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ORIGINAL ARTICLE

Effect of mild or moderate hepatic impairment on the pharmacokinetics of risdiplam

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Aim: This phase I, multicentre, open-label, nonrandomised, parallel-group, two-part study aimed to evaluate the effect of mild to moderate hepatic impairment on the pharmacokinetics (PK), safety and tolerability of a single oral dose of risdiplam.

Methods: Adult subjects (aged 18-70 years) with mild (Child-Pugh Class A; Part 1) or moderate (Child-Pugh Class B; Part 2) hepatic impairment were matched with subjects with normal hepatic function on sex, age, body mass index and smoking status. Each subject received a single oral dose of 5 mg of risdiplam. Plasma concentrations of risdiplam and its metabolite M1 were measured and PK parameters were compared. Adverse events, laboratory abnormalities, vital signs and electrocardiogram measurements were assessed.

Results: After a single dose (5 mg) of risdiplam, the risdiplam PK parameters area under the plasma concentration-time curve from time zero to infinity and maximum observed plasma concentration were approximately 20% and 5% lower, respectively, in subjects with mild hepatic impairment and approximately 8% and 20% higher, respectively, in subjects with moderate hepatic impairment compared with subjects with normal hepatic function. These differences were not statistically significant; all 90% confidence intervals for geometric least squares-means ratios spanned unity. No new risdiplam-related safety findings were observed in subjects with mild or moderate hepatic impairment.

Conclusion: Mild or moderate hepatic impairment did not have a clinically relevant impact on the PK of risdiplam. Therefore, no dose adjustment is required in patients with mild or moderate hepatic impairment when receiving risdiplam.

KEYWORDS
hepatic impairment, pharmacokinetics, risdiplam

1 | INTRODUCTION

Spinal muscular atrophy (SMA) is a severe, progressive neuromuscular disease characterised by motor neuron degeneration leading to

The authors confirm that Thomas C. Marbury was the Principal Investigator for this paper and had direct clinical responsibility for the study participants.

muscle weakness. SMA is caused by reduced levels of the survival of motor neuron (SMN) protein due to mutations and/or deletions of the *SMN1* gene, which encodes full-length, functional SMN protein.[1–5] The *SMN1* gene is located on chromosome 5q11.2-q13.3, where another closely related gene, *SMN2*, is found that also encodes SMN protein.[4] However, due to alternative splicing of exon 7, most *SMN2*-encoded SMN protein is nonfunctional.[1,6] Risdiplam (EVRYSDI®) is a small-molecule, *SMN2* pre-mRNA splicing modifier that targets the central nervous system through its ability to penetrate the blood-brain barrier and peripheral tissues, leading to increased levels of functional SMN protein throughout the body.[7,8]

Orally administered risdiplam has been approved by the US Food and Drug Administration (FDA) for the treatment of patients with SMA aged 2 months and older,[9] and by the European Medicines Agency (EMA) for patients aged 2 months and older with a clinical diagnosis of type 1, 2 or 3 SMA or with one to four *SMN2* copies.[10] Risdiplam safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy are being investigated in a clinical development programme that consists of four studies in a broad population of individuals with SMA. The FIREFISH study (NCT02913482)[11,12] includes infants with type 1 SMA aged 1-7 months (at enrolment), SUNFISH (NCT02908685) includes patients with type 2 or 3 SMA aged 2-25 years (at enrolment), JEWELFISH is evaluating patients with SMA aged 6 months−60 years (at enrolment) who previously received RG7800 (RO6885247), nusinersen (SPINRAZA®), olesoxime or onasemnogene abeparvovec (ZOLGENSMA®), and RAINBOWFISH (NCT03779334) includes infants from birth to 6 weeks of age (at first dose) with genetically diagnosed presymptomatic SMA.

Preclinical PK data have demonstrated that risdiplam is freely distributed into the central nervous system and peripheral tissues (including muscle, blood and brain) in animals via high passive permeability.[8] Plasma protein binding (PPB) in humans was assessed in vitro, with a free fraction of 11% for risdiplam and 7% for the metabolite M1. Risdiplam is predominantly bound to serum albumin, without any binding to alpha-1 acid glycoprotein.[9] In a study of healthy adult subjects, risdiplam exhibited linear PK over the dose range 0.6-18 mg, with a mean terminal half-life of 40-69 hours.[13] The PK profile of risdiplam has been characterised in paediatric patients with SMA in the ongoing FIREFISH and SUNFISH studies, and body weight and age have been identified as significant covariates.[9,10] Risdiplam is metabolised by flavin monooxygenase (FMO) 1 and 3, and cytochrome P450s 1A1, 2J2, 3A4 and 3A7. The majority (83%) of drug-related material circulating in plasma was the parent drug; the major circulating metabolite was the pharmacologically inactive metabolite M1.[9,10] Hepatic impairment can reduce the clearance of drugs eliminated by hepatic metabolism or biliary excretion and affect protein binding thereby influencing the process of distribution and elimination.[14] As risdiplam is predominantly metabolised in the liver, we sought to determine the impact of hepatic impairment on the metabolism of risdiplam. Therefore, we conducted a phase I, multicentre, open-label, nonrandomised, parallel-group, two-part study to evaluate the effect of mild to moderate hepatic impairment on the plasma PK, safety and tolerability of a single oral dose of 5 mg of risdiplam. In part 1 of the study, subjects with mild hepatic impairment were compared with subjects with normal liver function prior to the start of part 2. In part 2, subjects with moderate hepatic impairment were compared with subjects with normal liver function.

What is already known about this subject

- Risdiplam is primarily metabolised by the hepatic enzymes FMO1 and 3 and CYPs 1A1, 2J2, 3A4 and 3A7.
- Hepatic impairment can reduce the clearance of drugs eliminated by hepatic metabolism or biliary excretion.
- There is a need to develop dosing recommendations for risdiplam in individuals with hepatic impairment.

What this study adds

- No clinically relevant impact of mild or moderate hepatic impairment on the pharmacokinetics of a single oral dose of 5 mg of risdiplam was observed, compared with normal hepatic function.
- No new safety concerns were identified in individuals with mild or moderate hepatic impairment.
- Risdiplam dose adjustments are not required for mild or moderate hepatic impairment.

2 | METHODS

2.1 | Study oversight

All subjects provided written informed consent. All sites received approval from an Institutional Review Board (IRB) prior to study initiation. This study was conducted and monitored in accordance with the ethical principles and guidelines of the Declaration of Helsinki,[15] Council for International Organizations of Medical Sciences and International Conference on Harmonisation Good Clinical Practice,[16] and applicable laws or regulations.

2.2 | Study design and population

In part 1 of this two-part study, subjects with mild hepatic impairment and matched healthy subjects with normal hepatic function were enrolled. Preliminary PK, safety and tolerability data were used to support the dose selection for part 2, which included the moderate hepatic impairment cohort. In part 2, subjects with moderate hepatic impairment and matched healthy individuals with normal hepatic function were enrolled. Subjects received a single oral dose of 5 mg of risdiplam as drinking solution on day 1 after an overnight fast of at

least 8 hours. The total duration of study participation for each subject was approximately 8 weeks.

The primary objective of this study was to determine the effect of mild or moderate hepatic impairment on the plasma PK of a single dose of risdiplam compared with matched subjects with normal hepatic function. The secondary objective was to determine the effect of mild or moderate hepatic impairment on the safety and tolerability of a single dose of risdiplam compared with matched participants with normal hepatic function.

All subjects were required to be adult (aged 18-70 years) with a body mass index (BMI) of 18-36 kg/m^2 and a body weight of ≥50 kg. Subjects with normal hepatic function were matched to subjects with mild or moderate hepatic function in terms of sex, age (±10 years), BMI (±15%) and smoking status. These subjects were also required to be in good health, as determined by no clinically significant findings from medical history, physical examination, 12-lead electrocardiogram (ECG), vital sign measurements and clinical laboratory evaluations. A healthy subject could match one subject each in both the mild and moderate hepatic impairment groups. Subjects with hepatic impairment were eligible if they had documented chronic stable liver disease at screening (Child−Pugh Class A and B for mild and moderate hepatic impairment cohorts, respectively; Table 1), a diagnosis of cirrhosis due to parenchymal liver disease and were on a stable medication regimen, defined as not starting new drug(s) or changing drug dose(s) within 3 months of administration of risdiplam (day 1). Subjects were excluded if they were pregnant/lactating or of childbearing potential, had significant history or clinical manifestation of any metabolic, allergic, dermatological, renal, haematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine or psychiatric disorder, as determined by the investigator, or had previously completed or withdrawn from this study or any other study investigating risdiplam, and had previously received risdiplam.

2.3 | Study assessments and endpoints

Blood samples for measurement of risdiplam and its metabolite, M1, were taken pre-dose and 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504 and 552 hours post-dose. Blood samples were also collected and analysed for unbound risdiplam and unbound metabolite M1 concentrations at 3, 24 and 144 hours post-dose. Plasma concentrations of risdiplam and metabolite M1 were assayed by a specific and validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, validated according to current regulatory guidelines[17,18] in the concentration range 0.250-250 ng/mL. After sample preparation by protein precipitation with ethanol/acetonitrile, gradient separation was performed using a C18 column and mobile phases composed of aqueous ammonium carbonate, acetonitrile, 2-propanol and acetone. Detection was accomplished using heated electrospray MS/MS in positive ion multiple reaction monitoring mode. Stable isotope-labelled analogues of risdiplam and M1 were used as internal standards. During study sample analysis, the precision (CV) in quality control (QC) samples ranged from 1.7% to 7.6% for risdiplam and from 2.2% to 6.1% for M1. The accuracy ranged from 98.4% to 105.1% and from 97.3% to 106.4% for risdiplam and M1, respectively. No effect

TABLE 1 Child-Pugh classification for hepatic impairment

Assessment	1 point	2 points	3 points
Hepatic encephalopathy grade[a]	0	1 or 2[b]	3 or 4[b]
Ascites[c]	Absent	Slight	Moderate
Serum bilirubin, mg/dL (μmol/L)	<2 (<34)	2-3 (34-50)	>3 (>50)
Serum albumin, g/dL (g/L)	>3.5 (>35)	2.8-3.5 (28-35)	<2.8 (<28)
International normalised ratio	<1.7	1.7-2.3	>2.3
Total score	**Child-Pugh class**	**Severity**	
5 or 6 points	A	Mild impairment	
7-9 points	B	Moderate impairment	

[a]Hepatic encephalopathy grading:
- Grade 0: normal consciousness, personality, neurological examination, or normal electroencephalogram.
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, or 5 cps waves.
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, or slow triphasic waves.
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, or slower waves.
- Grade 4: unarousable coma, no personality/behaviour, decerebrate, or slow 2 to 3 cps delta activity.

[b]Participants with hepatic encephalopathy grade ≥2 were not enrolled into the study.

[c]Participants with evidence of severe ascites were not enrolled into the study. Ascites grading:
- Absent: no ascites was detectable by manual examination or by ultrasound investigation (if performed).
- Slight: ascites palpitation doubtful, but ascites measurable by ultrasound investigation (if performed).
- Moderate: ascites detectable by palpitations and by ultrasound investigation (if performed).
- Severe: necessity of paracentesis; did not respond to treatment.

Abbreviations: cps, cycles per second.

of hepatic-impaired patient plasma on the analytical method was observed as determined by analysis of control matrix and spiked QCs. The reproducibility during the reanalysis of 10% of the incurred samples was well within acceptance criteria: 97.4% of samples showed variability less than 20%. Plasma concentrations of unbound risdiplam and unbound metabolite M1 were determined by equilibrium dialysis followed by LC-MS/MS analysis, with diazepam used as a control to verify the correctness of dialysis. The precision ranged from 2.5% to 7.3% for risdiplam, 3.0% to 4.2% for M1 and 2.6% to 5.6% for diazepam, while the accuracy was within 100.8-102.4% for risdiplam, 99.9-101.1% for M1 and 98.4-103.2% for diazepam. The PPB recovery was within the predefined acceptance criteria (70-120%) for risdiplam, M1 and diazepam. The fraction unbound for diazepam was in the expected range 0.35-0.75%.

The PK parameters were determined from the plasma concentrations of risdiplam and metabolite M1 using noncompartmental methods with Phoenix WinNonlin (Version 8.1; Certara USA, Inc.). Primary PK parameters for risdiplam and metabolite M1 were area under the plasma concentration−time curve from time zero to infinity (AUC_{inf}) and maximum observed plasma concentration (C_{max}). Secondary PK parameters for risdiplam and its metabolite M1 were AUC from time zero to the last measurable concentration (AUC_{last}; used for PK comparison if AUC_{inf} could not be estimated with sufficient accuracy), time of the maximum observed plasma concentration (T_{max}), apparent plasma terminal elimination half-life ($t_{1/2}$), percentage of AUC due to extrapolation (%AUC_{extrap}) and apparent terminal elimination rate constant (λ_z). Secondary PK parameters assessed for risdiplam only were apparent total plasma clearance (CL/F), fraction of unbound drug, unbound AUC_{last} ($AUC_{last,u}$), unbound AUC_{inf} ($AUC_{inf,u}$), unbound C_{max} ($C_{max,u}$) and unbound CL/F (CL/F_u). The metabolite ratio (MR) was calculated as the molecular weight-adjusted metabolite-to-parent ratio for AUC_{inf}, C_{max} and AUC_{last} for the metabolite M1 versus the parent risdiplam. Evaluated secondary safety endpoints included incidence and severity of treatment-emergent adverse events (TEAEs), defined as an adverse event (AE) that occurred post-dose or that was present pre-dose and became more severe post-dose, incidence of laboratory abnormalities (haematology, clinical chemistry, coagulation and urinalysis), vital sign measurements, 12-lead electrocardiogram (ECG) parameters and physical examinations.

2.4 | Statistical methods

All subjects who received a dose of risdiplam were included in the safety analyses and all of these who had evaluable PK data were included in the PK analyses. An analysis of variance (ANOVA)[19] including the factor "hepatic impairment" (ie, mild, moderate or none) was used to estimate the effect of hepatic impairment on the primary PK parameters, which were log transformed prior to analysis. Data analysis was performed using SAS® Version 9.4. Statistical significance was deemed where the 90% confidence interval (CI) for the ratio of geometric least squares means (GLSM) was completely contained within the predefined interval of 0.80-1.25; this procedure was equivalent to Schuirmann's two one-sided tests at the 0.05 level of significance. Ratios of GLSM and the corresponding 90% CIs of AUC_{inf} and C_{max} of risdiplam between the groups of hepatically impaired participants and healthy participants with normal hepatic function were calculated. Data from parts 1 and 2 were analysed separately, and for each comparison only the matched control subjects were included. The secondary PK parameters were not participant to inferential statistical analysis.

No formal sample size calculation was performed; sample size determination was based on historical experience with such studies and per health authority guidelines.[20] The planned number of subjects for enrolment was up to 32, including eight subjects per hepatic impairment function group (ie, mild or moderate) and 8-16 subjects with normal hepatic function.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.

3 | RESULTS

3.1 | Subjects

Eight subjects with mild hepatic impairment (part 1) and eight subjects with moderate hepatic impairment (part 2) were enrolled and completed the study. Overall, 10 subjects with normal hepatic function were enrolled and completed the study: six of them were matched to subjects in both the mild and moderate hepatic impairment groups, two were matched to two subjects with mild hepatic impairment, and the remaining two were matched to two subjects with moderate hepatic impairment. Overall, demographic characteristics were similar across the hepatic impairment groups and controls (Table 2).

Seven of the eight subjects in the mild hepatic impairment group had an aetiology of hepatitis C, and for one subject it was alcohol induced. Two subjects in the moderate hepatic impairment group had an aetiology of hepatitis C, five listed alcohol and one subject listed hepatitis C and alcohol.

In the mild impairment group, one subject with a BMI of 33 had fatty liver (hepatic steatosis) in their medical history, with an aetiology of hepatitis C. Two subjects (one in the mild and one in the moderate group) reported portal hypertension − none had a shunt, which would have been exclusionary.

All of the subjects in the mild hepatic impairment group had ascites and albumin scores of 1 at screening and day −1. Six of the subjects in the moderate hepatic impairment group had an ascites score

TABLE 2 Demographic characteristics at baseline

	Part 1		Part 2	
	Mild hepatic impairment (n = 8)	Normal hepatic function (n = 8)	Moderate hepatic impairment (n = 8)	Normal hepatic function (n = 8)
Age, years, mean (range)	62 (56-69)	60 (53-67)	57 (44-64)	57 (45-67)
Gender, n (%)				
Female	4 (50)	4 (50)	4 (50)	4 (50)
Male	4 (50)	4 (50)	4 (50)	4 (50)
Race, n (%)				
Black or African American	2 (25)	0	1 (12.5)	0
White	6 (75)	8 (100)	7 (87.5)	8 (100)
Weight, kg, mean (range)	86.6 (61.0-103.2)	81.7 (60.0-105.7)	82.4 (68.1-106.4)	82.0 (60.0-105.7)
BMI, kg/m^2, mean (range)	31.1 (24.4-35.8)	29.1 (26.0-32.6)	29.2 (24.6-33.1)	29.4 (25.7-33.2)

BMI, body mass index.

TABLE 3 Primary PK parameters for risdiplam and metabolite M1: Part 1

	Risdiplam		Metabolite M1	
	Mild hepatic impairment (n = 8) Test	Normal hepatic function (n = 8) Reference	Mild hepatic impairment (n = 8) Test	Normal hepatic function (n = 8) Reference
AUC_{inf}, h*ng/mL				
GLSM	792	987	222	263
Ratio of GLSMs, test:reference (90% CI)	0.802 (0.627-1.03)		0.842 (0.588-1.21)	
C_{max}, ng/mL				
GLSM	21.7	22.8	3.73	3.92
Ratio of GLSMs, test:reference (90% CI)	0.950 (0.695-1.30)		0.953 (0.715-1.27)	

Abbreviations: AUC_{inf}, area under the plasma concentration−time curve from time zero to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; GLSM, geometric least squares mean; PK, pharmacokinetics.

of 2 (slight), and two subjects had a score of 3 (moderate or severe). At screening, seven subjects in the moderate group had an albumin score of 1 and one had a score of 2. At day −1, four subjects had an albumin score of 1 and four had a score of 2.

3.2 | PK

All participants from parts 1 and 2 were included in the PK analyses. Following administration of 5 mg of risdiplam, AUC_{inf} and C_{max} were approximately 20% (ratio of GLSM 0.802, 90% CI 0.627-1.03) and 5% (ratio of GLSM 0.950, 90% CI 0.695-1.30) lower, respectively, in subjects with mild hepatic impairment compared with subjects with normal hepatic function (Table 3). Subjects with moderate hepatic impairment had AUC_{inf} and C_{max} approximately 8% (ratio of GLSM 1.08, 90% CI 0.830-1.39) and 20% (ratio of GLSM 1.20, 90% CI 0.962-1.49) higher, respectively, compared with subjects with normal hepatic function (Table 4). These differences in AUC_{inf} and C_{max} were deemed not statistically significant and not clinically relevant.

The mean plasma-concentration versus time profiles of risdiplam and its metabolite M1 after administration of 5 mg of risdiplam appeared similar overall in subjects with mild or moderate hepatic impairment compared with normal hepatic function (Figure 1). Risdiplam concentration versus time profiles were characterised by a steady absorption phase (median T_{max} = 4 hours for both parts 1 and 2) in subjects with normal hepatic function (Tables 5 and 6). Subjects with mild hepatic impairment had the same median T_{max} of 4 hours, while those with moderate hepatic impairment had shorter median T_{max} of 2 hours.

TABLE 4 Primary PK parameters for risdiplam and metabolite M1: Part 2

	Risdiplam		Metabolite M1	
	Moderate hepatic impairment (n = 8) Test	Normal hepatic function (n = 8) Reference	Moderate hepatic impairment (n = 8) Test	Normal hepatic function (n = 8) Reference
AUC_{inf}, h*ng/mL				
GLSM	1040	971	261	275
Ratio of GLSMs, test: reference(90% CI)	1.08 (0.830-1.39)		0.947 (0.740-1.21)	
C_{max}, ng/mL				
GLSM	29.9	25.0	4.10	4.13
Ratio of GLSMs, test: reference(90% CI)	1.20 (0.962-1.49)		0.991 (0.810-1.21)	

Abbreviations: AUC_{inf}, area under the plasma concentration−time curve from time zero to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; GLSM, geometric least squares mean; PK, pharmacokinetics.

Other secondary PK parameters for risdiplam and/or metabolite M1 are also summarised in Tables 5 and 6. In part 1, risdiplam geometric mean $t_{1/2}$ was longer for subjects with normal hepatic function (55.0 hours) than for those with mild hepatic impairment (41.3 hours); individual values ranged from 47.1 to 71.9 hours for subjects with normal hepatic function and from 30.3 to 59.6 hours for those with mild hepatic impairment. In part 2, subjects with normal hepatic function had slightly longer geometric mean $t_{1/2}$ compared with those with moderate hepatic impairment (49.9 hours versus 45.6 hours, respectively); individual values ranged from 30.1 to 71.9 hours for subjects with normal hepatic function and from 30.5 to 69.0 hours for those with moderate hepatic impairment. The metabolite M1 appeared slowly in plasma, with a median T_{max} of 10 hours and 11 hours in parts 1 and 2, respectively, for subjects with normal hepatic function, 10 hours for those with mild hepatic impairment and 24 hours for those with moderate hepatic impairment. The geometric mean $t_{1/2}$ of metabolite M1 was in the same range across all groups. Similar to parent risdiplam, exposure parameters for the metabolite M1 were slightly higher for normal hepatic function participants than for mild impaired participants (approximately 16% for AUC_{inf} [ratio of GLSM 0.842, 90% CI 0.588-1.21] and 5% for C_{max} [ratio of GLSM 0.953, 90% CI 0.715-1.27]). The ratios for AUC_{inf} and C_{max} were very close to 1 for subjects with moderately impaired hepatic function versus those with normal function: 0.947 (90% CI 0.740-1.21) and 0.991 (90% CI 0.810-1.21), respectively. These differences were deemed not statistically significant. The MRs for AUC_{last}, AUC_{inf} and C_{max} ($MR_{AUClast}$, MR_{AUCinf} and MR_{Cmax}) were similar between normal hepatic and mild hepatic impairment groups in part 1, and between normal hepatic and moderate hepatic impairment groups in part 2.

The unbound free fraction for risdiplam at 3, 24 and 144 hours post-dose ranged from 11.2% to 12.8% (geometric mean) for subjects with normal hepatic function, from 12.9% to 13.7% for subjects with mild hepatic impairment and from 12.6% to 13.2% for subjects with moderate hepatic impairment. For M1, the free fraction ranged from 7.9% to 9.4% for subjects with normal hepatic function, from 9.0% to 10.1% for subjects with mild hepatic impairment and from 8.9% to 10.1% for subjects with moderate hepatic impairment. The exposure parameters for unbound risdiplam were comparable between subjects with normal hepatic function and those with mild or moderate impairment.

3.3 | Safety

All participants of parts 1 and 2 were included in the safety analyses. There were no findings of clinical concern in clinical laboratory evaluations, vital signs, ECGs or physical examinations. The incidences and characterisation of the TEAEs are summarised in Table 7. In part 1, in the mild hepatic impairment group, five subjects (62.5%) experienced seven AEs in total. Four subjects (50%) experienced five AEs that were considered related to risdiplam; four of these events were gastrointestinal disorders (vomiting [n = 2], diarrhoea [n = 1] and dyspepsia [n = 1]), and one was skin pruritus. One event of vomiting reached a maximum moderate intensity, occurring 9 days after dose administration; the rest of the TEAEs reported were of mild intensity. There were no AEs reported in the normal hepatic function group. No deaths, withdrawals from the study due to AEs or serious AEs (SAEs) were reported in part 1. All AEs occurring in part 1 resolved by the end of the study. In part 2, in the moderate hepatic impairment group, one subject (12.5%) experienced one SAE, which resolved by the end of the study. This event was gastrointestinal haemorrhage, which was considered to be mild in intensity and not related to risdiplam, but potentially related to a medical history of oesophageal varices and oesophagitis.

4 | DISCUSSION

This phase I, multicentre, open-label, nonrandomised, parallel-group, two-part study evaluating a single oral dose of 5 mg of risdiplam in

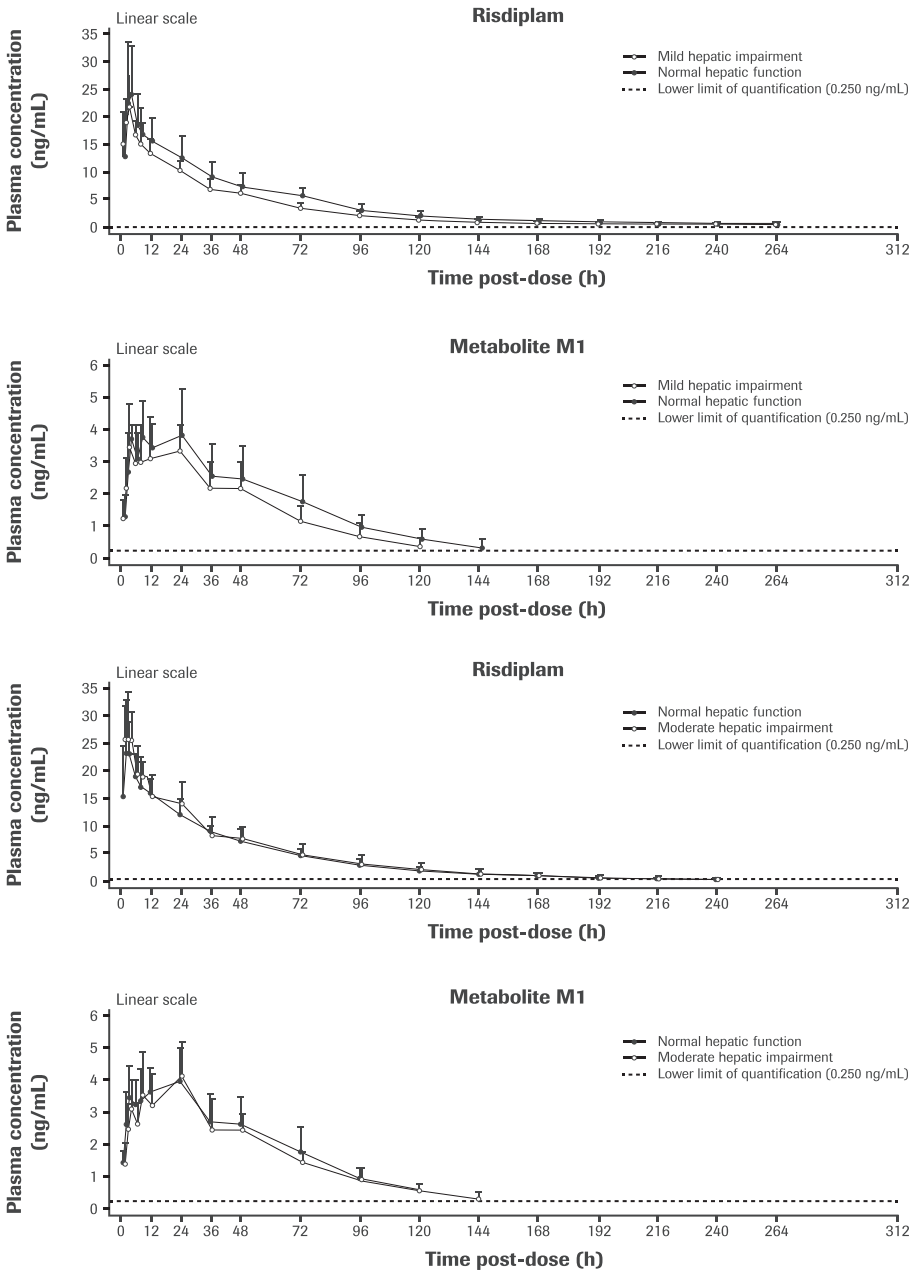

FIGURE 1 Mean (+SD) plasma concentration-time profiles of risdiplam and metabolite M1 in part 1 (A) and part 2 (B). SD, standard deviation

subjects with mild or moderate hepatic impairment and subjects with normal liver function demonstrated no impact of hepatic impairment on risdiplam PK. Differences in AUC_{inf} and C_{max} between participants with mild or moderate hepatic impairment compared with normal hepatic function were deemed not statistically significant as all 90% CIs for GLSM ratios spanned unity. The remaining PK parameters were also similar between cohorts. The plasma concentration-time profiles of risdiplam were comparable overall in subjects with varying degrees of hepatic impairment. Time to peak concentration appeared to be more rapid for those with moderate impairment, though with overlapping ranges versus the other groups. Consistent with the observed PK of the total risdiplam concentrations, the exposure parameters for unbound risdiplam were, in general, comparable between subjects with normal hepatic function and mild or moderate impairment. The unbound free fraction for risdiplam and its metabolite M1 was similar for all groups of hepatic function and consistent with the in vitro measurement. The gastrointestinal AEs reported for three subjects with mild hepatic impairment each resolved without requiring treatment: onset of diarrhoea on day 8 post-dose resolved on day 12, onset of dyspepsia on day 8 resolved on day 12, onset of vomiting on days 9 and 10 both resolved on the day of onset. These events were not considered to have impacted PK parameters as they occurred at least 1 week after risdiplam administration.

Safety data for risdiplam in studies of healthy subjects demonstrated a favourable safety profile for single oral doses up to 18 mg.[9,10] A single oral dose of 5 mg of risdiplam was chosen for this study to ensure sufficient safety margins in hepatically impaired subjects and to provide enough exposure to adequately characterise the

TABLE 5 Secondary PK parameters for risdiplam and metabolite M1: Part 1

Parameter	Risdiplam		Metabolite M1	
	Mild hepatic impairment (n = 8)	Normal hepatic function (n = 8)	Mild hepatic impairment (n = 8)	Normal hepatic function (n = 8)
AUC_{last}, h*ng/mL	773 (20.3)	961 (35.9)	197 (39.1)	245 (47.1)
$\%AUC_{extrap}$, %	2.3 (29.1)	2.5 (32.8)	7.5 (54.0)	6.3 (38.7)
T_{max}, median (range), h	4.0 (2.0-4.0)	4.0 (2.0-4.0)	10.0 (4.0-24.0)	10.0 (4.0-24.0)
CL/F, L/h	6.3 (20.0)	5.1 (35.2)	...	...
$t_{1/2}$, h	41.3 (29.1)	55.0 (16.2)	32.9 (19.1)	38.2 (18.7)
λ_z, h^{-1}	0.0168 (29.1)	0.0126 (16.2)	0.0211 (19.1)	0.0182 (18.7)
$MR_{AUClast}$	...	...	0.244 (24.8)	0.245 (13.8)
MR_{AUCinf}	...	...	0.258 (22.7)	0.255 (12.0)
MR_{Cmax}	...	...	0.165 (29.4)	0.164 (15.5)
$AUC_{last,u}$, h*ng/mL	104 (20.3)	116 (37.5)	...	...
$AUC_{inf,u}$, h*ng/mL	107 (20.2)	119 (36.8)	...	...
$C_{max,u}$, ng/mL	2.92 (23.4)	2.74 (52.6)	...	...
CL/F_u, L/h	46.9 (20.2)	42.1 (36.8)	...	...

Geometric mean (CV%) data are presented, unless otherwise stated.
Abbreviations: λ_z, apparent terminal elimination rate constant; $\%AUC_{extrap}$, percentage of area under the plasma concentration-time curve due to extrapolation; $AUC_{inf,u}$, unbound area under the plasma concentration-time curve from time zero to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to the last measurable concentration; $AUC_{last,u}$, unbound AUC_{last}; CL/F, apparent total plasma clearance; CL/F_u, unbound CL/F; $C_{max,u}$, unbound maximum observed plasma concentration; CV, coefficient of variation; $t_{1/2}$, apparent plasma terminal elimination half-life; MR_{AUCinf}, metabolic ratio based on AUC_{inf}; $MR_{AUClast}$, metabolic ratio based on AUC_{last}; MR_{Cmax}, metabolic ratio based on C_{max}; T_{max}, time of the maximum observed plasma concentration.

TABLE 6 Secondary PK parameters for risdiplam and metabolite M1: Part 2

Parameter	Risdiplam		Metabolite M1	
	Moderate hepatic impairment (n = 8)	Normal hepatic function (n = 8)	Moderate hepatic impairment (n = 8)	Normal hepatic function (n = 8)
AUC_{last}, h*ng/mL	1020 (29.7)	947 (31.2)	243 (24.9)	259 (33.9)
$\%AUC_{extrap}$, %	1.9 (33.5)	2.4 (30.5)	6.6 (28.8)	5.7 (23.6)
T_{max}, median (range), h	2.0 (1.0-4.0)	4.0 (1.0-4.0)	24.0 (10.0-24.0)	11.0 (4.0-24.0)
CL/F, L/h	4.8 (29.2)	5.2 (30.8)	...	...
$t_{1/2}$, h	45.6 (28.0)	49.9 (28.1)	34.5 (24.3)	35.0 (21.6)
λ_z, h^{-1}	0.0152 (28.0)	0.0139 (28.1)	0.0201 (24.3)	0.0198 (21.6)
$MR_{AUClast}$	...	...	0.227 (16.8)	0.262 (10.0)
MR_{AUCinf}	...	...	0.239 (16.8)	0.271 (10.3)
MR_{Cmax}	...	...	0.131 (16.3)	0.158 (15.0)
$AUC_{last,u}$, h*ng/mL	132 (31.4)	115 (32.5)	...	...
$AUC_{inf,u}$, h*ng/mL	134 (31.0)	118 (32.0)	...	...
$C_{max,u}$, ng/mL	3.84 (20.4)	3.04 (36.3)	...	...
CL/F_u, L/h	37.2 (31.0)	42.2 (32.0)	...	...

Geometric mean (CV%) data are presented, unless otherwise stated.
Abbreviations: λ_z, apparent terminal elimination rate constant; $\%AUC_{extrap}$, percentage of area under the plasma concentration-time curve due to extrapolation; $AUC_{inf,u}$, unbound area under the plasma concentration-time curve from time zero to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to the last measurable concentration; $AUC_{last,u}$, unbound AUC_{last}; CL/F, apparent total plasma clearance; CL/F_u, unbound CL/F; $C_{max,u}$, unbound maximum observed plasma concentration; CV, coefficient of variation; $t_{1/2}$, apparent plasma terminal elimination half-life; MR_{AUCinf}, metabolic ratio based on AUC_{inf}; $MR_{AUClast}$, metabolic ratio based on AUC_{last}; MR_{Cmax}, metabolic ratio based on C_{max}; T_{max}, time of the maximum observed plasma concentration.

TABLE 7 Summary of TEAEs

n (%)	Part 1		Part 2	
	Mild hepatic impairment (n = 8)	Normal hepatic function (n = 8)	Moderate hepatic impairment (n = 8)	Normal hepatic function (n = 8)
Total number of TEAEs	7	0	1	0
Total number of participants with at least one:				
AE	5 (62.5)	0	1 (12.5)	0
SAE	0	0	1 (12.5)	0
Study drug-related TEAE	4 (50.0)	0	0	0
Total number of TEAEs by preferred term				
Vomiting	2 (25.0)	0	0	0
Diarrhoea	1 (12.5)	0	0	0
Dyspepsia	1 (12.5)	0	0	0
Ear pain	1 (12.5)	0	0	0
Chest discomfort	1 (12.5)	0	0	0
Pruritus	1 (12.5)	0	0	0
Upper gastrointestinal haemorrhage	0	0	1 (12.5)	0

Events were coded using Medical Dictionary for Regulatory Activities (Version 21.1).
Abbreviations: AE, adverse event; SAE, serious AE; TEAE, treatment-emergent AE.

PK of risdiplam. In this study, the single dose of 5 mg of risdiplam was indeed considered safe in subjects with mild and moderate hepatic impairment. With the exception of one case of moderate-intensity vomiting, all TEAEs were of mild intensity. Four events in part 1 of the study were considered related to the study drug, but all of these events were mild and resolved by the end of the study. One SAE was reported in part 2 of the study but was not considered related to risdiplam. These safety findings of risdiplam in subjects with hepatic impairment are consistent with risdiplam safety data in a study of healthy volunteers in which no deaths, moderate or severe AEs, withdrawals due to AEs or SAEs were reported. All AEs resolved within a short period without sequelae.[13]

Risdiplam is almost completely eliminated via metabolism in the liver; therefore it may be surprising that no effect of hepatic impairment on risdiplam PK was observed in this study. Although risdiplam can be metabolised by a number of enzymes, including FMO1 and FMO3 and cytochrome P450s 1A1, 2J2, 3A4 and 3A7, it is metabolised approximately 75% by FMO3, a metabolic enzyme that is not as well understood as the cytochrome P450 family.[21] Based on the data obtained in this study, it can be hypothesised that FMO3 is not sensitive to mild and moderate hepatic impairment (per the Child–Pugh classification), and that the metabolic capacity of FMO3 remains unchanged in these patients.

4.1 | Limitations

A limitation of this study is the small sample size in each of the different groups, although the chosen sample size is consistent with regulatory guidelines for the detection of clinically relevant PK differences (at least eight subjects in the control and moderate impairment arms).[20] Therefore, caution should be used when generalising the PK and safety results to patients with different characteristics of hepatic impairment, in particular more severe hepatic impairment (Child-Pugh Class C). Extrapolation of the results of this study to the more severe stage of hepatic impairment is not advised.

5 | CONCLUSIONS

In this study, the PK profile and safety of risdiplam were assessed in subjects with mild or moderate hepatic impairment compared with subjects with normal hepatic function. Following the administration of a single oral dose of 5 mg of risdiplam, exposures (AUC_{inf} and C_{max}) were approximately 20% and 5% lower, respectively, in subjects with mild hepatic impairment and were approximately 8% and 20% higher, respectively, in subjects with moderate hepatic impairment than in matched healthy control subjects. The magnitude of these changes was not considered to be clinically meaningful. The unbound free fraction and the exposure parameters for unbound risdiplam were similar across the groups. The MRs for AUC_{last}, AUC_{inf} and C_{max} for subjects with hepatic impairment were comparable to those with normal liver function, ie, the extent of metabolism was not different for subjects with hepatic impairment versus subjects with normal hepatic function. Therefore, no dose adjustment of risdiplam is required in patients with mild or moderate hepatic impairment, and risdiplam's prescribing information has been updated accordingly.

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CONTRIBUTORS

H.K., H.A., I.A., K.H., B.J., A.Y. and A.G. contributed to the study design, data analysis and data interpretation. T.M. contributed to the study design, conduct of the study, data acquisition and data interpretation. All authors participated in the critical revision of the manuscript and approved the manuscript to be submitted for publication.

CONFLICT OF INTEREST

H.K., K.H., B.J. and A.Y. are current employees of and hold shares in F. Hoffmann-La Roche Ltd. H.A. and I.A. have no conflicts of interest to declare. T.M. is an employee and equity owner of the Orlando Clinical Research Center. A.G. is a current employee of F. Hoffmann-La Roche Ltd.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com).

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REFERENCES

1. Lefebvre S, Bürglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell*. 1995;80(1):155-165. doi:10.1016/0092-8674(95)90460-3
2. Burghes AH. When is a deletion not a deletion? When it is converted. *Am J Hum Genet*. 1997;61(1):9-15. doi:10.1086/513913
3. Liu Q, Dreyfuss G. A novel nuclear structure containing the survival of motor neurons protein. *EMBO J*. 1996;15(14):3555-3565. doi:10.1002/j.1460-2075.1996.tb00725.x
4. McAndrew PE, Parsons DW, Simard LR, et al. Identification of proximal spinal muscular atrophy carriers and patients by analysis of SMNT and SMNC gene copy number. *Am J Hum Genet*. 1997;60(6):1411-1422. doi:10.1086/515465
5. Wirth B, Herz M, Wetter A, et al. Quantitative analysis of survival motor neuron copies: identification of subtle *SMN1* mutations in patients with spinal muscular atrophy, genotype-phenotype correlation, and implications for genetic counseling. *Am J Hum Genet*. 1999;64(5):1340-1356. doi:10.1086/302369
6. Lorson CL, Hahnen E, Androphy EJ, Wirth B. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. *Proc Natl Acad Sci USA*. 1999;96(11):6307-6311. doi:10.1073/pnas.96.11.6307
7. Ratni H, Ebeling M, Baird J, et al. Discovery of risdiplam, a selective survival of motor neuron-2 *(SMN2)* gene splicing modifier for the treatment of spinal muscular atrophy (SMA). *J Med Chem*. 2018;61(15):6501-6517. doi:10.1021/acs.jmedchem.8b00741
8. Poirier A, Weetall M, Heinig K, et al. Risdiplam distributes and increases SMN protein in both the central nervous system and peripheral organs. *Pharmacol Res Perspect*. 2018;6(6):e00447. doi:10.1002/prp2.447
9. Genentech. EVRYSDI (risdiplam) US prescribing information. Accessed July, 2021. https://www.gene.com/download/pdf/evrysdi_prescribing.pdf
10. Roche. Evrysdi (risdiplam) summary of product characteristics. Accessed June, 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-product-information_en.pdf
11. Baranello G, Darras BT, Day JW, et al. Risdiplam in Type 1 spinal muscular atrophy. *N Engl J Med*. 2021;384(10):915-923. doi:10.1056/NEJMoa2009965
12. Darras BT, Masson R, Mazurkiewicz-Bełdzińska M, et al. Risdiplam-treated infants with Type 1 spinal muscular atrophy versus historical controls. *N Engl J Med*. 2021;385(5):427-435. doi:10.1056/NEJMoa2102047
13. Sturm S, Günther A, Jaber B, et al. A Phase 1 healthy male volunteer single escalating dose study of the pharmacokinetics and pharmacodynamics of risdiplam (RG7916, RO7034067), a *SMN2* splicing modifier. *Br J Clin Pharmacol*. 2018;85(1):181-193. doi:10.1111/bcp.13786
14. Palatini P, De Martin S. Pharmacokinetic drug interactions in liver disease: An update. *World J Gastroenterol*. 2016;22(3):1260-1278. doi:10.3748/wjg.v22.i3.1260
15. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. June 2021. Available from: https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2008.pdf
16. International Conference on Harmonisation (ICH). Integrated Addendum To ICH E6(R1): Guideline For Good Clinical Practice E6(R2). Accessed June 2021. Available from: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
17. European Medicines Agency. Guideline on bioanalytical method validation. 2021. Accessed February 2022. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-bioanalytical-method-validation_en.pdf
18. US Food and Drug Administration. Guidance for Industry: Bioanalytical Method Validation 2018. Accessed February 2022. Available from: https://www.fda.gov/media/70858/download
19. Snedecor G, Cochran WG. *Statistical Methods*. 8thed. Iowa State University Press; 1989.
20. US Food and Drug Administration. Guidance for industry pharmacokinetics in patients with impaired hepatic function: Study design, data

analysis, and impact on dosing and labeling. Accessed June 2021. Available from: https://www.fda.gov/media/71311/download

21. Cleary Y, Gertz M, Grimsey P, et al. Model-based drug-drug interaction extrapolation strategy from adults to children – risdiplam in pediatric patients with spinal muscular atrophy. *Clin Pharmacol Therap*. 2021;110(6):1547-1557. doi:10.1002/cpt.2384

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