Influence of different degrees of liver impairment on the pharmacokinetics of clazosentan

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Clazosentan is a selective endothelin A receptor antagonist, formulated for parenteral use, which is in clinical development for the treatment of aneurysmal subarachnoid haemorrhage.
- The human ADME study showed that most of clazosentan is excreted via the biliary route.
- The pharmacokinetics (PK) of clazosentan are similar in healthy subjects and those with severe renal impairment.

WHAT THIS STUDY ADDS

- The results of the present study showed that there was an increase in the exposure to clazosentan with increasing severity of liver impairment. Changes in PK in subjects with mild liver impairment compared with healthy subjects are unlikely to be clinically relevant.
- There are significant differences in the PK parameters of clazosentan in subjects with moderate and severe liver impairment compared with healthy subjects.
- The results of this study will allow confident dosing of clazosentan in individuals with moderate and severe liver impairment.

AIM

To investigate the effect of mild, moderate and severe liver impairment on the pharmacokinetics (PK), tolerability and safety of clazosentan, an intravenous endothelin receptor antagonist.

METHODS

Healthy subjects with normal liver function ($n = 8$), subjects with mild (Child Pugh A, $n = 8$), and with moderate (Child-Pugh B, $n = 8$) liver impairment received a continuous intravenous infusion of 1 mg h^{-1} and subjects with severe liver impairment (Child Pugh C, $n = 8$) received a continuous intravenous infusion of 0.5 mg h^{-1} clazosentan for a duration of 6 h. The pharmacokinetic (PK) parameters of clazosentan were determined by both model-independent and model-dependent methods.

RESULTS

Mean plasma concentrations of clazosentan increased with increasing severity of liver impairment. Geometric means of area under the plasma concentration–time curve from 0 to infinity ($\text{AUC}_{(0,\infty)}$) were 1.41 – $(90\% \text{ CI } 1.04, 1.90)$, 2.37 – $(90\% \text{ CI } 1.75, 3.19)$, and 3.79 – $(90\% \text{ CI } 2.81, 5.11)$ fold higher in subjects with mild, moderate and severe liver impairment, respectively, compared with healthy subjects. Similar results were obtained by non-compartmental and two-compartmental analysis. A significant positive correlation between clazosentan $\text{AUC}_{(0,\infty)}$ and Child-Pugh score ($r = 0.83$), bilirubin ($r = 0.78$) and prothrombin time ($r = 0.62$), and a significant negative correlation with albumin concentration ($r = 0.71$) was observed. Administration of clazosentan was well tolerated in all groups.

CONCLUSIONS

The increase in exposure to clazosentan in Child-Pugh A patients is not expected to be clinically relevant and no dose adjustment for these patients is proposed. It is recommended to reduce the dose of clazosentan to half in Child-Pugh B and to one fourth in Child-Pugh C patients.

Introduction

Endothelin-1 (ET-1) is one of the most potent vasoconstrictors known [1]. Its concentrations are increased in a number of different diseases such as pulmonary arterial hypertension [2] and aneurysmal subarachnoid haemorrhage (aSAH) [3]. The role of ET-1 in aSAH was confirmed by experimental studies showing the efficacy of endothelin receptor antagonists (ERAs) in preventing and reversing cerebral vasospasm after experimental SAH [4–8]. Clazosentan (Ro 61-1790, VML 588, AXV-034343) is a selective endothelin A (ET_A) receptor antagonist, formulated for parenteral use. Its chemical structure is published [8] and in patients clazosentan was shown to reduce the frequency and severity of cerebral vasospasm following severe aSAH, which is one of the major causes for morbidity and mortality in these patients [9, 10].

Previously, the tolerability, safety, and pharmacokinetics (PK) of clazosentan in healthy male and female subjects have been described. Clazosentan showed dose-proportional PK over the investigated dose range [11, 12]. It has also been shown that there are no notable differences in the PK of clazosentan between males and females, and/or between Caucasian and Japanese subjects [12, 13]. Dose-limiting adverse events in healthy subjects were headache, nausea and vomiting.

The PK profile of clazosentan can be described by a two-compartment model. The volume of distribution at steady state (V_{ss}) and clearance (CL) were approximately 18 l and 35 l h⁻¹, respectively. The two disposition half-lives were approximately 9 min and 2 h.

Clazosentan is currently being investigated in phase 3 studies as an intravenous (i.v.) infusion for reducing cerebral vasospasm-related morbidity and all-cause mortality in patients with aSAH. Some aSAH patients may have impaired liver function. As the majority of clazosentan is excreted as unchanged drug via bile [14], impaired liver function could affect the PK of clazosentan. The present study was designed to assess the effect of mild, moderate and severe liver impairment on the PK of clazosentan and to determine whether there is a need for dose adjustment in patients with liver impairment.

Methods

Subjects

After eligibility screening, male and female liver cirrhosis patients were categorized based on Child-Pugh classification as having mild, moderate or severe liver impairment [15, 16], and were allocated to groups A, B and C, respectively ($n = 8$ per group). The results of the Child-Pugh classification at screening had to be confirmed on day -1, if the screening assessment had taken place more than 1 week before day 1. Eight healthy male and female subjects (based on medical history and screening examination)

were enrolled in group D. The accepted age range was 30 to 75 years (inclusive). Subjects were excluded if they had known hypersensitivity to any excipients of the drug formulation, had received an experimental drug within the past 3 months or had a positive HIV serology at screening. Subjects who received any treatment with calcineurin inhibitors (cyclosporin A, pimecrolimus or tacrolimus) within 2 weeks prior to dosing were excluded from the study. Clinically relevant drug-drug interactions with cyclosporin A have been documented for the structurally related endothelin receptor antagonists bosentan and tezosentan [17, 18]. Therefore, a PK interaction between clazosentan and these drugs cannot be excluded.

In addition, subjects in the liver impairment groups who had suffered a myocardial infarction within the 3 months prior to the screening visit could not enter the study. Subjects with encephalopathy grade >1 (encephalopathy grading: one of the components of Child-Pugh classification [15, 16]) were excluded from the study. These subjects, because of neurological and behavioural disorders, are not able to understand and comply with the requirements of the study and to provide written informed consent.

Due to the teratogenic properties of clazosentan, participating women of childbearing potential were required to use a reliable method of contraception.

The Ethics Committee of the Republic of Moldova approved the study protocol and all subjects gave written informed consent before any screening procedures were performed. The study was conducted in full conformity with the principles of the Declaration of Helsinki and the European Medicines Agency (EMA) Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

Study design

This was an exploratory, phase 1, parallel-group, single-centre, open-label study. The planned administered dose was 1 mg h⁻¹ for a period of 6 h. For safety considerations, dosing in subjects in the liver impairment groups was staggered so that dosing in subjects with less severe liver impairment was started first. The dose could be adjusted for patients in liver impairment groups. After review of the interim PK results of subjects with moderate liver impairment (group B), which revealed a relevant increase in the exposure to clazosentan in these subjects compared with exposure in healthy subjects, the dose in subjects with severe liver impairment (group C) was reduced to half (0.5 mg h⁻¹ instead of 1 mg h⁻¹) in order to limit any possible risk to the subjects with severe liver impairment.

Blood sampling

Approximately 0.5 h after consumption of a light breakfast, infusion of drug was initiated at a constant rate of 10 ml h⁻¹. Blood samples of 3 ml were collected into potassium EDTA-containing tubes from an indwelling catheter or by direct venepuncture immediately before and at 0.5, 1,

2, 3, 4, 5 and 6 h after the start of the drug infusion as well as at 2, 5, 10, 15, 30 and 45 min, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 30 and 42 h after discontinuation of the infusion. In addition, one blood sample of 5 ml was taken 5 h after the start of the infusion for the assessment of plasma protein binding of clazosentan. Plasma was separated and stored at -20°C pending analysis. Tolerability and safety were evaluated by monitoring premature withdrawals, (serious) adverse events ((S)AEs), clinical laboratory variables, vital signs, 12-lead ECG recording and physical examination.

Bioanalytical methods

Quantification of clazosentan was performed by using a validated liquid chromatography (LC) assay coupled on-line with tandem mass spectrometry (MS/MS) [12, 19]. Clazosentan was extracted from plasma by protein precipitation with acetonitrile containing the internal standard (an analogue of clazosentan deuterated in four positions), before injection into the chromatographic system.

The quantification of samples was performed by plotting peak area ratios of clazosentan vs. the internal standard against the corresponding plasma nominal concentration. Analyst™ software (Version 1.4.1) was used to apply this internal standardization method. The performance of the assay was monitored by simultaneous analysis of independently prepared quality control samples of various concentrations. The lower limit of quantification (LOQ) in total plasma was 0.25 ng ml^{-1} . The inter-assay coefficient of variation and the inaccuracy were $\leq 7.4\%$ and $\leq 5.7\%$, respectively (at nominal concentrations of 0.750, 30.0 and 420 ng ml^{-1}). The calibration curves were linear in the range of 0.25 to 512 ng ml^{-1} . Linearity of the analytical method was demonstrated by correlation coefficients ≥ 0.9940 .

The *ex vivo* protein binding was determined by ultrafiltration of samples withdrawn 5 h after the start of the infusion from all subjects. Protein binding samples were centrifuged with 'Amicon Centrifree' centrifugal filter devices [20 min, 25°C and 440 g (relative centrifugal force)] to gain $150\text{ }\mu\text{l}$ ultra-filtrates. Each ultra-filtrate ($100\text{ }\mu\text{l}$) and $100\text{ }\mu\text{l}$ of unfiltered sample were extracted together with the internal standard by protein precipitation using acetonitrile. A quantitative determination with the filtrated and the unfiltered sample was performed in order to determine protein bound and non-bound clazosentan (free in plasma).

Pharmacokinetic and statistical evaluations

The sample size was not determined based on statistical power considerations. Actual blood sampling times were used for the PK evaluation when they deviated by more than 5% from the scheduled ones. The measured individual plasma concentrations of clazosentan were used to calculate PK parameters. The PK parameters of clazosentan

were determined with model-independent and model-dependent methods using WinNonlin Version 5.2 (Pharsight Corporation, Mountain View, CA). The area under the curve (AUC) was calculated according to the linear trapezoidal rule. $\text{AUC}_{\text{infusion}}$ is the AUC during the infusion, i.e. 0–6 h after start of the infusion. $\text{AUC}_{(0,t)}$ was calculated using the measured concentration–time values above the LOQ. $\text{AUC}_{(0,\infty)}$ was calculated by combining $\text{AUC}_{(0,t)}$ and $\text{AUC}_{\text{extra}}$. $\text{AUC}_{\text{extra}}$ represents an extrapolated value obtained by C_t/λ_z , where C_t is the last plasma concentration measured above the LOQ and λ_z represents the elimination rate constant determined by log-linear regression analysis of the measured plasma concentrations of the terminal elimination phase. The half-life of clazosentan was calculated as follows: $t_{1/2} = \ln 2/\lambda_z$. CL is the total systemic clearance, estimated by: $\text{CL} = \text{Dose}/\text{AUC}_{(0,\infty)}$. V_{ss} is the volume of distribution at steady state, estimated by: $V_{ss} = \text{CL} [(\text{AUMC}/\text{AUC}) - (\text{infusion time}/2)]$, where AUMC is the area under the first moment vs. time curve.

PK parameters were summarized using geometric mean and two-sided 95% CIs of the geometric mean.

For model-dependent analysis, concentration–time profiles of clazosentan were fitted to two-compartment and three-compartment models. The two models were compared for individual subjects based on visual review of the observed vs. predicted plots, diagnostic factors Akaike and Schwarz Criteria, assessment of obtained parameters and precision (standard error and CV%) of parameters and condition number. Based on these criteria for the majority of subjects the two-compartment model (PK model 9, i.v. infusion, micro-constant, no lag time, first order elimination) was revealed to be the best model. For six subjects, two subjects from group A, one subject from group B, and three subjects from group C the three-compartment model (model 19, i.v. infusion, macro-constant, no lag time, first order elimination) showed a better fit and was chosen for modelling. A weighting factor of $1/Y^2$ was applied.

Simulation of concentration–time profiles for a 24 h constant infusion of clazosentan (1 mg h^{-1} in groups A, B, D and 0.5 mg h^{-1} in group C) was performed using WinNonlin Version 5.2. For each subject the initial values of the parameters used for the simulation were derived from the 6 h constant infusion of clazosentan using the same model as described above.

Differences in PK parameters, obtained by non-compartmental and compartmental analysis, between the liver impairment groups and healthy subjects were explored using the ratios of geometric means (point estimates), and their 90% confidence intervals (CIs) (healthy subjects as reference). Log transformed PK parameters were analyzed by linear models with the independent factor 'group'. Geometric mean ratios and 90% CI were calculated from the corresponding back transformed marginal means with group D as reference.

The difference in percentage of unbound clazosentan in plasma between liver impairment groups and healthy

Table 1

Demographic variables and baseline characteristics

Group	n	Age (years)	Weight (kg)	Variable (mean $\pm$ SD)		Albumin (g l ⁻¹)	PT (s)	Child-Pugh score		Sex	
				Body mass index (kg m ⁻²)	Bilirubin (μ mol l ⁻¹)			Range		Male	Female
D	8	45 $\pm$ 11	72 $\pm$ 14	24.7 $\pm$ 3.7	10.8 $\pm$ 1.3	55.03 $\pm$ 4.07	13.48 $\pm$ 0.67	NA		3	5
A	8	47 $\pm$ 9	78 $\pm$ 19	26.3 $\pm$ 4.0	16.8 $\pm$ 9.1	49.01 $\pm$ 7.90	15.55 $\pm$ 1.26	5–6		4	4
B	8	53 $\pm$ 6	75 $\pm$ 12	25.7 $\pm$ 2.3	35.1 $\pm$ 11.0	42.98 $\pm$ 7.34	15.91 $\pm$ 1.61	7–9		5	3
C	8	50 $\pm$ 7	70 $\pm$ 13	24.2 $\pm$ 3.0	67.5 $\pm$ 61.1	28.30 $\pm$ 6.80	17.14 $\pm$ 1.60	10–13		4	4

A, subjects with mild liver impairment; B, subjects with moderate liver impairment; C, subjects with severe liver impairment; D, healthy subjects. NA, not applicable. The Child-Pugh score was not determined for healthy subjects.

subjects was explored by ratios of geometric means of percentage of unbound clazosentan (90% CI) of groups A, B, and C vs. healthy subjects (group D). Tolerability and safety endpoints were analyzed descriptively.

Results

Demographics

Table 1 summarizes the demographic variables and baseline characteristics of enrolled subjects. The four groups were well matched for BMI and age, with males and females in all groups.

All 32 enrolled subjects (eight in each group) completed the study as planned and were used for PK and safety analysis.

Pharmacokinetics

The subjects in groups A, B and D were administered a constant infusion of 1 mg h⁻¹ and subjects in group C were administered a constant infusion of 0.5 mg h⁻¹ of clazosentan for a period of 6 h. For the PK analysis the concentration-dependent PK parameters (AUC) were dose-adjusted, which enabled the comparison of the PK parameters between groups. Taking into consideration the dose-proportional PK of clazosentan, AUC values in group C were multiplied by two [11, 12].

The mean plasma concentration–time profiles of clazosentan in the subject groups during and following infusion of clazosentan are shown in Figure 1. Comparison of concentration–time profiles showed that mean concentrations of clazosentan increased with increasing severity of liver impairment. After termination of the infusion, the concentrations declined rapidly following a biphasic profile. All subjects in groups A and D had quantifiable clazosentan in plasma up to 5 h after the end of the infusion. In groups B and C, all subjects had quantifiable clazosentan in plasma up to 12 h and 8 h after the end of the infusion, respectively.

Visual inspection of the individual concentration–time profiles revealed that steady-state conditions were approached approximately 5 h after start of the infusion

Figure 1

Arithmetic mean $\pm$ SD plasma concentration–time profiles of clazosentan in subjects with mild, moderate and severe liver impairment (groups A, B and C) vs. healthy subjects (group D) after continuous i.v. infusion of 1 mg h⁻¹ (0.5 mg h⁻¹ for group C) for a period of 6 h. group A = 1 mg h⁻¹ (—■—); group B = 1 mg h⁻¹ (—▲—); group C = 0.5 mg h⁻¹ (—▼—); group D = 1 mg h⁻¹ (—□—)

Table 2

Summary of PK parameters of clazosentan after i.v. infusion of 1 mg h⁻¹ (0.5 mg h⁻¹ for group C) of clazosentan for a period of 6 h from non-compartmental analysis

Group	n	AUC _{infusion} (ng ml ⁻¹ h)	AUC _(0,t) (ng ml ⁻¹ h)	AUC _(0,∞) (ng ml ⁻¹ h)	t _{1/2} (h)	CL (l h ⁻¹)	V _{ss} (l)
D	8	161 (134, 194)	173 (142, 210)	174 (144, 211)	2.0 (1.5, 2.6)	34.5 (28.4, 41.9)	19.6 (15.3, 25.2)
A	8	215 (150, 307)	244 (168, 354)	245 (169, 356)	2.9 (1.7, 5.1)	24.5 (16.8, 35.5)	22.4 (15.7, 31.8)
B	8	330 (273, 398)	410 (330, 510)	412 (331, 513)	4.9 (3.4, 6.9)	14.5 (11.7, 18.1)	22.4 (18.8, 26.6)
C*	8	484 (361, 648)	642 (451, 913)	660 (464, 938)	14.7 (7.4, 29.1)	9.1 (6.4, 12.9)	28.3 (20.3, 39.5)

*The AUC_{infusion}, AUC_(0,t), and AUC_(0,∞) values of group C were multiplied by two in order to correct for dose. A, subjects with mild liver impairment; B, subjects with moderate liver impairment; C, subjects with severe liver impairment; D, healthy subjects. Data are expressed as geometric means (95% CI).

Table 3

Ratio of geometric means of PK parameters of clazosentan and 90% CIs from non-compartmental analysis

Comparison	Statistic	AUC _{infusion} (ng ml ⁻¹ h)	AUC _(0,t) (ng ml ⁻¹ h)	AUC _(0,∞) (ng ml ⁻¹ h)	t _{1/2} (h)	CL (l h ⁻¹)	V _{ss} (l)
A vs. D	Ratio of geometric means 90% CI	1.34	1.41	1.41	1.46	0.71	1.14
		1.02, 1.75	1.04, 1.90	1.04, 1.90	0.89, 2.39	0.53, 0.96	0.85, 1.52
B vs. D	Ratio of geometric means 90% CI	2.05	2.37	2.37	2.41	0.42	1.14
		1.56, 2.69	1.76, 3.20	1.75, 3.19	1.46, 3.96	0.31, 0.57	0.85, 1.52
C* vs. D	Ratio of geometric means 90% CI	3.00	3.71	3.79	7.29	0.26	1.44
		2.29, 3.94	2.75, 5.01	2.81, 5.11	4.43, 11.99	0.20, 0.36	1.08, 1.92

*The AUC_{infusion}, AUC_(0,t), and AUC_(0,∞) values of group C were multiplied by two in order to correct for dose. A, subjects with mild liver impairment; B, subjects with moderate liver impairment; C, subjects with severe liver impairment; D, healthy subjects.

for several subjects. However, true steady-state conditions were not reached during the infusion for all subjects, which was partly due to the increase in half-life of clazosentan in subjects with liver impairment, which delayed the attainment of steady-state conditions.

The PK parameters of clazosentan, obtained by non-compartmental analysis are summarized in Table 2. The ratios of geometric means (point estimates) of PK parameters and their 90% CIs, obtained by non-compartmental analysis with healthy subjects (group D) as reference are shown in Table 3. The geometric mean of AUC_(0,∞) was 1.41- (90% CI 1.04, 1.90), 2.37- (90% CI 1.75, 3.19) and 3.79- (90% CI 2.81, 5.11) fold higher in groups A, B and C, respectively, compared with healthy subjects (group D). There were decreases in geometric means of CL to 0.71 (90% CI 0.53, 0.96), 0.42 (90% CI 0.31, 0.57) and 0.26 (90% CI 0.20, 0.36) in groups A, B and C, respectively, compared with group D. The geometric mean of t_{1/2} showed a prolongation of 1.46- (90% CI 0.89, 2.39), 2.41- (90% CI 1.46, 3.96) and 7.29- (90% CI 4.43, 11.99) fold, in groups A, B and C, respectively, compared with healthy subjects (group D) (Table 3). Similar to non-compartmental analysis, results from the compartmental analysis showed a decrease in CL and an increase in the half-life of the first disposition phase (t_{1/2(α)}) and the half-life of the second disposition phase (t_{1/2(β)}) (or the half-

life of the third disposition phase, t_{1/2(γ)}) with increasing severity of liver impairment (data not shown).

There was no clear change in V_{ss} in both analyses.

Modelling and simulation were used to predict the concentration-time profiles after longer infusion, i.e. a 24 h constant infusion of 1 mg h⁻¹ in groups A, B D and 0.5 mg h⁻¹ in group C. Under these conditions clazosentan reached steady-state in all subjects. The results showed that the ratios of geometric means of predicted PK parameters after 24 h constant infusion were similar to 6 h infusion. The geometric mean of the AUC was 1.43- (90% CI 1.06, 1.92), 2.31- (90% CI 1.71, 3.11) and 3.59- (90% CI 2.67, 4.84) fold higher in groups A, B and C, respectively, compared with healthy subjects (group D).

The geometric mean (95% CI) of percentage of unbound clazosentan in plasma (measured in 5 h time point samples) was 2.2 (1.7, 2.7) for healthy subjects compared with 2.2 (1.8, 2.7), 3.5 (2.9, 4.2), and 4.9 (3.8, 6.3), in groups A, B and C, respectively.

The ratios of the geometric means of percentage of unbound clazosentan (90% CI) of groups A, B and C vs. healthy subjects (group D), were 1.04 (0.83, 1.30), 1.61 (1.29, 2.01) and 2.28 (1.83, 2.85), respectively.

Linear regressions between clazosentan exposure and Child-Pugh score, and its laboratory components

Figure 2

Relationship between $AUC_{(0,\infty)}$ and Child-Pugh score, and between $AUC_{(0,\infty)}$ and laboratory components of the Child-Pugh classification. (A □) subjects with mild liver impairment, (B ▼) subjects with moderate liver impairment, (C △) subjects with severe liver impairment, (D ○) healthy subjects

(bilirubin, albumin, and prothrombin time (PT)) are presented in Figure 2. Child-Pugh score and the three laboratory components of Child-Pugh classification showed a significant correlation with $AUC_{(0,\infty)}$. There was a significant positive correlation between Child-Pugh score and $AUC_{(0,\infty)}$ ($r = 0.83$), bilirubin concentration and $AUC_{(0,\infty)}$ ($r = 0.78$) and between PT level and $AUC_{(0,\infty)}$ ($r = 0.62$). There was a significant negative correlation between albumin concentration and $AUC_{(0,\infty)}$ ($r = 0.71$).

Tolerability and safety

One male subject with severe liver impairment (group C), experienced a SAE (a moderate hepatic encephalopathy progression), which was judged by the investigator as unrelated to the study drug and resolved without sequelae 5 days after the end of study visit (EOS).

In total there were 32 treatment-emergent AEs, of which 17 related to study drug, reported by 16 subjects. Five subjects in group A (62%) reported 13 AEs, four subjects in group B (50%) reported six AEs, four subjects in

group C (50%) reported nine AEs and three subjects in group D (37.5%) reported four AEs. The most frequently reported treatment-emergent AE was headache, with 8 of 32 AEs. There were two cases of reduction in blood pressure after the start of the clazosentan infusion in group C, which were reported as AEs. All treatment-emergent AEs were of mild or moderate intensity and resolved without sequelae.

No clinically relevant treatment-related effects on ECG, or clinical laboratory variables could be detected. In all groups, there was a decrease in mean and median systolic and diastolic blood pressure after study drug administration compared with baseline. The median decreases from baseline in systolic blood pressure during the infusion to 5 h after the start of the infusion were 7.5, 1.5, 11 and 4 mmHg in groups A, B, C and D, respectively. The median decreases in diastolic blood pressure from baseline to 5 h after infusion start were 7.5, 5.5, 4.5 and 2.5 mmHg for groups A, B, C and D, respectively. There was no relevant change in the median heart rate in any group.

Discussion

The objectives of this study were to evaluate the PK and describe the tolerability and safety of clazosentan in subjects with mild, moderate and severe liver impairment, due to liver cirrhosis, in comparison with healthy subjects. For the assessment of the severity of the liver impairment, the Child Pugh class (mild, moderate, and severe impairment) was used, as recommended by the Food and Drug Administration (FDA) [15] and EMEA [16]. The results showed an increase in the exposure to clazosentan with increasing severity of liver impairment, which is expected to be clinically relevant in subjects with moderate and severe liver impairment. On the basis of results obtained in the absorption, distribution, metabolism and excretion (ADME) study [14], which showed the excretion of the majority of clazosentan via bile, it was predicted that impaired liver function would significantly affect the PK of clazosentan and renal impairment would not have a major effect on its PK. The results of the present study, together with the recently performed PK study in subjects with severe renal impairment [19], confirm the importance of the liver and the minor role of the kidney in the elimination of clazosentan.

The inter-subject coefficients of variation in PK parameters were higher for subjects with liver impairment, especially in subjects with Child-Pugh C, compared with healthy subjects. One possible explanation could be the underlying complex pathophysiological changes occurring in liver impairment subjects, which are associated with variable non-uniform reduction in drug disposition. Overall, exposure to clazosentan was increased in subjects with liver impairment compared with healthy subjects and the increase in clazosentan exposure was consistent with increasing severity of liver impairment.

The results of this study suggest that the extent of change in PK parameters in subjects with mild liver impairment compared with healthy subjects is not sufficient to result in a clinically meaningful effect. Therefore, dose adjustment for these patients does not appear necessary. However, the results showed a significant increase in exposure to clazosentan in subjects with moderate and severe liver impairment. The increase in exposure to clazosentan was consistent with increasing severity of liver impairment. Based on the results of this study it is recommended to reduce the dose of clazosentan to half in patients with moderate and to one fourth in patients with severe liver impairment. Considering that clazosentan exhibits dose-proportional PK across the clinical dose range [11, 12], the results of this study can be applied to 5 mg h^{-1} and 15 mg h^{-1} , the doses used to investigate the efficacy of clazosentan in the ongoing phase 3 studies.

The reduction in systemic clearance and prolongation of elimination half-life in subjects with liver impairment is consistent with reduced excretion of the drug by the liver in these subjects. The reduced liver capacity in cirrhotic

subjects to eliminate drugs which are excreted almost un-metabolized through bile could be the result of multiple factors, such as impairment of active uptake of the drug into hepatocytes, efflux of the drug into the bile duct or impaired blood perfusion of hepatocytes [20].

True steady-state conditions were not reached during the infusion in all subjects. A possible explanation could be the increase in half-life of clazosentan in subjects with liver impairment due to reduced drug clearance in these subjects, which delayed the attainment of steady-state conditions. Modelling and simulation were used to predict the concentration–time profiles and PK parameters after longer infusion, i.e. a 24 h constant infusion of 1 mg h^{-1} in groups A, B, D and 0.5 mg h^{-1} in group C. Under these conditions steady-state was reached in all subjects. It was shown that the increase in exposure to clazosentan in subjects with mild, moderate and severe liver impairment was similar after 24 h and after 6 h continuous infusion. This indicates that the results of this study can also be applied to longer infusion times.

There was an increase in clazosentan exposure with increasing Child-Pugh score over the range of 5 to 13. The Child-Pugh score and three laboratory components of the Child-Pugh score, bilirubin, albumin and PT each showed a significant correlation with $\text{AUC}_{(0,\infty)}$, when these parameters were evaluated separately by linear regression. This suggests that the Child-Pugh score could be considered as a predictive marker of elevated exposure to clazosentan and the three laboratory components of the Child-Pugh score each contribute to this correlation.

Since clazosentan is highly protein bound (approximately 98%), a difference in protein binding was also explored between the liver impairment groups and healthy subjects. Mean percentage of unbound clazosentan in plasma was higher in the moderate and severe liver impairment groups (groups B and C) compared with healthy subjects (group D). It has been reported that only for those drugs administered intravenously and which have a high hepatic extraction ratio and high volume of distribution, changes in protein binding might influence the PK of the compound. Based on the PK of clazosentan (moderate extraction ratio and small volume of distribution) [14], the reduced plasma protein binding in patients with moderate and severe liver impairment is not expected to be clinically significant [21].

In general, clazosentan was well tolerated at the infused dose in this study. The reduction in mean and median systolic and diastolic blood pressure observed in all groups could be partly related to the systemic vasodilatory effect of clazosentan, which is common to ERAs. The more pronounced reduction in mean and median blood pressure in the liver impairment groups during the infusion and the two cases of hypotension reported as AEs in the severe liver impairment group would suggest that the subjects with severe liver impairment were possibly more sensitive to the vasodilatory effect of clazosentan.

However, it should be noted that the small number of subjects included in this PK study and the lack of a placebo group limit the interpretation of the effects of clazosentan on vital signs. Since one important aspect of the treatment of SAH patients is maintaining their blood pressure, in the ongoing phase 3 studies the close monitoring of vital signs during clazosentan treatment is part of the patient management guidelines.

In conclusion the observed changes in PK parameters of clazosentan in subjects with mild liver impairment compared with healthy subjects are not expected to be clinically relevant, and no dose adjustment is recommended for these patients.

Based on the results of this study, and taking into account the known dose-proportional pharmacokinetics of clazosentan, it is recommended to reduce the dose of clazosentan to half in patients with moderate liver impairment and to one fourth in patients with severe liver impairment (Child-Pugh classification).

The 6 h infusion of 0.5 mg h⁻¹ and 1 mg h⁻¹ clazosentan was generally well tolerated in this study. However, more data in a larger number of patients is necessary to evaluate adequately the safety of clazosentan in SAH patients with liver impairment.

Competing interests

Drs Bruderer and Dingemanse are employees of Actelion Pharmaceuticals Ltd. Dr Detishin was the principal investigator and Dr Tsvitbaum was the co-investigator of the clinical trial and received financial compensation for the clinical costs associated with conducting the study.

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