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Impact of renal impairment on the pharmacokinetic profile of intravenous difelikefalin, a kappa opioid receptor agonist for the treatment of pruritus

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Abstract

Background Difelikefalin is a selective kappa opioid receptor agonist that is approved for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adults undergoing hemodialysis (HD). In this study, we assessed the pharmacokinetics (PK) of intravenous (IV) difelikefalin in healthy subjects, in non–dialysis-dependent (NDD) subjects with varying stages of kidney disease, and in subjects with end-stage renal disease (ESRD) undergoing HD.

Methods The PK and safety of single IV doses of difelikefalin (3.0 mcg/kg) were initially evaluated in NDD subjects with mild, moderate, or severe renal impairment compared with matched healthy subjects. Based on those data, the PK and safety of 3 dose levels of IV difelikefalin (0.5, 1.0, or 2.5 mcg/kg) were compared with matched placebo in subjects undergoing HD with each dose administered following dialysis, 3 times over a 1-week treatment period).

Results Single IV dosing of difelikefalin in NDD subjects ($N=36$) with mild renal impairment demonstrated comparable exposure to healthy subjects with normal renal function, while subjects with moderate or severe renal impairment had higher total exposure. NDD subjects with severe renal impairment had higher total exposure compared with those with moderate renal impairment (i.e., exposure in severe NDD > moderate NDD > mild NDD ≈ healthy subjects). Clearance of difelikefalin correspondingly decreased with increasing renal impairment. In the multiple-dose study in subjects with ESRD undergoing HD ($N=19$), IV difelikefalin demonstrated dose proportionality and was shown to be mostly cleared by dialysis; steady state was achieved with the second dose on day 3. Safety findings for all subjects were consistent with the known profile of IV difelikefalin.

Conclusions IV difelikefalin was well tolerated. Similar exposure was observed in NDD subjects with mild renal impairment compared with healthy subjects with normal renal function, with reduced clearance and higher exposure in NDD subjects with moderate or severe renal impairment. Dose proportionality was demonstrated in subjects with ESRD undergoing HD administered IV difelikefalin 3 times per week following dialysis and was shown to be mostly cleared by dialysis.

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Keywords Difelikefalin, Kappa opioid receptor agonist, Pharmacokinetics, Tolerability, Chronic kidney disease, Pruritus

Introduction

Chronic kidney disease (CKD)–associated pruritus (CKD-aP) is a prevalent and distressing medical condition in advanced CKD and patients with end-stage renal disease (ESRD) on dialysis that is associated with sleep disturbances, increased incidence of depression, and impaired health-related quality of life (QoL) [1]. Severe pruritus in these patients has also been associated with increased morbidity and all-cause mortality [2, 3].

In August 2021 and April 2022, intravenous (IV) difelikefalin became the first drug approved by the US Food and Drug Administration and the European Medicines Agency, respectively, for the treatment of moderate-to-severe CKD-aP in adults undergoing HD [4–7], and it has also been approved in other parts of the world, including Japan and Canada [7].

Difelikefalin belongs to the opioid pharmacological class but was designed to selectively activate only kappa opioid receptors and is therefore differentiated from opioid narcotics [8], which preferentially bind to mu opioid receptors [9]. As such, clinical studies have demonstrated that difelikefalin does not have abuse potential or physical dependence properties [4, 5, 8, 10, 11] and is not a controlled substance under the Controlled Substance Act (CSA) [12]. In phase 2 and 3 randomized, double-blind studies, treatment with IV difelikefalin was generally well tolerated and demonstrated rapid, clinically meaningful, sustained itch reduction compared with placebo in patients undergoing HD with moderate-to-severe pruritus [4, 5].

Assessing the pharmacokinetic (PK) profile of difelikefalin is essential for understanding the drug's effects in a population with CKD. Because difelikefalin is eliminated mainly via the kidneys [13], it is important to understand how difelikefalin exposure changes in subjects with different levels of renal impairment. Here, we report findings from single-dose and multiple-dose studies in subjects with various degrees of renal impairment. The single-dose study characterized the PK and safety profile of a single IV dose of difelikefalin in non–dialysis-dependent (NDD) subjects with mild, moderate, or severe renal impairment compared with demographically matched healthy control subjects. Based on these results, a multiple-dose study was conducted to evaluate the PK and safety profile of repeated IV doses of difelikefalin in subjects with ESRD undergoing HD.

Methods

Single-dose administration

Study design

A single-dose, open-label, 2-center, parallel-group phase 1 study was conducted at 2 sites in the United States from August 2013 through study completion in December 2013 to evaluate the PK and safety of IV difelikefalin 3.0 mcg/kg in NDD subjects with varying degrees of renal impairment and demographically matched (for mean age, mean weight, and sex) to healthy control subjects. Subjects received difelikefalin as an IV bolus, followed by blood and urine sampling for 72 h for PK assessments. Subjects returned to the clinic 8 to 11 days after dosing for follow-up procedures and to determine if any adverse events (AEs) had occurred since the last study visit. Study drug (difelikefalin)/formulation information have been reported previously [13].

Eligibility criteria

The study enrolled subjects with varying degrees of renal impairment, as well as healthy control subjects, who were adults (≥18 years) with body weight≤140 kg and continuous nonsmokers or moderate smokers (≤20 cigarettes/day or equivalent). Subjects who were taking concurrent medications were on stable doses for ≥2 weeks, and doses were expected to remain stable during the study. Subjects with a clinical diagnosis of renal impairment were stratified based on screening estimated glomerular filtration rate (eGFR) value calculated using the Modification of Diet in Renal Disease (MDRD) equation [14] (mild: eGFR 60–89 mL/min/1.73 m^2 [Stage 2]; moderate: eGFR 30–59 mL/min/1.73 m^2 [Stage 3]; or severe: eGFR 15–29 mL/min/1.73 m^2 [Stage 4]). Eligible subjects had no clinically significant change in renal status≥1 month before study drug administration, were in generally good health, and were not currently or previously on dialysis. The control group included healthy subjects with normal renal function (eGFR≥90 mL/min/1.73 m^2). For all subjects, actual creatinine clearance determined by 24-hour urine collection could be used in place of or in conjunction with the MDRD equation. Healthy subjects were eligible for study inclusion if they were within 15 years of the mean age and within 20% of the mean body weight of the subjects with renal impairment.

Exclusion criteria were standard for single-dose phase 1 studies including healthy subjects and are described in detail in Additional file 1.

Assessments

Pharmacokinetics: The nominal dose (mcg/kg) for each subject was calculated using body weight at check-in. Blood samples for PK analyses were collected predose and at 0.0167, 0.0333, 0.0833, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 h after dosing (~6 mL per collection time). Two additional blood samples (12 mL total) were taken for the assessment of protein binding at the 0.0833- and 4-hour time points. Fluid intake was monitored, and urine was collected at the following intervals: −12–0 (prior to dosing), 0–2, 2–4, 4–8, 8–12, 12–24, 24–36, 36–48, 48–60, and 60–72 h after administration of the study drug.

Safety assessment: Safety, including AEs, physical examinations, vital signs, electrocardiograms, and standard laboratory tests, was monitored throughout the study.

Statistical analyses

The PK population included all subjects who received study drug and had measurable plasma and/or urine concentrations of difelikefalin that permitted an accurate PK assessment. PK parameters were summarized using descriptive statistics. To assess difelikefalin single-dose exposure in subjects with varying renal function, an analysis of covariance (ANCOVA) was performed on the ln-transformed values for maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to infinity (AUC_{inf}) to compare each impaired renal function group with the matched healthy control group. The ANCOVA model included group as a fixed effect, with continuous covariates of age, weight, and body mass index and a categorical covariate of sex. Each ANCOVA included calculation of least-square means (LSM), the difference between LSM of the renal impairment group (mild, moderate, or severe, as appropriate) and the healthy subject group, and the standard error and 90% confidence interval (CI) associated with each difference; these values were transformed back to the original scale and the geometric mean values were calculated. Ratios of geometric means and their 90% CIs are expressed as a percentage of the renal-impaired group over the matched healthy control group. Safety analyses were summarized descriptively.

Multiple-dose administration

Study design

A multiple-dose, randomized, double-blind, placebo-controlled, 2-part phase 2 study (NCT02229929, first registration: 03/09/2014) with ESRD subjects undergoing HD was conducted at 20 sites in the United States from July 2014 through study completion in July 2015 (Fig. 1; Part A [PK and safety]: single site; note that Part B of this study did not include PK assessments and is not described in this report). A sequential-group study design was used to evaluate the PK and safety of repeated doses of difelikefalin in subjects undergoing HD. Subjects received 1 of 3 IV bolus doses of difelikefalin (0.5, 1.0, or 2.5 mcg/kg) or matched placebo in a dose-escalation manner after each of 3 sequential HD sessions (i.e., total of 3 doses over 1 week). Doses were administered within 15 min after completing each HD session. Each dose cohort included 8 subjects (6 difelikefalin, 2 placebo), and dose escalation was conducted sequentially by cohort. Subjects were stratified by presence or absence of urine output (≥1 cup [8 oz]/day by history) and then randomized 3:1 (difelikefalin to placebo) within each dose group. Further information on randomization and blinding is included in Additional file 2.

All study protocols were approved by institutional boards (IRBs) before study commencement (single-dose study: Chesapeake IRB and Aspire IRB; multiple-dose study: Aspire IRB, Western IRBs, St Joseph Health IRB, Vanderbilt University IRB, Emory University IRB,

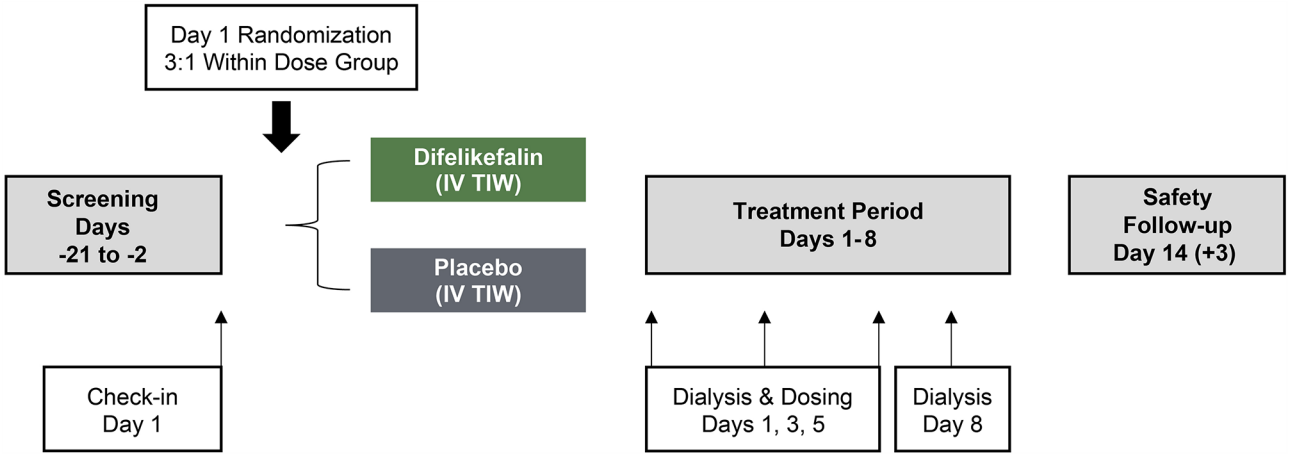

Fig. 1 Multiple-Dose Study Design in Part A. IV, intravenous; TIW, three times a week

Winthrop University Hospital IRB). Subjects provided written informed consent before participating in any study-related procedures. Research was carried out in accordance with the protocols, US regulations, the ethical principles set forth in the Declaration of Helsinki, and Good Clinical Practice guidelines.

Eligibility criteria

The study enrolled adults (≥18 years) with ESRD undergoing HD 3 times per week for at least the past 3 months with a dry body weight ≤135 kg (i.e., the target post-dialysis weight, as determined by the subject's nephrologist or dialysis unit during screening). Subjects were excluded if they had a history of missed HD sessions due to noncompliance in the past 2 months; were anticipated to receive a kidney transplant during the study; or had serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5x the reference upper limit of normal (ULN), or bilirubin >4x the ULN at screening.

Assessments

Pharmacokinetics Blood samples were collected via a peripheral line in the arm opposite to the dosing site at the following time points: dose 1 (day 1) pre-dialysis (i.e., within 5 min prior to starting dialysis); post-dialysis (i.e., within 10 min following the end of dialysis); 0.0833, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, and 44 (day 3, approximately 10 min prior to starting the second dialysis) hours after dosing; dose 2: 1 sample drawn approximately 44 h after dosing (pre-dialysis on day 5); dose 3: pre- and post-dialysis on day 5 (pre-dose) and at 0.0833, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, and approximately 68 (day 8, pre-dialysis) hours after dosing. A final PK sample was drawn post-dialysis on day 8 (approximately 72 h after day 5 dosing).

Safety assessment Safety, including AEs, physical examinations, vital signs, electrocardiograms, and standard laboratory tests, was monitored throughout the study.

Statistical analyses

The planned sample size ($n=6$ for difelikefalin and $n=2$ for placebo in each dose cohort) was considered appropriate for a PK and safety study with a dose-escalation design. The safety population consisted of all randomized subjects who received any study drug at any time during the study. Safety data were summarized descriptively with no formal statistical analysis.

Single-dose and multiple-dose administration

Pharmacokinetics

Plasma and urine samples were analyzed for difelikefalin using liquid chromatography with tandem mass spectrometric detection (AIT Bioscience), with lower limits of quantitation of 0.1 ng/mL in plasma and 1.0 ng/mL in urine. PK parameters were calculated using noncompartmental analysis (Phoenix™ WinNonlin® version 6.3 or later) from the plasma concentration-time data using actual elapsed plasma sampling times. Parameters included C_{max}, terminal elimination half-life ($t_{1/2}$), total clearance (CL for single-dose study and CL_{ss} for multiple-dose study), volume of distribution in the terminal elimination phase (V_z). Area under the plasma concentration-time curve (AUC) was derived for both studies (single-dose study: AUC_{inf}; multiple-dose study: AUC from time 0 to 48 h [AUC_{0-48}] and AUC for the dosing interval [AUC_{tau}] where tau=48 h for the first dose [day 1] and 72 h for the third dose [day 5]). Elimination by hemodialysis was calculated using concentrations immediately before and after hemodialysis on Day 8 (before and after dialysis occurring after the third dose). The accumulation ratio (R_{AC}) was derived for the multiple-dose study based on the ratio of AUC_{0-48} values (day 5:day 1). The fraction of dose excreted unchanged in urine (Fe) was determined only in the single-dose study. For the single-dose study, the plasma protein binding of difelikefalin in human plasma obtained from the dialysis subjects was determined by equilibrium dialysis.

Results

Study subjects

Single-dose administration: For the single-dose study, 36 subjects entered the study: 24 with renal impairment (mild: $n=8$, moderate: $n=8$, severe: $n=8$) and 12 healthy subjects. One subject with severe renal impairment withdrew on day 2 for personal reasons; data for this subject were included in PK analyses when possible. All 36 subjects were included in safety analyses. Healthy control subjects were demographically matched with subjects with renal impairment for mean [SD] age (years; mild: 59.9 [11.7]; moderate: 64.0 [11.2]; severe: 58.4 [8.8]; healthy control: 53.5 [6.8]), mean [SD] weight (kg; mild: 91.1 [13.7]; moderate: 83.9 [11.1]; severe: 87.2 [18.1]; healthy control: 81.8 [12.2]), and sex (male, n [%]; mild: 5 [62.5]; moderate: 4 [50.0]; severe: 6 [75.0]; healthy control: 8 [66.7]). Other demographics and baseline characteristics were mostly similar between subjects with renal impairment and healthy control subjects; however, the healthy control population was predominantly African American and subjects with renal impairment were predominantly White (Additional file 3). At baseline, 4 healthy control subjects had an eGFR<90 mL/min/m^2 based on serum creatinine measurement, but were deemed eligible based on a 24-hour creatinine clearance of >90 mL/min as per protocol.

Multiple-dose administration: In the multiple-dose study in subjects undergoing HD, there were 24 randomized subjects (difelikefalin 0.5 mcg/kg: $n=7$, difelikefalin

1.0 mcg/kg: $n=7$, difelikefalin 2.5 mcg/kg: $n=5$, placebo: $n=5$). All subjects completed the study and were included in safety and exploratory efficacy analyses. The PK population consisted of 19 subjects who received difelikefalin (0.5 mcg/kg: $n=7$, 1.0 mcg/kg: $n=7$, 2.5 mcg/kg, $n=5$). Baseline demographics and disease characteristics were generally similar among treatment groups (Additional file 3). Overall, mean age was 48.2 years and most subjects were male (71%). Mean duration of ESRD and of chronic HD was similar across groups.

PK analyses

Single-dose administration: After single IV doses of difelikefalin, mean plasma difelikefalin exposure generally increased with increasing severity of renal impairment (Fig. 2A and B). Peak plasma difelikefalin concentrations generally occurred with the first post-dose PK sample, at approximately 2 to 3 min across all treatment groups.

Mean C_{max} values were comparable between all renal impairment groups, with no apparent relationship to severity of renal impairment (Table 1). In general, mean exposures (AUC_{inf}) and apparent $t_{½}$ values increased with increasing degree of renal impairment, and clearance values decreased as degree of renal impairment increased (Table 1). Mean values for Fe were comparable in the control and mild impairment groups; however, Fe decreased with increasing renal impairment in the moderate and severe impairment groups (Table 1). The relationship between total clearance (CL) and renal function (represented by eGFR) shows that CL is directly correlated with renal function (Fig. 3).

Difelikefalin exposure in subjects with mild renal impairment was similar to that in subjects with normal renal function (% geometric mean ratio [95% CI]: 113% [98–130%]) (Table 2). Difelikefalin exposure in subjects with moderate renal impairment was 1.7-fold higher than in healthy subjects (171% [146–201%]) (Table 2). Exposure in subjects with severe renal impairment was 3.3-fold higher than in healthy subjects (334% [285–391%]) (Table 2). V_z values were similar among subjects with renal impairment and between subjects with renal impairment and subjects with normal renal function (Table 1).

Difelikefalin plasma protein binding was low to moderate in all groups, regardless of renal function status. The free fraction (f_u) ranged from 0.682 to 0.749 (Table 1).

Multiple-dose administration: Mean difelikefalin plasma concentration-time profiles for HD subjects from day 1 to day 8 are presented in Fig. 2C. After IV administration, difelikefalin concentrations were generally highest at the first sampling time point (5 min), with an elimination phase preceded by a relatively short distribution phase. Mean trough concentrations across days 3 to 8 varied from 0.379 to 0.694 ng/mL, 1.24 to 2.14 ng/mL, and 2.11 to 3.86 ng/mL for difelikefalin doses of 0.5 mcg/kg, 1.0 mcg/kg, and 2.5 mcg/kg, respectively. Difelikefalin reached steady state by day 3 (prior to the second dose). Dialysis effectively removed most difelikefalin (73–80%) from plasma.

HD subject PK parameters for day 1 (first dose) and day 5 (third dose) are presented in Table 1. In an analysis of the dose proportionality of C_{max} and AUC_{0-48} using a power model [15], slope values were all close to unity and the 95% CIs included 1, thus establishing dose proportionality of difelikefalin across the 3 doses studied. Mean $t_{1/2}$, CL_{ss} and V_z were comparable across the 3 difelikefalin doses; mean $t_{1/2}$ ranged from 23.2 to 31.1 h on day 1 and from 26.4 to 34.2 h on day 5 (Table 1). At day 5, the mean accumulation ratio (R_{AC} [range: 1.0–1.2]) was low in the 3 difelikefalin dose groups.

Safety

Single-dose administration: After single doses of difelikefalin, a total of 37 treatment-emergent AEs (TEAEs) were reported by 17/36 (47.2%) subjects; 17 TEAEs were considered related to study drug, and none were serious AEs (SAEs) (Additional file 4). Two laboratory AEs (increased ALT and AST; both laboratory values were increased by <2x ULN) were experienced by 1/36 (2.8%) subject; both AEs were considered unlikely to be related to study drug. Most TEAEs were mild in severity; 7 were moderate. The incidence of TEAEs was slightly higher in subjects with severe renal impairment compared with the other groups (Additional file 4). Mild paresthesia was the most common TEAE (reported by 5/36 [13.9%] subjects [3 with normal renal function and 1 subject each with mild and moderate renal impairment]); most TEAEs of paresthesia were transient and considered to be possibly related to study drug. Dizziness was reported by 4/36 (11.1%) subjects (2 subjects with moderate renal impairment and 2 with severe renal impairment); all of these TEAEs were mild or moderate and 2 cases were considered related to study drug. Mild headache was reported by 4/36 (11.1%) subjects (1 subject in each group); 3 of these TEAEs were considered probably or possibly related to study drug. Vomiting was reported in 3/36 (8.3%) subjects (2 with moderate renal impairment and 1 with severe renal impairment); these TEAEs were mild or moderate and 2 were considered probably or possibly related to study drug.

Multiple-dose administration: The most commonly reported TEAE with difelikefalin was paresthesia (difelikefalin 0.5-mcg/kg group: 57.1% [4/7]; 1.0-mcg/kg group: 14.3% [1/7]; 2.5-mcg/kg group: 20.0% [1/5]; Additional file 4), which was generally mild and transient with no apparent dose response; paresthesia was not reported in the placebo group. Headache was reported more frequently in the difelikefalin 0.5-mcg/kg group (57.1%

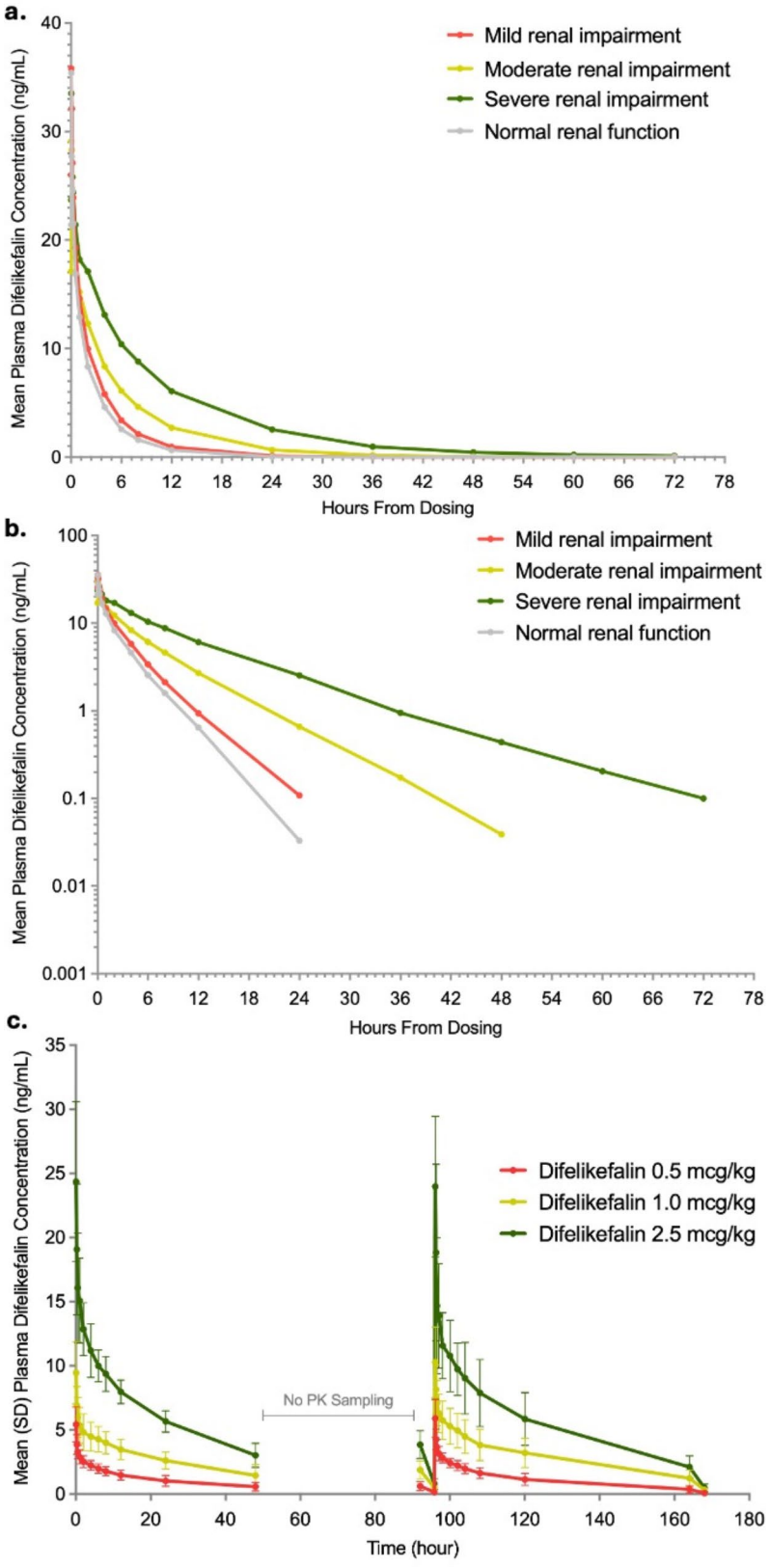

Fig. 2 Mean Difelikefalin Concentrations in NDD Subjects with Varying Degrees of (**a**, **b**) Renal Impairment and (**c**) HD Subjects*. *No PK assessments were performed between 48 and 92 h. Concentrations from day 1 to day 8 (linear scale) in the PK population. For the calculation of means, individual concentration values that were below the limit of quantitation (BLQ of 0.100 ng/mL) were treated as zero. IV bolus was administered after each dialysis session; dialysis occurred on days 1, 3, 5, and 8. PK, pharmacokinetic; SD, standard deviation

Table 1 Mean (SD) plasma PK parameters in NDD subjects with varying degrees of renal impairment and HD subjects

	Single-Dose PK Parameters Difelikefalin 3.0 mcg/kg			
Parameter, Mean (SD)	**Mild Renal Impairment (*n* = 8)**	**Moderate Renal Impairment (*n* = 8)**	**Severe Renal Impairment (*n* = 8)**	**Normal Renal Function (*n* = 12)**
C_{max}, ng/mL	47.0 (19.8)	32.9 (7.1)	41.1 (16.8)	40.5 (15.4)
AUC_{inf}, ng·h/mL	76.6 (15.9)	121 (28.7)	234 (48.4)	61.5 (10.2)
$t_{1/2}$, h	3.7 (0.7)	6.0 (1.2)	10.7 (1.8)	3.1 (0.8)
CL, mL/min	61.5 (15.1)	35.8 (7.5)	19.1 (4.5)	67.6 (11.5)
V_z, L	18.8 (2.6)	18.1 (3.7)	17.1 (2.8)	18.0 (5.1)
Fe, %	89.3 (5.1)	80.4 (8.4)	68.8 (12.0)	87.3 (6.3)
CLr, mL/min	55.1 (14.9)	28.6 (5.8)	12.8 (3.3)	58.8 (9.6)
f_u	0.749 (0.035)	0.682 (0.038)	0.714 (0.031)	0.718 (0.022)

	Multiple-Dose PK Parameters in HD Subjects					
Parameter,mean (SD)*	**Difelikefalin 0.5 mcg/kg (*n* = 7)**		**Difelikefalin 1.0 mcg/kg (*n* = 7)**		**Difelikefalin 2.5 mcg/kg (*n* = 5)**	
	Day 1	**Day 5**	**Day 1**	**Day 5**	**Day 1**	**Day 5**
C_{max}, ng/mL	5.43 (1.35)	5.90 (1.49)	9.46 (2.43)	9.92 (2.68)	24.4 (6.24)	24.0 (5.46)
AUC_{tau}, ng·h/mL	56.5 (15.7)	78.6 (28.7)	130 (31.9)	205 (66.0)	298 (33.4)	389 (120)
AUC_{0-48}, ng·h/mL	56.5 (15.7)	64.4 (17.6)	130 (31.9)	158 (47.2)	298 (33.4)	307 (92.6)
CL_{ss}, mL/min	—	12.76 (7.08)	—	8.02 (1.47)	—	9.37 (3.09)
V_z, L	—	23.65 (5.62)		23.10 (5.43)	—	24.81 (8.68)
$t_{1/2}$, h	—	26.4 (12.3)	—	34.2 (9.9)	—	30.9 (7.2)
R_{AC}	—	1.144 (0.139)	—	1.208 (0.108)	—	1.023 (0.251)

Values for the single-dose study are presented using the same units as the multiple-dose study. Summary statistics were rounded to 3 significant figures

*PK parameters for day 1 are for the first dose; steady-state PK parameters for day 5 are for the third dose

$AUC_{0\text{-}44,}$ area under the plasma concentration-time curve from time 0 to 44 h; $AUC_{tau,}$ area under the plasma concentration-time curve over the dosing interval (approximately 48 h for the first dose on day 1 and 72 h for the third dose on day 5); $CL_{ss,}$ total steady-state clearance; $C_{max,}$ maximum plasma concentration; CV, coefficient of variation; Fe, percent dose excreted unchanged in urine; f_u, unbound (free) fraction of difelikefalin in plasma; min-max, minimum-maximum; NDD, non–dialysis-dependent; R_{AC}, accumulation ratio based on AUC.; SD, standard deviation; $t_{1/2,}$ terminal elimination half-life; $T_{max,}$ time to maximum plasma concentration; $V_{z,}$ volume of distribution in the terminal elimination phase; $\lambda_{z,}$ the observed elimination rate constant

[4/7]) versus placebo (20.0% [1/5]). Somnolence was reported in 40.0% (2/5) of subjects in the difelikefalin 2.5-mcg/kg group; TEAEs of somnolence were mild or moderate, no action was taken with study drug dosing, and no additional treatments were given. There were no SAEs, severe TEAEs, TEAEs that led to drug discontinuations, or deaths during the multiple-dose PK study. No adverse trends in clinical chemistry or pre-dialysis hematology values, or apparent reductions in blood pressure, oxygen saturation, or respiratory rate were observed following difelikefalin dosing.

Discussion

These studies evaluated the PK and safety of IV difelikefalin in subjects with impaired renal function including subjects undergoing HD. After single-dose administration in NDD subjects, overall mean exposure was higher in subjects with moderate or severe renal impairment compared with healthy control subjects or mild renal impairment, demonstrating that compromised renal function affects difelikefalin clearance. This finding is in line with a previous study showing that difelikefalin is mainly renally excreted [13]. In all renal impairment groups, binding of IV difelikefalin to protein in human plasma was low, regardless of the degree of renal impairment, suggesting that renal impairment does not have a meaningful effect on the degree of difelikefalin protein binding.

The mean concentration-time profile for subjects with mild renal impairment was comparable to that of normal healthy subjects. Total body clearance was directly correlated with renal function (i.e., clearance increased with improved renal function). Subsequently, total exposure of difelikefalin was inversely correlated with renal function (i.e., increased exposure with decreased renal function). Compared with control subjects, the geometric mean ratios for AUC_{inf} were 113%, 171%, and 334% for mild, moderate, and severe impairment groups, respectively.

After multiple-doses in subjects with ESRD undergoing HD, IV difelikefalin demonstrated dose proportionality across the 0.5-, 1.0-, and 2.5-mcg/kg doses. Dialysis cleared 73–80% of circulating difelikefalin from plasma after approximately 4 h of dialysis. Following repeat dosing, steady state was achieved by the second dose (day 3) at all dose levels, indicating that IV difelikefalin is not

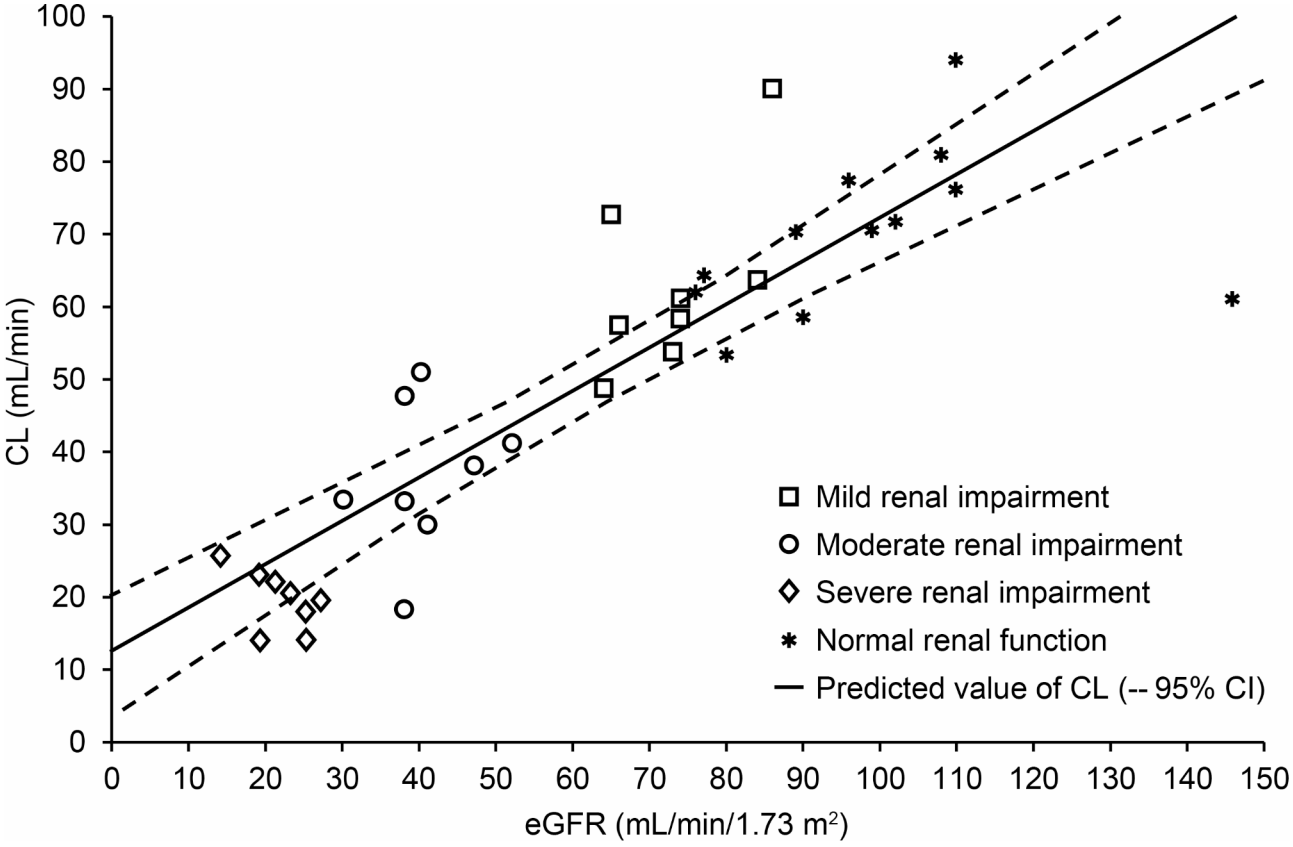

Fig. 3 Individual Total CL Versus eGFR Following Difelikefalin in NDD Subjects with Impaired or Normal Renal Function Treatment = IV difelikefalin 3.0 mcg/kg. CL value = intercept + slope * eGFR. Slope = 0.600157 (95% CI: 0.482284–0.718031). Intercept = 12.102759 (95% CI: 3.734794–20.470724). 95% CI is based on mean predicted values. $P < 0.0001$. CL, total clearance, eGFR, estimated glomerular filtration rate; NDD, non–dialysis-dependent

Table 2 Plasma difelikefalin PK parameters in subjects with impaired Versus normal renal function: PK Population

			Geometric LS means			
Parameter	**Test**	**Reference**	**Test**	**Reference**	**% Geometric mean ratio**	**90% Confidence interval**
AUC_{inf} (ng·h/mL)	Mild	Control	74.82	66.30	112.85	97.75–130.29
	Moderate	Control	113.29	66.30	170.86	145.56–200.57
	Severe	Control	221.37	66.30	333.89	285.24–390.83
	Moderate	Mild	113.29	74.82	151.40	129.69–176.75
	Severe	Mild	221.37	74.82	295.86	253.10–345.84
	Severe	Moderate	221.37	113.29	195.41	167.86–227.49
C_{max} (ng/mL)	Mild	Control	45.11	37.41	120.58	89.04–163.31
	Moderate	Control	32.07	37.41	85.73	61.12–120.25
	Severe	Control	37.43	37.41	100.06	71.77–139.51
	Moderate	Mild	32.07	45.11	71.10	51.28–98.57
	Severe	Mild	37.43	45.11	82.98	59.69–115.36
	Severe	Moderate	37.43	32.07	116.72	84.68–160.86

Parameters were ln-transformed prior to analysis

Geometric mean values for parameters are the exponentiated (back-transformed) LS means from the ANCOVA

The ANCOVA model includes group as a fixed effect with continuous covariates of age, weight, and BMI and a categorical covariate of gender

Geometric Mean Ratio = 100*(test/reference)

Mild = subjects with mild renal impairment

moderate = subjects with moderate renal impairment

severe = subjects with severe renal impairment

control = subjects with normal renal function

ANCOVA, analysis of covariance; AUC_{inf}, area under the plasma concentration-time curve from time 0 to infinity; BMI, body mass index; C_{max}, maximum plasma concentration

likely to accumulate in HD subjects with repeat administration over longer time periods.

The mean (SD) volume of distribution after IV administration of difelikefalin was 24.8 (8.68) L in subjects undergoing HD and 18.0 (5.11) L in subjects with normal renal function after administration of 2.5 to 3 mcg/kg. Total body clearance in subjects with mild renal impairment was comparable to that of healthy subjects. However, difelikefalin clearance in subjects with moderate and severe renal impairment was reduced by 47.0% and 71.7%, respectively, compared with healthy subjects. Clearance in HD subjects prior to dialysis was 14% of that observed in healthy subjects (cross-study comparison; reference is 2.5 mcg/kg HD group). Total systemic clearance was low in HD subjects, thus difelikefalin should be administered only once following each dialysis session (i.e., 3 times a week). The proposed dosing regimen is convenient for this patient population and should ensure treatment compliance in a population already burdened with complex medication schedules.

After an initial distribution phase, plasma concentrations of difelikefalin in HD subjects decrease slowly until mostly cleared during dialysis as difelikefalin concentrations observed 2 to 3 days after dosing and immediately prior to dialysis, were reduced by 73–80% at the end of dialysis. Dialysis effectively clears most difelikefalin from plasma. It was previously demonstrated that once treatment discontinued in hemodialysis patients, a single dialysis cycle reduced plasma concentrations by approximately 83%, and difelikefalin was no longer detectable in plasma after 2 dialysis cycles [11]. Based on the nominal dose administered, the percent of the difelikefalin dose excreted unchanged in urine following IV administration decreased with increasing renal impairment with approximate median values of 89%, 80%, and 69% in subjects with mild, moderate, and severe renal impairment compared with 87% in subjects with normal renal function.

The half-life increased by approximately 10-fold in HD subjects compared with subjects with normal renal function, with $t_{1/2}$ ranging between 10.7 h for severe renal impairment and 26.4 to 34.2 h in HD subjects prior to dialysis, compared with 3.1 h in subjects with normal renal function. Linear and dose-proportional PK were exhibited in HD subjects exposed to 1 week of repeated IV bolus doses ranging from 0.5 to 2.5 mcg/kg (i.e., total of 3 doses/week post-dialysis). Minimal accumulation was observed (RAC: 1.0–1.2).

Safety findings from these two studies showed that difelikefalin was well tolerated in NDD subjects with renal impairment and in subjects with ESRD undergoing HD. In both studies, there were no reports of side effects commonly associated with centrally acting kappa opioids (e.g., dysphoria and hallucinations) [16–19], or common mu-opioid side effects of constipation and euphoria [19]. Both studies had small sample sizes; thus, generalizability of the safety findings is limited. However, the safety profiles in both studies were consistent with the safety profile of IV difelikefalin in larger phase 2 and phase 3 studies [4, 5, 20, 21].

In summary, IV difelikefalin was well tolerated in all subjects, and dose proportionality was demonstrated in subjects with ESRD undergoing HD who were administered IV difelikefalin 3 times per week following dialysis. Difelikefalin was primarily eliminated via renal excretion, and difelikefalin total body clearance was directly correlated with renal function (eGFR). In subjects undergoing HD, difelikefalin was mostly cleared by dialysis. Exposure was similar in healthy subjects and NDD subjects with mild renal impairment and was higher in NDD subjects with moderate and severe renal impairment (i.e., exposure in severe NDD > moderate NDD > mild NDD ≈ healthy subjects).

Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC_{0-48}	Area Under the plasma concentration-time Curve from time 0 to 48 h
AUC_{0-tau}	Area Under the plasma concentration-time Curve (time 0 to days 1 and 5)
AUC_{inf}	Area Under the plasma concentration-time Curve from time 0 to infinity
BMI	Body Mass Index
C_0	predicted plasma concentration at time zero
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-aP	CKD–associated Pruritus
CL	total Clearance
CL_{ss}	total steady-state Clearance
C_{max}	maximum plasma concentration
CNS	Central Nervous System
CSA	Controlled Substance Act
CV	Coefficient of Variation
eGFR	estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
Fe	Fraction of dose excreted unchanged in urine
f_u	free fraction
HD	Hemodialysis
IRB	institutional Review Board
IV	Intravenous
KOR	Kappa Opioid Receptor
LSM	Least-Squares Mean
MDRD	Modification of Diet in Renal Disease
min-max	minimum-maximum
PK	Pharmacokinetic(s)
QoL	Quality of Life
R_{AC}	accumulation ratio based on AUC
SAE	Serious Adverse Event
SD	Standard Deviation
$t_{1/2}$	terminal elimination half-life
TEAE	Treatment-Emergent Adverse Event
TIW	Three Times a Week
T_{max}	Time to maximum plasma concentration
ULN	Upper Limit of normal
V_z	Volume of distribution
λ_z	elimination rate constant

Supplementary Information

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Supplementary Material 1: Additional File 1 Additional eligibility Criteria, Exclusion criteria for phase 1 study.

Supplementary Material 2: Additional File 2 Randomization and Blinding in the Multiple-Dose Study, Further information on randomization and blinding.

Supplementary Material 3: Additional File 3 Demographics and Baseline Characteristics, Additional demographics and baseline characteristics of subjects in single-dose study and multiple-dose study.

Supplementary Material 4: Additional File 4 Overview of TEAEs and Most Common (≥5%) TEAEs in the Single- and Multiple-Dose Studies (Safety Population).

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Author contributions
All authors contributed to the study conception and design. Material preparation was performed by all authors. TM contributed to study conduct and the collection of data. RS, FM, and PKN were responsible for the interpretation of the data and writing the first draft of the manuscript. All authors reviewed and participated in the editing of the different versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
Please contact Cara Therapeutics for data inquiries.

Declarations

Ethics approval and consent to participate
Both the phase 1 and phase 2 study protocols were approved by institutional boards (IRBs) before study commencement (CR845-CLIN 1005: Chesapeake IRB and Aspire IRB; CR845-CLIN 2005: Aspire IRB, Western IRBs, St Joseph Health IRB, Vanderbilt University IRB, Emory University IRB, Winthrop University Hospital IRB). Subjects provided written informed consent before any study-related procedures. Research was carried out in accordance with the protocols, US regulations, the ethical principles set forth in the Declaration of Helsinki, and Good Clinical Practice guidelines.

Consent for publication
Not applicable.

Competing interests
RS: Cara Therapeutics, Inc. – employment. PN: Cara Therapeutics, Inc. – consultant. TM: Orlando Clinical Research Center – employment. FM: Cara Therapeutics, Inc. – employment.

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