Influence of hepatic impairment on the pharmacokinetics and pharmacodynamics of the P2Y12 receptor antagonist selatogrel

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Abstract

Selatogrel is a potent and selective reversible P2Y12 receptor antagonist in development for early treatment of acute myocardial infarction via subcutaneous (s.c.) self-injection. Selatogrel is almost exclusively eliminated via the hepatobiliary route. Hepatic impairment is associated with reduced drug clearance and primary hemostasis. This single-center, open-label study investigated the effect of mild and moderate hepatic impairment on pharmacokinetics (PK) and pharmacodynamics (PD) of a single s.c. dose of selatogrel (16 mg). The study included groups of eight subjects with mild and moderate hepatic impairment, and matched healthy control subjects. Compared to healthy subjects, exposure to selatogrel in subjects with mild and moderate hepatic impairment was 30% and 108% (maximum plasma concentration [C_{max}]) and 47% and 212% (area under the concentration-time curve from zero to infinity [$AUC_{0-\infty}$]) higher, respectively. Hepatic impairment was associated with lower clearance and volume of distribution, whereas plasma protein binding was not affected. Marked inhibition of platelet aggregation (IPA > 80%) was attained within 30 min in all subjects and hepatic impairment prolonged IPA duration. Area under the effect curve was 60% and 160% higher in subjects with mild and moderate hepatic impairment, respectively. PK/PD modeling identified a change in the relationship between exposure and IPA, with a steeper concentration-effect relationship in healthy subjects compared to subjects with hepatic impairment. The combination of higher exposure and lower half-maximum inhibitory concentration resulted in longer lasting effect. In conclusion, hepatic impairment alters the PK/PD relationship leading to prolonged effects. Therefore, dose adjustments may be warranted in subjects with moderate hepatic impairment.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Selatogrel is a potent and selective P2Y12 receptor antagonist for subcutaneous self-administration by patients when they suspect onset of an acute myocardial infarction.

WHAT QUESTION DID THIS STUDY ADDRESS?
This study investigated the influence of mild and moderate hepatic impairment on the pharmacokinetics (PK) and pharmacodynamics (PD) of selatogrel.
WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Increased hepatic impairment was associated with higher exposure to selatogrel due to lower clearance and volume of distribution. The concentration-effect (inhibition of platelet aggregation) relationship changed in hepatic impairment leading to higher drug sensitivity.
HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
Hepatic impairment does not only change the PK of P2Y12 receptor antagonists but, due to its effect on primary hemostasis, also their PD.

INTRODUCTION

Early antithrombotic therapy is crucial in the treatment of patients with acute myocardial infarction (AMI) to prevent further occlusion of the artery, thereby preventing damage to the heart muscle and death until reperfusion can be achieved. Platelets play an important role particularly in the initial phase of thrombus formation.[1]

Selatogrel is a novel, potent, and reversible P2Y12 receptor antagonist characterized by rapid inhibition of platelet aggregation (IPA), short duration of action, and favorable safety profile after subcutaneous (s.c.) administration. It is currently in clinical development for the treatment of AMI prior to hospital admission in adult patients to early abort AMI and its clinical consequences. Hereto, selatogrel will be self-administered via an autoinjector. Selatogrel has been investigated in several clinical phase I and II studies, and a clinical phase III study in adult patients with a recent history of AMI is currently ongoing (NCT04957719).

In healthy subjects as well as in patients with chronic coronary syndrome and in patients with AMI, selatogrel showed quick onset of action with potent IPA achieved within 15 min after single s.c. doses of 8 mg and 16 mg.[2–5] Potent IPA was maintained over 8 h postdose and the effect was reversed ~24 h postdosing.[2,3] The pharmacokinetics (PK) of selatogrel are characterized by rapid absorption (median time to reach maximum plasma concentration [T_{max}] 45 min), distribution, and elimination (mean terminal half-life [$t_{1/2}$] ~7 h) at the anticipated therapeutic dose of 16 mg.[2]

Selatogrel is almost exclusively eliminated via the biliary route as evidenced by 92% of ^{14}C-radioactivity recovered in feces and only 2% in urine.[6] Metabolic profiling data indicated no extensive metabolism and excretion primarily as unchanged parent compound in urine and feces.[6] In contrast to approved oral P2Y12 inhibitors, elimination of selatogrel is independent of CYP enzymes and only to a minor extent impacted by OATP1B1/B3 inhibition.[7,8]

Selatogrel is classified as a multidrug resistance protein 2 (MRP2) substrate.[7] The selatogrel concentration, at which half the maximum effect (IC_{50}) of ADP-induced platelet aggregation is achieved, is 8.7 ng/ml.[9] A dose of 16 mg s.c. selatogrel provides fast and marked inhibition of highly activated platelets at the time of AMI onset without increased bleeding risk and is currently investigated in a phase III clinical trial.[4,10] Doses up to 32 mg have, however, been clinically investigated in the phase I program and were safe and tolerated.

Hepatic impairment affects blood coagulation as the liver plays an important role in both primary and secondary hemostasis.[11] Furthermore, hepatic impairment may result in lower plasma clearance of drugs mainly eliminated by biliary excretion and may also impact plasma protein binding.[12] Thus, how hepatic impairment influences the PK and/or pharmacodynamics (PD) of selatogrel needs further investigation.

Several clinical studies were performed to investigate the impact of different degrees of hepatic impairment on the PD of approved oral P2Y12 inhibitors.[8] No clinically relevant effects on the PD of prasugrel and ticagrelor were observed in subjects with mild or moderate hepatic impairment.[13,14] For clopidogrel the extent of IPA was even similar in subjects with severe hepatic impairment and healthy subjects.[15]

Overall, this study was designed to investigate PK, PD, safety, and tolerability of 16 mg s.c. selatogrel in subjects with mild and moderate hepatic impairment compared to matched healthy control subjects. Subjects with severe hepatic impairment have a high bleeding risk and were therefore excluded from the study.[16]

METHODS

The study protocol was approved by the German health authority (BfArM) as well as an Independent Ethics

Committee (Ethikkommission bei der Ärztekammer Schleswig-Holstein, Bad Segeberg, Schleswig Holstein, Germany). The study was conducted in full accordance with the principles of the Declaration of Helsinki and International Conference on Harmonization (ICH) good clinical practice guidelines. Each subject provided written informed consent prior to any treatment and study-related assessment. This study was disclosed on clinicaltrials.gov (NCT04406896).

Study design

This was a prospective, open-label, single-center, single-dose phase I study. The study comprised three groups consisting of subjects with mild hepatic impairment (Child-Pugh A, $n = 8$), moderate hepatic impairment (Child-Pugh B, $n = 8$), as well as matched healthy control subjects with normal liver function ($n = 8$). The primary study objective was to evaluate the effect of mild and moderate hepatic impairment on the PK of selatogrel.

Screening assessments were performed within 21 to 3 days (or within 28 to 10 days for women of childbearing potential) prior to study treatment administration. In the morning of the treatment day (day 1) a single s.c. dose of 16 mg selatogrel was administered by the medical investigator to the subjects in their right thighs under fasted conditions. The subjects stayed in the clinic until day 3 (i.e., until the 48 h postdose PK and PD blood sampling and safety assessments had been performed), upon which they could be discharged based on their medical condition. A safety follow-up phone call was performed 30–40 days after discharge from the clinic.

Administration of study treatment to hepatically impaired subjects was done sequentially by severity. Subjects with mild hepatic impairment were dosed first and only after an interim analysis of PK, PD, and safety and tolerability data of at least six subjects, the group of subjects with moderate hepatic impairment was dosed. Selection, enrollment, and dosing of healthy matched subjects were performed thereafter.

Subjects

Male and female subjects between 18 and 79 years (inclusive) with a body mass index (BMI) of 18.5–35.0 kg/m^2 were eligible for this study. Healthy subjects were eligible based on absence of clinically relevant findings during physical examination and assessment of clinical laboratory, 12-lead electrocardiogram (ECG), and vital sign data. Healthy subjects were matched to the average of subjects with mild and moderate hepatic impairment regarding

sex, body weight (±15%), and age (±10 years). To be enrolled in the study, healthy subjects had to have an estimated glomerular filtration rate (eGFR) greater than or equal to 80 ml/min/1.73 m^2 (based on the Modification of Diet in Renal Disease [MDRD] formula).[17]

Hepatic impairment due to liver cirrhosis was classified according to the Child-Pugh classification.[18,19] The Child-Pugh score was based on screening laboratory test results for bilirubin, serum albumin, prothrombin time, and state of hepatic encephalopathy, with or without ascites (based on sonography). A total score of five to six was assessed as mild hepatic impairment (Child-Pugh A) and a total score of seven to nine was assessed as moderate hepatic impairment (Child-Pugh B).

Subjects were excluded from the study if they had known platelet disorders or a history or clinical evidence of any disease and/or existence of any surgical or medical condition (e.g., cholecystectomy), which might have interfered with absorption, distribution, metabolism, or excretion of the study treatment (except for hepatic impairment, appendectomy, and herniotomy). In addition, subjects with hepatic impairment with encephalopathy greater than grade 2, severe ascites and/or pleural effusion, gastrointestinal bleedings within 1 month prior to Screening, esophageal varices greater than grade 2, or a platelet count less than $60 \times 10^9 \text{L}^{-1}$ were excluded.

Concomitant use of medication was prohibited in healthy subjects except for hormonal contraceptives and medications for treatment of adverse events (AEs). Subjects with mild and moderate hepatic impairment were required to be on stable concomitant medications. Women who were pregnant, lactating, or did not use effective contraception were not eligible.

Pharmacokinetic assessments

Blood samples of ~4 ml were collected by direct venipuncture or through an indwelling catheter in tubes containing ethylenediaminetetraacetic acid (EDTA) prior to dosing and at postdose time points (i.e., 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, and 48 h) to determine the plasma concentration of selatogrel. Blood samples were put on ice immediately after collection and plasma was prepared within 30 min by centrifugation at 1500 **g** and 4°C for 10 min and stored in polypropylene tubes below −70°C prior to analysis.

Plasma concentrations of selatogrel were determined using a validated liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS) assay with a lower limit of quantification (LLOQ) of 1.0 ng/ml.[9] The method was linear in the range from 1.0 to 2000 ng/ml. Deuterated selatogrel was used as internal standard. Calibration and

quality control samples were measured throughout the study and used to determine the inter-batch precision (≤11% coefficient of variation) and accuracy (−3.1 to +3.3% relative deviation).

Plasma concentrations were used to determine the PK parameters of selatogrel including maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to time of last measured concentration above the LLOQ (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$), T_{max}, $t_{1/2}$, apparent total body clearance (CL/F), and apparent volume of distribution (Vz/F). These PK parameters were determined by noncompartmental analysis with Phoenix WinNonlin version 8.0 (Certara, Princeton, NJ). For measurement of the unbound fraction (f_u) of selatogrel in plasma, blood samples were collected at 0.75 h and 3 h postdose: f_u was determined using equilibrium dialysis followed by analysis with an LC–MS/MS method adapted from the one described above. Triplicate 200 µl aliquots of each plasma sample were subjected to rapid equilibrium dialysis (Thermo Fisher Scientific, Waltham, MA) against 350 µl of fortified phosphate-buffered saline (PBS) on an orbital shaker at 450 rpm incubated at 37°C for 5 h. After dialysis, a 50 µl aliquot of the donor compartment was diluted with 50 µl of PBS, whereas a 50 µl aliquot of the receiver compartment was diluted with 50 µl of blank plasma, to generate samples of the same analytical matrix. The LC–MS/MS method was linear in the concentration range of 0.2–400 ng/ml with an LLOQ of 0.2 ng/ml. The interbatch precision was less than or equal to 9.8% with an interbatch accuracy of −1.8% to 7.1%.

Pharmacodynamic assessments

ADP-induced platelet aggregation was measured ex vivo using the point-of-care VerifyNow assay (Accumetrics, San Diego, CA). For PD assessments, 3 ml venous blood was collected predose (on the day before dosing, i.e., day −1, and on the treatment day prior to dosing, i.e., day 1) and at multiple postdose timepoints (0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, and 48 h) in tubes containing phenylalanine–proline–arginine–chloromethyl ketone (PPACK) as anticoagulant (i.e., a direct thrombin inhibitor). The whole-blood samples in PPACK tubes were processed according to the manufacturer's instructions using VerifyNow PRU test kits and analyzer. Percentage change in platelet aggregation from baseline based on P2Y12 reaction units (PRU) was calculated, as previously described.[9] Baseline was defined as the mean of the value measured at day −1 and the value measured prior to administration of study treatment on day 1. The area under the effect (i.e., IPA) over time curve from

time 0–48 h ($AUEC_{0-48h}$) was calculated according to the trapezoidal rule using the IPA (%) – time values from 0 to 48 h postdose based on the actual blood sampling timepoints.

Safety and tolerability assessments

Safety and tolerability were monitored throughout the study based on physical examination and repeated recording of AE, body weight, clinical laboratory, coagulation, vital sign, and 12-lead ECG data.

Statistical analysis

A descriptive analysis was performed for PK, PD, safety, and tolerability data. The sample size of eight subjects per group was based on empirical considerations. Differences in PK parameters between healthy subjects and subjects with hepatic impairment were explored using geometric mean ratios (GMRs) and 90% confidence intervals (CIs) with healthy subjects as reference. Mixed-effects modeling using log-transformed values of the PK parameters as dependent variable, and hepatic function as fixed effect was applied. GMRs and 90% CIs were calculated from the back-transformed least-squares means for treatment. Differences between treatments for T_{max} and f_u were explored using the nonparametric Wilcoxon signed rank test and Hodges-Lehmann estimates of median of differences and associated 90% CIs.

Pharmacokinetic/pharmacodynamic modeling

A population PK/PD model was used to estimate PK and PD parameters, assessing differences in concentration over time and relationships between exposure and response (i.e., the PD parameter IPA; Figure S1). There were 368 PK and 222 PD observations that were included for the population PK/PD analysis. Concentration measurements below the LLOQ were handled as censored values and simulated from a truncated distribution restricted to the range (0, LLOQ).[20] R version 3.6.1 (The R Project Foundation, Vienna, Austria) was applied for dataset preparation, exploratory analyses, and visualization of results. The PK/PD model was developed using the software Monolix 2020R1 (Lixoft, Antony, France). Parameters were estimated with the stochastic approximation expectation maximization algorithm.[21] Based on the final PK/PD model, 100 healthy subjects, 100 subjects with mild hepatic impairment, and 100 subjects with moderate

hepatic impairment receiving a single dose of 16 mg selatogrel were simulated. Selatogrel plasma concentrations were simulated every 0.1 h over 24 h and %IPA measurements were simulated every 0.5 h over 216 h. Simulations were performed with Simulx 2020R1 (Lixoft).

RESULTS

Study population

Overall, 24 subjects were enrolled, received study treatment, and completed the study. They were assigned to one of three groups according to hepatic function: mild hepatic impairment (Child-Pugh grade A; $n = 8$), moderate hepatic impairment (Child-Pugh grade B; $n = 8$), and healthy ($n = 8$).

Demographic characteristics were similar across the three groups with respect to age, height, weight, sex, and BMI (Table 1). Most subjects were men (17 of the 24 subjects), and all subjects were White. Seven subjects with mild hepatic impairment and all subjects with moderate hepatic impairment reported stable use of concomitant medications (e.g., diuretics,

proton pump inhibitors, or beta receptor blockers) for treatment of hepatic and other metabolic disorders. All concomitant medications were compliant with the study requirements.

One healthy subject was excluded from PK and PD analysis as he did not have measurable selatogrel plasma concentrations throughout and did not show a PD response. However, as he received an s.c. injection of selatogrel, the subject was included in the safety analysis.

Pharmacokinetics

In all three groups, selatogrel was rapidly absorbed with a median T_{max} of 0.5 h in healthy subjects and 0.75 h in subjects with mild and moderate hepatic impairment. Plasma concentrations of selatogrel were higher in subjects with mild and moderate hepatic impairment compared with healthy subjects (Figure 1). In subjects with mild hepatic impairment, C_{max} and $AUC_{0-\infty}$ were increased by 30 and 47%, respectively. In subjects with moderate hepatic impairment C_{max} and $AUC_{0-\infty}$ were increased by 108 and 212%, respectively (Table 2). CL/F was estimated as

TABLE 1 Demographics and characteristics of study subjects

Characteristics	Statistics	Mild hepatic impairment,[a] $n = 8$	Moderate hepatic impairment,[b] $n = 8$	Healthy subjects, $n = 8$
Sex				
Male	n (%)	5 (62.5)	6 (75.0)	6 (75.0)
Female	n (%)	3 (37.5)	2 (25.0)	2 (25.0)
Race				
White	n (%)	8 (100)	8 (100)	8 (100)
Age, years	Mean (SD)	64.5 (7.5)	55.4 (10.2)	60.0 (4.6)
Weight, kg	Mean (SD)	89.0 (17.4)	84.5 (15.9)	82.4 (8.9)
Height, cm	Mean (SD)	176 (9.6)	175 (7.9)	173 (9.1)
BMI, kg/m^2	Mean (SD)	28.6 (4.0)	27.7 (4.9)	27.6 (1.7)
Child-Pugh Score[c]				
Score 5	n (%)	6 (75.0)		
Score 6	n (%)	2 (25.0)		
Score 7	n (%)		5 (62.5)	
Score 8	n (%)		1 (12.5)	
Score 9	n (%)		2 (25.0)	
Albumin,[c] g/L	Mean (SD)	42.9 (3.2)	38.0 (3.9)	40.5 (3.1)
Prothrombin time[c] (s)	Mean (SD)	9.4 (0.7)	10.4 (0.6)	9.4 (0.4)
Total bilirubin[c] (mg/dL)	Mean (SD)	0.7 (0.2)	1.6 (1.3)	0.5 (0.2)

Abbreviations: BMI, body mass index; n, number of subjects; SD, standard deviation.

[a]Child-Pugh grade A.

[b]Child-Pugh grade B.

[c]Measured at screening.

FIGURE 1 Arithmetic mean (±SD) plasma concentration-time profiles of a single subcutaneous dose of 16 mg selatogrel in subjects with mild and moderate hepatic impairment and matched healthy controls on linear and semilogarithmic scale.
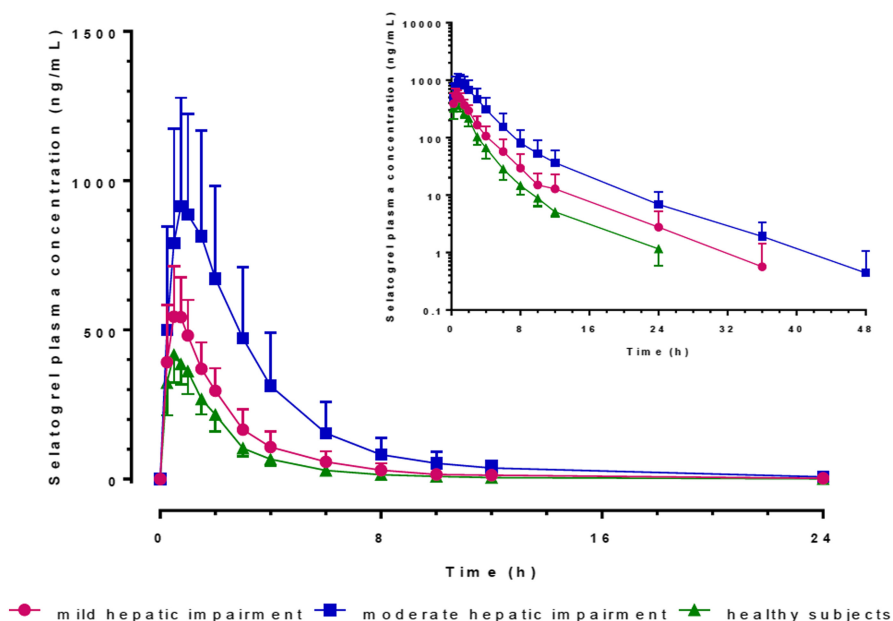

TABLE 2 Pharmacokinetic parameters of selatogrel

Parameter, unit	Healthy, $n = 7$	Mild hepatic impairment, $n = 8$	Moderate hepatic impairment, $n = 8$	LS-mean (90% CI) mild HI vs. healthy	LS-mean (90% CI) moderate HI vs. healthy
C_{max}, ng/ml	428 (366, 500)	556 (442, 701)	889 (622, 1271)	1.30 (0.98, 1.72)	2.08 (1.57, 2.75)
AUC_{0-t}, ng·h/ml	1047 (911, 1204)	1549 (1215, 1976)	3290 (2154, 5023)	1.48 (1.08, 2.03)	3.14 (2.29, 4.31)
$AUC_{0-\infty}$, ng·h/ml	1060 (926, 1214)	1562 (1226, 1991)	3305 (2168, 5037)	1.47 (1.08, 2.02)	3.12 (2.27, 4.27)
T_{max}, h	0.50 (0.25, 1.02)	0.75 (0.50, 1.00)	0.75 (0.50, 1.50)	0.00 (−0.25, 0.25)	0.25 (−0.02, 0.50)
$t_{1/2}$, h	4.92 (3.58, 6.76)	5.63 (4.82, 6.58)	5.80 (4.84, 6.95)	1.15 (0.91, 1.44)	1.18 (0.94, 1.48)
CL/F, L/h	15.10 (13.18, 17.29)	10.24 (8.04, 13.05)	4.84 (3.18, 7.38)	0.68 (0.50, 0.93)	0.32 (0.23, 0.44)
Vz/F, L	107.2 (69.3, 165.7)	83.2 (63.1, 109.8)	40.5 (27.8, 59.1)	0.78 (0.53, 1.13)	0.38 (0.26, 0.55)
$f_{u, 0.75h}$, %	0.90 (0.8, 1.0)	0.90 (0.8, 1.1)	0.80 (0.7, 1.4)	0.0 (−0.1, 0.1)	−0.1 (−0.2, 0.0)
$f_{u, 3h}$, %	0.90 (0.8, 1.0)	0.95 (0.9, 1.1)	0.90 (0.6, 1.5)	0.1 (0.0, 0.2)	0.0 (−0.1, 0.2)

Note: Data are displayed as geometric means (and 95% CI) or for T_{max} and f_u as median (and range).

Abbreviations: AUC_{0-t}, area under the plasma concentration time curve from time 0 to the time of last measurement; $AUC_{0-\infty}$, area under the plasma concentration time curve from time 0 to infinity; CI, confidence interval; CL/F, apparent clearance; C_{max}, maximum plasma concentration; f_u, fraction of unbound selatogrel in plasma; HI, hepatic impairment; LS-mean, least-squares mean; n, number of subjects; $t_{1/2}$, terminal half-life; T_{max}, time at which C_{max} is reached; Vz/F, apparent volume of distribution.

15.1 L/h for healthy subjects, 10.2 L/h in subjects with mild hepatic impairment (−32%), and 4.8 L/h in subjects with moderate hepatic impairment (−68%). The Vz/F decreased in a similar fashion with increasing severity of hepatic impairment from 107.2 L for healthy subjects to 83.2 L (−22%) for subjects with mild hepatic impairment and 40.5 L (−62%) for subjects with moderate hepatic impairment. The $t_{1/2}$ was only very slightly prolonged in subjects with mild and moderate hepatic impairment (i.e., 5.6 h and 5.8 h, respectively) compared with healthy subjects (4.9 h).

The unbound fraction of selatogrel was 0.90% at both, 0.75 h and 3.0 h postdose in healthy subjects and similar in subjects with mild and moderate hepatic impairment. All PK parameters are summarized in Table 2.

Pharmacodynamics

In subjects with mild and moderate hepatic impairment, the onset of effect was similar compared with healthy subjects, as indicated by a mean IPA of 97.8% and 94.7%, respectively, at 30 min postdosing versus 98.7% in healthy subjects (Figure 2). At this early timepoint, all 23 evaluable subjects had IPA values greater than 95%, except for one subject with moderate hepatic impairment who had an IPA of 80.5%.
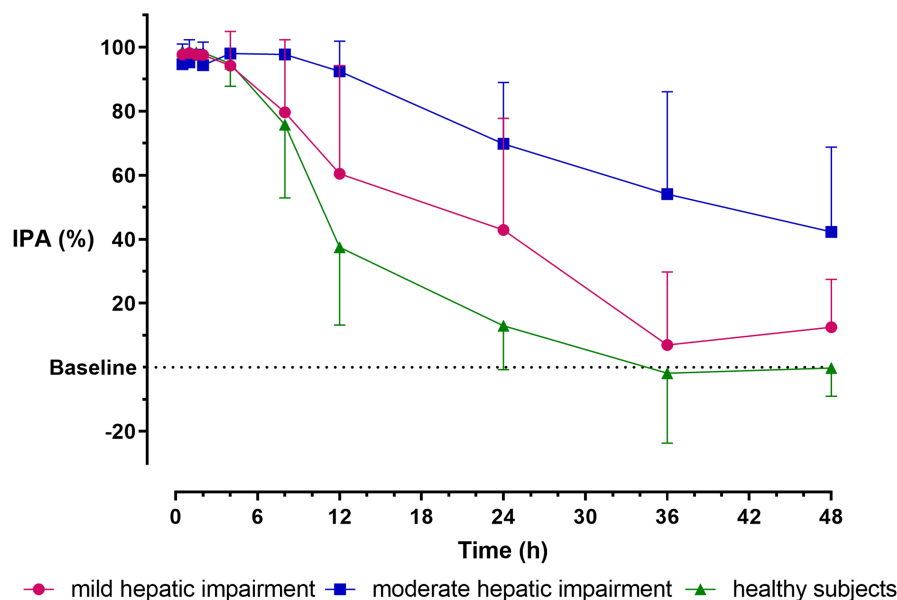
FIGURE 2 Inhibition of platelet aggregation (as percentage change from baseline), i.e., IPA (%) over 48 h following a single subcutaneous dose of 16 mg selatogrel in subjects with mild hepatic impairment, and moderate hepatic impairment, and healthy matched controls. Error bars represent standard deviation. IPA, inhibition of platelet aggregation.

Overall, the maximum PD effect achieved did not differ among the three study groups (i.e., mean IPA_{max} was 98.6% and 98.5% in subjects with mild and moderate hepatic impairment, respectively, and 98.8% in healthy subjects).

However, the duration of effect was prolonged in subjects with hepatic impairment. In subjects with mild hepatic impairment, mean IPA at 12 h post dose was 60.5% compared to 37.5% in healthy subjects and returned close to baseline levels (~10% IPA) at 36 h compared to 24 h in healthy subjects. In subjects with moderate hepatic impairment, the PD effect was further prolonged. Mean IPA at 12 h postdose was 92.5% and decreased to 42.4% at 48 h (i.e., the last sampling timepoint).

Consequently, $AUEC_{0-48h}$ was 55% and 158% higher in subjects with mild and moderate hepatic impairment, respectively, compared with healthy subjects (Table 3).

Pharmacokinetic/pharmacodynamic modeling

A two-compartment PK model with indirect PD effect described the data reasonably well (Table S1, Figures S1, S3). Based on the diagnostic plots, the PK/PD model appeared to capture the large variability but overpredicted the median %IPA in the limited number of subjects with moderate hepatic impairment at 12 and 24 h after selatogrel administration (Figure S1). The model confirmed clear differences between mild and moderate hepatically impaired subjects and healthy subjects in PK and, consequently, in PD (Figure 3). In addition, the relationship between exposure and effect (PK/PD relationship) appeared to differ. Hepatic impairment was associated with increased sensitivity toward selatogrel exposure (i.e., the

IC_{50}) and steepness of the concentration-effect curve (the gamma parameter or Hill coefficient) were reduced with higher degree of hepatic impairment (Figure 3, Table S1). Based on the simulated results, return to baseline (defined as 10% IPA) was estimated to occur 22.0 h after drug administration to healthy subjects and 38.5 and 97.0 h after drug administration to subjects with mild and moderate hepatic impairment, respectively (Table 4).

Safety

Overall, 10 subjects (4/8 with mild hepatic impairment, 2/8 with moderate hepatic impairment, and 4/8 healthy subjects) reported 11 AEs. All AEs were of mild intensity and considered related to study treatment by the investigator except for one. The most frequent AE in this study was dyspnea, reported by three subjects with mild hepatic impairment (37.5%), two subjects with moderate hepatic impairment, and three healthy subjects. All AEs resolved without need for treatment by the completion of the study. No clinically relevant changes in vital signs, body weight, laboratory variables, and ECG parameters were identified during the study.

DISCUSSION

The objective of this study was to assess the PK, PD, safety, and tolerability of a single dose of 16 mg s.c. selatogrel in subjects with mild and moderate hepatic impairment due to liver cirrhosis compared with matched healthy controls.

In healthy subjects, PK and PD parameters were in line with previous studies.[2,5] In subjects with mild and

TABLE 3 Pharmacodynamic parameters of selatogrel

Parameter	Healthy, $n = 7$	Mild hepatic impairment, $n = 8$	Moderate hepatic impairment, $n = 8$
$IPA_{0.5h}$, %	98.7 (0.52)	97.8 (1.11)	94.7 (7.04)
IPA_{12h}, %	37.5 (24.3)	60.5 (33.8)	92.5 (9.5)
IPA_{24h}, %	13.0 (13.7)	42.9 (34.9)	69.9 (19.1)
IPA_{48h}, %	−0.17 (8.8)	12.5 (15.0)	42.4 (26.4)
IPA_{max}, %	98.8 (0.59)	98.6 (0.57)	98.5 (0.72)
$AUEC_{0-48h}$, %·h	1333 (541)	2063 (949)	3434 (699)

Note: Data are displayed as arithmetic mean (and SD). IPA in percent is calculated as mean change in percentage from baseline for each time point. Baseline is defined as the mean of the value measured at day −1 and the value measured prior to administration of study treatment on day 1.

Abbreviations: IPA_{max}, maximum inhibition of platelet aggregation; $AUEC_{0-48h}$, area under the effect-time curve from 0 to 48 h postdose; SD, standard deviation; n, number of evaluable subjects in the study group.
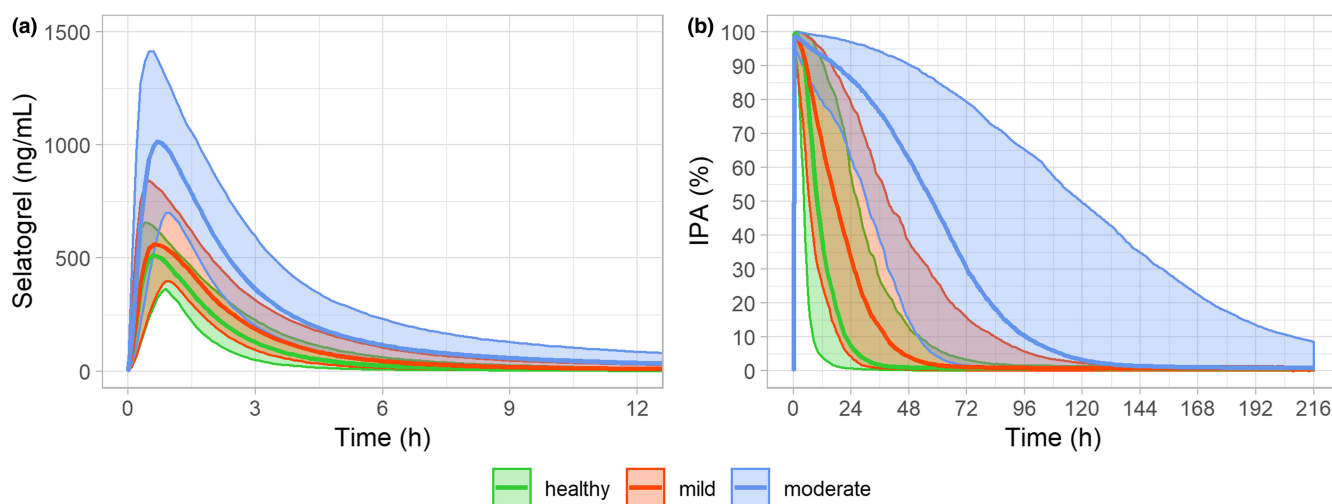

FIGURE 3 Simulated concentration vs time (a) and simulated IPA versus time (b) for healthy subjects and subjects with mild and moderate hepatic impairment. Bold lines represent the medians of selatogrel plasma concentration (left), and percentage (%) of inhibition of platelet aggregation (IPA), colored areas are 90% prediction intervals (i.e., ranges covering 90% of subjects). Healthy, healthy subjects; mild, subjects with mild hepatic impairment; moderate, subjects with moderate hepatic impairment.

moderate hepatic impairment, selatogrel was similarly quickly absorbed as in healthy subjects (i.e., within 30–45 min). However, exposure to selatogrel increased in subjects with mild and moderate hepatic impairment compared with healthy subjects. In subjects with mild hepatic impairment, the exposure increase was less than 50% (i.e., less than the 2-fold margin between the anticipated therapeutic dose of 16 mg and the highest tested dose of 32 mg) which was confirmed to be safe and well-tolerated.[2] In subjects with moderate hepatic impairment, exposure approximately doubled and tripled in terms of C_{max} and $AUC_{0-\infty}$, respectively. CL/F and Vz/F decreased with severity of hepatic function impairment in a similar fashion (by 32% and 22%, respectively, in subjects with mild hepatic impairment and by 68% and 62%, respectively, in subjects with moderate hepatic impairment). Half-life was

only impacted to a minor extent by hepatic impairment and was only slightly (<20%) prolonged with increasing liver disease severity. As selatogrel is almost entirely eliminated via the biliary route, this decrease in both CL/F and Vz/F may be due to reduced liver blood flow and impaired active and/or passive hepatic uptake of selatogrel in subjects with hepatic impairment.[6,7,22] This hypothesis is supported by literature data indicating lower expression of hepatic uptake transporters in liver disease.[23–25] In addition, it was hypothesized that the availability of protein-bound drugs to hepatocytes may be reduced due to capillarization of sinusoids.[22] Hepatic impairment also leads to a reduction in bile flow, and results in decreased clearance of endogenous and exogenous substrates, which could explain the decrease in CL/F in subjects with mild and moderate hepatic impairment observed in this study.

TABLE 4 Model-estimated time (h) to return to different IPA levels (median and 90% prediction interval)

	50% IPA	30% IPA	10% IPA
Healthy subjects	10.0 (4.5–27.0)	14.5 (6.0–35.0)	22.0 (8.5–52.5)
Subjects with mild hepatic impairment	18.0 (7.0–39.5)	25.5 (10.5–56.5)	38.5 (19.0–84.5)
Subjects with moderate hepatic impairment	58.0 (31.0–119.5)	72.5 (39.5–153.5)	97.0 (52.0–208.0)

Abbreviation: %IPA, percentage (%) of inhibition of platelet aggregation.

Selatogrel is highly bound to plasma proteins. Liver dysfunction can affect the decrease in plasma protein binding.[12] However, in this study, f_u was similar in healthy and hepatically impaired subjects. In healthy subjects, median f_u was 0.9%, in line with a value of 1.2% previously determined in vitro in human plasma. In subjects with hepatic impairment, f_u was similar but slightly more variable in subjects with moderate hepatic impairment (range: 0.5–1.6%) compared with healthy subjects or subjects with mild hepatic impairment.

All subjects irrespective of liver function showed rapid marked IPA (>80%). The duration of effect was prolonged with increasing severity of hepatic function impairment. Although effects reversed within 24h in healthy subjects, in subjects with moderate hepatic impairment IPA was still about 70% at 24h and 40% at 48h postdosing. Higher sensitivity is in accordance with previously reported data indicating that platelet function is reduced in patients with liver cirrhosis and the magnitude of reduction is associated with platelet count and severity of liver cirrhosis.[26] PK/PD modeling revealed that hepatic impairment was associated with a lower IC_{50} and showed higher variability in subjects with hepatic impairment compared to healthy subjects. The time-matched selatogrel plasma concentration versus %IPA data illustrate that moderate hepatic impairment is related to more pronounced hysteresis, most notably, in the disappearance of the effect (Figure S1). Because the estimated IC_{50} is low, 6.62, 3.38, and 0.20 ng/ml in healthy subjects, subjects with mild or moderate hepatic impairment, respectively (Table S1), a quick and pronounced onset of effect is observed in all study groups, and the hysteresis effect becomes apparent only in the late elimination phase.

Most interestingly, PK/PD modeling identified a change in the relationship between exposure and effect (IPA), with a steeper concentration-effect relationship in healthy subjects compared with patients with hepatic impairment. The combination of higher exposure and a lower IC_{50} resulted in longer lasting drug effect. This indicates that the P2Y12 receptor is more sensitive to selatogrel in subjects with hepatic impairment. Altered receptor sensitivity in liver cirrhosis has been reported for several drugs.[27] Whereas marked IPA over a longer period may not be of concern per se (patients on prasugrel or ticagrelor have strong IPA over months), for patients treated with selatogrel, a longer time interval may need to be considered when switching from selatogrel to clopidogrel and prasugrel, as their effect has been shown to be reduced when selatogrel is still present at the P2Y12 receptor.[5]

Despite the higher exposure and prolonged PD effects in subjects with hepatic impairment, there were no safety concerns. Subjects with moderate hepatic impairment reported the lowest number of AEs in this study.

In summary, this study showed that hepatic impairment affects both PK and PD of selatogrel as well as the PK/PD relationship. Therefore, caution is advised when administering selatogrel to patients with hepatic impairment. Although no safety concerns were observed in this small, well-controlled study, the PK and PD findings in subjects with moderate hepatic impairment suggest dose adjustments may be warranted. Further evaluation of the benefit/risk is needed in this population.

CONFLICT OF INTEREST

U.S., C.H., S.D., A.K., and J.D. were employees and/or shareholders of Idorsia Pharmaceuticals Ltd at the time the research was performed. Selatogrel is currently in clinical development by Idorsia Pharmaceuticals Ltd., Allschwil, Switzerland. H.W. and A.H. declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

U.S., C.H., A.K., and J.D. wrote the manuscript. U.S. and J.D. designed the research. H.W. and A.H. performed the research. U.S., C.H., S.D., and A.K. analyzed the data.

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