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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics, Tolerability, and Safety of Esmethadone in Subjects with Chronic Kidney Disease or Hepatic Impairment

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Abstract

Background and Objectives Esmethadone (dextromethadone; d-methadone; S-methadone (+)-methadone; REL-1017) is a low potency *N*-methyl-$_D$-aspartate (NMDA) receptor channel blocker that showed a rapid and sustained adjunctive antidepressant effects in patients with major depressive disorder with inadequate response to ongoing serotonergic antidepressant treatment. Previous studies indicated that esmethadone is partially excreted by the kidney (53.9% of the dose) and by the liver (39.1% of the dose).

Methods Here we studied the pharmacokinetics and safety of esmethadone after a single oral dose of 25 mg in subjects with different stages of kidney and liver impairment.

Results In subjects with a mild and moderate decrease in glomerular fraction rate (GFR), esmethadone C_{max} and $AUC_{0–inf}$ values did not differ compared with healthy subjects. In patients with severe renal impairment, the ratios of C_{max} and $AUC_{0–inf}$ values compared with healthy subjects were above 100% (138.22–176.85%) and, while modest, these increases reached statistical significance. In subjects with end stage renal disease (ESRD) undergoing intermittent hemodialysis (IHD), C_{max} and $AUC_{0–inf}$ values were not statistically different compared with healthy subjects. IHD did not modified plasma total esmethadone concentrations in blood exiting versus entering the dialyzer. Dose adjustment is not warranted in subjects with mild-to-moderate impaired renal function. Dose reduction may be considered for select patients with severe renal disfunction. In subjects with mild-or-moderate hepatic impairment, C_{max} and $AUC_{0–inf}$ were approximately 20–30% lower compared with healthy controls. The drug free fraction increased with the severity of hepatic impairment, from 5.4% in healthy controls to 8.3% in subjects with moderate hepatic impairment.

Conclusion Mild and moderate hepatic impairment has a minimal to modest impact on exposure to total or unbound esmethadone and dose adjustments are not warranted in subjects with mild and moderate hepatic impairment. Administration of esmethadone was well tolerated in healthy adult subjects, in subjects with mild or moderate hepatic impairment, and in subjects with mild moderate or severe renal impairment, including patients with ESRF undergoing dialysis.

Key Points

No dose adjustments of esmethadone are warranted with mild and moderate hepatic impairment.

No dose adjustments of esmethadone are warranted with mild-to-moderate impairment of renal function.

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1 Introduction

Esmethadone (d-methadone; dextromethadone; REL-1017) is the opioid inactive (S)-enantiomer of racemic methadone, showing low potency uncompetitive antagonist activity at *N*-methyl-$_D$-aspartate receptors (NMDARs) [1, 2]. Esmethadone is in phase 3 of clinical development as a promising rapid antidepressant drug for the adjunctive treatment of patients with major depressive disorder (MDD) and inadequate response to serotonergic antidepressants [3, 4]. Although the efficacy of esmethadone needs to be established in the ongoing phase 3 trials, other uncompetitive NMDAR antagonists have shown antidepressant activity with a rapid onset of action [5]. Intranasal esketamine has been approved by the Food and Drug Administration (FDA) for treatment-resistant depression and for MDD with suicidal ideation [6]. The oral twice daily combination dextromethorphan/bupropion has been shown to be effective [22, 23] and has been recently FDA approved for the treatment of MDD [7, 8].

Esmethadone shows a favorable pharmacokinetic profile with a 70–80% oral bioavailability and a half-life time longer than 30 h, allowing a single daily administration [9]. Specific in vitro and clinical studies have been carried out to determine the metabolic fate of esmethadone [10]. Although the main metabolic route of esmethadone is the biotransformation to 2-ethylene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) by cytochrome P450 (CYP) 3A4/5 and 2B6 [10], its pharmacokinetics is not affected by the co-administration of CYP3A4 inhibitors in healthy subjects [10–15]. The drug expressed an in vitro inhibitory effect on CYP2D6 that determined a significant increase of the CYP2D6 substrate dextromethorphan exposure [10]. Thus, esmethadone demonstrated a negligible effect on CYP3A4 induction and its metabolism was not meaningfully affected by strong CYP3A4 inhibitors while it can increase the exposure of CYP2D6-metabolized drugs [10].

The pharmacokinetic parameters have been determined after the oral administration of radiolabeled [^{14}C]-esmethadone in healthy male subjects [10]. Approximately half of the dose of [^{14}C]-esmethadone (53.9%) can be collected in the urine after a single administration and 39.1% was found in the feces, indicating a predominant renal extraction [10]. EDDP was the most abundant metabolite found in both urines and feces [10]. Since esmethadone is partially eliminated by the kidney and metabolized by the liver, patients with either renal or hepatic impairment may be at risk of increased systemic exposure. Thus, in the present work we carried out two clinical studies aiming at determining the pharmacokinetics of esmethadone in subjects with renal and hepatic impairment of different severity. The safety of the drug was also determined as secondary objective in these patients.

2 Methods

A central institutional review board (Advarra, 6100 Merriweather Drive, Columbia, MD) was used for the review and approval of the protocol and informed consent forms for all sites in studies 1 and 2 prior to enrollment, as well as all subsequent amendments to both. All subjects signed an approved informed consent forms prior to any procedures being performed. Number of protocols for study 1 was Pro00060570 (January 14, 2022), for study 2 was Pro00058624 (October 27, 2021).

2.1 Study 1

This was a phase 1, open-label, single-dose, parallel study to determine the pharmacokinetics of esmethadone in subjects with mild, moderate, and severe renal impairment, and end stage renal disease (ESRD) subjects receiving intermittent hemodialysis (IHD). The primary objective of the study was the determination of the impact of various severities of renal impairment on the pharmacokinetics of esmethadone following a single 25 mg oral dose. The secondary objective was safety assessment in the same cohort of patients. Accordingly, the primary endpoint was the determination of the pharmacokinetic parameters of esmethadone, and the secondary endpoint was the assessment of safety, including adverse events (AEs), vital signs, electrocardiograms (ECGs), clinical laboratory tests, and physical examination findings.

A total of 49 subjects were enrolled in the study and received at least one dose of esmethadone and 46 subjects (93.9%) completed the study. The study was composed of two parts. Subjects were divided into five groups according to their renal function: group 1 healthy control, group 2 mild impairment, group 3 moderate impairment, group 4 severe impairment not receiving IHD, and group 5 ESRD receiving IHD. Groups 1, 2, 3, and 4 were included in the first part of the study (Part 1), where subjects with normal renal function were matched to patients with renal impairment by gender, age (approximately ±10 years), and body mass index (BMI, approximately ±15%). Part 1 included screening, check in, one treatment period, and end of study. During the treatment period, subjects received a single oral dose of 25 mg esmethadone on day 1. The dose was administered with 240 mL of water, following a light snack or meal. Pharmacokinetic samples were collected at specified time points from predose (0 h) to 144 h postdose.

Group 5 was included in the second part of the study (Part 2) and included screening, check in, two treatment periods

with at least an 11-day washout between dosing in each treatment period (period 1 and 2), and end of study. During period 1 (week 1), the patients received a single oral dose of 25 mg esmethadone approximately 1 h after completing the third weekly intermittent hemodialysis (IHD) session, which took place at least 72 h before the first weekly IHD session of the subsequent week. During period 2 (week 2), subjects received a single oral dose of 25 mg esmethadone on the day of the third weekly IHD session, which took place at least 11 days after the first dose (period 1) and at least 72 h before the first weekly IHD session of the subsequent week.

During IHD, the total dialysate was collected and pooled at 1-h intervals (0–1, 1–2, 2–3, etc. for the entire duration of the IHD session). From each hourly interval, an aliquot sample of dialysate was collected for pharmacokinetic analysis. Also, during period 2 IHD, arteriovenous samples were drawn at the following postdose time points: 1, 1.5, 2, 2.5, 3, 4, and 5 h for pharmacokinetic analysis. Each dose was administered with 240 mL of water, following a light snack or meal. Pharmacokinetic samples were collected at specified time points from predose (0 h) to 72 h postdose.

2.1.1 Diagnosis and Main Inclusion Criteria for Study 1

Male and female healthy subjects, or patients with mild, moderate, or severe renal impairment, or ESRD, ≥ 18 and ≤ 65 years of age with a BMI ≥ 18 and ≤ 35 kg/m^2, who were able to give consent and follow the protocol requirements of the study were enrolled in this study. The full description of inclusion and exclusion criteria are available in the supplementary material. The degree of renal impairment was calculated by the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD–EPI) equation. Subject eligibility was based on screening results, and subjects were assigned to one of the groups according the following eGFR interval values: control ($n = 12$) GFR ≥ 90 mL/min; mild decrease in GFR (60–89 mL/min, $n = 8$); moderate decrease in GFR (30–59 mL/min, $n = 9$); severe decrease in GFR not receiving IHD (15–29 mL/min, $n = 9$); and ESRD receiving IHD (< 15 mL/min, $n = 11$). Healthy subjects had normal renal function and were comparable to patients with renal impairment in terms of gender, age (approximately ±10 years), and BMI (approximately ±15%).

2.2 Study 2

This was a phase 1, open-label, single-dose, parallel study to evaluate the pharmacokinetics of esmethadone in adults with mild-or-moderate hepatic impairment. The primary objective of the study was the determination of the impact of hepatic impairment on the pharmacokinetics of esmethadone following a single 25 mg oral dose. The secondary objective was the assessment of the safety in the same cohort of patients. Also in this study, the primary endpoint was the determination of the pharmacokinetic parameters of esmethadone and the secondary endpoint was the assessment of safety, including AEs, vital signs, ECGs, clinical laboratory tests, and physical examination findings.

A total of 29 subjects were enrolled in the study, and 27 (93.1%) subjects completed the treatment. The study was composed of screening, check in, treatment period, and end of study. Subjects were divided into three groups according to their hepatic function: group 1: healthy (control, $n = 8$); group 2: mild impairment (Child–Pugh A, $n = 13$, score 5); and group 3: moderate impairment (Child–Pugh B, $n = 8$, score 8). During the treatment period, subjects received a single oral dose of 25 mg esmethadone on day 1. Each dose was administered with 240 mL of water following an overnight fast of at least 10 h.

2.2.1 Diagnosis and Main Criteria for Inclusion for Study 2

Male and female adults (≥ 18 and ≤ 65 years of age) with a BMI ≥ 18 and ≤ 35 kg/m^2, who were able to give consent and follow the protocol requirements of the study. Subjects with hepatic impairment (mild and moderate) were rated at screening using the Child–Pugh classification for severity of liver disease [16, 17]. The full description of inclusion and exclusion criteria are available in the supplementary materials. Healthy subjects were required to have normal hepatic function and coupled to patients with liver dysfunction in terms of gender, age (approximately ±10 years), and BMI (approximately ±15%).

2.3 Safety: Adverse Events (Studies 1 and 2)

An AE was defined as any untoward medical occurrence associated with the use of a drug, whether considered drug related or not. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptoms, or disease temporally associated with the use of the drug, irrespective of the causal relationship.

2.4 Genotype Testing

To avoid any confounding effect related to the CYP2B6-mediated metabolic variability, poor metabolizers for CYP2B6 were excluded from the study. The metabolizing genotype of CYP450 2B6 was evaluated for all subjects during the screening. A buccal sample was collected by swabbing the inside of the oral cavity, and DNA was extracted for genetic analysis to determine the selected variants of their CYP450 gene. The analysis was performed with Agena MassARRAY 4 system. DNA was amplified using PCR with primers designed to amplify large portions of the target areas

(> 1 kb) for copy number variation (CNV) determinations and shorter areas adjacent to variable nucleotides for single-nucleotide polymorphism (SNP) determinations. A shrimp alkaline phosphatase (SAP) reaction was then utilized to deactivates the phosphate groups of unincorporated nucleotides from use in multiple-base extension reactions. Then, a single-base extension (SBE) reaction added the mass-modified dideoxynucleotide terminators with thermosequenase to the amplicons according to their template strands. The molecular weights of the amplicons were determined via matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry. The specific terminators added in the SBE reaction were determined by matching the molecular weights of the subject sample amplicons to those of known sequences from their respective loci. CNV quantities were calculated by comparing the ratio of amplicons detected from copy number variable regions to the amount of amplicons detected from regions with established copy number quantities. Specific assays included for CYP2B6 were *1 (normal haplotype - polymorphisms not detected), *6 (rs3745274, decreased function), and *18 (rs28399499, nonfunctional).

2.5 Pharmacokinetic Measurements

Study 1. In part 1, blood samples for pharmacokinetic analysis were collected at predose (0 h) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, and 144 h postdose; these samples were drawn from an indwelling catheter or via venipuncture. Blood samples for protein binding were collected at 1 and 12 h postdose. In part 2, the blood samples for plasma pharmacokinetic analysis were collected at predose (0 h), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, and 72 h postdose in periods 1 and 2. Blood samples for protein binding were collected at 1 and 12 h postdose.

During period 2, the total dialysate was collected and pooled at 1-h intervals (0–1, 1–2, 2–3, etc. for the duration of the IHD session). From each hourly interval (including any partial interval at the end of dialysis), an aliquot sample of dialysate was collected for pharmacokinetic analysis. Additionally, during period 2, arteriovenous samples were drawn from the hemodialysis line at 1, 1.5, 2, 2.5, 3, 4, and 5 h postdose. Arterial samples were drawn from blood entering the dialyzer, and venous samples were drawn from blood exiting the dialyzer. A total of 20 blood samples (3 mL), including two additional samples for protein binding assessment, were collected from each subject in part 1, while a total of 32 blood samples (3 mL), including four additional samples for protein binding assessment, were collected from each subject in part 2.

Study 2. A total of 57 mL (17 × 3 mL samples, plus two additional samples for assessment of protein binding) were collected from each subject for the pharmacokinetic analysis. Samples for the analytical determination of total esmethadone were collected at the following times: predose (0 h), and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 h postdose, whereas samples for the measurement of the unbound fraction of esmethadone were collected at 1 and 12 h postdose.

2.6 Statistical Analysis

The pharmacokinetic parameters for esmethadone were calculated using noncompartmental analysis. To be evaluable for pharmacokinetic analysis, subjects must have had at least four quantifiable plasma concentrations of esmethadone. Pharmacokinetic calculations were performed using PhoenixWinNonlin (version 8.2.2, Certara), R Software (version 3.4.0, R Foundation for Statistical Computing), RStudio Workbench (version 1.4.1717, Rstudio), and SAS (version 9.4, SAS Institute Inc.).

The effect of renal or hepatic impairment on plasma esmethadone pharmacokinetic parameters was assessed statistically. C_{max}, $AUC_{0–inf}$, $AUC_{0–last}$, and apparent total body clearance (CL/*F*) were natural log-transformed and fit with a mixed-effects linear model containing a fixed effect for categorical renal function. Parameter estimates from this model were back transformed by exponentiation to yield geometric least squares means (LSMs). Ratios of geometric LSMs with associated 90% confidence intervals (CIs) were reported to compare patients with mild, moderate, and severe impairment with subjects with normal renal function, as well as patients with mild and moderate hepatic impairment with subjects with normal liver function.

The effect of hemodialysis was assessed by comparing the aforementioned pharmacokinetic parameters (C_{max}, $AUC_{0–inf}$, $AUC_{0–last}$, and CL/*F*) calculated for patients with ESRD on dialysis (Period 2) to those of patients with ESRD off dialysis (Period 1).

The test used for comparisons was the nonparametric Mann–Whitney test, by which the time to the maximum observed concentration (T_{max}) of subjects with mild, moderate, and severe renal impairment with that of subjects with normal renal function, as well as subjects with mild and moderate hepatic impairment with those with normal liver function was compared. The median differences were estimated with the Hodges–Lehmann estimator, and the associated 90% CIs were presented.

The relationship between esmethadone pharmacokinetic parameters (C_{max}, $AUC_{0–inf}$, $AUC_{0–last}$, and CL/*F*) and eGFR as a continuous variable marker of renal function was assessed. Linear regression analysis was performed on natural log-transformed pharmacokinetic parameters and natural log-transformed eGFR. Estimates of the slope and intercept associated 90% CIs, and the coefficient of determination (R^2)

were calculated. For all the analyses, a P value < 0.05 was considered statistically significant.

Safety and tolerability parameters were summarized using descriptive statistics, where appropriate.

Descriptive statistics for continuous variables [the number of non-missing observations (n), mean, standard deviations (SD), standard error (SE) of the mean, median, minimum, and maximum] are presented for the observed and change from baseline values for all vital signs, ECGs, and clinical laboratory evaluations. Descriptive statistics for categorical variables include subject counts and percentages. All abnormalities in clinical laboratory parameters and physical examinations are listed. All safety analyses were performed by SAS (version 9.4, SAS Institute Inc.).

3 Results

3.1 Pharmacokinetic Profile of Esmethadone According to Renal Function (Study 1)

In the first clinical trial, we investigated the esmethadone pharmacokinetics in patients with renal insufficiency following a single oral dose of 25 mg, in subjects with different degrees of renal impairment (mild, moderate, severe, and ESRD).

A total of 49 subjects were enrolled in the study and received at least one dose of esmethadone. Of those enrolled, 46 subjects (93.9%) completed the study, 2 subjects (4.1%) discontinued due to AEs and 1 subject (2.0%) due to a protocol deviation. The enrolled population consisted of 12 subjects in group 1 (healthy control), 8 subjects in group 2 (mild impairment), 9 subjects in group 3 (moderate impairment), 9 subjects in group 4 (severe impairment not receiving IHD), and 11 subjects in group 5 (ESRD receiving IHD).

The overall mean age of the population was 55.2 ± 7.71 years, ranging between 35 and 65 years with a 73.5% prevalence of males and 65.3% of White race (Table 1). The baseline median BMI was 28.8 kg/m^2 (minimum to maximum range: 20.8–35.1 kg/m^2). Subjects in group 5 were younger (51.8 ± 9.7 years) and prevalently males (90.9%). A considerably lower proportion of males was present in group 2 (37.5%). The average BMI was similar across groups 2, 3, and 4 (varied between 29.06 and 30.38 kg/m^2) and slightly lower in groups 1 (26.78 kg/m^2) and 5 (27.17 kg/m^2).

The renal impairment was based on the calculated eGFR using the CKD–EPI equation and values were within the predetermined ranges for each group, ranging from 102.7 ± 6.7 mL/min for healthy control to 6.8 ± 2.5 mL/min for ESRD patients receiving IHD (Table 1).

All total esmethadone plasma concentrations were quantifiable by 1 h for groups 1–4, by 1.5 h for group 5 (ESRD) off dialysis, and by 2 h for group 5 on dialysis. Total plasma esmethadone mean concentrations peaked at 2–3 h for groups 1–4, while for group 5 it was observed at 5–6 h. The concentration of esmethadone remained quantifiable for 144 h (the last sampling time point), except one profile in group 3 (quantifiable up to 96 h) (Fig. 1). Plasma total esmethadone concentration profile in ESRD off and on dialysis (periods 1 and 2) were essentially superimposable (Fig. 2).

Table 1 Demographics characteristics of recruited subjects divided by renal group

	Group 1: Control (normal) GFR ($N = 12$)	Group 2: Mild decrease in GFR ($N = 8$)	Group 3: Moderate decrease in GFR ($N = 9$)	Group 4: Severe decrease in GFR not receiving IHD ($N = 9$)	Group 5: ESRD receiving IHD ($N = 11$)	Total ($N = 49$)
Variable						
Age (years, mean ± SD)	56.3 ± 5.9	55.9 ± 4.8	55.0 ± 11.2	57.6 ± 4.6	51.8 ± 9.7	55.2 ± 7.7
Sex, male (%)	9 (75.0)	3 (37.5)	7 (77.8)	7 (77.8)	10 (90.9)	36 (73.5)
Race, *n* (%)						
White	9 (75.0)	5 (62.5)	7 (77.8)	8 (88.9)	3 (27.3)	32 (65.3)
Black or African American	3 (25.0)	3 (37.5)	2 (22.2)	1 (11.1)	8 (72.7)	17 (34.7)
Ethnicity, *n* (%)						
Hispanic or Latino	5 (41.7)	2 (25.0)	5 (55.6)	6 (66.7)	1 (9.1)	19 (38.8)
Not Hispanic or Latino	7 (58.3)	6 (75.0)	4 (44.4)	3 (33.3)	10 (90.9)	30 (61.2)
Weight (kg, mean ± SD)	84.3 ± 13.8	85.3 ± 14.9	92.2 ± 13.4	85.8 ± 17.1	85.5 ± 12.9	86.5 ± 14.0
BMI (kg/m^2, mean ± SD)	26.8 ± 3.3	29.1 ± 3.6	30.4 ± 3.5	30.1 ± 4.1	27.2 ± 4.8	28.5 ± 4.0
eGFR mean ± SD (mL/min/1.73 m^2)	102.7 ± 6.7	69.2 ± 5.4	41.0 ± 9.1	24.9 ± 4.6	6.8 ± 2.5	

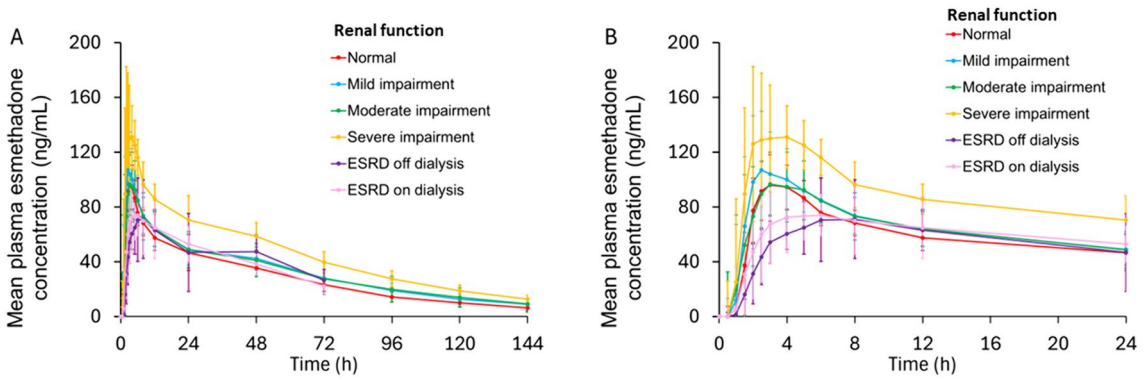

Fig. 1 Mean plasma total esmethadone concentration-time profile according to renal function. Panel **A**: linear, full collection period; Panel **B**: linear, truncated to 8 h

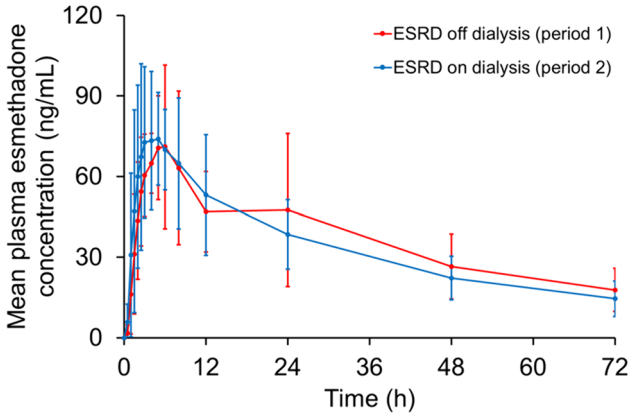

Fig. 2 Mean plasma total esmethadone concentration-time profile in ESRD off (period 1) and on dialysis (period 2). In period 1 subjects received esmethadone after IHD session while in period 2 before it

Esmethadone T_{max} was 2.0–2.5 h in groups 1–4, 5 h in group 5 (ESRD) off dialysis, and 3.50 h in group 5 on dialysis. Elimination half-lives ($t_{1/2}$) were comparable across groups (33.4–42.1 h). Similar values of C_{max}, $AUC_{0–inf}$, $AUC_{0–last}$, and CL/*F* were observed in the different groups (Table 2).

Statistical comparison of plasma total esmethadone parameters across renal function groups indicated that point estimates for geometric LSM ratios were above 100% for C_{max}, $AUC_{0–last}$, and $AUC_{0–inf}$, ranging from 108.51 to 176.85% across groups (Fig. S1). The 90% CIs for geometric LSM ratios contained 100% for all three parameters for mild and moderate decrease in GFR. The 90% CIs for geometric LSM ratios did not contain 100% for all three parameters for severe decrease in GFR (Fig. S1). The geometric LSM ratios between patients with and without dialysis for C_{max}, $AUC_{0–last}$, and $AUC_{0–inf}$ were 114.37%, 95.89%, and 88.12%, respectively. The 90% CIs for geometric LSM ratios contained 100% for all three parameters (Fig. S2).

Plasma total esmethadone mean concentrations in blood entering and exiting the dialyzer peaked at 3 h postdose.

Table 2 Observed pharmacokinetic parameters of esmethadone in patients with different renal function

	Group 1: Control (normal) GFR (*N* = 12)	Group 2: Mild decrease in GFR (*N* = 8)	Group 3: Moderate decrease in GFR (*N* = 9)	Group 4: Severe decrease in GFR not receiving IHD (*N* = 9)	Group 5: ESRD receiving IHD, off dialysis (*N* = 11)	Group 5: ESRD receiving IHD, on dialysis (*N* = 10)
C_{max} (ng/mL)	101 ± 20.4	120 ± 37.6	112 ± 29.5	146 ± 47.7	79.9 ± 27.1	91.5 ± 26.8
T_{max} (h)	2.5	2.0	2.5	2.0	5.0	3.5
$AUC_{0–last}$ (h ng/mL)	2980 ± 716	3600 ± 989	3600 ± 1450	4680 ± 1770	2580 ± 1060	2390 ± 704
AUC_{0-inf} (h ng/mL)	3220 ± 835	4000 ± 1180	4160 ± 2030	5680 ± 1330	3540 ± 1440	3010 ± 998
$T_{1/2}$	37.4 ± 6.5	42.1 ± 9.1	43.6 ± 15.2	42.6 ± 8.0	39.1 ± 15.5	35.6 ± 14.0
CL/*F* (L/h)	7.31 ± 1.60	6.24 ± 2.72	6.75 ± 3.75	4.13 ± 0.93	7.81 ± 4.76	8.34 ± 3.25
Vz/*F* (L)	386 ± 71	357 ± 85	363 ± 84	252 ± 67	367 ± 138	371 ± 115

All profiles that were quantifiable at 1-h postdose remained quantifiable through 5 h (the last sampling time point). Mean concentration profiles in blood entering and exiting the dialyzer were nearly identical (Fig. 3).

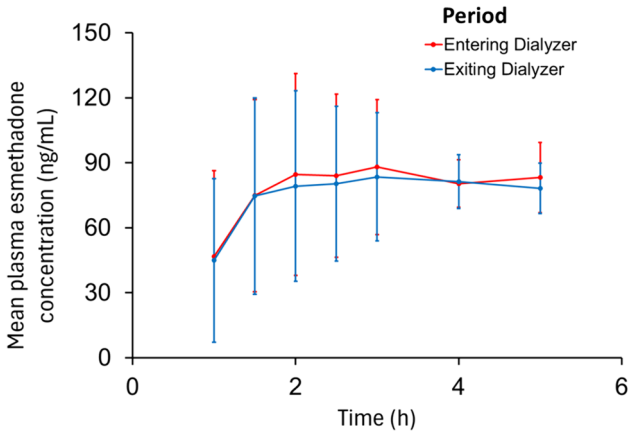

Fig. 3 Mean plasma total esmethadone concentration–time profile in blood entering (arterial) and exiting (venous) the dialyzer for subjects with ESRD on dialysis

3.2 Safety Analysis (Study 1)

A total of 49 subjects were enrolled with three discontinuations (one for protocol deviation, two for AEs). The AE discontinuations were a non-drug-related hospitalization for infected surgical site from prior toe amputation, and a grade 3 hypertensive event possibly related to drug but with complicating factor of an antihypertensive treatment being discontinued a week prior to study entry (not reported upon entry).

Overall, the highest incidence of treatment emergent adverse events (TEAEs) was observed in ESRD subjects (group 5); four subjects with eight events in period 1 (dosed off dialysis) and two subjects with five events in period 2 (same patients dosed on dialysis) (Table 3).

The most commonly reported TEAEs were related to gastrointestinal and nervous system disorders. Seven TEAEs were considered related to study drug. One in severe subjects (hypertensive event), two in ESRD period 1 subjects (nausea, dizziness) and four in ESRD period 2 patients (dry mouth, nausea, vomiting, fatigue).

There were no abnormal laboratory findings deemed clinically meaningful following esmethadone administration (in any chemistry, hematology, and urine parameters). No significant alteration in vital signs (except for those

Table 3 Summary of treatment related TEAEs and serious AEs by renal group

Adverse event (AE)	Group 1: Control (normal) GFR (N = 12)	Group 2: Mild decrease in GFR (N = 8)	Group 3: Moderate decrease in GFR (N = 9)	Group 4: Severe decrease in GFR not receiving IHD (N = 9)	Group 5: ESRD receiving IHD, off dialysis (N = 11)	Group 5:ESRD receiving IHD, on dialysis (N = 10)
Number of TEAEs	3	0	2	1	8	5
Number of subjects with any TEAE	2 (17%)	0	2 (22%)	1 (11%)	4 (36%)	2 (20%)
Any treatment-related TEAE	0	0	0	1 (11%)	1 (9%)	1 (10%)
TEAEs						
Vision blurred	0	0	0	0	1 (9%)	0
Constipation	0	0	1 (11%)	0	0	0
Dry mouth	0	0	0	0	0	2 (20%)
Nausea	0	0	0	0	1 (9%)	1 (10%)
Vomiting	0	0	0	0	1 (9%)	1 (10%)
Chest discomfort	0	0	0	0	1 (9%)	0
Fatigue	0	0	0	0	0	1 (10%)
Malaise	0	0	0	0	1 (9%)	0
Dizziness	0	0	0	0	1 (9%)	0
Vascular disorders	0	0	0	1 (11%)	0	0
Epistaxis	0	0	0	0	1 (9%)	0
Hypertensive emergency*	0	0	0	1 (11%)	0	0

*Later determined to be hypertensive urgency in communication with the investigator

observed during the grade 3 hypertensive event reported in one subject), physical examination, C-SSRS measures, and ECG parameters were noted in response to esmethadone administration.

3.3 Pharmacokinetic Profile of Esmethadone According to Hepatic Function (Study 2)

Twenty-nine subjects were enrolled in the study. Demographics and baseline characteristics of subjects were largely balanced across the groups (Table 4). There were 18 females (62.1%) and 11 males (37.9%) at ages ranged from 41 to 65 years. BMI ranged from 19.2 to 34.2 kg/m^2. The subjects were mostly White (75.9%) and evenly split in terms of ethnicity.

Across all groups, total esmethadone concentrations were generally quantifiable starting at 0.5 to 1 h postdose, and peak concentrations were observed at approximately 2.0 to 2.5 h postdose (Fig. 4). The time of maximum concentration (T_{max}) was similar in the three groups with a median value of 1.75–2.50 h (Table 5). The C_{max} of total esmethadone was 43.9% and 48.3% higher in healthy controls (135 ng/mL) compared with subjects with mild (93.8 ng/mL) and moderate (91.0 ng/mL) impairment, respectively. Similarly, AUC_{0-inf} for total esmethadone (4220 h ng/mL) was 48.5% and 24.4% higher in healthy controls compared with subjects with mild (2840 h ng/mL) and moderate (3390 h ng/mL) impairment, respectively. Consistent with the observed effect on AUC_{0-inf}, apparent CL/*F* was 33.7% and 20.5% lower in healthy controls (5.31 L/h) compared with subjects with mild (7.89 L/h) and moderate (6.60 L/h) hepatic impairment, respectively. Subjects with moderate hepatic impairment have 54.7% and 34.4% longer terminal elimination $t_{½}$ (57.1 h) compared with subjects with mild hepatic impairment (36.9 h) and healthy controls (42.5 h). Volume of distribution (*Vz*/*F*) increased with the severity of hepatic impairment, starting from 326 L in healthy controls, moving to 420 L for mild impairment, and reaching to 544 L for moderate impairment (Table 5).

Total esmethadone plasma concentration remained quantifiable for 144 h postdose (Fig. 4). Mean concentrations of total esmethadone were lower in patients with mild and

Table 4 Demographics characteristics of recruited subjects divided by hepatic impairment group

Variable	Group 1: normal hepatic function (*N* = 8)	Group 2: mild hepatic impairment (*N* = 13)	Group 3: moderate hepatic impairment (*N* = 8)	Total (*N* = 29)
Age (years, mean ± SD)	53.9 ± 3.9	56.5 ± 6.4	57.6 ± 6.1	56.1 ± 5.7
Sex, male (%)	2 (25.0)	6 (46.2)	3 (37.5)	11 (37.9)
Race, *n* (%)				
White	6 (75.0)	9 (69.2)	7 (87.5)	22 (75.9)
Black or African American	1 (12.5)	3 (23.1)	1 (12.5)	5 (17.2)
Asian	(12.5)	1 (7.7)	0	2 (6.9)
Ethnicity, *n* (%)				
Hispanic or Latino	6 (75.0)	6 (46.2)	4 (50.0)	16 (55.2)
Not Hispanic or Latino	2 (25.0)	7 (53.8)	4 (50.0)	13 (44.8)
Weight (kg, mean ± SD)	76.7 ± 12.9	76.3 ± 15.7	80.7 ± 14.5	77.6 ± 14.7
BMI (kg/m^2, mean ± SD)	28.7 ± 5.1	27.3 ± 3.9	28.7 ± 3.7	28.0 ± 4.1

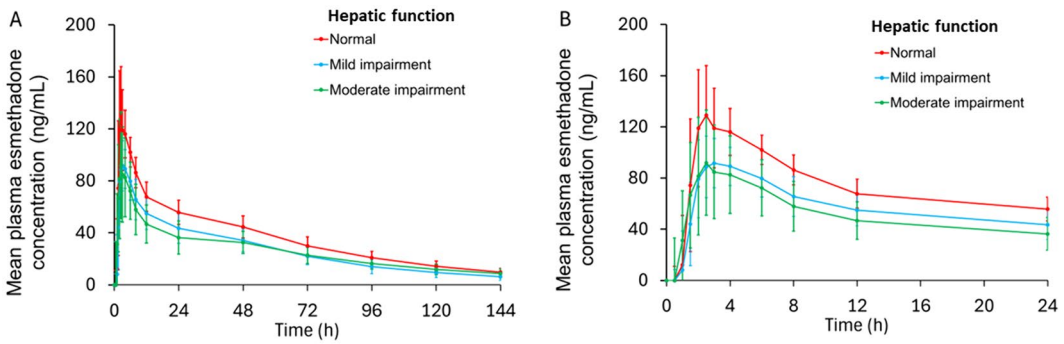

Fig. 4 Mean plasma total esmethadone concentration-time profile in relation to hepatic function. **A** Linear, full collection period and **B** linear, truncated to 24 h

Table 5 Observed pharmacokinetic parameters of esmethadone in patients with different hepatic function

Variable	Group 1: normal hepatic function ($N = 8$)	Group 2: mild hepatic impairment ($N = 13$)	Group 3: moderate hepatic impairment ($N = 8$)
C_{max} (ng/mL)	139 ± 33.5	97.1 ± 22.4	99.9 ± 43.8
T_{max} (h)	1.75	2.5	2.0
AUC_{0-last} (μg ng/mL)	3930 ± 961	2840 ± 990	2970 ± 1090
AUC_{0-inf} (μg ng/mL)	4380 ± 1190	3110 ± 1130	3650 ± 1490
$T_{1/2}$ (h)	43.2 ± 7.7	38.9 ± 11.4	61.6 ± 27.5
CL/*F* (L/h)	5.55 ± 1.94	9.27 ± 7.51	7.13 ± 3.06
Vz/*F* (L)	332 ± 74.4	440 ± 144	597 ± 297

moderate liver dysfunction compared with subjects with normal hepatic function (Fig. 4). The mean concentration-time profiles demonstrated a similar time course for peak concentrations and elimination from plasma, although the moderate impairment group had a slightly shallower slope compared with the others during the elimination phase.

Statistical analyses showed that esmethadone C_{max} was approximately 30% lower for subjects with mild-or-moderate hepatic impairment relative to healthy controls, with the geometric LSM ratio (90% CIs) equal to 69.6% (52.9–91.5%) for mild impairment and 67.5% (50.1–91.1%) for moderate impairment (Table S3). AUC_{0-last} and AUC_{0-inf} were approximately 30% lower for subjects with mild hepatic impairment relative to healthy controls, with a geometric LSM ratio equal of 68.6% (49.3–95.4%) for AUC_{0-last} and 67.3% (47.6–95.2%) for AUC_{0-inf} (Table S3). While there was a trend for 20–27% lower geometric LSMs for AUC_{0-last} and AUC_{0-inf} in subjects with moderate hepatic impairment relative to healthy controls, there was no statistical difference (51.3–104.3% for AUC_{0-last} and 55.4–116.8% for AUC_{0-inf}) (Table S3).The C_{max} for unbound esmethadone was similar across hepatic function groups, with estimates of 7.33 ng/mL (38.0%) for healthy controls, 6.80 ng/mL (37.9%) for mild impairment, and 7.59 ng/mL (40.8%) for moderate impairment. On the contrary, unbound esmethadone AUC_{0-inf} was higher for subjects with moderate impairment, such as 283 h ng/mL (61.4%) compared with healthy controls at 229 h ng/mL (42.3%) and subjects with mild impairment at 206 h ng/mL (66.2%).

3.4 Safety Analysis (Study 2)

A summary of TEAEs, treatment-related TEAEs, as well as AEs leading to death and SAEs in the different hepatic groups is provided in Table 6. There was one serious TEAE (bile duct stone), but there were no TEAEs leading to death.

A total of 12 TEAEs were reported by 8 subjects (28%) over the course of the study. Of these, 7 TEAEs in 6 subjects were considered related to the drug (possibly, probably, definitely). All the treatment related TEAEs were mild or moderate in intensity and included constipation (3), headache (2), abdominal discomfort (1), and dry mouth (1). Except for constipation ($n = 3$, 10%) and headache ($n = 2$, 7%), all TEAEs were reported by single subjects.

4 Discussion

It has been estimated that approximately 70% of patients with MDD have a comorbid chronic physical condition, which may include age related diseases, such as renal and hepatic disfunction [18]. Conventional small-molecule drugs are excreted by the kidney, the liver, or both. Esmethadone showed a favorable elimination by both organs. Indeed, after a single oral administration, half of the dose of esmethadone is collected in the urine and approximately 40% in the feces in form of its main metabolite EDDP [10]. Nevertheless, a possible impairment of drug excretion can be predicted in patients with either liver or kidney disfunction. For this reason, we performed two clinical trials aiming at determining the pharmacokinetic profile of esmethadone, and its tolerability, in subjects with different stages of either liver or kidney disfunction.

Our results demonstrated that mild-to-moderate renal impairment does not determine a significant change in the total plasma esmethadone exposure; however, severe renal impairment increases its permanence in the body. Mild-to-severe renal impairment showed no impact on T_{max}, but a significant prolongation was observed in ESRD patients, either off dialysis (up to 5.0 h) or on dialysis (up to 3.5 h). Thus, the study findings suggest that dose adjustment is not warranted in the population of patients with mild-to-moderate impairment of renal function. Instead, for severe renal impairment, the ratios of total plasma esmethadone exposure increase from 138.2% to 176.9%, compared with healthy controls. Although the increased exposure caused by severe renal impairment is unlikely to be meaningful for most patients due to the relatively large therapeutic index of esmethadone [3, 9], selected patients may need dose adjustment.

Table 6 Summary of treatment emergent AE by system organ class, and preferred term by hepatic group

Variable	Group 1: normal hepatic function ($N = 8$)	Group 2: mild hepatic impairment ($N = 13$)	Group 3: moderate hepatic impairment ($N = 8$)	Total (N=29)
Number of TEAEs	5	6	1	12
Number of subjects with any TEAE	4 (50%)	3 (23%)	1 (13%)	8 (28%)
Number of treatment related TEAEs	3	3	1	7
Number of subjects with any treatment-related TEAE	3 (38%)	2 (15%)	1 (13%)	6 (21%)
Number of serious TEAEs	0	1 (8%)	0	1 (3%)
TEAEs				
Abdominal discomfort	0	0	1 (13%)	1 (3%)
Constipation	2 (25%)	1 (8%)	0	3 (10%)
Diarrhea	1 (13%)	0	0	1 (3%)
Dry mouth	1 (13%)	0	0	1 (3%)
Bile duct stone	0	1 (8%)	0	1 (3%)
Back pain	0	1 (8%)	0	1 (3%)
Headache	0	2 (15%)	0	2 (7%)
Urine odor abnormal	1 (13%)	0	0	1 (3%)

Group 1: healthy control; group 2: mild impairment; group 3: moderate impairment. TEAE: treatment-emergent AE

Importantly, in patients with ESRD, dialysis did not significantly change systemic exposure of esmethadone, suggesting that dose adjustment is not warranted due to dialysis. In case of drug overdose, esmethadone is unlikely to be amenable to removal by dialysis. These results are consistent with a previous study conducted in HIV-positive addicted patient on methadone (60 mg per day) treated by hemodialysis for ESRD [19].

The direct comparison of the pharmacokinetic parameters of control groups ($N = 12$ study 1; $N = 8$ study 2) showed significant differences in esmethadone pharmacokinetic parameters, such as C_{max} (101 ± 20.4 ng/mL versus 139 ± 33.5 ng/mL, p value = 0.0130 with the Mann–Whitney test), and AUC_{0-last} (2980 ± 716 h ng/mL versus 3930 ± 961 h ng/mL, p value = 0.0497 with the Mann–Whitney test). These changes might be the result of different subject's demographic characteristics, such as sex and ethnicity (75% versus 25% were males in the first and second study, respectively; 41.7% versus 75% were Hispanic or Latinos in the first and second study, respectively). Secondly, in the two studies esmethadone was administered either under fed (study 1) or fasting (study 2) conditions. Study 1 (fed) subjects assumed esmethadone with a light snack or meal; study 2 (fast) subjects assumed esmethadone following a fast of at least 10 h. Although these conditions were not intentional, but simply derived from different clinical decisions of the investigators involved in the two studies, have provided an interesting observation. Indeed, the results suggest that the presence of food may modestly increase esmethadone's systemic exposure, although it is not possible to draw a final statement without a direct comparison of fasted versus fed conditions.

The second relevant aspect of our studies is represented by the fact that the administration of a single oral dose of 25 mg esmethadone was well tolerated both healthy subjects and subjects with mild-to-moderate ESRD. One serious AE of right foot osteomyelitis was reported in one subject in group 5. However, this infection was due to a recent toe amputation and was not considered related to the esmethadone treatment. In addition, one nonserious grade 3 AE of hypertensive crisis was reported to be probably related to drug administration, although this subject, with severe renal impairment, had self-stopped his ongoing antihypertensive therapy with nifedipine. The reintroduction of nifedipine resolved the hypertensive episode. No clinically important abnormalities were observed in clinical laboratory tests, vital signs, or ECGs and no suicidal behaviors or nonsuicidal self-injury behaviors were recorded.

Our results are consistent with the finding that the excretion of methadone is unaffected by impaired hepatic or renal function [20, 21]. In cases of anuria, methadone is excreted almost exclusively as pyrrolidine metabolite via the gastrointestinal tract and thus it can be safely administered to chronic kidney disease (CKD) patients [20, 22]. A dose reduction could be considered in patients with reduced GFR of 10–15 mL/min and a serum creatinine level above 8 mg/dL (700 mmol/L) [20].

The results of the second study indicated that increasing severity of hepatic impairment had minimal effects on the extent of overall esmethadone exposure. Impaired liver function resulted in minimal differences in the

concentration-time profiles of total esmethadone, with slightly lower total exposure (< 33% decrease in total esmethadone C_{max} and $AUC_{0\text{-inf}}$) in subjects with mild and moderate liver dysfunction with respect to healthy controls. T_{max} was similar across all hepatic function groups (median of 1.75–2.5 h).

When comparing unbound esmethadone exposure parameters, there were approximately 10% reductions in C_{max} and AUC_{0-inf} in subjects with mild hepatic impairment and higher C_{max} (4%) and AUC_{0-inf} (23%) in those with moderate impairment compared with healthy controls. Esmethadone is highly protein bound across all liver function groups [23, 24], and the free fraction increased with increasing severity of hepatic impairment from 5.4% in healthy controls, 7.3% in mild impairment, and 8.3% in moderate impairment. The reduction in protein binding could potentially be due to baseline differences in plasma protein levels in subjects with hepatic impairment [25]. Consistent with reduced protein binding, the apparent volume of distribution (Vz/F) increased with the severity of hepatic impairment (approximately 30% in mild impairment and 60% in moderate impairment relative to healthy controls).

Overall, the results of the study support that mild and moderate hepatic impairment have a modest impact on exposure to total or unbound esmethadone and suggest that dose adjustments are not warranted for these populations. Similar results were observed in patients with liver fibrosis or possible advanced cirrhosis, where concentration-to-dose ratio of methadone did not increase with higher degree of liver fibrosis [26]. Accordingly with the minor effect of hepatic function of drug exposure, esmethadone was well tolerated in both healthy subjects and with mild-or-moderate hepatic impairment when administered as a single oral dose of 25 mg. There was one SAE of bile duct stone in a single subject; this SAE was considered not related to the treatment. There were no persistent clinically significant abnormalities in clinical laboratory tests, vital signs, or ECGs.

In conclusion, our study indicated that a single 25 mg dose esmethadone is well tolerated in subjects with mild-to-severe renal impairment, and with end stage renal disease receiving IHD. However, select patients with severe renal impairment may need dose adjustment due to a modest statistically significant increase in esmethadone exposure. Mild and moderate hepatic impairment did not meaningfully impact the pharmacokinetic parameters of 25 mg esmethadone.

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Data Availability Statement The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Ethics Approval A central institutional review board (Advarra, 6100 Mer[1]riweather Drive, Columbia, MD) was used for the review and approval of the protocol.

Consent to Participate All subjects signed an approved informed consent forms prior to any procedures being performed.

Consent for publication All patients provided consent.

Code availability Not applicable.

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