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ORIGINAL RESEARCH ARTICLE

Effect of Renal or Hepatic Impairment on the Pharmacokinetics of Mirabegron

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Abstract
Background and Objectives Mirabegron, a selective β3-adrenoceptor agonist for the treatment of overactive bladder (OAB), is eliminated by renal and metabolic routes. The potential influence of renal or hepatic impairment on the pharmacokinetics of mirabegron was evaluated.
Methods Two separate open-label, single-dose, parallel-group studies were conducted. Male and female subjects ($n = 8$ per group) were categorized according to their baseline renal function (mild, moderate, severe or no impairment as determined by estimated glomerular filtration rate [eGFR] using the abbreviated modification of diet in renal disease formula) or hepatic function (mild, moderate or no impairment as determined by the Child-Pugh classification). All subjects received a single oral 100 mg dose of mirabegron. Non-compartmental pharmacokinetic parameters were determined from plasma and urine concentration-time data of mirabegron and metabolites.
Results Compared with healthy subjects who were similar overall in terms of age, sex and body mass index (BMI), the geometric mean area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC_∞) for mirabegron was 31, 66 and 118 % higher in subjects with mild, moderate and severe renal impairment, respectively. Peak plasma concentrations (C_{max}) increased 6, 23 and 92 %, respectively, in subjects with mild, moderate and severe renal impairment. Renal clearance but not apparent total body clearance of mirabegron correlated well with renal function. Compared with healthy subjects matched for age, sex and BMI, mirabegron AUC_∞ values were 19 and 65 % higher in subjects with mild and moderate hepatic impairment, respectively. Mirabegron C_{max} was 9 and 175 % higher, respectively, compared with matched healthy subjects. No clear relationship was evident between pharmacokinetic parameters and Child-Pugh scores. Protein binding was approximately 71 % in healthy subjects and was not altered to a clinically significant extent in subjects with renal or hepatic impairment. No consistent changes in mirabegron elimination half-life were observed in subjects with renal or hepatic impairment. There was high pharmacokinetic variability and significant overlap in exposures between subjects with renal or hepatic impairment and healthy subjects.

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Conclusion Mirabegron AUC_{∞} and C_{max} increased 118 and 92 %, respectively, in subjects with severe renal impairment, and 65 and 175 %, respectively, in subjects with moderate hepatic impairment. Pharmacokinetic changes observed in subjects with mild or moderate renal impairment or mild hepatic impairment are of small magnitude and likely to be without clinical importance.

1 Introduction

Mirabegron (YM178) is a potent and selective β3-adrenoceptor agonist, approved for the treatment of overactive bladder (OAB) in Japan and the United States, and under evaluation for the same indication in Europe [1]. OAB has been defined by the International Continence Society as "urgency, with or without urgency incontinence, usually with frequency and nocturia" [2, 3]. Mirabegron is the first of a new class of drugs with a different mode of action compared with antimuscarinic medications, the current standard of care for the treatment of patients with OAB [4]. Mirabegron oral controlled absorption system (OCAS) modified-release tablets, at doses of 50 and 100 mg/day, demonstrated superior efficacy compared with placebo in the treatment of the symptoms of OAB in 12-week, phase-III studies [4, 5]. Mirabegron was generally safe and well tolerated with a low incidence of treatment-emergent adverse events (TEAEs) [5, 6]. When administered as a single, oral radioactive solution dose to healthy subjects, approximately 55 % of the radioactivity was excreted in the urine (comprising 25 % mirabegron), while 34 % was recovered in the faeces, mainly as unchanged mirabegron [7]. Mirabegron is metabolized to at least ten pharmacologically inactive metabolites via multiple pathways involving amide hydrolysis, (direct) glucuronidation, dealkylation and oxidation [7]. *In vitro* studies have shown the involvement of butyrylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT) and possibly alcohol dehydrogenase in the metabolism of mirabegron [7, 8]. In addition, cytochrome 450 (CYP) 3A4 was the primary responsible isoenzyme for the hepatic oxidative metabolism of mirabegron *in vitro* [7], with a minor role of CYP2D6. However *in vivo* results indicate that these isozymes play a limited role in the overall elimination [9, 10]. As renal excretion and hepatic metabolism account for a substantial part of mirabegron elimination, it is important to assess whether impaired renal or hepatic function has an impact on the pharmacokinetics of mirabegron. This report presents the results of two studies investigating the pharmacokinetics and tolerability of mirabegron in subjects with renal or hepatic impairment of various severities compared with healthy adult subjects.

2 Methods

2.1 Subjects

2.1.1 Renal Impairment Study

Eligible subjects were men and women, aged 18–79 years, of any race, with a body weight of at least 45 kg and a body mass index (BMI) of 18–40 kg/m^2, who met pre-defined criteria for sub-categorization according to renal function. The degree of renal function was determined by pre-dose estimated glomerular filtration rate (eGFR) based on the abbreviated Modification of Diet in Renal Disease (MDRD) formula (eGFR-MDRD) [11, 12]. Subjects were assigned to one of four groups: normal (eGFR-MDRD $\geq$ 90 mL/min/1.73 m^2; $n = 8$); mild impairment (eGFR-MDRD 60–89 mL/min/1.73 m^2; $n = 8$), moderate impairment (eGFR-MDRD 30–59 mL/min/1.73 m^2; $n = 8$); or severe impairment (eGFR-MDRD 15–29 mL/min/1.73 m^2; $n = 9$). Creatinine clearance estimated by the Cockcroft-Gault method (CL_{CR}-CG) [13] was used as secondary information.

The subjects with normal renal function were selected to be similar to the pooled group of renally impaired subjects in terms of sex and the range of BMI and age. Exclusion criteria for subjects with renal impairment included obstructive uropathy or other causes of renal impairment not related to parenchymal renal disorder and/or disease of the kidney.

2.1.2 Hepatic Impairment Study

Eligible subjects were men and women, aged 18–80 years, of any race, with a BMI of 18–32 kg/m^2, who were genotyped and categorized as being extensive metabolizers of CYP 2D6 substrates, and who met pre-defined criteria for sub-categorization according to hepatic function. The degree of hepatic function was determined by the Child-Pugh classification [14], based on scores for encephalopathy, ascites, serum bilirubin, serum albumin and prothrombin time. Subjects were assigned to one of three groups: healthy with normal hepatic function ($n = 16$); mild hepatic impairment (5–6 in the Child-Pugh classification; $n = 8$); or moderate hepatic impairment (7–9 in the Child-Pugh classification; $n = 8$). The subjects with normal hepatic function were matched (1:1) to the hepatically impaired volunteers by age (within a 10 % range), sex and BMI (within a 5 % range). Exclusion criteria for subjects with hepatic impairment included biliary obstruction or other causes of hepatic impairment not related to parenchymal disorder and/or disease of the liver, fluctuating or rapidly deteriorating hepatic function, biliary

liver cirrhosis, history or presence of severe hepatic encephalopathy (grade > 2), advanced ascites, oesophageal variceal bleeding within the past 2 months, severe portal hypertension or surgical or non-surgical portosystemic shunt or a thrombocyte level <40,000 × 10^9/L and/or prothrombin time >18 s and/or haemoglobin <9 g/L.

In both studies, female subjects were at least 2 years post-menopausal, surgically sterile or practising effective birth control if sexually active and not pregnant or lactating. Matched healthy male and female subjects were determined by the absence of clinically significant deviations from normal in medical history, physical examination, electrocardiography and clinical laboratory measurements. All subjects were willing and able to comply with the study requirements.

2.2 Study Designs

Both studies were of open-label, single-dose, parallel-group design. In both studies, subjects received a single oral dose of mirabegron OCAS 100 mg. The design of both trials followed the US Food and Drug Administration (FDA) [15, 16] and the European guidance documents [17, 18] on the design and conduct of *in vivo* renal or hepatic impairment studies. Subjects were fasted for at least 8 h prior to dosing. Standard meals were allowed after at least 4 h post-dose for the renal impairment study and 2 h post-dose for the hepatic impairment study. In the renal impairment study, subjects were confined to the study site from two nights before dosing and for the duration of the pharmacokinetic assessments. In the hepatic impairment study, subjects remained at the study site from the day before dosing until 96 h post-dose; thereafter subjects were allowed to leave the study site and return for the last pharmacokinetic samples.

Concomitant medication was not permitted for healthy subjects, with the exception of contraceptives and occasional use of paracetamol (acetaminophen) or ibuprofen in the renal impairment study and paracetamol in the hepatic impairment study. Subjects with renal or hepatic impairment were to be stable on their usual medication for at least 2 and 4 weeks, respectively, prior to pre-study screening and were allowed to continue their current treatment, with the exception of anticholinergics/antispasmodics and CYP2D6 substrates with a narrow therapeutic range for renal impairment subjects.

Both studies were carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and all subjects provided written informed consent before entering a study. Protocols were approved by the Independent Ethics Review Committee or Institutional Review Board at the sites where the studies were conducted.

2.3 Pharmacokinetic Sampling and Bioanalysis

In the renal impairment study, plasma and urine samples for pharmacokinetic assessment of mirabegron and eight circulating metabolites (M5 [deacylated mirabegron (M16)-N^{ω}-acetylated], M8 [mirabegron-*N*-α-oxidation body (phenylacetic acid derivative)], M11 [mirabegron-*O*-glucuronide], M12 [mirabegron ketone oxidation body (M18)-*N*-*COO*-glucuronide], M13 [mirabegron-*N*-*COO*-glucuronide], M14 [mirabegron-N^{ω}-glucuronide], M15 [mirabegron-*N*-*O*-glucuronide] and M16 [deacylated mirabegron]) were obtained at prespecified time points until 120 h post-dose. In the hepatic impairment study, plasma samples for mirabegron and metabolite concentrations were collected up to 144 h post-dose in healthy subjects and up to 240 h post-dose in hepatically impaired subjects. Urine samples for mirabegron concentrations were collected up to 96 h post-dose for all hepatic groups. In both studies, an additional plasma sample was obtained at 4 h after dosing for determination of protein binding of mirabegron. Plasma samples were loaded on a Vivaspin Ultrafiltration tube to obtain ultrafiltrate. Plasma, plasma ultrafiltrate and urine samples were analysed using validated liquid chromatography analytical methods coupled with tandem mass spectrometric detection (LC-MS/MS) using an atmospheric pressure chemical ionization (APCI) interface for mirabegron and a heated electrospray ionization interface for the metabolites [19]. Either solid-phase extraction or liquid–liquid extraction was used to extract the analytes of interest from matrix constituents. The calibration ranges for mirabegron were 0.2–100 ng/mL in plasma, 1–100 ng/mL in plasma ultrafiltrate and 10–5,000 ng/mL in urine. The calibration ranges for the metabolites in plasma were 1.0–200 ng/mL for M8, 0.5–250 ng/mL for M11, M12, M13 and M15, 1.0–500 ng/mL for M14 and 0.5–100 ng/mL for M5 and M16. The ranges in urine were 5.0–1,000 ng/mL for M5, M8 and M16 and 5.0–2,000 ng/mL for M11 to M15. Precision of quality control standards assayed during sample analysis, expressed as percent relative standard deviation, was <8.9 % for plasma, <5.0 % for plasma ultrafiltrate and <6.8 % for urine. The accuracy (relative error) of the assays over the quality control (QC) range ranged from −7.7 to 4.2 % for plasma, −2.2 to 3.3 % for plasma ultrafiltrate and −9.1 to 2.5 % for urine.

2.4 Pharmacokinetic Methods

Concentration data of mirabegron and metabolites in plasma and urine were analysed by non-compartmental methods using WinNonlin version 5.2 or higher (Pharsight Corporation, Mountain View, CA, USA) or SAS version 9.1 or later (SAS Institute, Cary, NC, USA) to obtain

values for the following pharmacokinetic parameters as applicable: maximum (peak) observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve (AUC; calculated using the linear-log trapezoidal method) from immediately prior to dosing (time zero) to the time of the last measurable plasma concentration (AUC_{last}) as well as extrapolated to infinity (AUC_{∞}), metabolic ratio (MR_p; assessed as metabolite AUC_{last} divided by mirabegron AUC_{last}), elimination half-life ($t_{½}$), apparent total body clearance from plasma after oral administration (CL/F), cumulative amount of drug as a percentage of the dose excreted in the urine from time zero to the time of the last measurable urine concentration (Ae_{last} %) as well as extrapolated to infinity (Ae_{∞} %), renal clearance (CL_R) and excretion ratio (ER; calculated as unbound CL_R divided by eGFR-MDRD; which, if greater than unity, indicates that tubular secretion is dominant in renal excretion). Unbound parameters for mirabegron were calculated by multiplying (C_{max}, AUC_{last} or AUC_{∞}) or dividing (CL/F or CL_R) the individual parameter by its fraction unbound in plasma (f_u). Actual sampling times were used for the calculation of pharmacokinetic parameters, and nominal sampling times were used for the mean concentration-time figures.

2.5 Statistical Methods

No formal sample size calculations were performed. The sample size was determined based on precedent set by other pharmacokinetic studies similar in design and not on statistical consideration of power. Summary statistics were calculated for all pharmacokinetic parameters for mirabegron and metabolites by renal or hepatic function group.

To assess the effect of renal impairment on the pharmacokinetics of mirabegron, an analysis of variance (ANOVA) was performed on the natural log-transformed pharmacokinetic parameters, with renal function group as a fixed effect. For the hepatic study, a paired analysis was performed on the natural log-transformed pharmacokinetic parameters. For both studies, the primary pharmacokinetic parameters were AUC_{∞} and C_{max} of total (bound and unbound) mirabegron. The least squares mean of the difference between impaired and healthy subjects and associated 90 % confidence interval (CI) was transformed to the original scale in order to obtain the geometric mean ratios for AUC_{∞} and C_{max} and the 90 % CIs for these ratios. Equivalence between healthy subjects and subjects with renal impairment was considered to be demonstrated if the 90 % CI for a pharmacokinetic parameter was wholly contained in the default equivalence limits of 0.80 and 1.25, although the study was not powered for this. In the hepatic impairment study, a wider equivalence range of 0.70–1.43 was defined because of anticipated high intersubject variability. For both studies, an exploratory correlation analysis was performed between selected pharmacokinetic parameters of mirabegron and α1-acid glycoprotein (AGP) or albumin concentrations. In addition, in the renal impairment study, the relationships between measures of renal function and selected pharmacokinetic parameters of mirabegron as well as the relationship between unbound CL/F and CL_R of mirabegron were investigated using linear regression techniques. All statistical analyses were performed using SAS version 9.1 or later (SAS Institute).

2.6 Tolerability Assessments

These included physical examinations, supine vital signs, resting 12-lead electrocardiograms, safety clinical laboratory tests (biochemistry, haematology and urinalysis) and adverse event monitoring.

3 Results

3.1 Subject Characteristics

Thirty-three subjects were enrolled in the renal impairment study, 32 of whom completed the study. After receiving mirabegron, one subject with severe renal impairment was removed from the study by the investigator because of lack of venous access; this subject was replaced. In the hepatic impairment study, 32 subjects were enrolled and all completed the study. The majority of subjects in the renal impairment study and all subjects in the hepatic impairment study were white (Table 1). The ranges for BMI and age were similar in subjects with renal impairment and their healthy controls. All renal function groups included males and females but the proportion of males and females differed between the groups. Subjects with hepatic impairment and matched healthy subjects were balanced for age, sex and BMI. In the renal impairment study, some subjects would be reclassified to a different renal function group if CL_{CR}-CG was used as the classification methodology, although none of the subjects shifted by more than one renal classification category. Mean CL_{CR}-CG was lower in the mild hepatically impaired group than in the matched healthy group. Plasma AGP concentrations were increased in subjects with renal impairment and decreased in subjects with hepatic impairment compared with healthy control subjects. Serum albumin concentrations were similar between healthy and hepatic impairment subjects and reduced in renal impairment subjects. Most of the subjects with renal or hepatic impairment were taking concomitant medication for various indications typical for these patient populations. None of the subjects took prohibited

Table 1 Demographic and other baseline characteristics

Parameter	Class	Renal function group				Hepatic function group			
		Healthy ($n = 8$)	Mild ($n = 8$)	Moderate ($n = 8$)	Severe ($n = 9$)	Healthy [matched to mild] ($n = 8$)	Mild ($n = 8$)	Healthy [matched to moderate] (n = 8)	Moderate (n = 8)
Sex (n)	Male	4	3	6	5	4	4	5	5
	Female	4	5	2	4	4	4	3	3
Race (n)	White	5	6	8	7	8	8	8	8
	Black	2	0	0	2	0	0	0	0
	Asian	1	0	0	0	0	0	0	0
	Native Hawaiian-OPI	0	2	0	0	0	0	0	0
Age (y)	All subjects	60	68	68	65	48	50	48	47
		50–72	54–76	52–77	42–75	40–58	45–60	28–62	28–58
Weight (kg)	All subjects	74.8	76.4	88.0	73.3	69.4	67.9	82.1	79.9
		49.3–93.0	54.1–118	54.3–119	53.2–83.2	57–106	49–88	70–97	60–88
BMI (kg/m^2)	All subjects	27.4	28.4	29.8	27.0	23.5	23.1	27.0	27.0
		20.0–35.0	21.7–39.6	21.9–37.5	19.3–30.6	20.7–31.0	19.9–29.8	24.5–32.0	23.7–32.0
eGFR-MDRD[a] (mL/min/1.73 m^2)	All subjects	106	77.0	47.8	21.7	–	–	–	–
		90–135	66–88	33–59	15–29				
CL_{CR}-CG[b] (mL/min/1.73 m^2)	All subjects	105	75.9	50.6	24.6	102	76.5	108	110
		75–134	58–106	42–63	19–33	65–144	53–111	70–179	94–147
AGP (g/L)	All subjects	0.58	0.69	0.99	0.86	0.62	0.47	0.57	0.48
		0.28–0.91	0.44–0.85	0.77–1.18	0.59–1.08	0.50–0.91	0.29–0.88	0.36–0.74	0.32–0.74
Albumin (g/L)	All subjects	42.3	38.3	38.6	38.1	40.5	43.9	40.7	41.9
		38–45	35–40	35–41	34–46	38–44	39–50	39–43	36–48

All data are mean (range) except where stated otherwise

AGP α1-acid glycoprotein, *BMI* body mass index, *CL_{CR}-CG* estimated creatinine clearance by Cockcroft-Gault, *eGFR-MDRD* estimated GFR by modification of diet in renal disease, *GFR* glomerular filtration rate, *OPI* other Pacific Islander, – indicates not reported

[a] For serum creatinine (S_{cr}) traceable to isotope dilution mass spectroscopy (IDMS), eGFR-MDRD = $175 \times (S_{cr}\,[mg/dL]^{-1.154}) \times (Age^{-0.203}) \times (0.742$ if female) $\times$ (1.210 if black); for serum creatinine not traceable to IDMS, eGFR-MDRD = $186 \times S_{cr}\,[mg/dL]^{-1.154}) \times (Age^{-0.203}) \times (0.742$ if female) $\times$ (1.210 if black)

[b] For serum creatinine traceable to IDMS, CL_{CR}-CG = [(140–age) $\times$ (weight in kg) $\times$ (0.85 if female)] $\times$ [1.73] / [S_{cr} (mg/dL) $\times$ 68 $\times$ body surface area (m^2)]. For serum creatinine not traceable to IDMS, CL_{CR}-CG = [(140–age) $\times$ (weight in kg) $\times$ (0.85 if female)] $\times$ [1.73] / [S_{cr} (mg/dL) $\times$ 72 $\times$ body surface area (m^2)]

concomitant medication, apart from one subject with normal renal function, who used stable doses of metformin and lisinopril.

3.2 Pharmacokinetics of Mirabegron

Mean pharmacokinetic parameters for both studies are summarized in Table 2. Analysis of the effects of renal or hepatic impairment on the pharmacokinetics of mirabegron is summarized in Table 3.

3.2.1 Renal Impairment Study

Plasma exposure of mirabegron was slightly higher in subjects with mild renal impairment, and was noticeably increased in moderately or severely impaired subjects relative to that in healthy controls (Fig. 1). In the mild, moderate and severe groups, mean mirabegron AUC_∞ was increased by 31, 66 and 118 %, respectively, compared with the healthy group; for C_{max}, the increases were 6, 23 and 92 %, respectively (Table 3). None of the 90 % CIs for the ratios for AUC_∞ and C_{max} were entirely contained within the default no effect limits of 0.80 and 1.25. Mirabegron protein binding was slightly increased in subjects with moderate or severe renal impairment, thus changes in unbound mirabegron AUC_∞ and C_{max} were slightly lower than those observed for total AUC_∞ and C_{max}. Unbound AUC_∞ was 26, 38 and 84 % higher in volunteers with mild, moderate or severe renal impairment, respectively. Unbound mirabegron C_{max} was unchanged in the mild and moderate groups, but increased 62 % in the severe group compared with the healthy group. There was high

Table 2 Summary of mirabegron pharmacokinetic parameters in healthy subjects and subjects with renal or hepatic impairment

Parameter	Renal function group				Hepatic function group			
	Healthy ($n = 8$)	Mild ($n = 8$)[a]	Moderate ($n = 8$)	Severe ($n = 8$)	Healthy [matched to mild] ($n = 8$)	Mild ($n = 8$)	Healthy [matched to moderate] ($n = 8$)	Moderate ($n = 8$)
AUC_∞ (ng·h/mL)	558 [45]	771 [63]	992 [52]	1,239 [53]	615 [60]	770 [51]	486 [51]	784 [46]
C_{max} (ng/mL)	45.2 [60]	57.0 [88]	60.8 [69]	93.8 [75]	66.9 [111]	71.9 [70]	41.5 [77]	113 [60]
t_{max} (h)	2.5 [1–6]	4.0 [1–6]	4.0 [2–8]	4.0 [2–6]	2.0 [1–3]	3.0 [1–8]	2.5 [1–4]	3.0 [2–6]
$t_{½}$ (h)	43.0 [15]	55.1 [25]	47.3 [23]	52.1 [23]	56.7 [21]	67.7 [51]	55.4 [19]	51.2 [22]
CL/F (L/h)	228 [58]	181 [66]	160 [102]	105 [62]	197 [36]	197 [96]	279 [70]	166 [66]
f_u	0.32 [21]	0.29 [21]	0.27 [34]	0.27 [15]	0.27 [15]	0.30 [18]	0.30 [9]	0.29 [15]
Ae_{last} (%)	5.7 [45]	6.3 [34]	3.9 [35]	2.3 [47]	5.5 [51]	5.1 [54]	4.0 [35]	7.8 [38]
CL_R (L/h)	11.8 [29]	11.2 [37]	5.5 [43]	2.3 [36]	11.9 [37]	8.2 [33]	11.1 [27]	12.3 [13]
ER	5.6 [28]	7.8 [22]	6.3 [37]	6.7 [39]	–	–	–	–

Values are mean [%CV]; median [range] for t_{max}

Ae_{last}% Cumulative amount of drug as percentage of the dose excreted in the urine from time zero to the time of the last measurable urine concentration, *AUC_∞* area under the plasma concentration-time curve from time zero to infinity, *CL/F* apparent total body clearance from plasma, *CL_R* renal clearance, *C_{max}* maximum observed plasma concentration, *ER* excretion ratio (ratio of unbound CL_R to eGFR-MDRD), *f_u* fraction unbound in plasma, *$t_{½}$* = elimination half-life, *t_{max}* time to C_{max}, – indicates not reported

[a] f_u and ER for mild group $n = 7$

Table 3 Comparison of mirabegron pharmacokinetic parameters for subjects with renal or hepatic impairment versus healthy subjects

Parameter	Renal impairment			Hepatic impairment	
	Mild ($n = 8$)[a]	Moderate ($n = 8$)	Severe ($n = 8$)	Mild ($n = 8$)	Moderate ($n = 8$)
AUC_∞	1.31 (0.78, 2.20)	1.66 (0.99, 2.80)	2.18 (1.30, 3.67)	1.19 (0.69, 2.05)	1.65 (0.95, 2.85)
C_{max}	1.06 (0.53, 2.10)	1.23 (0.62, 2.44)	1.92 (0.97, 3.81)	1.09 (0.42, 2.80)	2.75 (1.08, 6.98)
Unbound AUC_∞	1.26 (0.74, 2.13)	1.38 (0.83, 2.29)	1.84 (1.11, 3.07)	1.30 (0.73, 2.30)	1.57 (0.95, 2.60)
Unbound C_{max}	1.00 (0.51, 1.99)	1.02 (0.53, 1.97)	1.62 (0.84, 3.14)	1.18 (0.44, 3.15)	2.62 (1.10, 6.25)
$t_{½}$	1.26 (1.04, 1.51)	1.09 (0.90, 1.30)	1.19 (0.99, 1.43)	1.19 (1.08, 1.32)	0.92 (0.77, 1.10)
f_u	0.91 (0.74, 1.11)	0.83 (0.68, 1.01)	0.84 (0.69, 1.03)	1.09 (0.95, 1.25)	0.95 (0.83, 1.09)
CL_R	0.93 (0.67, 1.28)	0.44 (0.32, 0.61)	0.19 (0.14, 0.26)	0.70 (0.53, 0.91)	1.14 (0.92, 1.41)

Values are geometric least squares mean ratio (90 % confidence interval)

AUC_∞ area under the plasma concentration-time curve from time zero to infinity, *CL_R* renal clearance, *C_{max}* maximum observed plasma concentration, *f_u* fraction unbound in plasma, *$t_{1/2}$* elimination half-life

[a] f_u for mild group $n = 7$

interindividual variability (expressed as % coefficient of variation [CV]) in mirabegron AUC_∞ and C_{max} in all renal function groups and considerable overlap in exposures between the different groups, as reflected in the wide 90 % CIs for the group comparisons (Table 3). Absorption of mirabegron appeared delayed by approximately 1.5 h in subjects with renal impairment compared with those with normal renal function (Table 2). Although $t_{½}$ estimates were on average 12, 4 and 9 h longer in the mild, moderate and severe groups, respectively, compared with the healthy group, plasma concentration-time profiles indicate that the slopes of the terminal phase were approximately parallel for the different renal function groups (Fig. 1). Mirabegron CL_R and Ae_{last} % were decreased in the moderate and severe renal impairment groups compared with the healthy group (Tables 2, 3). Mirabegron was actively secreted in the kidney, with mean excretion ratios of 5.6 in the healthy group and 7.8, 6.3 and 6.7, respectively, in the mild, moderate and severe groups (Table 2). Unbound CL_R was linearly related to eGFR-MDRD (Fig. 2) and CL_{CR}-CG, with correlation coefficients (r) of 0.83 and 0.84, respectively. Other unbound pharmacokinetic parameters (AUC_∞, C_{max}, CL/F) did not correlate well with these renal function measures (Fig. 3 for CL/F); r values ranged from 0.41 to 0.51. A shallow inverse correlation existed between the unbound fraction of mirabegron and AGP levels but not

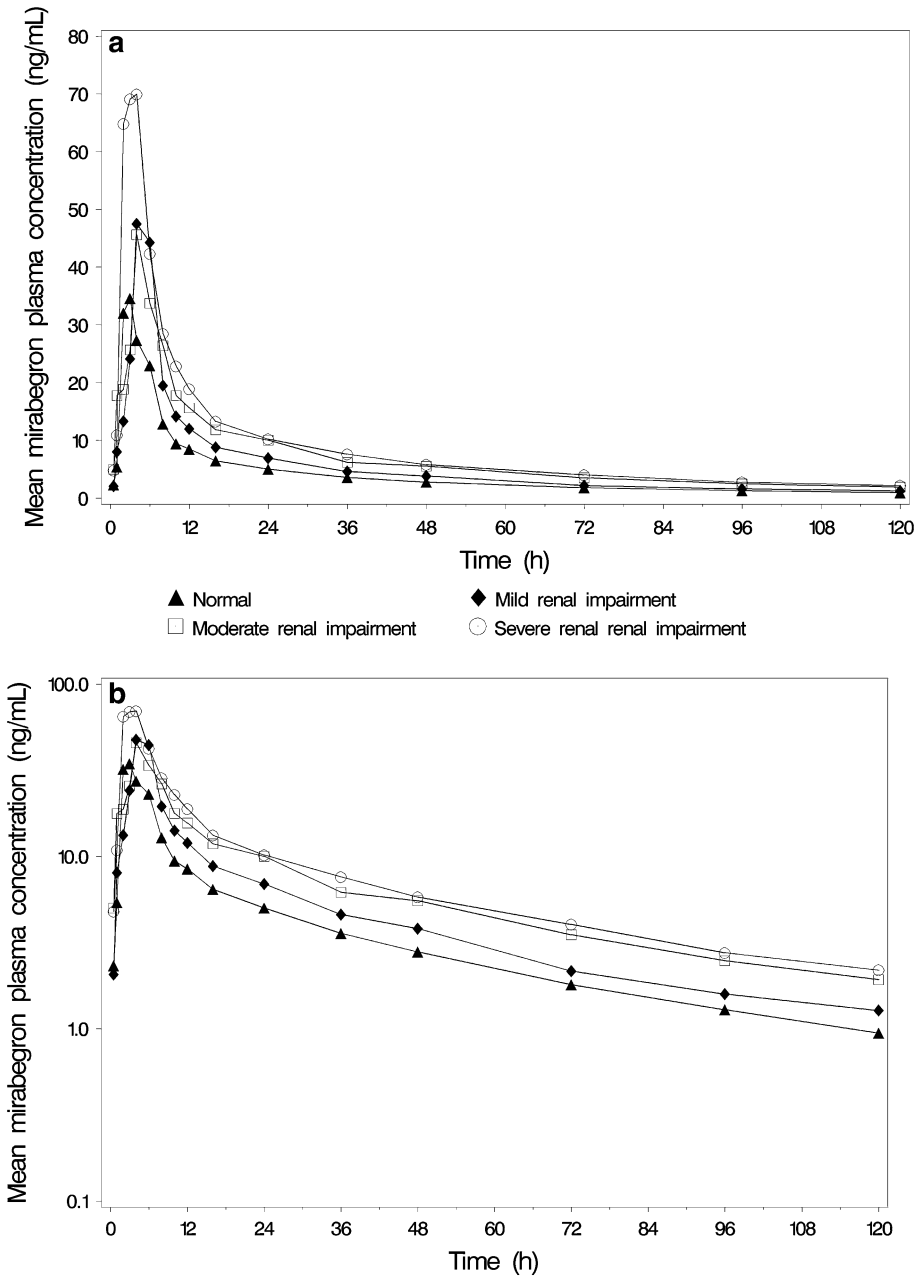

Fig. 1 Mean total mirabegron plasma concentrations versus time on a linear scale (**a**) and semi-logarithmic scale (**b**) following single-dose administration of mirabegron oral controlled absorption system 100 mg in healthy subjects and subjects with renal impairment

albumin levels (data not shown). For both AGP and albumin, the correlation with unbound mirabegron AUC_{∞} was weak.

3.2.2 *Hepatic Impairment Study*

Plasma exposure of mirabegron was slightly higher in subjects with mild hepatic impairment, and noticeably increased in moderately impaired subjects relative to that in matching controls (Fig. 4). Mean AUC_{∞} and C_{max} values of mirabegron were increased by 19 and 9 %, respectively, in mildly impaired subjects compared with subjects with normal hepatic function (Table 3). Moderate hepatic impairment increased mean AUC_{∞} and C_{max} by 65 and 175 %, respectively, compared with subjects with normal hepatic function. The unbound fraction of mirabegron in plasma was not statistically significantly different from that in subjects with normal hepatic function, despite an approximate 20 % decrease in mean plasma AGP concentrations in the hepatically impaired subjects compared with control subjects, and thus changes in unbound pharmacokinetic parameters were similar to those obtained for total AUC_{∞} and C_{max}. None of the 90 % CIs of total and unbound AUC_{∞} and C_{max} ratios were contained within the

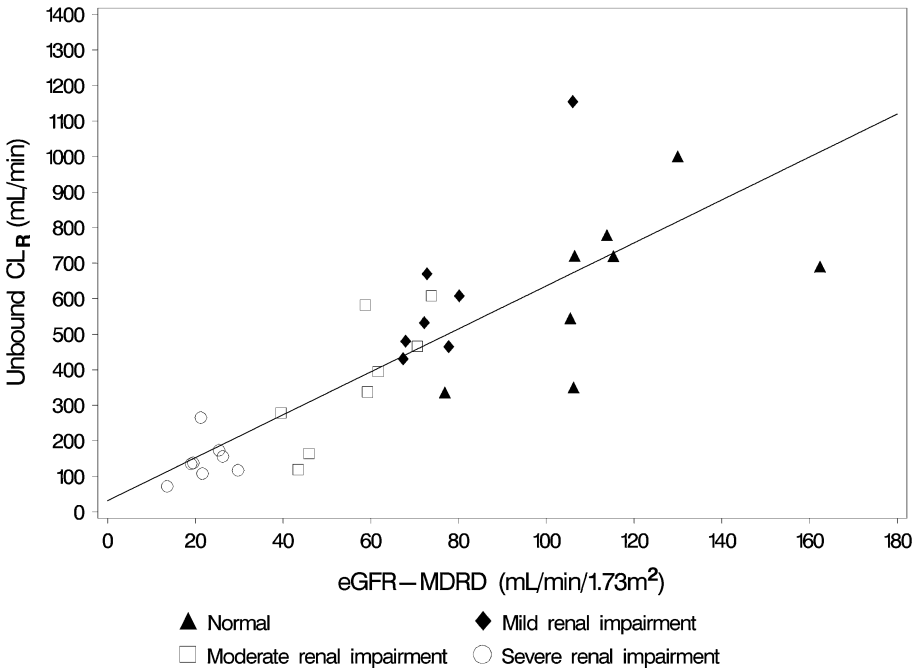

Fig. 2 Relationship between individual unbound renal clearance (CL_R) of mirabegron and estimated glomerular filtration rate based on the abbreviated Modification of Diet in Renal Disease formula (eGFR-MDRD) following single-dose administration of mirabegron oral controlled absorption system 100 mg in healthy subjects and subjects with renal impairment. The diagonal line represents the linear regression line with an intercept of 31.1 mL/min and a slope of 6.05

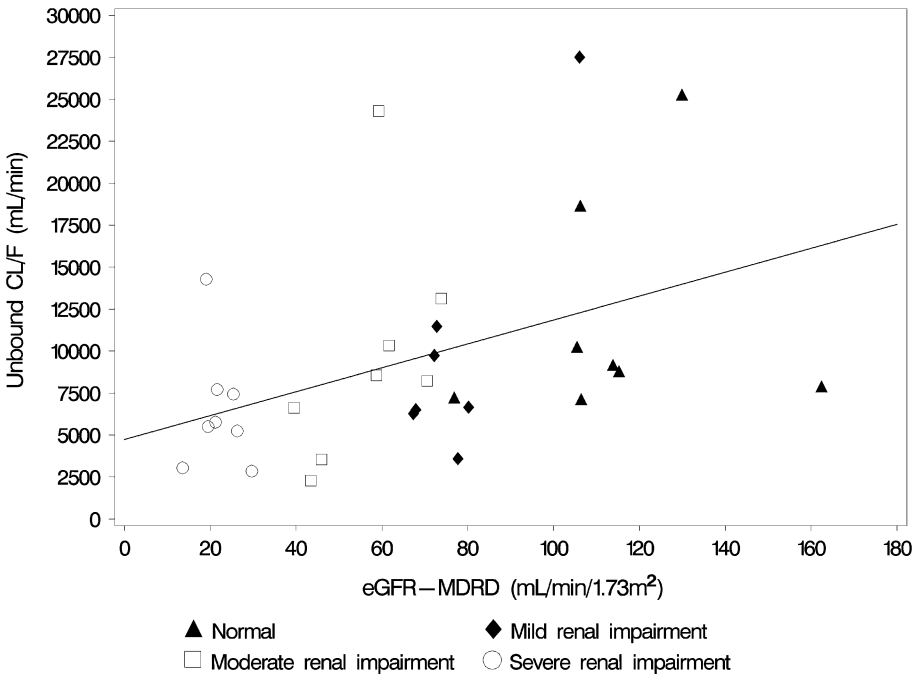

Fig. 3 Relationship between individual unbound apparent clearance (CL/F) of mirabegron and estimated glomerular filtration rate based on the abbreviated Modification of Diet in Renal Disease formula (eGFR-MDRD) following single-dose administration of mirabegron oral controlled absorption system 100 mg in healthy subjects and subjects with renal impairment. The *diagonal line* represents the *linear regression line* with an intercept of 4,725 mL/min and a *slope* of 71.2

prespecified 0.70–1.43 boundaries. There was high inter-individual variability in mirabegron AUC_∞ and C_{max} in all hepatic function groups and considerable overlap in exposures between the different groups, as reflected by the wide 90 % CIs for the group comparisons (Table 3). Mirabegron t_{max} was delayed by approximately 0.5–1.0 h in

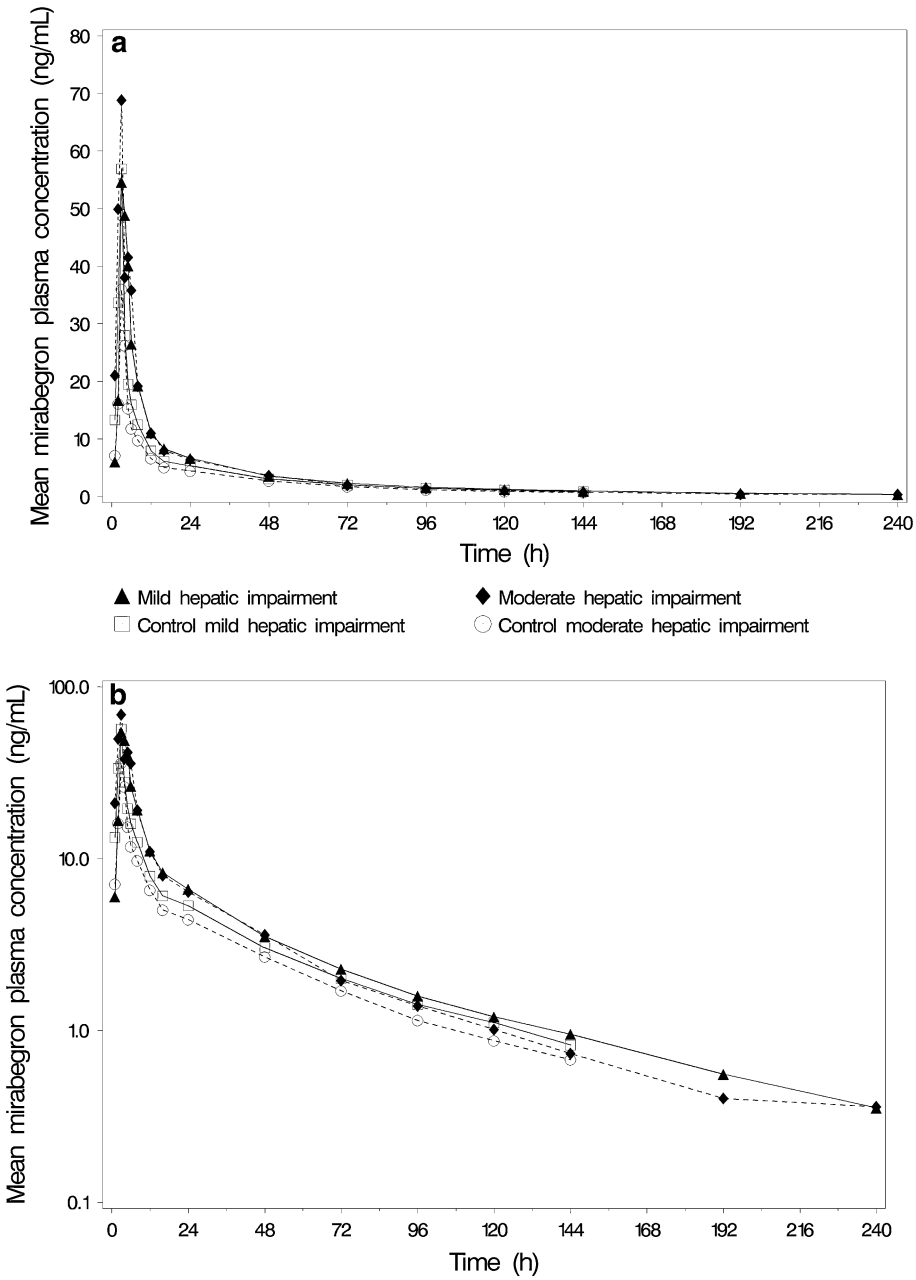

Fig. 4 Mean total mirabegron plasma concentrations versus time on a linear scale (**a**) and semi-logarithmic scale (**b**) following single-dose administration of mirabegron oral controlled absorption system 100 mg in healthy subjects and subjects with hepatic impairment

subjects with hepatic impairment compared with those with normal hepatic function (Table 2). Mean plasma concentrations in the different hepatic function groups declined with approximately parallel terminal slopes (Fig. 4); the 90 % CIs of the $t_{½}$ ratios were contained within the prespecified no effect boundaries of 0.70–1.43 for both impairment groups. Compared with the healthy control group, mirabegron CL_R was reduced by 30 % in subjects with mild hepatic impairment, consistent with a slightly decreased mean CL_{CR}-CG in this group (Table 1). No significant difference in CL_R was observed between the normal and moderately impaired hepatic function groups and Ae_{last} % was comparable for all groups. No clear relationship was evident between individual C_{max} and AUC_{∞} values and the scores of the five parameters included in the Child-Pugh scale (Fig. 5). A shallow inverse correlation existed between the unbound fraction of mirabegron and AGP levels but not albumin levels (data not shown). For both AGP and albumin, the correlation with unbound mirabegron AUC_{∞} was weak.

3.3 Pharmacokinetics of Metabolites

In both studies, plasma concentration-time profiles of the metabolites were truncated at various time points when the metabolite concentrations fell below the lower limit of

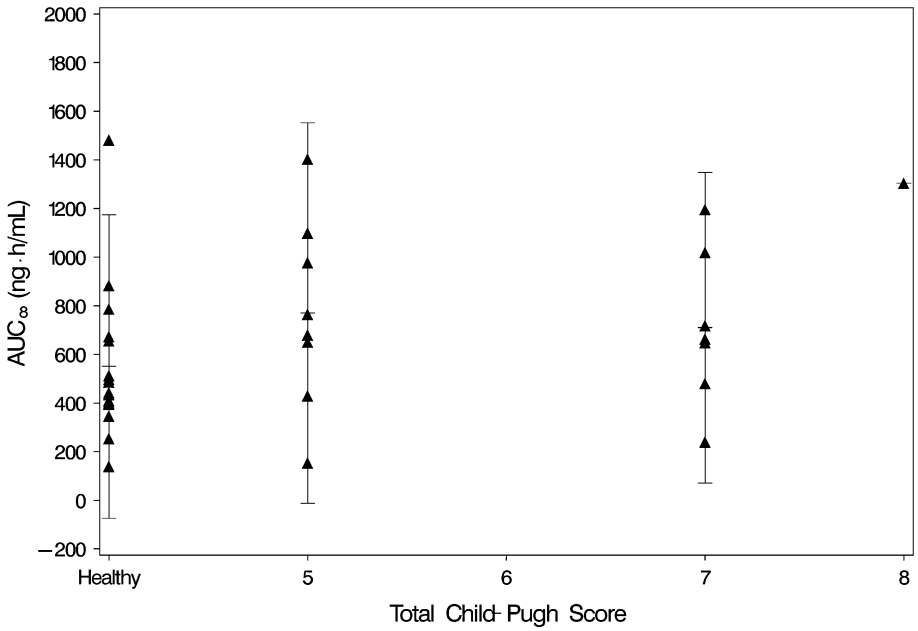

Fig. 5 Relationship between individual area under the plasma-concentration time curve from time zero to infinity (AUC_{∞}) of mirabegron and Child-Pugh score following single-dose administration of mirabegron oral controlled absorption system 100 mg in healthy subjects and subjects with renal impairment. *Diamonds* represent individual values. *Vertical lines* represent mean ± 2 standard deviations

quantification, resulting in highly variable AUC estimates (data not shown). Renal impairment increased plasma exposure to all metabolites to a greater extent than for mirabegron itself. The greatest increases were observed for M8 and M14, with approximately 1,300 and 330 % higher metabolite-to-mirabegron AUC_{last} ratios (MR_p), respectively, in the severe group compared with the normal group (Table 4). The increases in MR_p were accompanied by apparent increases in metabolite $t_{½}$ values in the moderate and severe but not the mild group (data not shown). With the exception of values for M5, M14 and M16 in the severe group (mean $t_{½}$ of 62.9, 53.1 and 59.0 h, respectively), mean $t_{½}$ estimates were shorter than mirabegron $t_{½}$ for all metabolites and all renal function groups, which is likely due to assay insensitivity. Plasma concentrations of the metabolites were quantifiable over a shorter period of time compared to mirabegron, which may have affected the accuracy of the estimate of metabolite $t_{½}$ values. Inter-subject variability in urine pharmacokinetic parameters was high for all metabolites. Relative to the healthy group, increases in mean Ae_{last} values >50 % were observed for metabolites M12, M14, M15 and M16 in the mild group, for metabolites M13, M14 and M15 in the moderate group, and for M8 in the severe group. There were no decreases >50 % in mean Ae_{last} for any urine metabolite compared with the healthy group. For all metabolites, CL_R was decreased in the moderate and severe renal impairment groups compared with the healthy group.

In subjects with mild or moderate hepatic impairment, a substantial (defined as >50 %) increase in MR_p was observed for metabolites M5 and M13, and for M12 in the mild hepatic impairment group only (Table 4). Hepatic impairment had no consistent effect on the MR_p for the other metabolites. Part of these increases in MR_p may be attributed to the prolonged period during which plasma concentrations of the metabolites were quantifiable in the hepatic impairment groups compared with the healthy control groups. For all metabolites, plasma concentrations in the three different hepatic function groups declined with approximately parallel terminal slopes, suggesting that there were no major changes in mean metabolite $t_{½}$ values in the impairment groups compared with healthy controls (data not shown). Mean $t_{½}$ estimates were shorter than mirabegron $t_{½}$ for all metabolites and all hepatic function groups. As indicated above, this is likely due to assay insensitivity.

3.4 Tolerability

3.4.1 Renal Impairment Study

A single dose of mirabegron 100 mg was well tolerated in healthy and renally impaired subjects. Two subjects reported TEAEs assessed by the investigator as possibly related to trial drug exposure (one subject in the mild group experienced dizziness, nausea, headache and palpitations and one subject in the moderate group experienced constipation). The events were mild in severity and were resolved by the last evaluation date (6 days after administration). There were no clinically relevant mean changes from baseline in clinical laboratory tests and blood pressure and no clinically significant results were observed for electrocardiograms. Increases in pulse rate were observed in all renal function groups.

Table 4 Mean metabolite-to-mirabegron AUC_{last} ratios in healthy subjects and subjects with renal or hepatic impairment

Metabolite	Renal function group				Hepatic function group			
	Healthy ($n = 8$)	Mild ($n = 8$)	Moderate ($n = 8$)	Severe ($n = 8$)	Healthy [matched to mild] ($n = 8$)	Mild ($n = 8$)	Healthy [matched to moderate] ($n = 8$)	Moderate ($n = 8$)
M5	0.18 [53][c]	0.18 [43][c]	0.22 [90][c]	0.30 [56]	0.09 [87][d]	0.24 [36][d]	0.09 [65][d]	0.21 [30][d]
M8	0.008 [101][a]	0.012 [117][a]	0.017 [66][b]	0.11 [63]	0.008 [48][b]	0.008 [69][d]	0.019 [70][a]	0.004 [80][b]
M11	0.37 [44]	0.39 [22]	0.62 [51]	1.42 [45]	0.35 [35]	0.33 [34]	0.34 [26]	0.25 [55]
M12	0.35 [57]	0.42 [38]	0.65 [48]	0.78 [118]	0.17 [56]	0.34 [30]	0.22 [65]	0.23 [77]
M13	0.038 [70][b]	0.041 [45][d]	0.11 [153][d]	0.10 [172]	0.018 [73][d]	0.044 [29]	0.019 [85][c]	0.067 [105][d]
M14	0.14 [35]	0.18 [77]	0.30 [37]	0.60 [46]	0.11 [41]	0.14 [29]	0.16 [48]	0.14 [79]
M15	0.063 [50][d]	0.081 [34]	0.11 [52]	0.18 [57]	0.051 [38]	0.087 [49]	0.053 [59]	0.055 [37]
M16	0.039 [57][b]	0.57 [73][c]	0.11 [41]	0.14 [23]	0.062 [49]	0.054 [54][d]	0.048 [70]	0.065 [61]

Values are mean [%CV]

AUC_{last} area under the plasma concentration-time curve from time zero to the time of the last measurable plasma concentration, *M5* deacylated mirabegron (M16)-*N^{ω}*-acetylated, *M8* mirabegron-*N*-α-oxidation body (phenylacetic acid derivative), *M11* mirabegron-*O*-glucuronide, *M12* mirabegron ketone oxidation body (M18)-*N-COO*-glucuronide, *M13* mirabegron-*N-COO*-glucuronide, *M14* mirabegron-*N^{ω}*-glucuronide, *M15* mirabegron-*N-O*-glucuronide, *M16* deacylated mirabegron

[a] $n = 3$, [b] $n = 5$, [c] $n = 6$, [d] $n = 7$

3.4.2 Hepatic Impairment Study

A single dose of mirabegron 100 mg was well tolerated in healthy and hepatically impaired subjects. The only TEAE reported in the study was a single subject with moderate hepatic impairment who experienced a mild case of watery diarrhoea, which lasted for 8 h, and was assessed by the investigator as having a possible relationship to mirabegron administration. The event resolved without any treatment or medication. There were no clinically significant findings in electrocardiograms, clinical laboratory parameters or physical examination results during the study. A decrease in mean systolic blood pressure was observed in all hepatic function groups. No clear trend was seen in mean diastolic blood pressure or mean pulse rate.

4 Discussion

The results of these studies demonstrated an effect of renal and hepatic impairment on the pharmacokinetics of mirabegron. Mean mirabegron exposure increased with the degree of renal or hepatic impairment. Mirabegron was generally well tolerated in subjects with mild, moderate or severe renal or mild or moderate hepatic impairment in these single-dose studies.

Residual renal function (i.e. eGFR-MDRD or CL_{CR}-CG) was positively correlated with a decline in mirabegron CL_R, consistent with renal clearance being a substantial route (25 %) of elimination for mirabegron [20]. The relative contribution of active tubular secretion to renal elimination of mirabegron (as reflected in ER) did not significantly change with declining renal function. However, as expected for a drug that is largely non-renally cleared, the relationships between measures of renal function and other pharmacokinetic parameters such as unbound C_{max}, AUC_{∞} or CL/F were weak. This observation is consistent with previous findings that the major determinant of the variability in mirabegron pharmacokinetics is variability in the absorption process [20]. There is accumulating evidence from animal data and clinical studies that renal impairment, particularly severe impairment, can lead to alterations in bioavailability and non-renal clearance by affecting some pathways of intestinal and hepatic drug-metabolizing enzymes and transporters [21–24]. As intestinal efflux is thought to limit the absorption of mirabegron in healthy subjects [20], an increase in bioavailability as a result of reduced efflux transporter activity may account for part of the observed increase in mirabegron exposure in renally impaired subjects.

In subjects with hepatic impairment, no significant changes in mirabegron $t_{½}$ were observed, and thus the increased mirabegron plasma exposure with impaired hepatic function is likely explained by an increase in bioavailability rather than a decrease in non-renal clearance. Mirabegron AUC_{∞} or C_{max} did not strongly correlate with any of the measures of the Child-Pugh score, which may be because of small subject numbers. Also, although the Child-Pugh scale is the most commonly used method for classifying subjects with hepatic impairment in clinical trials, it was not developed for the purpose of predicting drug elimination capacity.

Mirabegron was not highly bound (71 %) to plasma proteins in healthy subjects, subjects with mild or moderate

hepatic impairment and subjects with mild renal impairment. Protein binding was slightly increased in subjects with moderate or severe renal impairment, which is ascribed to an increase in plasma AGP concentrations in these subjects. The increase in protein binding contributed only to a minor extent to the observed increase in mirabegron exposure in these subjects. *In vitro* data suggest that albumin is the major binding protein (34–37 % bound), followed by AGP (24–32 % bound) (data on file) [25]. In both studies, the unbound fraction of mirabegron was shown to be inversely related to AGP concentrations, whereas no clear correlation was observed with serum albumin levels. This may be related to the fact that AGP levels varied about four-fold between subjects, whereas variations in albumin levels were much smaller. No relationship was apparent between other pharmacokinetic parameters and AGP or albumin concentrations, indicating that small variations in the unbound fraction of mirabegron have minimal impact on the overall variability in the pharmacokinetics.

Renal impairment increased exposure to all circulating metabolites to a greater extent than for mirabegron itself. This observation is consistent with metabolism accounting for a larger percentage of overall elimination in subjects with renal impairment, to compensate for their reduced renal clearance of mirabegron. Higher metabolite concentrations are not expected to be clinically important because all metabolites are pharmacologically inactive (data on file) [26]. All metabolites appeared to show a progressive increase in $t_{½}$ and reduction in CL_R with declining renal function, suggesting that renal dysfunction affects their elimination, which is as expected for metabolites that, apart from M8 and M16, are not further metabolized and are excreted by the kidney [7]. The apparent increase of metabolite $t_{½}$ with declining renal function may also be attributed to improved definition of the terminal phase because of higher plasma concentrations in the moderate and severe impairment groups. There was no evidence of metabolites with a substantially longer $t_{½}$ than mirabegron in any of the renal function groups, suggesting that all eight circulating metabolites are most likely to show formation-rate-limited kinetics.

In subjects with moderate hepatic impairment, none of the metabolites demonstrated a consistent reduction in exposure relative to mirabegron despite the reduced apparent clearance of mirabegron, suggesting that the activity of the enzymes involved in mirabegron metabolism was not impaired.

5 Conclusion

Mirabegron AUC_∞ and C_{max} increased 118 and 92 %, respectively, in subjects with severe renal impairment and 65 and 175 %, respectively, in subjects with moderate hepatic impairment. Pharmacokinetic changes observed in subjects with mild or moderate renal impairment or mild hepatic impairment are of small magnitude and likely to be without clinical importance.

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