


Evaluation of the Pharmacokinetics and Safety of a Single Oral Dose of Fasiglifam in Subjects with Mild or Moderate Hepatic Impairment

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Abstract

Background and Aims Fasiglifam, a potent, selective novel agonist of G protein-coupled receptor 40, stimulates insulin secretion at elevated blood glucose levels in a glucose-dependent manner. This study evaluated the potential effect of hepatic impairment on the pharmacokinetics and safety of a single dose of fasiglifam and its metabolite M-I. Fasiglifam's clinical development was halted due to liver safety concerns.

Methods In this phase I, open-label study, subjects with mild or moderate hepatic impairment, along with matched controls (gender, weight, age, and smoking status), received a single, 25-mg oral dose of fasiglifam. Blood samples were collected through 336 h post-dose for pharmacokinetic evaluation.

Results Overall, 73% of subjects were male with a mean age of 54 years. Compared with normal hepatic function subjects ($n = 14$), mean systemic fasiglifam exposure (C_{\max} and AUC_{∞}) was reduced in mild ($n = 8$) and moderate ($n = 8$) hepatic impairment subjects by approximately 20–40%. However, the observed percent unbound drug plasma concentration appeared comparable across all groups. Mean oral clearance was higher and terminal half-life lower in subjects with mild or moderate hepatic impairment compared with normal hepatic function subjects. Fasiglifam M-I systemic exposure increased by

approximately twofold in subjects with mild or moderate hepatic impairment compared with those with normal hepatic function. Fasiglifam was well tolerated, and there were no reports of hypoglycemia.

Conclusion Hepatic status did not significantly impact systemic exposure of fasiglifam in this study, in fact, a decrease was observed, suggesting no dose reduction would be required for patients with hepatic impairment.

Key Points

Fasiglifam, a potent, selective G protein-coupled receptor 40 agonist, is primarily cleared by the liver.

Hepatic impairment does not impact pharmacokinetics of a single, 25-mg dose of fasiglifam, suggesting no dose reduction is needed.

A single, 25-mg dose of fasiglifam was well tolerated with no reports of hypoglycemia.

1 Introduction

Of the estimated 415 million people globally and 29.1 million people in the United States who have diabetes, approximately 90–95% have type 2 diabetes mellitus (T2DM) [1, 2]. Although a number of therapeutic options are available for the treatment of T2DM patients, there are certain risks associated with antidiabetic drugs [3]. The use of insulin secretagogues such as glinides and sulfonylureas is often associated with hypoglycemia, as they stimulate

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insulin secretion even at low blood-glucose concentrations [4]. Over the past decade, G protein-coupled receptor 40 (GPR40) has gained considerable attention as a potential therapeutic target for the treatment of T2DM [5]. Expressed in pancreatic β cells and activated by long-chain free fatty acids, GPR40 stimulates insulin secretion in a glucose-dependent manner [6].

Fasiglifam (TAK-875; [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl] acetic acid hemi-hydrate), a potent and highly selective agonist of GPR40 [7], stimulates insulin secretion only at elevated glucose levels [8, 9] and was being developed for the treatment of T2DM. Fasiglifam's novel mechanism of action amplifies the agonistic activity of the endogenous ligand γ -linolenic acid by binding to an allosteric site of GPR40 [10]. In clinical trials, fasiglifam provided significant glycemic control, was well tolerated, and was associated with a low incidence of hypoglycemia [11–13]. However, because of liver safety concerns, the clinical development of fasiglifam was terminated in December 2013. This decision was a result of liver test data in patients enrolled in phase III studies indicating drug-induced liver injury.

In healthy volunteers, single doses of fasiglifam (25–800 mg) demonstrated linear pharmacokinetics (PK) and were rapidly absorbed, reaching peak plasma concentrations in 3–4 h, with a terminal elimination half-life ($t_{1/2}$) of 28–30 h [14]. Fasiglifam is highly protein bound (>99.4%) and primarily eliminated by hepatic metabolism via glucuronidation or conjugation with taurine [15], with the metabolic pathways as depicted in Fig. 1. Therefore, changes in liver function may potentially impact the metabolism of fasiglifam by altering its overall clearance. Although the contribution of oxidative metabolism to hepatic clearance of fasiglifam is minimal, the major inactive circulating metabolite M-I is formed by oxidative cleavage of the ether linkage of the parent molecule [14]. Metabolite M-I has a longer half-life than the parent compound, ranging from 36 to 53 h, resulting in a greater accumulation of metabolite M-I compared with parent drug [14]. Although fasiglifam absolute oral bioavailability (F) was not evaluated in humans, fasiglifam has a high F in preclinical species. The oral bioavailability of fasiglifam is 76.0 and 92.4% in rats and dogs, respectively [7]. Therefore, fasiglifam can be considered as a medium to low extraction drug in animals, and it is also anticipated to have a high absolute oral bioavailability in humans. Diabetes is associated with an increased risk of acute liver failure and chronic liver disease [16–18], and conversely, various liver diseases are associated with an increased risk for the development of T2DM [19, 20]. Liver disease is known to be an important cause of death in T2DM patients [21]. Management of patients with T2DM and liver disease can

be complicated due to pre-existing elevated liver enzyme levels, potential liver-related alterations in drug metabolism, interactions between coadministered drugs, and hepatotoxicity [18]. In addition, US Food and Drug Administration guidelines recommend a PK study in patients with impaired hepatic function if hepatic metabolism and/or excretion accounts for a substantial portion (>20% of the absorbed drug) of the elimination of a parent drug or active metabolite [22]. At present, there are no clinical data available on the effect of impaired hepatic function on the PK of fasiglifam. Therefore, we sought to investigate the effect of hepatic impairment on the PK of a single, oral, 25-mg dose of fasiglifam and its metabolite M-I in subjects with varying degrees of hepatic function. Our secondary objective was to evaluate the safety and tolerability of a single, oral, 25-mg dose of fasiglifam in subjects with varying degrees of hepatic function.

The use of a single dose of fasiglifam was chosen for two reasons. First, the PK of fasiglifam and its circulating metabolite exhibit time independence following once-daily dosing [15], and therefore, the PK profile obtained after single dose is predictable of PK at steady-state. Second, a single dose should be sensitive enough to detect the effect of hepatic impairment on PK parameters such as oral clearance. The 25-mg dose was selected to minimize potential increased exposure to the drug and its metabolite, fasiglifam M-I, in subjects with impaired hepatic function.

2 Materials and Methods

2.1 Study Design

This study was conducted in compliance with institutional review board regulations, Good Clinical Practice regulations and guidelines, and all applicable local regulations. This was an open-label, parallel-group, single-site, phase I study designed to evaluate the effect of mild or moderate hepatic impairment on the PK of fasiglifam and its metabolite M-I. This study was conducted in accordance with regulatory guidelines for determining the impact of hepatic impairment on study drug PK [22].

Subjects checked in on day – 1 and were administered a single dose of fasiglifam 25 mg on day 1. The confinement period lasted from day – 1 to day 14. All subjects received a single dose of fasiglifam 25 mg (Takeda Pharmaceutical Co Ltd, Osaka, Japan) at 8 a.m. on day 1, after fasting for approximately 10 h. Standardized meals containing 30% fat were provided to all subjects during the confinement period.

Subjects with normal hepatic function were matched to subjects with hepatic impairment by sex, weight at screening ($\pm 30\%$), age (± 10 years), and smoking status

filtration, separation of the analytes was achieved by high-performance liquid chromatography (HPLC) on an ACQUITY BEH Shield RP₁₈ column (Waters; Milford, MA, USA), with a mobile phase consisting of methanol:10 mmol/L ammonium formate (2:1, v/v). The eluting analytes were detected by tandem mass spectrometry via electrospray ionization in the negative ion mode, with the following transitions (*m/z*): fasiglifam (523 → 148), fasiglifam M-I (361 → 197), fasiglifam-*d*₅ (528 → 148), and fasiglifam M-I-*d*₅ (366 → 198). The linear range for fasiglifam and fasiglifam M-I was validated over 5–10,000 ng/mL, and the lower limit of quantification (LLOQ) was at the lower end of the range. Respective interassay precision and accuracy were 4.72–11.7 and –10.8 to 1.38% for fasiglifam, and 4.99–7.98 and –10.2 to –23.4% for fasiglifam M-I. Method validation and analysis of study samples were conducted by PPD (Middleton, WI, USA), and were adequate to characterize the plasma concentration profiles of fasiglifam and fasiglifam M-I.

The *in vitro* plasma protein binding of spiked [¹⁴C]-labeled fasiglifam at a concentration of 1017 ng/mL [1000 ng/mL as TAK-875 (anhydrous)] in plasma from healthy subjects and subjects with mild and moderate hepatic impairment were elucidated by an ultracentrifugation method. Radioactivity was measured by liquid scintillation counting.

The PK parameters of fasiglifam and fasiglifam M-I were derived using standard noncompartmental analysis methods with Phoenix WinNonlin Version 6.3 (Pharsight Corp., Cary, NC). The PK parameters assessed for fasiglifam and fasiglifam M-I (unless otherwise specified) included maximum observed plasma concentration (C_{\max}); time to reach C_{\max} (t_{\max}); area under the plasma concentration–time curve (AUC) from time 0 to the time of last quantifiable concentration (last), calculated using the linear trapezoidal rule (AUC_{last}); area under the plasma concentration–time curve from 0 to infinity calculated from $AUC_{\text{last}} + \text{last}/\lambda_z$, where last is the last quantifiable concentration (AUC_{∞}); terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration–time curve during the terminal phase (λ_z); $t_{1/2}$ calculated as $\ln(2)/\lambda_z$; apparent clearance after extravascular administration, calculated as dose/AUC_{∞} after a single dose (CL/F) (calculated for fasiglifam only); apparent volume of distribution calculated as $(\text{CL}/F)/\lambda_z$ (V_z/F) (calculated for fasiglifam only); area under the unbound plasma concentration–time curve from time 0 to infinity ($AUC_{\infty,u}$), calculated as $AUC_{\infty} \times \text{percent unbound}$ (calculated for fasiglifam only); maximum observed unbound plasma concentration ($C_{\max,u}$) (calculated for fasiglifam only).

2.5 Statistical Analysis

The safety analysis set included all subjects who received the study drug, and was used for demographic and safety summaries. The PK analysis set included all subjects who received study drug and had evaluable PK data. Descriptive statistics [*N*, mean, standard deviation (SD), percent coefficient of variation, median, minimum, and maximum] were used to summarize the plasma PK parameters of fasiglifam, its metabolite M-I, and the percent unbound parent drug in plasma.

A sample size of 30 subjects in total (eight each with mild or moderate hepatic impairment and 14 with normal hepatic function) was considered sufficient for determining the PK and safety profile of a single, oral, 25-mg dose of fasiglifam. This sample size was not determined based on statistical power; however, an exploratory statistical analysis was performed to evaluate the effect of hepatic impairment on the PK of fasiglifam and fasiglifam M-I. An analysis of variance (ANOVA) was performed on t_{\max} , λ_z , and the natural logarithms of C_{\max} , AUC_{last} , AUC_{∞} , $C_{\max,u}$, and $AUC_{\infty,u}$, with the hepatic function group (normal, mild impairment, moderate impairment) as a fixed factor. Within the ANOVA framework, comparisons of each hepatic impairment group (test) versus the normal hepatic function group (reference) were made using appropriate contrast statements.

2.6 Safety Evaluation

Physical examinations were performed at screening (baseline), check-in, and study exit/early termination. At subsequent physical examinations (post baseline), changes were assessed and recorded as clinically significant or not clinically significant. Vital signs were recorded at screening; check-in; day 1 prior to dosing and 1, 2, 4, 8, and 12 h after dosing; days 2 through 14 in the morning; and on study exit (day 15)/early termination. Participants were also monitored for adverse events (AEs) and the incidence of hypoglycemia. Clinical laboratory tests including hematology and serum chemistry were measured at screening, day –1, day 2, day 3, day 7, and study exit (day 15). Blood glucose was monitored by fingerstick on day 1 prior to dosing, lunch, and dinner; days 2 through 14 prior to breakfast, lunch, and dinner; and on study exit/early termination. Glucose was also measured via fingerstick whenever signs or symptoms of hypoglycemia occurred.

3 Results

3.1 Subject Disposition and Baseline Characteristics

Of the 44 subjects who were initially screened, 30 were enrolled and completed the study. Two subjects in the normal hepatic function group each matched to one subject in each hepatic impairment group; hence, a total of 14 healthy subjects were enrolled. Demographic characteristics were comparable across all three groups, with the exception of mean weight and body mass index, which were higher in the group with moderate hepatic impairment than in the other groups (Table 1). No subject with normal hepatic function had any concurrent medical condition. All of the subjects in the normal hepatic function group stated they never consumed alcohol, while half of the subjects in the mild and moderate hepatic impairment groups had a history of alcohol abuse. Eleven subjects who had hepatic impairment used one to four concomitant medications during the study. Six subjects were taking medication to control hypertension, three were taking antianxiety medications, two were taking supplements, two were taking pain medication, and one each were taking medication for T2DM (insulin), cardioprotection, low platelet count, benign prostatic hyperplasia, and myalgia.

3.2 Pharmacokinetic Analyses

Following the administration of a single, oral, 25-mg dose of fasiglifam, mean plasma concentrations of fasiglifam were decreased in subjects with mild and moderate hepatic impairment compared with subjects with normal hepatic

function (Fig. 2). The concentration–time profiles of the fasiglifam M-I metabolite are also presented in Fig. 3.

The measured percent unbound fasiglifam values (mean ± SD) were 0.14 ± 0.04, 0.13 ± 0.02, and 0.13 ± 0.05 for subjects with normal hepatic function, mild hepatic impairments, and moderate hepatic impairment, respectively. The mean percent unbound fasiglifam in plasma was similar in subjects with normal hepatic function and subjects with mild or moderate hepatic impairment.

Descriptive statistics for the noncompartmental plasma PK parameter estimates of fasiglifam following the administration of a single, 25-mg dose of fasiglifam to subjects with normal hepatic function and mild or moderate hepatic impairment are summarized in Table 2. Mean AUC_{∞} values of fasiglifam in the mild (17,490 ng·h/mL) and moderate (17,828 ng·h/mL) hepatic impairment groups were decreased by almost half that of the normal hepatic function group (35,482 ng·h/mL). A scatter plot of mean AUC_{∞} values of fasiglifam is shown in Fig. 4. Fasiglifam median t_{max} was similar in subjects with normal and moderately impaired hepatic function, but was 30 min longer in subjects with mild hepatic impairment. Oral clearance was increased in subjects with hepatic impairment, while V_z/F was similar, compared with the normal hepatic function group. Hence, the estimated $t_{1/2}$ of fasiglifam was shortened by 50 and 43% in the mild and moderate hepatic impairment groups, respectively, compared with the normal hepatic function group.

Statistical analyses of the effect of mild or moderate hepatic impairment versus normal hepatic function on the plasma PK parameters of fasiglifam are presented in

Table 1 Subject demographics and baseline characteristics

Characteristic	Hepatic impairment status		
	Normal (n = 14)	Mild (n = 8)	Moderate (n = 8)
Age, years, mean (SD)	53.4 (6.94)	55.3 (6.23)	55.4 (4.53)
Sex, male, n (%)	10 (71.4)	5 (62.5)	7 (87.5)
Race, n (%)			
Black or African American	2 (14.3)	1 (12.5)	2 (25.0)
White or Caucasian	12 (85.7)	7 (87.5)	6 (75.0)
Height, cm, mean (SD)	168.4 (8.45)	166.8 (8.66)	173.0 (9.93)
Weight, kg, mean (SD)	79.61 (11.288)	76.76 (5.455)	99.41 (20.049)
BMI, kg/m ² , mean (SD)	28.03 (2.938)	27.69 (2.256)	32.88 (3.467)
Albumin, g/dL, n (%)			
> 3.5	14 (100.0)	8 (100.0)	6 (75.0)
2.8–3.5	0 (0.0)	0 (0.0)	2 (25.0)
< 2.8	0 (0.0)	0 (0.0)	0 (0.0)

Mild hepatic impairment = Child–Pugh class A; moderate hepatic impairment = Child–Pugh class B
 BMI body mass index, SD standard deviation

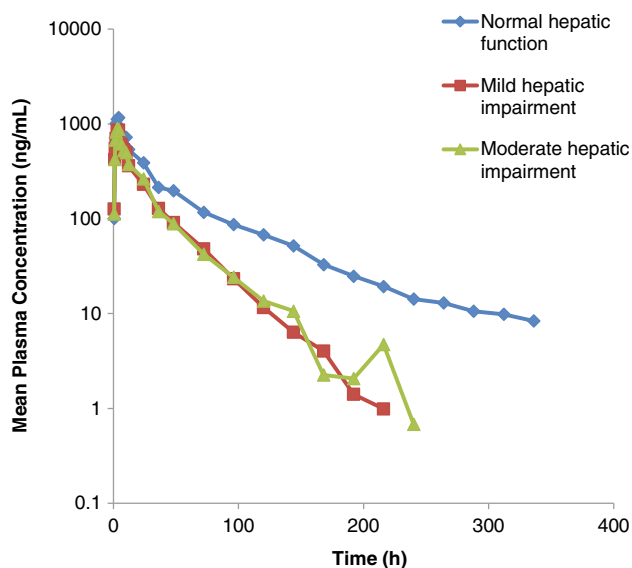


Fig. 2 Mean concentration–time profile of fasiglifam. Mild hepatic impairment = Child–Pugh class A; moderate hepatic impairment = Child–Pugh class B

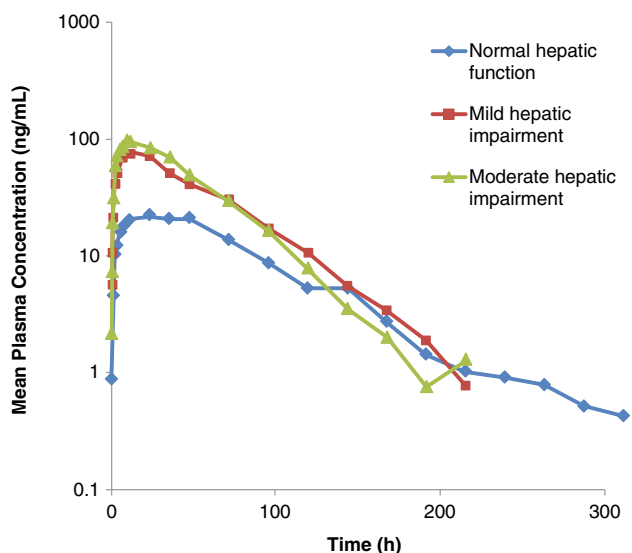


Fig. 3 Mean concentration–time profile of fasiglifam metabolite M-I. Mild hepatic impairment = Child–Pugh class A; moderate hepatic impairment = Child–Pugh class B

Table 3. Ratios of the central values of C_{\max} , $C_{\max,u}$, AUC_{last} , AUC_{∞} , and $AUC_{\infty,u}$ for the test groups (subjects with hepatic impairment) and the reference group (subjects with normal hepatic function) were estimated. Mean C_{\max} and $C_{\max,u}$ values of fasiglifam were approximately 18–24% lower in subjects with mild or moderate hepatic impairment than in subjects with normal hepatic function; these differences were not statistically significant. Exposure to fasiglifam, as measured by mean AUC_{last} , AUC_{∞} , and $AUC_{\infty,u}$, was reduced by 39–46% in subjects with

mild or moderate hepatic impairment compared with subjects with normal hepatic function (Table 3). Despite the limited numbers of subjects with hepatic impairment, overall ANOVA on the effect of hepatic impairment revealed a significant reduction for all AUC parameters.

Descriptive statistics for the noncompartmental plasma PK parameter estimates of fasiglifam M-I following the administration of a single, 25-mg dose of fasiglifam to subjects with normal hepatic function and mild or moderate hepatic impairment are summarized in Table 4. The mean AUC_{∞} values of fasiglifam M-I were generally similar in subjects with mild or moderate hepatic impairment and approximately 156% higher than in subjects with normal hepatic impairment (Fig. 5). The mean C_{\max} values of fasiglifam M-I were 125 and 174% higher in subjects with mild and moderate hepatic impairment, respectively, than in subjects with normal hepatic function (Table 5). In general, mean plasma concentrations of TAK-875 M-I over time in subjects with mild or moderate hepatic impairment were higher than those in subjects with normal hepatic function.

3.3 Safety Analyses

Treatment-emergent AEs (TEAEs) occurred in 12.5% of subjects in both the mild and moderate hepatic impairment groups and in 7.1% of the group with normal hepatic function. The TEAEs that were considered by the investigator to be related to study drug were hypertension (one subject with normal hepatic function) and blood creatine kinase increase (one subject with mild hepatic impairment). All TEAEs were mild or moderate in intensity. No deaths, other serious AEs (SAEs), or TEAEs leading to discontinuation occurred in the study. None of the subjects had an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value $> 3 \times$ upper limit of normal or a total bilirubin of > 2.0 mg/dL, and no cases of hypoglycemia were observed during the study. Baseline and study exit (day 15) liver tests including ALT, AST, alkaline phosphatase (ALP), total bilirubin, and gamma-glutamyl-transferase (GGT) for all three treatment groups are included in Table 6. Baseline liver tests were generally higher in the mild and moderate hepatic impairment groups compared to the normal hepatic function group, except for total bilirubin. In all three treatment groups, there were no notable findings in change from baseline measurements for any of the liver tests.

Table 2 Summary of fasiglifam plasma pharmacokinetic parameter estimates

	Hepatic impairment status		
	Normal (<i>n</i> = 14)	Mild (<i>n</i> = 8)	Moderate (<i>n</i> = 8)
<i>t</i> _{max} , h	3.00 (2.0, 4.0)	3.50 (1.5, 4.0)	3.00 (2.0, 4.0)
<i>C</i> _{max} , ng/mL	1254.7 ± 371.5	1027.1 ± 272.9	960.8 ± 195.1
<i>AUC</i> _{last} , ng·h/mL	34,078.8 ± 23,981.3	17,217.5 ± 6924.1	17,914.5 ± 4122.1
<i>AUC</i> _∞ , ng·h/mL	35,481.8 ± 26,997.6	17,490.0 ± 7038.6	17,828.2 ± 3507.9 ^a
<i>t</i> _{1/2} , h	51.4 ± 26.7	25.5 ± 12.5	29.2 ± 14.2 ^a
<i>CL</i> / <i>F</i> , L/h	1020.6 ± 743.8	1855.8 ± 1296.9	1450.7 ± 297.8 ^a
<i>V</i> _z / <i>F</i> , mL	58,060.7 ± 25,565.1	53,033.7 ± 12,567.6	56,482.9 ± 18,142.3
<i>C</i> _{max,u} , ng/mL	1.6 ± 0.3	1.4 ± 0.5	1.3 ± 0.5
<i>AUC</i> _{∞,u} , ng·h/mL	43.0 ± 21.4	22.7 ± 8.9	25.0 ± 10.7 ^a

Mild hepatic impairment = Child–Pugh class A; moderate hepatic impairment = Child–Pugh class B

Data are presented as mean ± SD, except for *t*_{max}, which is presented as median (min, max)

*AUC*_∞ area under the plasma concentration–time curve from time 0 to infinity, *AUC*_{∞,u} area under the plasma concentration–time curve from time 0 to infinity for unbound drug, *AUC*_{last} area under the plasma concentration–time curve from time 0 to the time of last quantifiable concentration, *CL*/*F* oral clearance, *C*_{max} maximum observed plasma concentration, *C*_{max,u} maximum observed plasma concentration for unbound drug, *SD* standard deviation, *t*_{1/2} terminal elimination half-life, *t*_{max} time to reach *C*_{max}, *V*_z/*F* apparent volume of distribution

^a*n* = 6

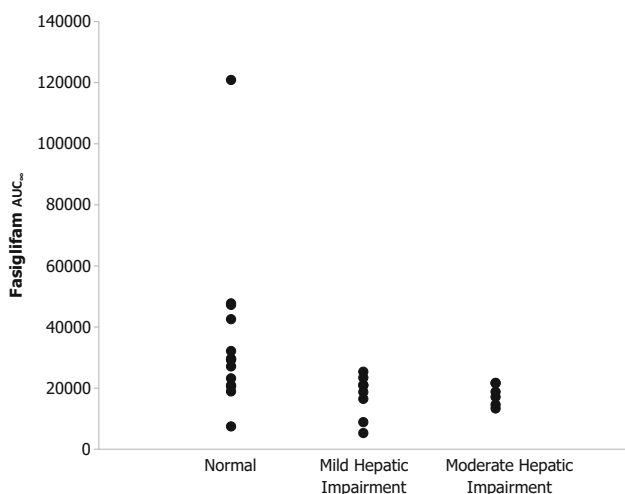


Fig. 4 Scatter plot of fasiglifam *AUC*_∞. *AUC*_∞ area under the plasma concentration–time curve from time 0 to infinity. Mild hepatic impairment = Child–Pugh class A; moderate hepatic impairment = Child–Pugh class B

4 Discussion

Hepatic diseases can alter the absorption and disposition of drugs and therefore impact their safety and efficacy, although different types of hepatic disease have varying effects on drug PK [24]. When hepatic impairment leads to increased drug exposure of twofold or greater, dose reductions are generally recommended [22]. Unexpectedly, in this single-dose study, hepatic impairment did not increase exposure to fasiglifam in subjects with mild or

moderate hepatic impairment. On the contrary, a decreasing trend in fasiglifam exposure was observed with progressive hepatic impairment, while exposure to the inactive metabolite M-I increased. The *V*_z/*F* did not change with decreased hepatic function, while *CL*/*F* increased.

Fasiglifam is highly protein bound; in this study, >99.8% of the 25-mg dose was protein bound. For highly bound plasma protein drugs, a small change in binding can result in a large change in the percentage of the unbound fraction [24]. Therefore, it is possible that small changes in plasma albumin, a reflection of decreasing hepatic function, may cause a large increase in the fraction of unbound fasiglifam, and contribute to its increased oral clearance. However, the assay used in this study may have not been sensitive enough to accurately measure the free fasiglifam fraction. It may be that the observed increase in M-I levels reflects an increase in available fasiglifam levels due to changes in plasma protein levels. This would then lead to the higher clearance of fasiglifam observed in the hepatic impairment groups. However, any relevant changes in the free fraction of fasiglifam should have impacted both *CL*/*F* and *V*_z/*F*. However, no appreciable differences in the apparent volume of distribution values were noted between hepatic impairment groups and normal subjects. Since fasiglifam M-I does not bind to GPR-40, the increase in exposure is of minimal clinical relevance.

Another possible explanation for lower fasiglifam but higher metabolite plasma concentrations may be a decrease in the contribution of enterohepatic recycling of fasiglifam by chronic hepatic impairment. Studies in rats

Table 3 Statistical analysis of the plasma pharmacokinetic parameters of fasiglifam

Parameter	Mild hepatic impairment vs normal hepatic function Ratio (90% CI) ^a	Moderate hepatic impairment vs normal hepatic function Ratio (90% CI) ^a
C_{max}	0.82 (0.67–1.01)	0.78 (0.64–0.96)
$C_{max,u}$	0.82 (0.65–1.03)	0.76 (0.60–0.95)*
AUC_{last}	0.54 (0.37–0.80)*	0.61 (0.41–0.90)*
AUC_{∞}	0.54 (0.36–0.81)*	0.60 (0.38–0.94)
$AUC_{\infty,u}$	0.54 (0.37–0.78)**	0.60 (0.40–0.91)*

Mild hepatic impairment = Child–Pugh class A; moderate hepatic impairment = Child–Pugh class B

AUC_{∞} area under the plasma concentration–time curve from time 0 to infinity, $AUC_{\infty,u}$ area under the plasma concentration–time curve from time 0 to infinity for unbound drug, AUC_{last} area under the plasma concentration–time curve from time 0 to the time of last quantifiable concentration, CI confidence interval, C_{max} maximum observed plasma concentration, $C_{max,u}$ maximum observed plasma concentration for unbound drug

* $p < 0.05$, ** $p < 0.01$

^aRatios of the central values for the test groups (subjects with hepatic impairment) and the reference group (subjects with normal hepatic function) and 90% CIs were calculated using natural logarithm-transformed data

Table 4 Summary of plasma pharmacokinetic parameter estimates of fasiglifam M-I following administration of a single 25-mg dose of fasiglifam to subjects with normal hepatic function and subjects with mild or moderate hepatic impairment

Parameter	Normal	Mild	Moderate
t_{max} (h)	24.00 (1.5, 48.0)	24.00 (10.0, 36.0)	12.00 (10.0, 36.0)
C_{max} (ng/mL)	27.04 ± 14.3	88.21 ± 90.4	102.70 ± 98.5
AUC_{last} (ng·h/mL)	2060.01 ± 1626.9	4898.20 ± 5471.3	5501.88 ± 5589.1
AUC_{∞} (ng·h/mL)	2059.61 ± 1149.7	5737.80 ± 5694.2	5357.24 ± 5458.2
$t_{1/2}$ (h)	44.26 ± 16.1	32.96 ± 9.3	44.36 ± 32.3
AUC_{last} ratio	0.06 ± 0.0	0.32 ± 0.4	0.32 ± 0.3

Mild hepatic impairment = Child–Pugh class A; moderate hepatic impairment = Child–Pugh class B

Data presented as mean ± SD, except for t_{max} , which is presented as median (min, max)

AUC_{∞} area under the plasma concentration–time curve from time 0 to infinity, AUC_{last} area under the plasma concentration–time curve from time 0 to the time of last quantifiable concentration, AUC_{last} ratio ratio of the AUC_{last} of fasiglifam M-I to that of fasiglifam, C_{max} maximum observed plasma concentration, SD standard deviation, $t_{1/2}$ terminal elimination half-life, t_{max} time to reach C_{max}

demonstrated that approximately 60% of fasiglifam and/or its metabolites excreted into the bile was reabsorbed and subjected to enterohepatic circulation (unpublished data). Individual plasma concentration–time profiles in this study for subjects with normal hepatic function had a secondary peak at approximately 8–10 h (data not shown) after fasiglifam administration that may correlate with digestion of the evening meal and suggest the occurrence of enterohepatic recycling. If the elimination of fasiglifam in humans is similar to that in rats and dogs, in which an ester glucuronide conjugate of fasiglifam is a major biliary component [25], enterohepatic recycling of fasiglifam and interference in this process by chronic hepatic impairment could result in an overall decrease in parent drug exposure. Additionally, chronic hepatic impairment can affect glucuronidation [24].

However, the absence of urinary data for the parent molecule and metabolite M-I can be considered as the main

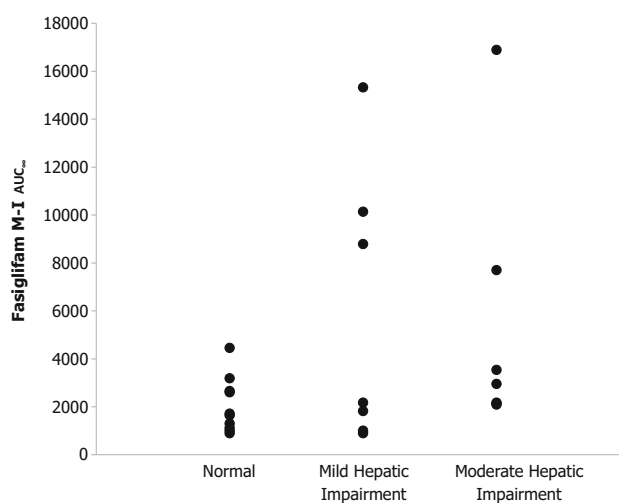
**Fig. 5** Scatter plot of fasiglifam M-I AUC_{∞} . AUC_{∞} area under the plasma concentration–time curve from 0 to infinity. Mild hepatic impairment = Child–Pugh class A; moderate hepatic impairment = Child–Pugh class B

Table 5 Statistical analysis of the plasma pharmacokinetic parameters of fasiglifam M-I following administration of a single 25-mg dose of fasiglifam to subjects with normal hepatic function and subjects with mild or moderate hepatic impairment

Parameter	Mild hepatic impairment vs normal hepatic function	Moderate hepatic impairment vs normal hepatic function
	Ratio (90% CI) ^a	Ratio (90% CI) ^a
C_{max}	2.25 (1.18–4.31)*	2.74 (1.43–5.23)*
AUC_{last}	1.84 (0.79–4.30)	2.56 (1.10–5.98)
AUC_{∞}	1.87 (0.92–3.78)	2.15 (1.06–4.36)

Mild hepatic impairment = Child–Pugh class A; moderate hepatic impairment = Child–Pugh class B

AUC_{∞} area under the plasma concentration–time curve from time 0 to infinity, AUC_{last} area under the plasma concentration–time curve from time 0 to the time of last quantifiable concentration, CI confidence interval, C_{max} maximum observed plasma concentration

* $p < 0.05$

^aRatios of the central values for the test groups (subjects with hepatic impairment) and the reference group (subjects with normal hepatic function) and 90% CIs were calculated using natural logarithm-transformed data

Table 6 Summary of liver test values at baseline and at study exit (day 15)

	Hepatic impairment status					
	Normal ($n = 14$)		Mild ($n = 8$)		Moderate ($n = 8$)	
	Baseline ^a	Day 15 ^b	Baseline ^a	Day 15	Baseline ^a	Day 15
ALT, U/L	24.4 ± 8.1	26.5 ± 9.2	49.6 ± 19.0	48.4 ± 22.7	41.4 ± 24.6	43.5 ± 28.8
AST, U/L	27.8 ± 4.6	24.8 ± 3.6	41.3 ± 8.7	37.0 ± 12.7	37.3 ± 23.4	40.5 ± 25.7
ALP, U/L	64.2 ± 15.0	64.8 ± 12.8	76.1 ± 17.7	68.0 ± 16.2	89.4 ± 18.0	84.8 ± 14.7
Total bilirubin, $\mu\text{mol/L}$	11.4 ± 6.0	9.2 ± 4.4	9.4 ± 4.5	7.5 ± 2.2	11.3 ± 3.3	11.3 ± 4.0
GGT, U/L	22.4 ± 7.7	28.2 ± 15.0	66.3 ± 35.2	60.9 ± 36.5	79.1 ± 68.4	73.4 ± 55.4

Mild hepatic impairment = Child–Pugh class A; moderate hepatic impairment = Child–Pugh class B

Data are presented as mean ± SD

ALP alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, GGT gamma-glutamyltransferase, SD standard deviation

^aBaseline is defined as the last measurement collected on or before the first dose of study drug

^b $n = 13$

limitation of this study, which renders assessment of compensatory changes in the urinary elimination due to hepatic impairment difficult. Furthermore, the conjugated forms of fasiglifam were not quantitated in this study because of the lack of availability of reliable bioanalytical methodology.

In the current study, a single dose of fasiglifam was well tolerated in this population. Overall, few AEs were reported and ranged from mild to moderate in intensity. In addition, none of the subjects experienced increased transaminases $> 3 \times$ upper limit of normal after a single dose of fasiglifam, and there were no clinically important changes in baseline liver test measurements identified in subjects with hepatic impairment. No cases of hypoglycemia were seen in this study, and this is in line with findings from previous observations [12, 15].

In conclusion, fasiglifam exposure was lower in subjects with hepatic impairment compared with individuals with normal hepatic function. Based on the results of this single-dose study, no dose reduction would have been required in patients with mild or moderate hepatic impairment. Since the completion of this study, however, Takeda decided to voluntarily terminate the current development activities as a result of liver safety concerns identified in late phase III clinical development. This study, however, may provide useful data in the development of other similar antidiabetic compounds.

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Compliance with Ethical Standards

All authors fulfill International Committee of Medical Journal Editors (ICMJE) criteria for authorship.

Conflict of interest John Marciniak and Majid Vakilynejad are employees of Takeda Development Center Americas Inc., Deerfield, IL, USA. Akifumi Kogame and Yoshihiko Tagawa are former employees of Takeda Pharmaceutical Company Limited, Kanagawa, Japan.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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