therapy, and surgery at baseline. Covariates were kept in the model according to the criteria of forward inclusion and backward exclusion: log-likelihood ratio test, inclusion at the 1% significance level, and exclusion at the 0.1% significance level. The relationship between lenvatinib AUC and time to progression based on independent review assessments was evaluated using the Kaplan-Meier method.

#### Receiver Operating Characteristics Analysis

To investigate the best cutoff value of lenvatinib exposure and body weight to predict high-risk group of the occurrence of TEAEs leading to study drug withdrawal or dose reduction during cycle 1, a receiver operating characteristics (ROC) curve was used. The classification table cross-classifies the binary response with prediction of whether the subject experiences TEAEs leading to study drug withdrawal/reduction during cycle 1 for some cutoff value based on the logistic model. Specifically, each cutoff value is associated with a particular value of specificity and sensitivity. Sensitivity, defined as the proportion of subjects who experienced TEAEs leading to study drug withdrawal or dose reduction during cycle 1 who were correctly classified to do so (true-positive test), was calculated as:

$$\text{Sensitivity} = \frac{\text{True positives}}{\text{True positives} + \text{False negatives}}$$

Specificity was defined as the proportion of subjects who did not experience TEAEs leading to study drug withdrawal or dose reduction during cycle 1 and were correctly classified not to experience it (true-negative test) calculated as:

$$\text{Specificity} = \frac{\text{True negatives}}{\text{True negatives} + \text{False positives}}$$

The ROC curve is a plot of sensitivity on the y-axis and 1 – specificity on the x-axis. Each point on the ROC curve represents a particular sensitivity and specificity value corresponding to a unique cut-off value. The best cutoff point was determined as the point closest to the top-left part of the plot with sensitivity and specificity, namely the criterion was calculated as:

$$\text{minimum}((1 - \text{sensitivities})^2 + (1 - \text{specificities})^2)$$

**Table 2.** Base and Final Population Pharmacokinetic Parameter Estimates of Lenvatinib

Parameter	Base Model		Final Model		
	Population Mean (% RSE)	Interindividual Variability (%CV <sup>a</sup> )	Population Mean (%RSE)	Interindividual Variability (%CV <sup>a</sup> )	Bootstrap Median (2.5-97.5 percentile)
$CL/F [L/h] = \Theta_{CL} \cdot (WGT/75)^{\Theta_{WGT1}} \cdot \Theta_{INDU}^{INDU} \cdot \Theta_{INHIB}^{INHIB} \cdot \Theta_{TM}^{TM} \cdot \Theta_{ALP}^{ALP}$					
Basal CL/F in L/h [ $\Theta_{CL}$ ]	6.50 (2.49)	40.0	6.43 (2.19)	32.6	6.42 (6.07-6.76)
Body weight on CL/F, Q1/F and Q2/F [ $\Theta_{WGT1}$ ]	–	–	0.708 (6.58)	–	0.711 (0.538-0.886)
Inducer on CL/F [ $\Theta_{INDU}$ ]	–	–	1.30 (0.534)	–	1.30 (1.23-1.38)
Inhibitor on CL/F [ $\Theta_{INHIB}$ ]	–	–	0.922 (0.922)	–	0.921 (0.893-0.951)
Population (healthy vs subjects) on CL/F [ $\Theta_{TM}$ ]	–	–	1.19 (3.26)	–	1.19 (1.11-1.27)
ALP (> ULN vs $\leq$ ULN) on CL/F [ $\Theta_{ALP}$ ]	–	–	0.852 (1.24)	–	0.855 (0.807-0.910)
$Q1/F [L/h] = \Theta_{Q1} \cdot (WGT/75)^{\Theta_{WGT1}}$					
Basal Q1/F in L/h [ $\Theta_{Q1}$ ]	3.91 (3.20)	–	3.96 (3.03)	–	3.99 (3.57-4.49)
$Q2/F [L/h] = \Theta_{Q2} \cdot (WGT/75)^{\Theta_{WGT1}}$					
Basal Q2/F in L/h [ $\Theta_{Q2}$ ]	0.724 (3.34)	–	0.726 (2.91)	–	0.738 (0.639-0.845)
$V1/F [L] = \Theta_{V1} \cdot (WGT/75)^{\Theta_{WGT2}}$					
Basal V1/F in L [ $\Theta_{V1}$ ]	45.6 (5.07)	55.2	47.0 (4.40)	49.5	46.8 (43.9-49.8)
Body weight on V1/F, V2/F, and V3/F [ $\Theta_{WGT2}$ ]	–	–	1.08 (5.42)	–	1.08 (0.876-1.28)
$V2/F [L] = \Theta_{V2} \cdot (WGT/75)^{\Theta_{WGT2}}$					
Basal V2/F in L [ $\Theta_{V2}$ ]	31.4 (6.97)	64.3	31.2 (6.76)	62.4	31.1 (28.3-33.7)
$V3/F [L] = \Theta_{V3} \cdot (WGT/75)^{\Theta_{WGT2}}$					
Basal V3/F in L [ $\Theta_{V3}$ ]	33.6 (4.64)	47.7	34.5 (4.14)	42.0	34.7 (31.6-37.7)
$K_a$ (L/h)	1.02 (6.06)	44.5	1.04 (6.80)	46.5	1.04 (0.933-1.13)
D1 (hours)	1.05 (5.45)	68.5	1.06 (5.77)	68.4	1.06 (0.987-1.14)
F1 (capsule vs tablet formulation)	0.832 (0.982)	–	0.867 (1.00)	–	0.867 (0.815-0.908)
Proportional (%CV) (Clinical pharmacology studies)	18.4 (0.888)	–	17.3 (0.883)	–	17.1 (15.5-18.8)
Proportional (%CV) (Patient studies)	30.7 (2.03)	–	30.2 (2.00)	–	30.1 (27.7-32.2)
Proportional (%CV) (TAD $\leq$ 2 hours)	44.9 (3.75)	–	44.8 (3.87)	–	44.8 (40.7-48.8)
Additional (ng/mL) (TAD $\leq$ 2 hours)	7.29 (16.2)	–	7.35 (16.3)	–	7.50 (4.62-9.85)

Correlation between CL/F and V1/F for final model: R = 0.599.

%CV, coefficient of variation; %RSE indicates percentage relative standard error of the estimate; ALP, alkaline phosphatase measurement; CL/F, apparent plasma clearance of drug after extravascular administration; CYP3A4, cytochrome P450 3A4; D1, duration of 0-order absorption; INDU, CYP3A4 inducers; INHIB, CYP3A4 inhibitors;  $K_a$ , absorption rate; Q1, intercompartment clearance between V1 and V2; Q2, intercompartment clearance between V2 and V3; TAD, time after dose; TM, population 0 (cancer subjects) or 1 (healthy subjects); ULN, upper limit of normal; V1/F, apparent volume of central compartment; V2/F and V3/F, apparent volume of peripheral compartments; WGT, weight;  $\Theta$ , population parameters.

<sup>a</sup>The %CV for both intersubject and proportional residual variability is an approximation taken as the square root of the variance  $\times$  100.

All data analyses were performed using R Version 3.1.0 with a pROC package.<sup>34</sup>

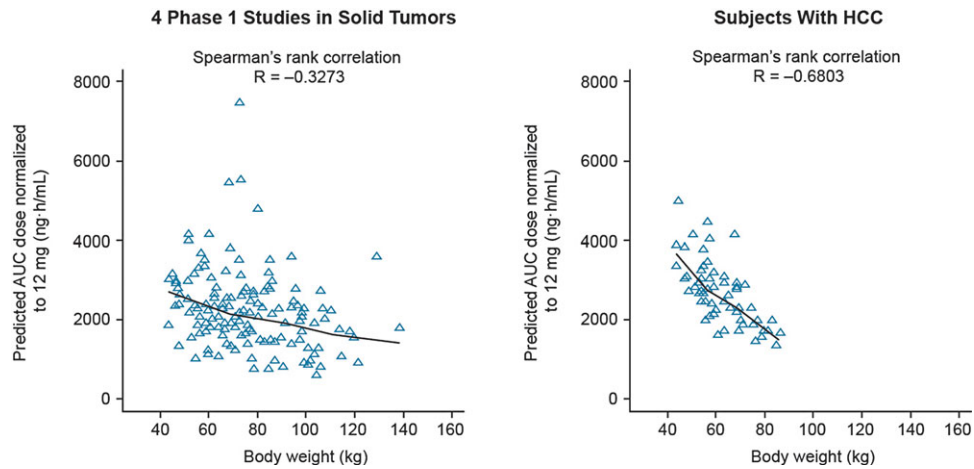
## Results

### PK Model

The parameter estimates, precision of the estimate, bootstrapped median, and 95%CI for the final lenvatinib PK model are presented in Table 2. Interindividual variability was estimated for all parameters except Q2/F, Q3/F, and relative bioavailability of capsule to tablet formulation. Lenvatinib CL/F was observed to increase with increasing body weight (power = 0.708) and to decrease by 15% with alkaline

phosphatase above the upper limit of normal. Effect of the HCC population (HCC vs other cancer type) on CL/F was tested in the covariate analysis; however, this was not a statistically significant effect on the lenvatinib PK model, including body weight and alkaline phosphatase effects.

The final PK model for lenvatinib included body-weight effects on both clearance and volume parameters, whereby both parameters increased with increasing body weight. As a consequence, the relationship between the AUC and body weight demonstrated an increase in AUC as body weight decreased in subjects with HCC. Figure 1 shows the weight-related increase in individual AUC dose normalized to 12 mg for



**Figure 1.** Relationship between model-predicted lenvatinib exposure and body weight. AUC indicates area under plasma concentration–time curve at steady state; HCC, hepatocellular carcinoma.

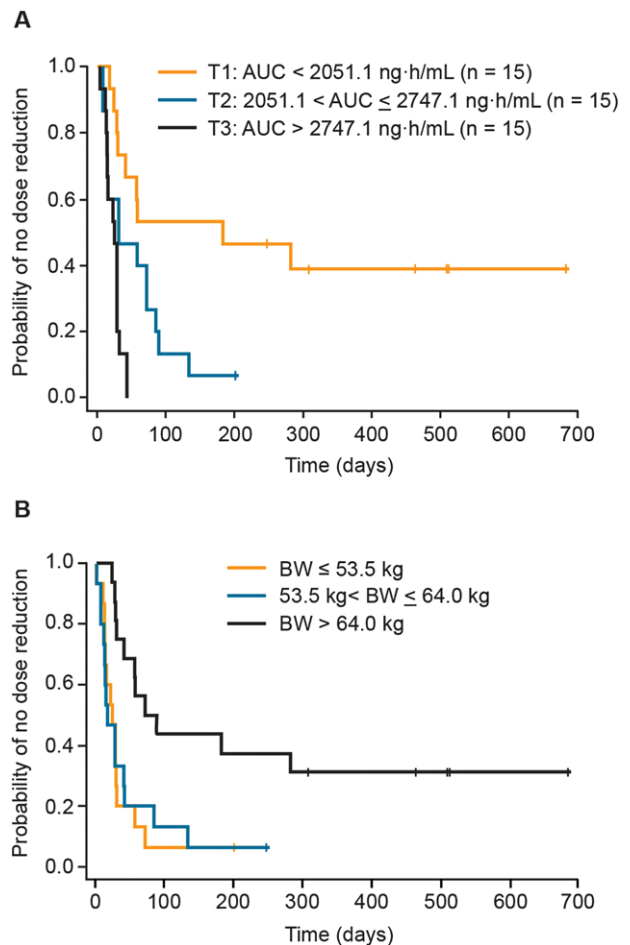
subjects with HCC in study 202. Of note, a stronger correlation between dose-normalized AUC and body weight was observed in subjects with HCC compared with that observed in the 4 studies of subjects with solid tumors.

**Exposure–Response Relationship Analysis of Occurrence of TEAEs Leading to Study Drug Withdrawal or Dose Reduction**

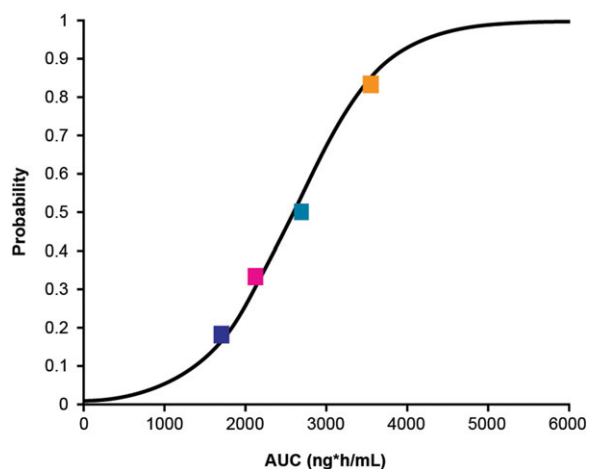
For the phase 2 component of study 202, Kaplan-Meier plots of time to first TEAE leading to study drug withdrawal or dose reduction stratified by 3 groups based on lenvatinib AUC and body weight are presented in Figure 2. A clear exposure–response relationship was observed with higher lenvatinib AUC (Figure 2A) and lower body weight (Figure 2B), resulting in earlier drug withdrawal or dose reduction.

Of the 45 subjects in the exposure–response population, 21 subjects (46.7%) experienced TEAEs leading to dose reduction or discontinuation during cycle 1. The median body weight of these subjects with early dose withdrawal or reduction was 54.3 kg (n = 21; 1 subject was not evaluable; range: 42.8 to 78.8 kg), whereas the median body weight of subjects without early dose modification was 67.6 kg (range: 48.1 to 85.5 kg). The median AUC based on the starting dose of subjects with early dose withdrawal or reduction was 2950 ng·h/mL (range: 1560 to 4250 ng·h/mL), whereas the median AUC based on the starting dose of subjects without early dose modification was 2050 ng·h/mL (range: 1370 to 3270 ng·h/mL).

The occurrence of TEAEs leading to study drug withdrawal or dose reduction during cycle 1 as a function of lenvatinib exposure was modeled with the logit function. Lenvatinib AUC based on the starting dose as linear function was the best predictor for the probability of TEAEs leading to dose reduction of



**Figure 2.** Kaplan-Meier plots of time to first TEAE leading to lenvatinib withdrawal or dose reduction stratified by tertiles of (A) lenvatinib AUC or (B) body weight. AUC indicates area under plasma concentration–time curve at steady state; TEAE, treatment-emergent adverse event.



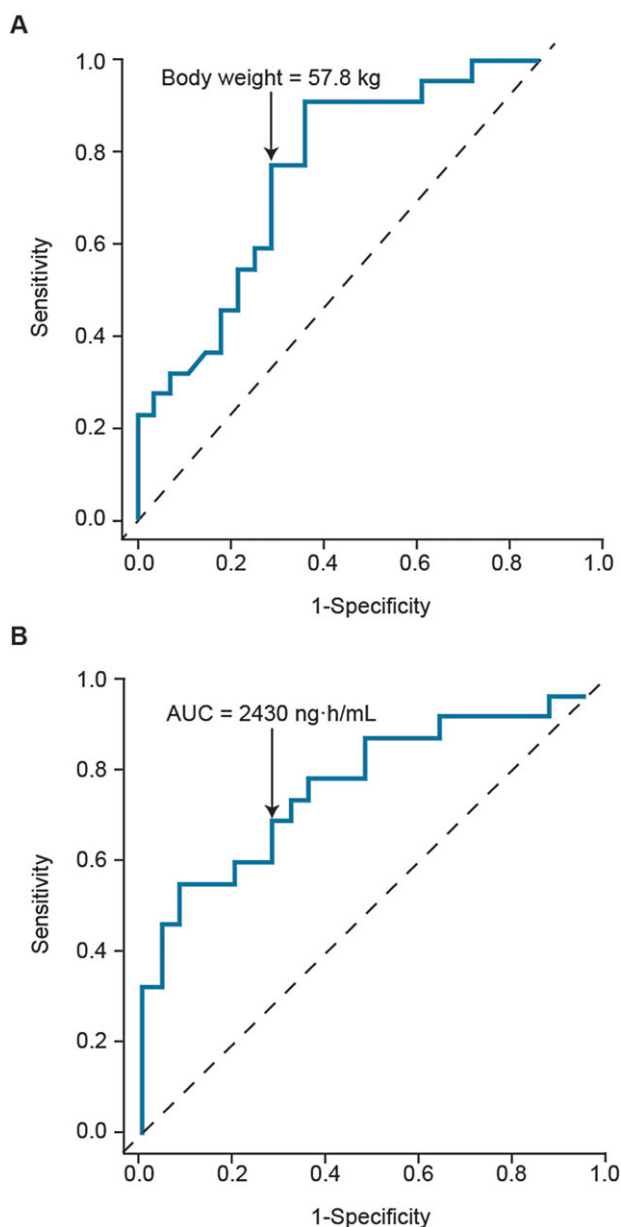
**Figure 3.** Plot of model-predicted probability of the occurrence of TEAEs leading to dose reduction or discontinuation during cycle 1 vs lenvatinib AUC. Filled squares represent the observed probability of responders for each AUC group, plotted at the median AUC of each group. Q1 group  $\leq 25$ th percentile; Q2 group  $> 25$ th percentile and  $\leq 50$ th percentile; Q3 group  $> 50$ th percentile and  $\leq 75$ th percentile; Q4 group  $> 75$ th percentile. AUC indicates area under plasma concentration–time curve at steady state; TEAE, treatment-emergent adverse event.

discontinuation during cycle 1. The effects of demographics, liver function markers, ECOG performance status, factor of carcinogenesis, portal vein involvement, previous systemic chemotherapy and surgery, and prior antihypertensive treatment were tested, and these effects did not influence the exposure–response relationship.

Based on the result of the analyses, a model (Logit = intercept + slope · AUC) that included an intercept and a linear term with respect to lenvatinib AUC was selected as the final model for the logistic analysis of the occurrence of TEAEs leading to study drug withdrawal or dose reduction during cycle 1. The model parameters estimated (NONMEM) for the final model were these: intercept =  $-4.71$  (percentage relative standard error of the estimate = 29.3; 95%CI  $-7.41$  to  $-2.01$ ), and slope of lenvatinib AUC effect (per 1000 ng·h/mL) = 1.82 (percentage relative standard error of the estimate = 28.8; 95%CI 0.793 to 2.85). Model-predicted probability of TEAE leading to study drug withdrawal or dose reduction during cycle 1 is shown in Figure 3.

#### Assessment of Lenvatinib Starting Dose for Phase 3 Studies of Subjects With HCC

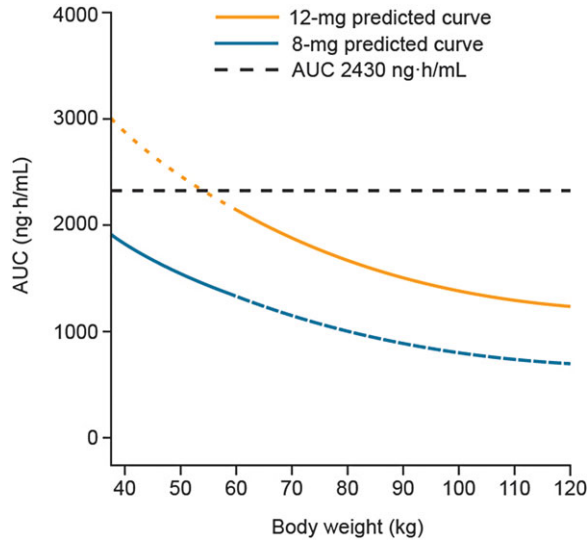
A clear relationship was observed between the occurrence of TEAEs leading to dose reduction or discontinuation during cycle 1 and body weight. Subjects with low body weight experienced early dose reduction or discontinuation. This can be explained by the higher lenvatinib AUC in subjects with low body weight.



**Figure 4.** ROC curve for the occurrence of TEAEs leading to dose reduction or discontinuation during cycle 1. (A) body weight. (B) lenvatinib AUC. AUC indicates area under plasma concentration–time curve at steady state; ROC, receiver operating characteristics; TEAE, treatment-emergent adverse event.

Therefore, an exploratory analysis was performed to assess whether the starting dose of lenvatinib should be adjusted by body weight in future HCC clinical trials.

A ROC curve was used to investigate the best cutoff values of body weight (Figure 4A) and lenvatinib AUC (Figure 4B) to predict the high-risk group for the occurrence of TEAEs leading to study drug withdrawal or dose reduction during cycle 1. The ROC curve indicated that the best cutoff value for body weight was 57.8 kg with 0.77 sensitivity and 0.67 specificity, and area under the ROC curve was 0.75. In addition, the ROC curve

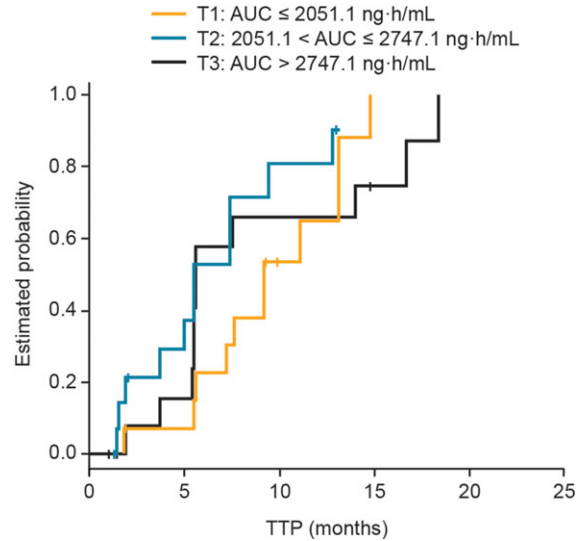


**Figure 5.** Simulated body weight vs lenvatinib AUC for 12-mg and 8-mg dose groups. AUC indicates area under plasma concentration–time curve at steady state.

indicated that the best cutoff value of lenvatinib AUC is 2430 ng·h/mL with 0.71 sensitivity and 0.71 specificity, with an area under the ROC curve of 0.79. Based on the final PK model, simulated body weight (range: 40 to 120 kg) vs lenvatinib AUC in 12- and 8-mg dose groups is shown in Figure 5. With body weight of 57.8 kg and AUC of 2430 ng·h/mL as the threshold to predict the high-risk group of occurrence of TEAEs leading to study drug withdrawal or dose reduction during cycle 1, Figure 5 suggests that dosing adjusted for body weight (specifically a lenvatinib 12-mg dose in subjects with body weight  $\geq 60$  kg and an 8-mg dose for subjects with body weight  $< 60$  kg) was recommended to avoid the early dose reduction or discontinuation. Within the body-weight range of 40 kg to 120 kg, the predicted AUC of subjects with body weight  $< 60$  kg is calculated at between 1540 and 2050 ng·h/mL, and the predicted AUC of subjects with body weight  $\geq 60$  kg is calculated at between 1410 and 2310 ng·h/mL. The AUC range between the 2 dose groups was similar, which supports the adequacy of the proposed dosing regimens based on a body-weight cutoff at 60 kg. No relationship between lenvatinib exposure and response was observed, as evidenced by Kaplan-Meier analysis of independent reviewer assessments of time to progression, stratified by tertiles of lenvatinib AUC based on the starting dose of 12 mg (Figure 6).

**Discussion**

In the phase 2 part of study 202, lenvatinib 12 mg QD demonstrated promising clinical activity with an objective response rate of 37% based on independent



**Figure 6.** Kaplan-Meier estimates of TTP, stratified by tertiles of lenvatinib AUC. AUC indicates area under plasma concentration–time curve at steady state; TTP, time to progression.

radiologic review per modified Response Evaluation Criteria in Solid Tumors and a median time to progression of 7.4 months. However, 74% of subjects (34/46) who received lenvatinib required a dose reduction, and although lenvatinib TEAEs were manageable with the dose reductions, these data indicate that a lower starting dose may be optimal for some subjects. The goal of the current modeling analysis was to identify a dose regimen that can achieve optimal efficacy with improved safety.

In order to describe the PK profile of lenvatinib in subjects with HCC, PK data from 8 phase 1 studies in healthy adults, 4 phase 1 studies in subjects with mixed tumor types, and data from study 202 in subjects with HCC were pooled and analyzed using the population PK approach. The model also included covariate functions. Healthy subjects had a 19% higher lenvatinib CL/F than patients with cancer, CL/F decreased by 14.8% with ALP  $>$  the upper limit of normal, concomitant administration of CYP3A4 inducers increased CL/F by 30%, and CYP3A4 inhibitors decreased CL/F by 7.8%. The magnitude of these effects is within the intersubject variability for CL/F (32.6%) and, hence, of no clinical relevance. These results are similar to the results seen in the previous analysis reported by Gupta et al.<sup>31</sup> Effect of body weight was included in clearance and volume parameters, whereby both parameters increased with increasing body weight. Model estimates of body-weight effect are similar to the result seen in the previous analysis. Body weight was the main covariate that explained the interindividual variability of CL/F; however, only 10.5% of CL/F interindividual variability could be explained by body weight in this



PK model. Other covariates explained 14.3% of CL/F interindividual variability and remaining interindividual variability was unknown variability. Meanwhile, in the phase 2 part of study 202, dose reductions were frequent and early in the course of treatment. Indeed, 21 subjects (46.7%) of the 45 subjects in the exposure–response population experienced TEAEs leading to dose reduction or discontinuation during cycle 1. A clear relationship was seen between the occurrence of TEAEs leading to dose reduction or discontinuation during cycle 1 and body weight, whereby patients with low body weight experienced the early dose reduction or discontinuation. This can be explained by the higher lenvatinib exposure in patients with low body weight, as body weight affects lenvatinib PK. Therefore, adjusting the starting dose according to body weight could be an effective way to manage the toxicity of lenvatinib in subjects with HCC.

The effect of tumor type (HCC vs others) on lenvatinib PK was not statistically significant in this analysis. Subjects with HCC in study 202 had low body weight (median 58.8 kg) and low liver function (71% had alkaline phosphatase >upper limit of normal). Therefore, the observed higher concentrations of lenvatinib in study 202<sup>22</sup> may be explained by body weight and alkaline phosphatase effects on lenvatinib PK. However, our analysis was limited by the small number of subjects with HCC. Thus, further evaluation in phase 3 studies with large data sets are required to determine the effect of HCC on CL/F. No differences in CL/F were observed in the population PK analysis between HCC Child-Pugh class A and B groups, which is similar to the results seen in the hepatic impairment PK study.<sup>21</sup>

Lenvatinib AUC was the best predictor for the probability of developing TEAEs leading to dose reduction or discontinuation during cycle 1. There was a clear exposure–response relationship for time-to-first TEAE leading to study drug withdrawal or dose reduction, which was evident in the Kaplan-Meier plots, and a higher lenvatinib AUC resulted in earlier dose reduction. The effects of the demographics, liver function markers, ECOG performance status, factor of carcinogenesis, portal vein involvement, previous systemic chemotherapy and surgery, and prior antihypertensive therapy did not influence the relationship between lenvatinib exposure and TEAEs.

High toxicity is a common reason for the failure of phase 3 clinical trials with tyrosine kinase inhibitors.<sup>4</sup> Based on the observation that subjects with low body weight experienced early dose reduction or discontinuation in this study, a 2-level dose regimen based on body weight is expected to be effective to manage toxicity. Therefore, we utilized exploratory ROC curves to assess the utility of adjusting the starting dose of lenvatinib

by body weight in future HCC clinical studies and to determine the best cutoff value for body weight and lenvatinib exposure. The ROC curve indicated that the best cutoff value of body weight was 57.8 kg; therefore, we propose the dosing regimen based on a body-weight cutoff at 60 kg; 12-mg dose in subjects with body weight  $\geq 60$  kg and 8-mg dose for subjects with body weight  $< 60$  kg. The simulation suggests that this dosing regimen be recommended to avoid the early dose reduction or discontinuation (Figure 5), based on the 2430 ng·h/mL of AUC as threshold to predict the high-risk group for early dose reduction or discontinuation. In addition, the AUC range between the 2 dose groups was similar, which supports the adequacy of the proposed dosing regimens.

Finally, our results must be interpreted with the following limitations: we explored the early dose modification as the safety endpoint; therefore, cumulative or chronic drug toxicity is not considered. In addition, all TEAEs leading to study drug withdrawal or dose reduction was treated as 1 event in this exposure–response analysis, namely the same exposure–response relationship was assumed for all TEAEs.

## Conclusions

For further clinical development of lenvatinib in patients with HCC Child-Pugh class A, a starting dose of 12 mg is recommended for subjects with a body weight of  $\geq 60$  kg as well as an 8-mg dose for subjects with a body weight  $< 60$  kg to minimize early dose reduction or discontinuation. Although the starting dose in the phase 3 study will be lower for subjects with low body weight, it is predicted that efficacy may be similar to the phase 2 results because the estimated exposure to lenvatinib is similar between subjects with lower body weight and those with higher body weight. Overall, the modeling proposes a dose regimen for future studies in subjects with HCC that is predicted to achieve optimal efficacy and enhanced safety.

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