EU Risk Management Plan

for

Kapruvia (Difelikefalin)®

RMP version to be assessed as part of this application:

RMP Version number:	3.2
Data Lock Point for this RMP:	22 August 2025
Date of final sign off:	16 April 2026
Rationale for submitting an updated RMP:	Submission of final study results for the phase 3 trials of oral difelikefalin (CR845-310501, CR845-310301 and CR845-310302; Additional Pharmacovigilance Activities) Removal of the important potential risk of 'Cardiac Failure and Arrhythmias Including Atrial Fibrillation (AF) in Hemodialysis (HD) Patients with a Medical History of AF' from the list of safety concerns in response to Pharmacovigilance Risk Assessment Committee (PRAC) preliminary assessment report for Procedure No. EMA/VR/0000316094 and in line with Good Pharmacovigilance Practices (GVP) Module V (Rev. 2)

Summary of significant changes in this RMP:	Part II Module SV per up-to-date exposure figures, inclusion of postmarketing methodology Part III.2 and Part III.3: Per clinical trials update Part II Modules SVII.2, SVII.3.1, SVIII, Part V Modules V.1, V.3 and Part VI Modules II.A, II.B updated to reflect the removal of the important potential risk of 'Cardiac Failure and Arrhythmias Including Atrial Fibrillation (AF) in Hemodialysis (HD) Patients with a Medical History of AF' from the list of safety concerns. Part III.1 and Annex 4 were updated in RMP version 3.1 to remove the Specific Adverse Reaction Follow-Up Questionnaire; however, this questionnaire for 'Cardiac Failure and Arrhythmias Including Atrial Fibrillation in Patients on HD with a Medical History of AF' was subsequently reintroduced unchanged in RMP version 3.2 in response to the EMA request. Annexes 2 and Annexes: per clinical trials update

Details of the currently approved RMP:

RMP Version number:	2.0
Approved with procedure:	EMEA/H/C/005612/IB/0002
Date of approval (opinion date):	21 September 2022
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Following the acquisition of Vifor Pharma by CSL on 09 August 2022, Vifor Pharma is now operating under the brand CSL Vifor and is a dedicated business unit of CSL. The Vifor Pharma legal entities will continue to use the Vifor Pharma entity names until the appropriate legal and regulatory approvals are obtained.

Abbreviations

Term / Abbreviation	Description
AD	Atopic Dermatitis
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
BBB	Blood-Brain Barrier
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-aP	Chronic Kidney Disease-associated Pruritus
CNS	Central Nervous System
CV	Cardiovascular
CYP	Cytochrome P450
DLP	Data Lock Point
DOPPS	Dialysis Outcomes and Practice Patterns Study
ECG	Electrocardiogram
EMA	European Medicines Agency
ESRD	End-stage Renal Disease
EU	European Union
HD	Haemodialysis
HR	Hazard Ratio
IR	Incidence Rate
ISS	Integrated Summary of Safety
IV	Intravenous
KOR	Kappa Opioid Receptor
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PT	Preferred Term
QoL	Quality of Life
RMP	Risk Management Plan
RR	Relative Risk
SmPC	Summary of Product Characteristics

Term / Abbreviation	Description
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
US	United States

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Part I: Product(s) Overview

Table Part I-1: Product(s) Overview

Active substance(s) (INN or common name)	Difelikefalin
Pharmacotherapeutic group(s) (ATC Code)	All other therapeutic products, other therapeutic products (V03AX04)
Name of Marketing Authorisation Holder / Applicant	Vifor Fresenius Medical Care Renal Pharma France
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Kapruvia
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: KOR agonist
	Summary of mode of action: Difelikefalin is a selective KOR agonist with a peripheral mechanism of action.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	See Section 1.3.1
Indication(s) in the EEA	Current: Treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients on haemodialysis.
	Proposed: Not applicable
Dosage in the EEA	Current: 0.5 µg/kg dry body weight (ie, the target post dialysis weight) 3 times per week
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 50 µg/ml solution for injection
	Proposed: Not applicable

Is / will the product be subject to additional monitoring in the EU?	Yes

ATC = Anatomical Therapeutic Chemical; EEA = European economic area; EU = European Union; INN = International Nonproprietary Name; KOR = kappa opioid receptor; RMP = risk management plan

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication and target population

Indication

Kapruvia is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease (CKD) in adult patients on haemodialysis (HD).

CKD-associated pruritus (CKD-aP), also known as uraemic pruritus, is a common, bothersome and under-recognised condition in patients with CKD, including those on dialysis (Mettang and Kremer, 2015; Rayner et al, 2017). CKD-aP can be defined as itching related to kidney failure, with no other comorbid condition explaining the itch (Verduzco and Shirazian, 2020). The clinical presentation of CKD-aP varies widely between patients (Verduzco and Shirazian, 2020). It can occur without any skin changes, can cooccur with dry skin (in 50-85% patients) or may present alongside secondary skin manifestations caused by intense scratching activity, including excoriations with and without impetigo, linear crusts, papules, ulcerations and prurigo nodularis (Verduzco and Shirazian, 2020). The distribution of itching with CKD-aP is often symmetrical, and can either be generalised (in up to 50% of patients) or localised, predominantly to the back, face and dialysis access arm (Mettang and Kremer, 2015; Shirazian et al, 2017; Verduzco and Shirazian, 2020). The severity, persistence and spatial distribution of CKD-aP may also fluctuate widely over time (Verduzco and Shirazian, 2020). Severity of itching can progress from itching that is barely noticeable, to more extreme itching that causes constant restlessness (Mettang and Kremer, 2015; Shirazian et al, 2017).

CKD-aP is associated with several adverse clinical and psychosocial outcomes in patients on HD (Verduzco and Shirazian, 2020), including discomfort, restlessness, poor sleep quality, depression, reduction in quality of life (QoL) and reduced adherence to dialysis (Rayner et al, 2017; Verduzco and Shirazian, 2020). Patients on HD with moderate-to-extreme pruritus have greater all-cause, cardiovascular (CV)- and infection-related mortality rates than patients without pruritus (Pisoni et al, 2006). The higher mortality rates associated with extreme pruritus may be related to several factors including, sleep disruption, missed HD sessions and

higher levels of inflammation and immune system dysregulation in these patients (Fishbane et al, 2020; Pisoni et al, 2006; Ramakrishnan et al, 2014).

The diagnosis of CKD-aP is challenging due to its variable clinical presentation (Verduzco and Shirazian, 2020). Diagnosis is further complicated in patients with CKD who may also experience itching associated with comorbidities, such as diabetes mellitus, CV disease or chronic liver disease, as well as the medications administered to manage these comorbidities (Mettang and Kremer, 2015; Verduzco and Shirazian, 2020). As such, CKD-aP often remains unrecognised and may be substantially underreported (Verduzco and Shirazian, 2020). The Dialysis Outcomes and Practice Patterns Study (DOPPS) is an international prospective cohort study that captures data on demographics, comorbidities, medication use and clinical outcomes for adult patients on HD from dialysis facilities in 20 countries, and monitors clinical practice patterns in these facilities (Kimmel et al, 2006). One analysis of the DOPPS database indicated a lack of awareness of CKD-aP among medical staff, with approximately 69% of medical directors surveyed shown to underestimate the prevalence of pruritus in their dialysis facility (Rayner et al, 2017).

The scientific understanding of CKD-aP pathogenesis is evolving (Verduzco and Shirazian, 2020). Emerging evidence suggests that while probably multifactorial, it predominately involves immune system dysfunction (microinflammation in the skin, and possible systemic inflammation), an imbalance in the endogenous opioid system (overexpression of mu-opioid receptors signalling and downregulation of kappa opioid receptor [KOR] signalling). Toxin deposition (of vitamin A, aluminium, calcium, phosphorus and magnesium) and peripheral neuropathy (activation of diseased afferent sensory neurons or interneurons) may contribute to the itch (Kimmel et al, 2006; Mettang and Kremer, 2015; Tey and Yosipovitch, 2011; Verduzco and Shirazian, 2020).

Incidence and prevalence:

There is a wide range of prevalence estimates of CKD-aP in patients on dialysis, which may be partly due to variation in patient characteristics between studies, as well as the lack of a universal measure for defining CKD-aP (Shirazian et al, 2017; Verduzco and Shirazian, 2020). In 2010, it was estimated that 2.62 million people received dialysis treatment globally, and the need for dialysis was projected to double by 2030 (Liyanage et al, 2015). Data from an international DOPPS study showed as many as 70% of patients on HD reported pruritus, with approximately 40% reporting moderate-to-extreme pruritus (Pisoni et al, 2006). In Europe, the prevalence of patients on HD with moderate-to-extreme pruritus ranged from

26% in Germany to 48% in the United Kingdom (Rayner et al, 2017). The prevalence of pruritus (any severity) in patients undergoing peritoneal dialysis ranges from 28 to 65% (Li et al, 2015; Min et al, 2016; Wu et al, 2016). There are mixed results regarding whether the prevalence of CKD-aP differs significantly between patients undergoing peritoneal dialysis or HD (Min et al, 2016; Verduzco and Shirazian, 2020; Wu et al, 2016).

Demographics of the target population (age, gender, racial and / or ethnic origin) and risk factors for the disease:

Evidence from large-scale studies of dialysis patients suggests that gender and age may be associated with the prevalence of CKD-aP. Multivariable logistic regression analyses of the DOPPS population identified that patients on HD with at least moderate CKD-aP were slightly older (adjusted odds ratio for age per 10 years = 1.06) (Rayner et al, 2017). Analyses of the DOPPS database found that male patients on HD were more likely to have moderate-to-extreme CKD-aP than female patients on HD (adjusted odds ratio = 1.1, $p < 0.005$) (Pisoni et al, 2006). However, a retrospective analysis of > 73,000 United States (US) patients with end-stage renal disease (ESRD) undergoing dialysis and having CKD-aP symptoms, found that patients who self-reported higher degrees of itching were more likely to be female and younger (Ramakrishnan et al, 2014). Hence, the relationship between CKD-aP severity and age / gender has not been fully defined. In the same retrospective analysis of US dialysis patients, the severity of CKD-aP symptoms did not appear to be influenced by race (Ramakrishnan et al, 2014).

CKD-aP is a serious itching condition that is directly related to kidney failure, and frequently observed in those with CKD or ESRD who are undergoing dialysis (Mettang and Kremer, 2015; Verduzco and Shirazian, 2020).

Studies in patients with CKD undergoing dialysis have shown that CKD-aP severity is associated with a higher level of median C-reactive protein; lower levels of serum albumin, haemoglobin; and presence of hepatitis B or C (Kimata Kiata et al, 2014; Pisoni et al, 2006; Ramakrishnan et al, 2014; Rayner et al, 2017). Furthermore, patients on dialysis with certain comorbid conditions, including diabetes mellitus, CV disease, chronic obstructive pulmonary disease, liver disease, hypertension, lung disease, congestive heart failure are more likely to self-report higher degrees of itching (Pisoni et al, 2006; Ramakrishnan et al, 2014). The most common comorbidity in patients undergoing HD is CV disease, occurring in up to 70% of patients, with the most prevalent conditions (> 20%) being coronary artery disease, heart failure, peripheral arterial disease and atrial fibrillation (AF) (United States Renal Data

System, 2018). Cardiac events are the leading cause of death for patients undergoing HD, with cardiac arrest being the most common reason. Other common CV causes of death are acute myocardial infarction, congestive heart failure and cerebrovascular disease and arrythmia (United States Renal Data System, 2019).

Main existing treatment options:

Currently, there are no approved treatments specifically targeting CKD-aP in Europe, and commonly prescribed therapies offer limited efficacy or are associated with significant side effects (Fishbane et al, 2020).

On 23 August 2021, the US Food and Drug Administration approved difelikefalin (Korsuva™) injection for the treatment of moderate-to-severe pruritus associated with CKD in adult patients undergoing HD.

An analysis of the international DOPPS database showed that, in the real-world clinical practice, nephrologists most commonly manage severe pruritus by reducing serum phosphorus or parathyroid hormone levels in patients with hyperphosphataemia or hyperparathyroidism, adjusting dialysis prescriptions and prescribing medications aimed at relieving pruritus. Medications for patients with itching symptoms included oral and topical antihistamines, corticosteroids, gabapentin and pregabalin (Rayner et al, 2017). Nalfurafine, a centrally acting, small molecule KOR agonist, is an approved treatment for CKD-aP. However, this drug is not approved in Europe (in January 2014, the Marketing Authorisation Application was withdrawn based on Committee for Medicinal Products for Human Use opinion that the benefit of nalfurafine in the treatment of uraemic pruritus had not been sufficiently demonstrated) and currently is approved only in Japan and South Korea.

The current 2025 European S2k Guideline on Chronic Pruritus specifically recommends difelikefalin for the treatment of CKD-aP. In addition, the following off-label treatments are also recommended for the management of CKD-aP, but reporting also a caveat of association with much higher hazards of altered mental status, falls and fractures: the antiepileptic drugs gabapentin and pregabalin. Other therapies such as selected antidepressants (eg, sertraline and doxepin); the opioid receptor agonist, nalfurafine or nalbuphine (not licensed in Europe) or leukotriene receptor antagonists are only reported as suggested options (Weisshaar et al, 2025). Many of these medications have been used largely as off-label treatments for CKD-aP (Combs et al, 2015; Mettang, 2010; Reszke and Szepietowski, 2018), however, the off-label therapies are not always well tolerated by patients, and the evidence of their antipruritic

efficacy is limited and lacking support from randomised, well-controlled studies (Simonsen et al, 2017).

Natural history of the indicated condition in the population, including mortality and morbidity:

Dialysis patients with moderate-to-extreme pruritus have a higher rate of all-cause, CV- and infection-related mortality than patients who are not bothered by pruritus, which may in part be related to sleep disturbance, missed HD sessions and higher levels of inflammation and immune system dysregulation that are associated with severe pruritus (Fishbane et al, 2020; Pisoni et al, 2006; Ramakrishnan et al, 2014; Shirazian et al, 2017). Furthermore, CKD-aP adversely affects QoL, with itching severity significantly associating with lower health-related QoL scale scores (Mathur et al, 2010). Patients with moderate-to-extreme pruritus can experience impairment of sleep and social functioning, which if left untreated can cause the development of depression (Mathur et al, 2010; Shirazian et al, 2017). Poor mood, reductions in QoL and depression symptoms of CKD-aP may further increase mortality risk in HD patients with CKD-aP compared with those without the condition (Shirazian et al, 2017).

Important comorbidities:

The following comorbidities and laboratory findings are associated with greater risk of CKD-aP in patients undergoing dialysis: diabetes mellitus, lung disease, CV disease, cancer, chronic obstructive pulmonary disease, neurological disease, liver disease, higher body mass index, smoking, hypertension, elevated white blood cell count, lower haemoglobin and lower serum albumin (Ramakrishnan et al, 2014; Shirazian et al, 2017). Diabetes and hypertension are highly prevalent in this population and are the primary causes of CKD (Atkins, 2005; Weisbord et al, 2005). The most common comorbidity in patients undergoing HD is CV disease, occurring in up to 70% of patients, with the most prevalent conditions (> 20%) being coronary artery disease, heart failure, peripheral arterial disease and AF (United States Renal Data System, 2018). In addition, approximately 20-40% of patients undergoing HD suffer from moderate-to-severe pruritus, a generalised, persistent and intractable itch (Shirazian et al, 2017), which further impairs health and QoL and severely impacts patients' mental health (Pisoni et al, 2006; Plewig et al, 2019). In addition, patients on HD who are extremely bothered by itchy skin have a higher rate of all-cause mortality (hazard ratio [HR] = 1.24, 95% confidence interval [CI]: 1.08, 1.41) than patients on HD who are not bothered by itchy skin, including higher rates of CV-related mortality (HR = 1.29, 95% CI: 1.06, 1.57) and

infection-related mortality (HR = 1.44, 95% CI: 1.05, 1.96) (Sukul et al, 2020). Additionally, a retrospective analysis identified an increased burden of infection-related conditions, including septicaemia and bacteraemia in patients with CKD-aP (Ramakrishnan et al, 2014).

Part II: Module SII - Nonclinical part of the safety specification

Toxicity

Key safety findings from nonclinical toxicity studies with difelikefalin and their relevance to human usage are summarised below in Table SII-1.

Table SII-1: Key Nonclinical Safety Findings - Toxicity

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Single-dose Toxicity	
Decreased activity / lethargy associated with decreased body weight gain and food consumption at ≥ 50 mg/kg was observed in rats following a single IV dose, but no mortality occurred at doses up to 100 mg/kg (CR845-TOX042). Similar findings were observed in monkeys with a maximum tolerated single dose of 8 mg/kg IV (CR845-TOX043). These doses, corrected by allometric scaling, far exceed the human clinical dose of 0.5 µg/kg.	No evidence for any potential risk to human.
Repeat-dose Toxicity	
In rats (CR845-TOX044, SBL069-078, SBL069-104) and monkeys (CR845-TOX045, SBL069-076, SBL069-103, CR845-TOX085) dosed with IV difelikefalin for up to 26 and 39 weeks, respectively, the primary effects were related to decreased activity / altered behaviour and potentially secondary sequelae (eg, decreased food consumption, body weight changes). The effects were transient and resolved after 1 to 2 weeks of dosing. Two 39-week monkey studies were conducted (SBL069-103, CR845-TOX085). In 1 study (CR845-TOX085), a single female at 1 mg/kg/day was euthanised prematurely on Day 253 due to notable weight loss and a moderately enlarged, nonpainful abdomen. Histopathological evaluation of this animal revealed findings attributable to weight loss. The death was considered unlikely related to the test item although a relationship could not be completely ruled out. An exacerbation of the common, age-related, rodent-specific renal changes, ie, chronic progressive nephropathy, was noted predominantly in males at 25 mg/kg/day for up to 6 months (SBL069-104). The associated lesions are rodent-specific, and a common background finding in aged animals, and the changes are not considered to represent a risk to humans. An inconsistent effect on the rat testis (seminiferous tubule atrophy / degeneration with cellular debris in the epididymal lumen) was observed predominantly at the high dose of 25 mg/kg. The finding was initially noted in the 28-day study (CR845-TOX044). When the housing was switched from wire-bottomed cages to polycarbonate, solid-bottomed cages in the 13-week study (SBL069-078), the finding was not observed at comparable doses. Testicular findings were, however, increased at 25 mg/kg/day in the 6-month IV study (SBL069-104). There were no	No evidence for any potential risk to human.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
effects on male fertility in a reproductive toxicity study at 25 mg/kg/day IV (please see below), and similar findings were not observed in the monkey. The NOAEL in the rat chronic study was 2.5 mg/kg/day in males (210-fold clinical exposure based on AUC) and 25 mg/kg/day in females (2200-fold clinical exposure based on AUC). The NOAEL in monkeys was 1 mg/kg/day (4800-fold clinical exposure based on AUC) in one of the 39-week studies (SBL069-103). A conservative NOAEL in the second study was considered to be 0.25 mg/kg/day (650-fold (females) and 800-fold (males) clinical exposure based on AUC) because of the premature death (CR845-TOX085).	
Genotoxicity	
Difelikefalin was not mutagenic in the Ames test (CR845-TOX029) and not clastogenic in the in vitro chromosomal aberration assay (CR845-TOX031) or in vivo mouse micronucleus test (CR845-TOX054).	No evidence for any potential risk to human.
Carcinogenicity	
There was no evidence of carcinogenic potential following daily administration of difelikefalin at SC doses of up to 30 mg/kg/day (> 1000-fold clinical exposure based on AUC) for 26 weeks in transgenic rasH2 mice (CR845-CARC086) or up to 1 mg/kg/day (> 1000-fold clinical exposure based on AUC) for 104 weeks in rats (CR845-CARC088). In mice, there was an increased incidence of small, focal, unilateral renal infarcts, which were generally of minimal-to-moderate severity, observed at a low incidence in control mice, and of unknown pathogenesis. These findings did not demonstrate a clear dose-dependency, especially in males and appear specific to transgenic rasH2 mice, as similar findings have not been observed in chronic toxicology studies of up to 6 months in rats and 9 months in monkeys.	No evidence for any potential risk to human.
Reproductive and Developmental Toxicity	
Except for the testicular findings observed at 25 mg/kg/day in the rat (see above), there were no consistent effects on male or female reproductive organs in the repeat-dose toxicity studies in rats or monkeys. **Fertility and Early Embryonic Development:** In the rat, no effects of difelikefalin were observed on male fertility, mating parameters or testicular morphology and female fertility or embryonic development at IV doses up to 25 mg/kg/day (CR845-TOX073). The clinical observations and effects on body weight and food consumption were similar to those in the repeat-dose toxicity studies at the same dose levels. In females at ≥ 2.5 mg/kg/day, there were effects on oestrous cyclicity (prolonged dioestrus) associated with a slight increase in days to mating although for the latter, the mean values were within the historical range of the testing facility. The findings were considered of negligible toxicological relevance because of the magnitude of the change and as the effects did not adversely affect fertility, implantation or early embryonic development at any dose level. The NOAEL for general toxicity, male mating and fertility indices, fertility indices in females and early embryonic development was the high dose of 25 mg/kg/day (1900-fold (females) and 2900-fold (males) clinical exposure based on AUC). The NOAEL for female mating was 0.25 mg/kg/day (15-fold clinical exposure based on AUC) based on the slight increase in female time to mating. The change in time to	No evidence for any potential risk to human.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
mating, considered of negligible toxicological relevance, was secondary to alterations in oestrous cyclicity at 2.5 mg/kg/day (170-fold clinical exposure based on AUC). **Embryofoetal Development:** In rats, maternal toxicity, characterised by persistent decreased body weight parameters and food consumption, was observed at doses up to 25 mg/kg/day (CR845-TOX075). However, there were no test item-related effects on ovarian or uterine parameters or embryofoetal survival. No changes in foetal morphology and no evidence of teratogenicity were observed at any dose level, with the exception of a low incidence of skeletal variations at 25 mg/kg/day (wavy ribs and incompletely ossified ribs). The wavy ribs were not considered adverse because these types of variations typically resolve with further growth and development. In the rabbit, notable maternal toxicity (ie, mainly notable decreased body weight parameters, including weight loss and food consumption) was observed (CR845-TOX076). At 0.1 mg/kg/day, there was a decrease in total number of pregnancies. The underlying aetiopathology remains unclear because 5 of the 6 nonpregnant females exhibited no evidence of implantation or pregnancy while the ovaries (ie, follicular development and corpora lutea) were normal. If, however, the fewer pregnancies were difelikefalin related, they would likely be secondary to the maternal toxicity as there were no effects on embryofoetal development and no evidence of teratogenicity at any dose. The developmental NOAEL in the rat was 25 mg/kg/day (2100-fold clinical exposure based on AUC) and $\geq$ 0.1 mg/kg/day in rabbit (30-fold clinical exposure based on AUC). The maternal NOAEL could not be established due to the magnitude and persistence of the effects on body weight in both rats and rabbits. **Pre- and Postnatal Development:** In the pre- and postnatal study in rats, maternal toxicity (mainly persistently reduced body weight, weight gain and food consumption) were reported, but there were no test item-related effects on maternal (F0) reproductive function and no developmental effects in the F1 generation at doses up to 10 mg/kg/day (CR845-TOX077). Based on the magnitude and persistence of the reduced maternal body weight gain, weight loss and decreased food consumption, the maternal NOAEL was considered to be 0.6 mg/kg/day. The reproductive function NOAEL for the F0 generation was 10 mg/kg/day (780-fold clinical exposure based on AUC). The F1 generation developmental NOAEL was also 10 mg/kg/day.	
Local Tolerance	
A local tolerance study in the rabbit showed that there should not be any concern if difelikefalin is misadministered into the perivascular tissue (SBL069-105). In addition, the site of administration was evaluated grossly and microscopically in the repeat-dose toxicity studies in rats and monkeys dosed for up to 26 and 39 weeks, respectively (please see above). No notable difelikefalin-related injection site reactions were observed after IV dosing.	No evidence of any potential risk to human.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Immunotoxicity	
Immune parameters were evaluated in rats and monkeys as part of the 13-week repeat-dose toxicity studies in which animals were dosed up to 25 mg/kg/day in the rat (SBL069-078) and 1 mg/kg/day in the monkey (SBL069-076). There were no effects on peripheral blood immunophenotyping in the rat and monkey, immunohistochemistry of the thymus and spleen in the monkey or T-cell-dependent antibody response to KLH in the monkey.	No evidence for immunotoxic potential.
Dependence / Abuse Potential	
IV difelikefalin did not exhibit rewarding or reinforcing properties in rats (CR845-TOX036, CR845-TOX081). The discriminative stimulus properties of difelikefalin were not similar to the positive control pentazocine (CR845-TOX079). In addition, difelikefalin did not produce tolerance or sensitisation during prolonged administration nor did it produce a syndrome of behavioural or physical dependence upon withdrawal in rats (CR845-TOX080).	No liability to produce withdrawal-induced physical dependence upon dosing discontinuation after prolonged exposure, and no risk of abuse potential.
Phototoxicity	
Difelikefalin does not absorb light within the range of natural sunlight (290-700 nm) and, therefore, no further phototoxicity testing was needed.	No evidence for any potential risk to human.

AUC = area under the concentration-time curve; IV = intravenous; KLH = keyhole limpet haemocyanin; NOAEL = no observed adverse effect level; SC = subcutaneous

Safety pharmacology

Key safety findings from safety pharmacology studies with difelikefalin and their relevance to human usage are summarised below in Table SII-2.

Table SII-2: Key Nonclinical Safety Findings - Safety Pharmacology

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Secondary Pharmacology Screen	
There were no or negligible affinities in a comprehensive panel of receptors, transporters, ion channels or enzymes studied at a concentration of 10 µM (> 1000-fold human Cmax) including human MOR, DOR and ORL1 (CR845-PHARM003, CR845-PHARM004, CR845-PHARM071, CR845-PHARM091, CR845-PHARM092).	No evidence for any off-target activity and potential risk in human.
Central Nervous System	
In rats (CR845-SP055), IV difelikefalin predominantly produced an overall decrease of activity and altered behavioural responses at the lowest dose tested of 1 mg/kg (Cmax > 300-fold human Cmax) or greater but this did not prevent rats from performing when motivated, as exemplified by normal function in the rotarod test at doses ≤ 1 mg/kg (CR845-SP034). In mice, no effect on locomotor activity (SBL069-129) but impaired rotarod response (CR845-SP033 and SBL069-130) was observed at ≤ 0.1 and 0.7 mg/kg, respectively (16- and 114-fold the clinical dose on a body area dose equivalency).	While nonclinical studies suggest a low risk to humans, a low rate of generally well-tolerated CNS adverse events have been reported in humans.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Cardiovascular System	
In monkeys (CR845-SP039), IV administration of difelikefalin resulted in decreased blood pressure, heart rate and body temperature, which seemed to correlate with the decreased spontaneous activity at doses of ≥ 0.25 mg/kg (Cmax > 200-fold human Cmax); the haemodynamic changes were not considered adverse. There were no effects on quantitative (PR, QRS or QT / QTc intervals) or qualitative ECG assessments. At the NOAEL of 4 mg/kg Cmax was > 3000-fold human Cmax. The in vivo assessment is consistent with the in vitro hERG assay (CR845-SP037), which also indicated that difelikefalin is unlikely to have an effect on the QT interval at plasma concentrations up to 1 mM (> 115,000-fold human Cmax).	No evidence for any potential risk in human.
Respiratory System	
In rats (CR845-SP040), although mean respiratory rate was decreased, the mean tidal volume was slightly higher than controls, which likely reflects physiological compensation for the reduced respiratory rate, rather than a direct effect of difelikefalin. There was no overall effect on minute volume. Difelikefalin does not appear to induce respiratory depression in rats. At the NOAEL of 25 mg/kg, Cmax was > 8000-fold human Cmax.	No evidence for any potential risk in human.
Gastrointestinal System	
IV (and oral) administration of difelikefalin had minimal to no effect on GI transit time or gastric emptying in rats in comparison to morphine, which produced a marked inhibition of both gastric emptying and GI transit following a charcoal meal (CR845-SP041, CR845-SP204). In a rat model of postoperative ileus, morphine further inhibited gastric emptying and GI transit (as measured by total transit or small intestinal transit), whereas IV difelikefalin produced no significant effect compared to saline-treated animals (CR845-PHARM015). Overall, these findings indicate that difelikefalin, unlike morphine, does not affect GI motility in the rat. At the NOAEL of 10 mg/kg Cmax for gastric emptying and GI transit was > 4000-fold human Cmax.	No evidence for any potential risk in human.

Cmax = maximum concentration; CNS = central nervous system; DOR = delta opioid receptor; ECG = electrocardiogram; GI = gastrointestinal; hERG = human ether-a-go-go-related gene; IV = intravenous; MOR = mu opioid receptor; NOAEL = no observed adverse effect level; ORL1 = opioid receptor like-1

Other toxicity-related information or data

No other toxicity-related studies have been conducted than those presented above.

Difelikefalin is neither a substrate for major cytochrome P450 (CYP) enzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 (CR845-DMPK027), nor an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 (CR845-DMPK026, CR845-DMPK087, PBC069-123) and has minimal to no potential for induction of CYP1A2, CYP2B6 or CYP3A (CR845-DMPK077). It is not an inhibitor of glucuronidation enzymes UGT1A3, UGT1A9 or UGT2B7 either (CR845-DMPK211).

In addition, difelikefalin is not an inhibitor of major drug transporters BCRP, BSEP, LAT1, MATE1, MATE2-K, MRP2, OAT1, OAT3, OATP1A2, OATP1B1, OATP1B3, OCT1, OCT2, OCT3, P-glycoprotein, PEPT1 or PEPT2 (CR845-DMPK028, CR845-DMPK060, CR845-DMPK078, CR845-DMPK093, CR845-DMPK095, CR845-DMPK210) and is not a substrate for ASBT, BCRP, BSEP, LAT1, MATE1, MATE2-K, MRP2, OAT1, OAT2, OAT3, OATP1A2, OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, OCT3, OCTN1, OCTN2, OSTαβ, P-glycoprotein, PEPT1 or PEPT2 (CR845-DMPK028, CR845-DMPK061, CR845-DMPK078, CR845-DMPK093, CR845-DMPK095).

In conclusion, the nonclinical data suggest that difelikefalin should possess minimal to no drug-drug interaction potential in humans, either as a victim or a perpetrator. No human drug-drug interaction studies were considered necessary.

Part II: Module SIII - Clinical trial exposure

SIII.1 Duration of exposure

As of the Data Lock Point (DLP) of this Risk Management Plan (RMP), a total of 3124 subjects (3116 adults and 8 adolescents) have been exposed to intravenous (IV) difelikefalin across 27 studies: 12 phase 1 studies (including 2 studies conducted in Japan by Cara's licensee, Maruishi Pharmaceutical Co., Ltd.), 4 phase 2 / 3 postoperative pain studies, 4 phase 2 studies in subjects with CKD on HD with moderate-to-severe CKD-aP (including 1 study conducted in Japan by Kissei Pharmaceuticals Co., Ltd), 1 phase 2a study in adolescents on HD, 1 phase 3 study in previously treated HD subjects with pruritus (Kissei Pharmaceutical Co., Ltd.) and 5 phase 3 studies in subjects with CKD on HD with moderate-to-severe CKD-aP (including 1 study in China).

During the initial submission, the overall clinical exposure to difelikefalin IV formulation presented in the completed clinical development programme for the approved indication the treatment of moderate-to-severe pruritus associated with CKD-aP in adult patients undergoing HD, consisted of 18 completed clinical studies with 1879 subjects (some of whom participated in the double-blind and open-label extension phases of the studies) who received at least 1 dose of difelikefalin IV, 1592 of whom were undergoing HD (84.7%) and 287 of whom were not undergoing HD (15.3%). Of the 1879 subjects 1454 received the 0.5 µg/kg IV dose; 1400 subjects were undergoing HD (96.3%) and 54 were not.

Of the 1306 subjects with CKD-aP who were undergoing HD and treated with difelikefalin in phase 3 placebo-controlled and open-label studies (Studies CR845-CLIN3101, CR845-CLIN3102, CR845-CLIN3103, CR845-CLIN3105), the majority (1089 subjects [83.4%]) had a continuous exposure duration of ≥ 3 months; in addition, 711 subjects (54.4%), 533 subjects (40.8%) and 400 subjects (30.6%) had continuous exposure durations of ≥ 6, ≥ 9 and ≥ 12 months, respectively. These data include patients treated up to 64 weeks with difelikefalin (see Table SIII.1-1). A total of 714 subjects received at least 1 dose of placebo treatment; of those, 552 subjects were undergoing HD and 162 were not.

In the phase 1 studies, 287 non-HD CKD patients and 73 HD CKD patients received difelikefalin in doses ranging from 0.5 µg/kg to ≤ 10 µg/kg. In the phase 2 studies, in total 496 CKD patients on HD received difelikefalin at a dose of 0.5 µg/kg.

Since the previous RMP version, 4 additional studies—KOR-CHINA-101, KOR-CHINA-301, MR13A9-4 (PR-13A9-P2-B) and MR13A9-5—and 1 paediatric study (KOR-PED-201) have contributed a total of 636 additional subjects treated with difelikefalin. While these additional cohorts significantly expand the geographic and ethnic diversity of the safety database, their relative size compared to the existing safety pool means they do not substantially change the overall cumulative exposure profile. Additionally, the phase 2b paediatric study KOR-PED-202 had been approved at the time of the DLP, although no patients had yet been enrolled. In accordance with Good Pharmacovigilance Practice, Module V, Rev. 2, the cumulative exposure tables have not been updated, but the contribution of these studies is acknowledged for transparency.

Table SIII.1-1: Overview of Completed Clinical Trials with Intravenous Formulation

Tradename Clinical Trial Protocol No.	Phase	Therapeutic Area	Duration	Difelikefalin Total (N)	Control Total (N)
CR845-CLIN1001	1	Healthy volunteers	Single dose	37	17
CR845-CLIN1003	1	HD	Single dose	18	6
CR845-CLIN1004	1	Healthy volunteers	24 hours	28	14
CR845-CLIN1005	1	Healthy volunteers and subjects with mild, moderate or severe renal impairment not on dialysis	Single dose	36	0
CR845-CLIN1006	1	Healthy recreational polydrug users	Single dose	42	0
CR845-CLIN1009	1	Healthy volunteers	Single dose	15	0

Tradename Clinical Trial Protocol No.	Phase	Therapeutic Area	Duration	Difelikefalin Total (N)	Control Total (N)
CR845-100201	1	Healthy volunteers	Single dose	57	-[a]
CR845-100302	1	HD / non-HD	Single dose	12	0
CR845-100303	1	HD	3 weeks	35	14
PR-13A9-P1-A[b]	1	Healthy volunteers	Step 1: single dose; Step 2: 21 hours	66	22
PR-13A9-P1-B[b]	1	HD	1 week	14	5
KOR-CHINA-101[c]	1	HD	5 weeks	30	0
CR845-CLIN-2101	2	HD with moderate-to-severe CKD-aP	8 weeks	129	45
CR845-CLIN-2005 DB	2	HD with moderate-to-severe CKD-aP	2 weeks	33	32
PR-13A9-P2-A[b]	2	HD with moderate-to-severe CKD-aP	2 weeks	84	21
PR-13A9-P2-B[b]	2	HD with moderate-to-severe CKD-aP	8 weeks	184	63
KOR-PED-201[c]	2a	HD	Single dose	8	0
CR845-CLIN2001	2	Acute postoperative pain	Single dose	63	51
CR845-CLIN2002	2	Acute postoperative pain	1 or 2 doses within 1 day	119	84
CR845-CLIN2003	2	Acute postoperative pain	Up to 6 doses over 48 hours	34	17
CR845-CLIN3001 Part A[d]	2 / 3	Acute postoperative pain	Up to 5 doses within 24 hours	69	23
CR845-CLIN3001 Part B[d]	2 / 3	Acute postoperative pain	Up to 5 doses within 24 hours	324	163
CR845-CLIN3101	3	HD with moderate-to-severe CKD-aP	Up to 52 weeks	288	0
CR845-CLIN3102 DB (pivotal)	3	HD with moderate-to-severe CKD-aP	12 weeks	189	188
CR845-CLIN3102 OLE	3	HD with moderate-to-severe CKD-aP	Up to 52 weeks	313	0
CR845-CLIN3103 DB (pivotal)	3	HD with moderate-to-severe CKD-aP	12 weeks	235	236
CR845-CLIN3103 OLE	3	HD with moderate-to-severe CKD-aP	Up to 52 weeks	399	0
CR845-CLIN3105	3	HD with moderate-to-severe CKD-aP	12 weeks	222	0

Tradename Clinical Trial Protocol No.	Phase	Therapeutic Area	Duration	Difelikefalin Total (N)	Control Total (N)
MR13A9-5[b]	3	HD with moderate-to-severe CKD-aP	12 weeks	172	89
KOR-CHINA-301 DB[c]	3	HD with moderate-to-severe CKD-aP	12 weeks	129	130
KOR-CHINA-301 OLE[c]	3	HD with moderate-to-severe CKD-aP	14 weeks	216	0

CKD-aP = chronic kidney disease-associated pruritus; DB = double-blinded; FDA = Food and Drug Administration; HD = haemodialysis; IV = intravenous; KOR = kappa opioid receptor; OLE = open-label extension; US = United States

[a] Safety population: 57 subjects (54 difelikefalin 0.5 µg/kg, 53 difelikefalin 3 µg/kg, 50 moxifloxacin and 53 placebo). Difelikefalin 0.5 or 3 µg/kg or placebo as IV bolus or moxifloxacin 400 mg orally, in crossover fashion.

[b] Clinical trials sponsored by Maruishi Pharmaceutical Co, Ltd.

[c] Studies sponsored by Vifor Fresenius Medical Care Renal Pharma France

[d] Study CR845-CLIN3001 was placed on clinical hold by US FDA (19 February 2016) after the prespecified protocol stopping criterion of 3 subjects with serum sodium levels > 150 mmol/L was reached. As a result of effective risk mitigation measures, such as discontinuation of IV doses ≥ 5 mcg/kg, addition of new study stopping rules and revision of the perioperative fluid management, the clinical hold was lifted on 15 April 2016. 'CR845-CLIN3001 Part B' refers to data collected after the clinical hold was lifted and 'CR845-CLIN3001 Part A' refers to data collected before the study was placed on clinical hold.

The presentation of the clinical exposure data in this RMP is primarily focusing on the following 2 pools of the Integrated Summary of Safety (ISS) datasets from the following clinical trials:

1. The ISS Primary Safety Pool (consisting of the 2 pivotal, 12-week, placebo-controlled, double-blinded phase 3 clinical trials CR845-CLIN3102 and CR845-CLIN3103).

   In this safety pool, 424 subjects in the pooled difelikefalin group (0.5 µg/kg) and 424 subjects in the pooled placebo group received at least 1 dose of their assigned treatment, with a median duration of treatment (and duration of cumulative exposure) of 85.0 days for both treatment groups (range of 3 to 93 days for subjects treated with difelikefalin and range of 3 to 94 days for subjects treated with placebo).

2. The ISS Difelikefalin Exposure Safety Pool (consisting of the phase 3 clinical trials: CR845-CLIN3101 (open-label safety study up to 52 weeks), CR845-CLIN3102 (12-week double–blinded study and up to 52-week open-label extension study), CR845-CLIN3103 (12-week double-blinded study and up to 52 weeks open-label extension study) and CR845-CLIN3105 (12-week open-label safety study).

All 1306 subjects in the Difelikefalin Exposure Safety Pool received ≥ 1 dose of study treatment. The median duration of continuous exposure was 6.9 months (range 0 to 17 months). The majority of subjects (1089 subjects, 83.4%) had a continuous exposure duration of ≥ 3 months, and 711 subjects (54.4%), 533 subjects (40.8%) and 400 subjects (30.6%) had continuous exposure durations of ≥ 6, ≥ 9 and ≥ 12 months, respectively. The median duration of cumulative exposure was 6.7 months (range 0 to 16 months).

These studies have all been conducted in adult HD patients with moderate-to-severe CKD-aP (see Table SIII.1-1). Details about clinical trial exposure for completed phase 3 clinical trials from the Difelikefalin Exposure Safety Pool are presented in Table SIII.1-2, Table SIII.1-3, Table SIII.1-4, Table SIII.1-5, Table SIII.1-6 and Table SIII.1-7.

Table SIII.1-2: Duration of Continuous Exposure for Completed Clinical Trials in Adults (Difelikefalin Exposure Safety Pool)

CKD-aP in Patients on Haemodialysis		
Duration of Continuous Exposure[a]	**Persons**	**Person-Time**
≥ 2 months	1089	779.29
≥ 6 months	711	660.4
≥ 9 months	533	551.21
≥ 12 months	400	440.28
Total person-time	**1306**	**811.29**

Notes: Total = All subjects receiving ≥ 1 dose.
One month is considered equivalent to 4 weeks. Twelve months are considered equivalent to 48 weeks.
CKD-aP = chronic kidney disease-associated pruritus
[a] A subject will be considered to have a continuous exposure to study drug if any single gap in exposure is < 4 weeks. If the gap in exposure is ≥ 4 weeks, then the subjects' longest exposure to study drug was used to calculate the length of continuous exposure.

Table SIII.1-3: Duration of Treatment Exposure for Completed Clinical Trials in Adults (Difelikefalin Exposure Safety Pool)

CKD-aP in Patients on Haemodialysis		
Duration of Treatment[a]	**Persons**	**Person-Time**
≥ 1 week	1295	810.85
≥ 2 weeks	1280	810.04
≥ 1 month	1234	806.24
≥ 3 months	1093	780.56

CKD-aP in Patients on Haemodialysis		
Duration of Treatment[a]	**Persons**	**Person-Time**
≥ 6 months	718	664.72
≥ 9 months	541	559.23
≥ 12 months	412	453.04
Total	**1306**	**811.29**

Notes: Total = All subjects receiving ≥ 1 dose.
One month is considered equivalent to 4 weeks. Twelve months are considered equivalent to 48 weeks.
CKD-aP = chronic kidney disease-associated pruritus
[a] Duration of treatment is calculated in days as: (date of first dialysis after last dose) - (date of first dose) + 1.

Table SIII.1-4: Cumulative Exposure Data from Completed Clinical Trials in Adults by Age Group (Difelikefalin Exposure Safety Pool)

CKD-aP in Patients on Haemodialysis		
Age Group	**Persons**	**Person-Time**
< 45 years	182	114.38
≥ 45 years	1124	696.91
< 65 years	881	553.54
≥ 65 years	425	257.75
< 75 years	1171	734.73
≥ 75 years	135	76.56
Total	**1306**	**811.29**

CKD-aP = chronic kidney disease-associated pruritus

Table SIII.1-5: Cumulative Exposure Data from Completed Clinical Trials in Adults by Gender (Difelikefalin Exposure Safety Pool)

CKD-aP in Patients on Haemodialysis		
Age Group	**Persons**	**Person-Time**
Female	539	336.21
Male	767	475.08
Total	**1306**	**811.29**

CKD-aP = chronic kidney disease-associated pruritus

Table SIII.1-6: Cumulative Exposure Data from Completed Clinical Trials in Adults by Ethnic and Racial Origin (Difelikefalin Exposure Safety Pool)

CKD-aP in Patients on Haemodialysis		
Ethnic / Racial Origin	**Persons**	**Person-Time**
Ethnicity		
Hispanic or Latino	370	235.1
Not Hispanic or Latino	927	571.79
Unknown	4	2.72
Not reported	5	1.67
Total	**1306**	**811.29**
Race		
White	692	416.91
Black or African American	494	326.28
Asian	57	31.77
American Indian or Alaska Native	26	18.19
Native Hawaiian or Other Pacific Islander	14	5.97
Other / unknown / not reported	23	12.16
Total	**1306**	**811.29**

CKD-aP = chronic kidney disease-associated pruritus

Table SIII.1-7: Dose Administered and Compliance (Difelikefalin Exposure Safety Pool)

	CR845 0.5 µg/kg (N = 1306) n (%)
Number of Doses (Times) Administered – n (%)	
1-12	105 (8.0%)
13-24	59 (4.5%)
25-36	267 (20.4%)
37-48	77 (5.9%)
49-60	73 (5.6%)
61-72	49 (3.8%)
73-84	58 (4.4%)
85-96	65 (5.0%)
97-108	47 (3.6%)
109-120	49 (3.8%)

	CR845 0.5 µg/kg (N = 1306) n (%)
121-132	61 (4.7%)
133-144	90 (6.9%)
145-156	180 (13.8%)
≥ 157	126 (9.6%)
Number of Subjects with Extra Doses - n (%)	
1 extra dose during the study	427 (32.7%)
2 extra doses during the study	184 (14.1%)
3 extra doses during the study	41 (3.1%)
≥ 4 extra doses during the study	35 (2.7%)
% Compliance	
n	1306
Mean	92.53
SD	8.659
Median	94.95
Range (min, max)	(34.4, 100.0)
Total	**1306**

max = maximum; min = minimum; n = number; SD = standard deviation

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table SIV.1-1 highlights the populations excluded from clinical trials with difelikefalin.

Table SIV.1-1: Exclusion Criteria

Criteria	Reason for Exclusion	Missing Information?	Rationale
Use in pregnant and lactating women	Pregnant or lactating women were not enrolled in any of the clinical studies.	Yes	There have been no reports of difelikefalin use in pregnant or lactating women in any of the clinical studies. The effects of difelikefalin on labour and delivery in humans are not known and therefore, these are considered as missing information.

Criteria	Reason for Exclusion	Missing Information?	Rationale
Use in patients < 18 years old	The safety and efficacy of difelikefalin in the paediatric population has not been established, but will be investigated as part of a Paediatric Investigational Plan.	No	The safety of difelikefalin in paediatric patients has been partially established. The KOR-PED-201 study with targeted population as adolescents (aged 12 to 17 years) demonstrated that the pharmacokinetic exposure in adolescents was comparable to that observed in adults on haemodialysis. Furthermore, the safety profile of difelikefalin in this population was consistent with the known safety profile in adults. Additional data from KOR-PED-202 study is expected to provide further information on the safety and tolerability of this population. The safety and efficacy of difelikefalin in children below 12 years has not yet been established. No data are available in patients below 12 years. A Paediatric Investigation Plan (EMEA-002565-PIP02-19-M01) has been agreed with the Paediatric Committee of the EMA, and therefore not considered as missing information.
Use in CKD patients not on HD	Subjects with CKD not requiring HD were excluded from phase 3 clinical trials.	No	There is currently limited information on the use of difelikefalin in patients with CKD not requiring HD. This population is not targeted for the approved indication in the current Marketing Authorisation Application
Known or suspected hypersensitivity to any of the constituents of the investigational product (difelikefalin)	Enrolling subjects with known hypersensitivity to constituents of difelikefalin would place these patients at increased risk for additional hypersensitivity reactions.	No	If the patient is known to have a history of hypersensitivity reactions to the active substance or to any of the excipients, difelikefalin should not be given. This exclusion criteria will remain as a contraindication.
Patients receiving peritoneal dialysis	Patients receiving peritoneal dialysis were excluded from the clinical trials.	No	There is no information on the use of IV difelikefalin in patients on peritoneal dialysis. This population is not targeted for the approved indication in the current Marketing Authorisation Application, and therefore not considered as missing information. The IV route of administration limited the study population to those with 3 times per

Criteria	Reason for Exclusion	Missing Information?	Rationale
			week IV access, namely HD subjects. These subjects should not be excluded from treatment with difelikefalin if they are switched from peritoneal dialysis to HD.
Known history of allergic reaction to opiates (such as hives)	Patients with a history of allergic reactions to opiate use were excluded from phase 2 and 3 clinical trials (based on the parallel conduct of clinical studies in postoperative indication, where other opioids were used as rescue medication). In the completed studies CLIN1001, CLIN100303, CLIN210301, as well as in the completed / ongoing / planned clinical trials with oral difelikefalin in other patient populations with pruritus (conducted by the Applicant's development partner) these patients are no longer excluded.	No	These subjects should not be excluded from receiving treatment with difelikefalin because there is no cross-reaction / hypersensitivity across drugs targeting different opioid receptors.
New or change of treatment received for itch or new or change of prescription for opioids, gabapentin or pregabalin within 14 days prior to screening	These patients were excluded from the pivotal clinical trials as the unknown effects of changes in the medications on the clinical outcomes and their small numbers could have falsely skewed the clinical efficacy findings. These protocol requirements were not related to safety, but only set to allow for unbiased evaluation of efficacy in these clinical trials. Accordingly, the restrictions about changes to current anti-itch prescriptions did not apply to the open-label extension phases of the pivotal studies CLIN3102 and CLIN3103, where changes to, or initiation of, other anti-itch medications were allowed and their safety was evaluated.	No	Patients with recent changes in their anti-itch medications or with changes to their prescription opioids should not be excluded from treatment with difelikefalin, as determined by the prescribing physician. In clinical practice the prescriber should not be restricted in changing anti-itch medications, including antihistamines, corticosteroids, gabapentin and pregabalin or opioids when starting the treatment with difelikefalin or changing its dose (eg, in case of dry body weight change). These changes may include stopping or dose reduction of other anti-itch medications, as per the clinical judgement of the prescriber, in order to adapt the treatment to the patient's current needs and to reduce or avoid prescriptions that are dosed unnecessarily high or no more required.

Criteria	Reason for Exclusion	Missing Information?	Rationale
Has localised itch restricted to the palms of the hands or pruritus only during the dialysis session	These patients were excluded from the clinical trials as it could not be excluded that their itch was related to another cause or an allergic response to the dialysis treatment itself.	No	Patients with recent localised itch to the palms or pruritus only during dialysis should not be excluded from treatment with difelikefalin if no reversible cause for the itch is discernible and the benefit outweighs the risk, as determined by the prescribing physician.
Any acute or chronic medical or neuropsychiatric condition (eg, encephalopathy, coma, delirium	Patients included in the clinical trials must have a stable condition to accurately determine efficacy and safety in the clinical studies. Inclusion of patients with acute or chronic medical or neuropsychiatric conditions could falsely skew clinical trial results. Excluding these patients from the clinical trials was a logistical decision to ensure that ethical standards are met and to comply with the study protocol and procedures (eg, compliance with clinical questionnaire and study conduct).	No	Patients with CKD-aP should not be excluded from receiving treatment with difelikefalin regardless of underlying comorbidities, if the benefit outweighs the risk, as determined by the prescribing physician.
Recent history of alcohol, narcotic or other drug abuse or substance dependence	Clinical trial specific exclusion criteria due to the risk for inability to comply with the protocol and related questionnaires.	No	Patients with CKD-aP should not be excluded from receiving treatment with difelikefalin based on past history of substance abuse or dependence if the benefit outweighs the risk, as determined by the prescribing physician.
History of severe mental illness or cognitive impairment (dementia)	Patients included in the clinical trials must have a stable condition to accurately determine efficacy and safety in the clinical studies. Inclusion of patients with acute or chronic medical or neuropsychiatric conditions could falsely skew clinical trial results. Study specific exclusion criteria due to the risk for inability to comply with the protocol and related questionnaires. Excluding these patients from the clinical trials was a logistical decision to ensure that ethical standards are	No	This exclusion criteria was not related to safety. As long as there is no suspicion that the blood-brain barrier is disrupted, no particular safety risks or different safety profiles are expected for patients with a history of severe mental illness or cognitive impairment.

Criteria	Reason for Exclusion	Missing Information?	Rationale
	met and to comply with the study protocol and procedures.		
Subjects with a dry body weight of < 40 or > 130 kg	These patients were excluded as very low weight adults could represent severe malnutrition and large weights would require more than 1 vial of difelikefalin.	No	Patients with body weights below 40 or above 130 kg should not be excluded from receiving treatment with difelikefalin if the benefit outweighs the risk, as determined by the prescribing physician.
Subjects with significant (severe) hepatic impairment	These patients were excluded from the clinical trials as they represent a high mortality population and could have confounded the safety profile of the study drug.	Yes	The influence of mild-to-moderate hepatic impairment on the PK of difelikefalin was evaluated in a population PK analysis which concluded that no dose adjustments were needed. Because insufficient PK data are available for HD subjects with severe hepatic impairment, PK and any dose adjustments in this patient population could not be assessed or predicted. Treatment in patients with severe hepatic impairment is not recommended with difelikefalin. Therefore, the use in patients with severe hepatic impairment is considered as missing information.
Subjects with a concomitant disease or any medical condition that, in the opinion of the Investigator, could pose undue risk to the patient, impede completion of the study procedures or would compromise the validity of the study measurements, including NYHA Class IV congestive heart failure.	Patients included in the clinical trials must have a stable condition to accurately determine efficacy and safety in the clinical studies, and to ensure that ethical standards are met and to comply with the study protocol and procedures. Patients with diagnosed NYHA Class IV systolic or diastolic congestive heart failure were excluded from the clinical trials as they represent a high mortality population and could have confounded the safety profile of the study drug.	No	Difelikefalin has not been studied in patients with NYHA Class IV systolic or diastolic congestive heart failure. However, these patients should not be excluded from receiving treatment with difelikefalin if the benefit outweighs the risk, as determined by the prescribing physician. Wording has been added into EU SmPC Section 4.4, that difelikefalin has not been studied in patients with NYHA Class IV heart failure. In the pivotal clinical studies a small numerical imbalance of cardiac failure and AF events was observed in the difelikefalin treated patients compared to placebo, including patients with a medical history of AF who discontinued or missed their AF treatment. No causal relationship was established.

Criteria	Reason for Exclusion	Missing Information?	Rationale
Subjects with CKD associated mild pruritus	These patients were excluded from the clinical trials as the expected change in their itch scores would be small making it more difficult to show clinical significance between groups.	No	There is currently limited information on the use of difelikefalin in patients with CKD associated mild pruritus. This population is not targeted for the approved indication in the current Marketing Authorisation Application.
Subjects receiving UVB treatment	These patients were excluded from the clinical trials as UVB treatment could have altered the studies primary endpoints.	No	Patients receiving UVB treatment should not be excluded from receiving treatment with difelikefalin if the benefit outweighs the risk, as determined by the prescribing physician.

AF = atrial fibrillation; CKD = chronic kidney disease; CKD-aP = chronic kidney disease-associated pruritus; EMA = European Medicines Agency; EU = European Union; HD = haemodialysis; IV = intravenous; NYHA = New York Heart Association; PK = pharmacokinetic; SmPC = Summary of Product Characteristics; UVB = ultraviolet B

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Table SIV.2-1: Limitations to Adverse Drug Reaction Detection

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	To date, 2515 subjects were exposed to difelikefalin IV formulation within the clinical development programme for the approved indication.	It is recognised that controlled randomised trials are not feasible for capturing rare ADRs. Postmarketing surveillance will provide additional safety information on rare ADRs.

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Due to prolonged exposure	In 2 double-blinded, placebo-controlled clinical studies, difelikefalin has been investigated for 12 weeks, followed by open-label extension long-term exposure for periods of up to 52 weeks of use. No unexpected safety signals emerged during long-term treatments of up to 52 weeks, with the nature and rate of the reported safety events aligning with published morbidity and mortality data of patients with CKD-aP undergoing HD. Additionally, difelikefalin has been investigated in the regional phase 3 study KOR-CHINA-301, conducted in Chinese HD patients with moderate-to-severe pruritus, (double-blind placebo-controlled period of 12 weeks followed by 14 weeks open label extension); this study confirmed the known safety profile of difelikefalin, further supporting its tolerability in a broader population.	The ability to detect ADRs which are due to prolonged exposure, cumulative effects or prolonged latency may have been affected by the duration of conducted clinical trials.
Due to cumulative effects which have a long latency	In addition to 12-week treatment periods, long-term safety study data for difelikefalin are available for up to 52 weeks.	None

ADR = adverse drug reaction; CKD-aP = chronic kidney disease-associated pruritus; HD = haemodialysis; IV = intravenous

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3-1: Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	There are no adequate and well-controlled studies of difelikefalin in pregnant women. Studies in animals have not shown direct or indirect reproductive toxicity.
Breastfeeding women	Limited available evidence from animal studies suggests that difelikefalin may be excreted in human milk.

Type of Special Population	Exposure
Children less than 18 years of age	The safety of difelikefalin in paediatric patients has been partially established. A Paediatric Investigation Plan (EMEA-002565-PIP02-19-M01) has been agreed with the Paediatric Committee of the EMA. In the KOR-PED-201 study, a total of 8 adolescents (aged 12 to 17 years) on HD were enrolled in an open-label, single-arm study to evaluate the PKs of a single intravenous dose of difelikefalin (0.5 µg/kg based on dry body weight). The study demonstrated that the PK exposure in adolescents was comparable to that observed in adults on HD. Furthermore, the safety profile of difelikefalin in this population was consistent with the known safety profile in adults. Additional data from KOR-PED-202 study is expected to further provide further information on the safety and tolerability of this population. The safety and efficacy of difelikefalin in children below 12 years has not yet been established. No data are available in patients below 12 years.
Patients with severe hepatic impairment	The influence of mild-to-moderate hepatic impairment on the PK of difelikefalin was evaluated in a population PK analysis which concluded that no dose adjustments were needed. The influence of severe hepatic impairment on the PK of difelikefalin in subjects undergoing HD has not been evaluated; therefore, no adequate clinical data is available.
Patients with impaired BBB	Difelikefalin is a peripherally acting KOR agonist with restricted access to the CNS. The BBB integrity is important for minimising difelikefalin uptake into the CNS. Patients with clinical important disruptions to the BBB (eg, primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis, advanced Alzheimer's disease) may be at risk for difelikefalin entry into the CNS. To ensure that ethical standards are met, to comply with the study protocol and procedures and efficacy and safety can be accurately determined in the clinical trials, patients with certain risks of unstable medical conditions were excluded as per study investigators opinion (see Table SIV.1-1). However, no specific clinical investigations were performed to detect or quantify significant BBB disruptions during enrolment for patients studied in clinical trials, therefore this particular condition is defined as missing information.

BBB = blood-brain barrier; CNS = central nervous system; EMA = European Medicines Agency; HD = haemodialysis; KOR = kappa opioid receptor; PK = pharmacokinetic

Part II: Module SV – Postauthorisation experience

Difelikefalin was initially developed under the code CR845 by Cara Therapeutics Inc. (hereby referred as Cara) as a part of the global clinical development programme. The first approval of a company-sponsored clinical trial conducted with difelikefalin in any country was granted on 28 March 2008, marking the Developmental International Birth Date. Subsequently, difelikefalin injection was approved for marketing in the US on 23 August 2021 for the treatment of moderate-to-severe CKD-aP in adults undergoing HD.

On 25 April 2022, the European Commission granted marketing authorisation to Vifor Fresenius Medical Care Renal Pharma for difelikefalin (Kapruvia®) for the treatment of

moderate-to-severe CKD-aP in adult HD patients within the European Union (EU) and European Economic Area. In addition, difelikefalin was approved in Japan on 23 September 2023 by Maruishi Pharmaceutical Co., Ltd. for the improvement of pruritus in patients receiving HD.

On 15 April 2025 the Marketing Authorization for difelikefalin in US (NDA 214916) was transferred from Cara to Vifor Internation AG (a CSL Vifor group company) and acquired the global rights from Cara. Vifor Fresenius Medical Care Renal Pharma is the joint company of Fresenius Medical Care and CSL Vifor (hereby referred as CSL Vifor). CSL Vifor has assumed full responsibility for the product's pharmacovigilance activities, including safety data management, signal detection, and regulatory reporting. Historical safety data from Cara have been successfully integrated into CSL's global safety database to ensure continuity in safety surveillance and compliance with applicable regulatory requirements.

SV.1 Postauthorisation exposure

SV.1.1 Method used to calculate exposure

Depending on the market, the product is available as vials containing 1 mL extractable solution (ie, containing 50 mcg difelikefalin per vial) or as vials containing 1.3 mL extractable solution (ie, containing 65 mcg difelikefalin per vial).

Patient exposure is calculated based on Patient-Years:

$$\text{Patient-Years} = \frac{\text{Total Vials}^{a}}{\text{3 vials per patient per week}^{b} \times 52}$$

[a] Total Vials = Total number of vials commercially dispensed / shipped to Pharmacies

[b] Administration Dose for a patient with an average weight of 80 kg: 1 vial; 3 HD treatments (1 vial each) per week per patient = 3 vials per patient per week (1 year = 52 weeks)

SV.1.2 Exposure

Cumulatively, 2,394,852 vials were sold worldwide (excluding CCI) which is equivalent to postmarket exposure of approximately 15,351.62 patient years.

From commercial launch (13 December 2023) till the DLP of this report, unit sales to wholesalers in CCI was as follows:

CCI

CCI

CCI

Patient exposure data for CCI are not available due to limitations on availability of data at the patient level.

Table SV.1.2-1: Exposure Table

Region	Exposure (Units)	
	Patient-Years	Number of Vials
North America	7109.15	1,109,028
Europe	7658.38	1,194,708
Middle East	200.85	31,332
Asia Pacific	383.23	59,784
Total	**15,351.62**	**2,394,852**

Note: Sales data are available on a monthly basis only, including data from the first to the last day of each month. This exposure data is cumulative till July 2025.

Part II: Module SVI - Additional European Union requirements for the safety specification

Potential for misuse for illegal purposes

Difelikefalin is subject to medical prescription only and shall be administered to patients intravenously at the end of defined HD sessions in a controlled clinical environment by healthcare professionals. In all clinical studies of difelikefalin, there were no adverse event (AE) reports related to misuse with IV difelikefalin at doses up to 80-fold the clinical dose for the approved indication.

The potential for misuse of difelikefalin for illegal purposes is considered low.

There were no signals of abuse, diversion, dependence or withdrawal with difelikefalin in clinical studies or from the postmarketing setting.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial risk management plan submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the risk management plan

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The clinical safety profile for difelikefalin had been based on 27 clinical studies in various clinical indications, including the approved indication of CKD-aP in adult HD patients, as well as postsurgical acute pain. These studies included 2 phase 3, double-blind, placebo-controlled randomised 12-week studies with up to 52-week open-label extensions and 2 phase 3 open-label safety studies (see Table SIII.1-1). These 4 phase 3 studies evaluated difelikefalin in subjects with moderate-to-severe CKD-aP undergoing HD, the intended population for the drug. The conclusions presented in this section are primarily from the Primary Safety Pool and Difelikefalin Exposure Safety Pool (see Part II: Module SIII), which evaluated the intended dose of difelikefalin in the intended population in the 12-week placebo-controlled studies (including 424 patients) and the up to 52-week long-term exposure studies (including 1306 patients), respectively.

Among the treatment–emergent AEs (TEAEs), adverse drug reactions (ADRs) were identified based on: 1) frequency of reporting (≥ 2% of subjects exposed to drug); 2) whether the AE rate for subjects exposed to drug exceeded that of placebo (≥ 1% higher than placebo); 3) extent of dose-response; 4) extent to which AE was consistent with pharmacology of the drug; 5) timing of AE relative to time of drug exposure and 6) whether the AE was known to be caused by related drugs.

The results of the analysis from the pivotal phase 3 studies for TEAEs from the Primary Safety Pool for potential ADRs reported in ≥ 2% of subjects on difelikefalin and ≥ 1% higher than placebo are:

- Diarrhoea (24 of 424 (5.7%) in the placebo group and 38 of 424 (9.0%) in the difelikefalin group)

- Nausea (19 of 424 (4.5%) in the placebo group and 28 of 424 (6.6%) in the difelikefalin group)

- Headache (11 of 424 (2.6%) in the placebo group and 19 of 166 (4.5%) in the difelikefalin group)

During 12 weeks of difelikefalin treatment, these events were reported to be mostly mild or moderate in severity (≤ 0.9% reported as severe), few led to study drug discontinuation (n ≤ 4 subjects), and the incidence of nonfatal serious events was low (< 2%). During extended 52 weeks treatment, these TEAEs were mild or moderate in the majority of subjects (≤ 0.5% reported as severe), few led to study drug discontinuation (n ≤ 1 subjects) and the incidence of nonfatal serious events was low (≤ 0.7%).

Difelikefalin is the single drug approved in the EU for the treatment of CKD-aP, there remains a significant unmet need for safe and effective treatments in this susceptible population which is known to be associated with significant, multiple comorbid conditions (see Part II: Module SI). Based on the associated medical conditions from ESRD- and HD-associated procedures, the clinical impact of the above mentioned risks in this target population occurring from difelikefalin treatment is considered small and these risks should therefore not be classified as important. These ADRs are listed in the EU Summary of Product Characteristics (SmPC) Section 4.8.

From the Primary Safety Pool, the following TEAEs reported in ≥ 2% of subjects on difelikefalin and ≥ 1% higher than placebo have also been observed and are discussed in more details below:

- Somnolence (10 of 424 subjects (2.4%) in the placebo group and 18 of 424 (4.2%) in the difelikefalin group),

- Dizziness (16 of 424 subjects (3.8%) in the placebo group and 29 of 424 (6.8%) in the difelikefalin group),

Additional TEAEs which occurred at a frequency of < 2% or without a ≥ 1 percentage point higher incidence than placebo, and selected as TEAE of special interest are also discussed below:

- Mental status changes (3 of 424 subjects (0.7%) in the placebo group and 6 of 424 (1.4%) in the difelikefalin group), and confusional state (6 of 424 subjects (1.4%) in the placebo group and 8 of 424 (1.9%) in the difelikefalin group).

TEAEs of special interest

Based upon available phase 2 clinical study results during the clinical development programme in the HD population (CR845-CLIN2101), the medical concepts of somnolence and dizziness were identified as TEAEs of special interest. Subsequently, these AEs have been monitored prospectively and closely throughout completion of the phase 3 clinical trials to gather additional clinical information for event characterisation.

The physicochemical properties of difelikefalin (ie, a hydrophilic, synthetic D-amino acid peptide with high polar surface area and charge at physiological pH) have been designed to minimise passive diffusion or active transport through the blood-brain barrier (BBB). In line with these properties, the nonclinical data demonstrate negligible passive diffusion or active transport of difelikefalin across membranes with no detection in the brain or poor distribution to the central nervous system (CNS), based on whole-body autoradiography and tissue dissection studies in rats and / or monkeys. In the nonclinical data, difelikefalin preferentially activates KORs outside of the CNS, which should mitigate central side effects, especially dysphoria and psychomimetic effects, which are associated with the activation of centrally located KORs. The peripheral action of difelikefalin is supported by the pharmacology studies CR845-PHARM010-01 and CR845-PHARM063, as well as the absence of typical dose-limiting CNS side effects of difelikefalin in humans, which are seen with the centrally acting KOR agonists at pharmacologically active doses.

Difelikefalin is a selective KOR agonist, which has no activity at mu or delta-opioid receptors. The selective activity of difelikefalin at KORs avoids mu-associated side effects, such as respiratory depression, dependence and euphoria (Yaksh and Wallace, 2017). Difelikefalin also differs from clinically used mixed agonist-antagonist opioids (such as pentazocine) and other selective small organic heterocycle KOR agonists explored to date (such as enadoline), which for the most part are CNS-penetrant agonists (Delgado-Aros et al, 2003; Delvaux et al, 2004; Mangel et al, 2008; Pande et al, 1996; Reece et al, 1994).

As expected from the physicochemical properties of the compound and the nonclinical studies, the clinical safety profile of difelikefalin corresponds to that of a specific KOR agonist with a primarily peripheral mode of action. The absence of typical dose-limiting side

effects in humans - that are associated with most centrally acting KOR agonists at pharmacologically active doses - indicate that observed CNS-like effects (eg, somnolence, dizziness, mental status changes and confusion state) in the target patient population are likely not to be mediated by a direct activity at central KORs. The CNS-like safety profile of difelikefalin at the recommended therapeutic dose was comparable across CKD-aP patients on HD, healthy subjects, and non-HD patients treated for a different indication (postoperative pain).

Somnolence

In clinical practice, to treat patients suffering from CKD-aP, several off-label treatments have been used, such as antihistamines, corticosteroids, gabapentin, and pregabalin; however, these drugs are limited by a lack of proven antipruritic efficacy and poor tolerability (including side effects such as somnolence). In the Primary Safety Pool, antihistamines for systemic use have been used as concomitant medications in 39.2% of the pooled difelikefalin and 43.4% in the pooled placebo subjects. Overall, 180 subjects (42.5%) in the pooled difelikefalin group and 188 subjects (44.3%) in the pooled placebo group used anti-itch medication (eg, diphenhydramine, hydroxyzine and hydrocortisone). In the Difelikefalin Exposure Safety Pool, 546 subjects (41.8%) from the pooled difelikefalin group reported at least 1 concomitant anti-itch medication.

In the Primary Safety Pool, 95 pooled difelikefalin subjects (22.4%) and 104 pooled placebo subjects (24.5%) reported medical history related to HD or conditions that worsened during HD. Somnolence was reported in 2.4% and 1.7% of pooled difelikefalin and placebo subjects, respectively.

During 12 weeks treatment, somnolence was observed as a TEAE reported in ≥ 2% of pooled difelikefalin subjects with an incidence ≥ 1 percentage point higher than in placebo subjects (4.2% in the difelikefalin group, and 2.4% in the placebo group). Somnolence was severe in 1 difelikefalin subject (0.2%), and the incidence of nonfatal serious events was low (0.2%). For somnolence, the median time to onset of the first somnolence event was shorter (by ≥ 10 days) in the pooled difelikefalin group than in the pooled placebo group. In most cases, somnolence occurred within the first 3 weeks of treatment and tended to resolve over time with continued dosing. There were no subjects who discontinued difelikefalin due to somnolence during 12 weeks treatment. In the Primary Safety Pool, the incidences of this related TEAE in the pooled difelikefalin group was at least twice that in the placebo group (1.9% in the pooled difelikefalin and 0.9% in the placebo groups). In the Difelikefalin

Exposure Safety Pool, which includes only subjects treated with difelikefalin (n = 1306), the incidence of somnolence assessed as related to treatment by clinical Investigator was 1.1%, no patient discontinued treatment due to somnolence; 1 patient experienced a nonfatal serious event of somnolence.

In summary, the incidence rates (IRs) for somnolence in the pooled difelikefalin group of the Difelikefalin Exposure Safety Pool showed no notable increases over corresponding rates in the pooled difelikefalin group of the Primary Safety Pool: 39.4 events per 1000 patient-years for the Difelikefalin Exposure Safety Pool versus 204.0 events per 1000 patient-years for the Primary Safety Pool. Subjects who used prior anti-itch medication showed a higher risk of somnolence than subjects who did not; similarly, subjects who used concomitant opioids had an increased risk of somnolence compared with subjects who did not. The incidence of somnolence was also higher in pooled difelikefalin subjects (5.8%) who took opioids compared to pooled placebo in the same subgroup (1.6%). The incidence of somnolence was higher in difelikefalin-treated subjects 65 years of age and older (7.0%) than in difelikefalin-treated subjects less than 65 years of age (2.8%).

Based on the observed characteristics of somnolence episodes in clinical investigations, taking into consideration concomitant mediation, and the analysis of the primary and Difelikefalin Exposure Safety Pools (including long-term treatment), it is not expected that somnolence may have a negative impact on the current favourable benefit / risk profile of difelikefalin in treated CKD patients on HD. Somnolence did not lead to deleterious consequences and therefore should not be considered as an important risk. Somnolence is listed as an ADR in the EU SmPC Section 4.8.

Dizziness

ESRD patients may experience episodes of dizziness any time during or after dialysis sessions due to possible fluctuations in blood pressure. In the Primary Safety Pool, 95 pooled difelikefalin subjects (22.4%) and 104 pooled placebo subjects (24.5%) reported medical history related to HD or conditions that worsened during HD. Dizziness was reported in 9.4% and 9.0% of pooled difelikefalin and placebo subjects, respectively.

Over 12 weeks treatment, dizziness was observed as a TEAE reported in ≥ 2% of pooled difelikefalin subjects with an incidence ≥ 1 percentage point higher than in placebo subjects (6.8% in the difelikefalin group, and 3.8% in the placebo group). Dizziness was severe in 1 difelikefalin subject (0.2%), and the incidence of nonfatal serious events was low (0.2%).

The median time to onset of the first event of dizziness was shorter (by ≥ 10 days) in the pooled difelikefalin group than in the pooled placebo group. In most cases, dizziness occurred within the first 3 weeks of treatment with a median duration of 1 day. Four subjects discontinued difelikefalin due to dizziness during 12 weeks of treatment (0.9%). In the Primary Safety Pool, the incidences of this related TEAE in the pooled difelikefalin group was at least twice that in the placebo group (1.4% and 0.2% respectively). In the Difelikefalin Exposure Safety Pool (which includes only subjects treated with difelikefalin (n = 1306) and additional treatment up to 52 weeks), 7.9% of patients experienced dizziness. A severity grade of severe was reported in 0.3% of subjects. With 6 patients experiencing nonfatal serious events of dizziness, the incidence was low (0.5%). Seven subjects discontinued treatment due to dizziness during long-term treatment (0.5%). The incidence of related events (assessed by clinical Investigators) was 0.9%.

The IRs for dizziness in the pooled difelikefalin group of the Difelikefalin Exposure Safety Pool showed no notable increases over corresponding rates in the pooled difelikefalin group of the Primary Safety Pool: 151.6 events per 1000 patient-years for the Difelikefalin Exposure Safety Pool versus 316.2 events per 1000 patient-years for the Primary Safety Pool. From a subgroup analysis in the Primary Safety Pool, differences were observed for dizziness in subjects who used concomitant CNS-depressant medication and were treated with difelikefalin. These subjects had an increased risk of dizziness (7.3% for concomitant use of CNS-depressant medication and 4.8% for no concomitant use of CNS-depressant medication); however, the small number of subjects who did not use concomitant CNS-depressant medications limits clinically meaningful interpretation of this difference. (In total, 341 subjects (80.4%) from the pooled difelikefalin group and 363 subjects (85.6%) from the pooled placebo group reported concomitant use of CNS-depressant medications.)

Dizziness episodes can occur in ESRD patients in a temporal relationship to dialysis sessions. In patients being treated with difelikefalin during clinical trials, dizziness episodes did not lead to deleterious consequences in this patient population. Based on the characteristics from clinical observations and analysis of Primary and Difelikefalin Exposure Safety Pools, dizziness should not be considered as an important risk. Dizziness is listed as an ADR in the EU SmPC Section 4.8.

Mental status changes

The ESRD patient population suffer from many different medical conditions (including diabetes, hypertension, CV disorders, and infections) which require various medications to

manage these medical conditions. Many of these medications may at times cause different psychiatric symptoms.

In addition, medical conditions such as electrolyte disturbances, hypertension, hypoglycaemia, and dialysis - regularly observed in CKD patients on HD - may be the reason for confusional state or mental status changes conditions. In this population, CKD-aP is observed as a clinically relevant complication, which may further impair the HD patients' QoL and severely impact their physical and mental health.

Based upon the phase 2 clinical study results during the clinical development programme in the HD population (CR845-CLIN2101), the medical concept of mental status changes was identified as a TEAE of special interest. Mental status changes have been closely and prospectively monitored throughout completion of the phase 3 clinical trials to gather additional clinical information for further characterisation of this medical condition.

In the Primary Safety Pool, the Preferred Terms (PTs) of mental status changes and confusional state occurred as TEAEs at a frequency of $< 2\%$ and without a ≥ 1 percentage point higher incidence than placebo:

- Confusional state (8 of 424 subjects (1.9%) in the difelikefalin group and 3 of 424 (0.7%) in the placebo group), 1 of 424 subjects (0.2%) in the difelikefalin group and 0 of 424 (0.0%) in the placebo group were considered serious

- Mental status changes (6 of 424 subjects (1.4%) in the difelikefalin group and 3 of 424 (0.7%) in the placebo group). Five of 424 subjects (1.2%) in the difelikefalin group and 2 of 424 (0.5%) in the placebo group) were considered serious

None of these episodes were considered treatment-related per the Investigators, but rather causally linked with other aetiologies (eg, medical history; concomitant medication, clinical conditions associated with the underlying ESRD, consequence of timely associated AEs or (missed) dialysis procedures). Confusion is already known in this target HD patient population, due to as dynamic changes which may occur during the dialysis process may contribute to it.

Based on the similar clinical aetiology and manifestations, and both Medical Dictionary for Regulatory Activities (MedDRA) PTs being allocated under the MedDRA System Organ

Class (SOC) of Psychiatric Disorders, these 2 terms have been grouped to be analysed and presented under 1 medical concept, with mental status changes as the leading term.

In the Primary Safety Pool, mental status changes (including confusional state) was reported in 3.3% of subjects randomised to difelikefalin compared to 1.4% of subjects who received placebo. Half (50%) of these events occurred within the first 4 weeks of treatment. Mental status changes were assessed as serious in 1.4% (6 / 424) of difelikefalin-treated subjects (compared to 0.5% of subjects who received placebo), and led to discontinuation in 0.7% (3 / 424) of difelikefalin-treated subjects (compared to 0.2% of subjects who received placebo).

In the Difelikefalin Exposure Safety Pool, mental status changes (including confusional state) was reported as TEAEs in 4.5% (59 / 1306) of patients receiving difelikefalin for up to 1 year. The median duration of these events was 4.5 days. Mental status changes were assessed as serious in 2.2% (also in association with infection-associated events) and led to discontinuation in a very small number of 3 subjects (< 0.3%) of difelikefalin-treated patients. In 0.4% of patients, treatment was considered as related to IV difelikefalin

The vast majority of events have been single episodes with continuation of difelikefalin treatment, and most events tended to resolve over time with continued dosing.

The IRs for mental status changes in the Difelikefalin Exposure Safety Pool showed no notable increases over corresponding rates in the pooled difelikefalin group of the Primary Safety Pool: 60.4 events per 1000 patient-years for the Difelikefalin Exposure Safety Pool versus 61.2 events per 1000 patient-years for the Primary Safety Pool.

For mental status changes (including confusional state), no new clinical important identified or potential risk is expected with impact on the benefit / risk profile of difelikefalin in this target population. This conclusion is based on the analysis and observations from the primary as well as Difelikefalin Exposure Safety Pool:

- Characteristics of target population and its underlying disease and comedications profile
- Approximately 75% of patients had alternative aetiology / confounders (in patients who reported events of mental status changes and confusional rate)

- The vast majority of events occurred as single episodes (all patients with TEAE confusional state experienced a single episode; more than 85% of patients with TEAE mental status change experienced a single episode)

- The majority of events did not require dose changes or study drug discontinuation (from the difelikefalin safety exposure pool, < 0.3% lead to treatment discontinuation (3 / 1306 patients)

- The majority of events were of mild or moderate severity (0.8% from difelikefalin safety exposure pool reported with a severity grade of severe (11 / 1306 patients)

- No safety concerns from duration or time to first onset of these events

- Individual events reported together with or as a consequence of associated serious events leading to hospitalisation (eg, infections)

- Limited incidence of these psychiatric disorder events occurring during up to 52 weeks long-term treatment

Therefore, mental status changes do not qualify for the list of safety concerns in this RMP. Mental status changes (including confusion state) are listed as ADRs in the EU SmPC Section 4.8.

Hyperkalaemia

Patients with ESRD on dialysis have a high risk of developing hyperkalaemia, particularly when undergoing maintenance HD. The key approaches to clinical management of hyperkalaemia in patients with ESRD are dialysis, dietary potassium restriction, administration of potassium binders and avoidance of medications that increase hyperkalaemia risk. Serum potassium is measured regularly in patients on dialysis, and patient management (eg, potassium concentration in the dialysis fluid) is adapted accordingly.

In the Primary Safety Pool, 26.2% (difelikefalin pool) and 28.3% (placebo pool) of patients reported hyperkalaemia in their medical history.

During the 12-week placebo-controlled treatment period (Primary Safety Pool), hyperkalaemia was reported as a TEAE with a slightly higher frequency in the difelikefalin group (20 / 424, 4.7%) compared to placebo group (15 / 424 patients, 3.5%). Hyperkalaemia

was evaluated as severe in 1.7% (7 / 424) and 0.5% (2 / 424), and was reported as serious in 1.9% (8 / 424) and 1.9% (8 / 424) of subjects in the difelikefalin and placebo groups, respectively. However, hyperkalaemia did not lead to study drug discontinuation in any of these cases. None of these events was considered to be treatment-related by the Investigator. The median time to first onset of hyperkalaemia was 43.0 days in the difelikefalin group and 59.0 days in the placebo group. Median duration of hyperkalaemia was ≤ 5 and ≤ 6 days, in difelikefalin and placebo groups, respectively.

During the treatment period up to 52 weeks (Difelikefalin Exposure Safety Pool), hyperkalaemia was observed in 8.3% of patients (108 / 1306), was assessed as severe in 2.1% (28 / 1306), and was serious in 3.2% (42 / 1306). Hyperkalaemia led to study drug discontinuation in only < 0.1% of these subjects (1 / 1306). In CR845 - CLIN3105, 1 subject experienced a severe hyperkalaemia episode on study Day 7, which was considered by the Investigator as associated to the subject's medical history (including congestive heart failure, diabetes and hypokalaemia). Subject had concurrent events of urinary tract infection, blood glucose decreased and acute respiratory failure. In the Difelikefalin Exposure Safety Pool, none of the events reported as hyperkalaemia were considered to be treatment-related by Investigator. The median time to first onset of hyperkalaemia was 91 days.

Compared with the Primary Safety Pool, the Difelikefalin Exposure Safety Pool showed no notable increase of the incidence of serious hyperkalaemia.

In the Primary Safety Pool, no subject with a central laboratory treatment-emergent potassium of > 7 mmol/l reported a TEAE in the Cardiac Disorders SOC at the time of the observed increased potassium. In the Difelikefalin Exposure Safety Pool, among subjects with a treatment-emergent potassium > 7 mmol/l, there were 2 subjects; 1 subject in CR845-CLIN3101 and 1 subject in CR845-CLIN3103OLE, who had a mild, concomitant TEAE of atrioventricular block first degree reported at the time of the increased potassium. Both TEAEs were considered not related to study drug. The Investigator assessed the TEAE for 1 subject attributable to the use of a beta-blocker.

Based on the clinical observations and analysis from Primary and Difelikefalin Safety Exposure Pools (eg, only 1 patient discontinued drug treatment; none of the episodes assessed as treatment-related by the Investigator; and only 2 subjects reported a cardiac TEAE concomitantly with elevated potassium values), hyperkalaemia should not be considered as an important risk in this patient population on HD. However, as hyperkalaemia generally is

an important condition in HD-dependent patients, the Applicant proposes to add additional wording to Section 4.4 of the SmPC.

Potential for drug abuse

As part of the development programme and final clinical evaluation, a comprehensive assessment of abuse potential associated with the administration of difelikefalin has been performed, including relevant chemistry and manufacturing, in vitro pharmacology, animal pharmacology, safety and toxicology and clinical data.

Nonclinical studies indicate no rewarding or reinforcing properties of difelikefalin in rodents, with failure to generalise to the mixed agonist / antagonist opioid comparator C-IV pentazocine at large multiples of the clinical human dose. This lack of similarity to pentazocine is consistent with the observed low CNS penetration of difelikefalin and its lack of similarity to the psychoactive effects of KOR and mu opioid receptor agonists. A human abuse potential study in recreational polydrug users with opioid and hallucinogen experience (CR845-CLIN1006) demonstrated that difelikefalin, at doses of 5 and 15 µg/kg IV, ie, 10- to 30-fold higher than the proposed therapeutic dose of 0.5 µg/kg, presents an abuse potential profile not meaningfully different from placebo and significantly lower compared to C-IV pentazocine on the primary endpoint (peak drug liking). For the majority of secondary measures related to abuse potential, the magnitude of the effects was also small and generally more similar to those produced by placebo than by pentazocine. There were no dysphoric or euphoric effects consistent with CNS penetrant KOR agonists or mu opioids, respectively. The signals for potential abuse were not only small but also of short duration, and not dose dependent. The dose-effect ceiling is in line with a low CNS penetration and demonstrates that IV doses larger than 15 µg/kg of difelikefalin would not lead to a higher likelihood of abuse potential; in addition, higher doses would translate into an unlikely usable volume of injection. Thus, the profile of difelikefalin observed in nonclinical and clinical studies is not consistent with those of Schedule IV opioids and it appears very unlikely that difelikefalin will be regarded as an attractive drug of abuse for individuals seeking conventional mu opioid effects and / or hallucinogenic CNS kappa opioid effects.

No AEs related to difelikefalin suggesting misuse, abuse, diversion or dependence were documented based on a total population of > 3400 subjects exposed to IV or oral difelikefalin. Through subjective and objective scales of withdrawal, AEs or vital signs, discontinuation of difelikefalin did not produce any signs or symptoms of withdrawal, as evaluated in nonclinical studies, a dedicated human physical dependence study or

discontinuation of difelikefalin at the end of the treatment period of one of the pivotal trial. Thus, difelikefalin does not appear to produce physical dependence following chronic administration.

The most commonly reported potentially abuse-related AEs following administration of IV difelikefalin in healthy subjects were paraesthesia, hypoaesthaesia, dizziness and somnolence across a wide range of doses (up to 80 times the planned clinical dose). In the absence of meaningful signals for euphoria or hallucinations, these AEs are not considered to be abuse related. Isolated occurrences of abuse-related AEs in the targeted population were generally attributed to concomitant medication or the subject's underlying ESRD and do not appear indicative of potential for abuse.

Given the available evidence, difelikefalin is expected to have no meaningful abuse potential and no physical dependence and no relevant impact on its positive benefit / risk profile.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the risk management plan

Important identified risks are currently not defined for difelikefalin.

Important potential risk: cardiac failure and arrhythmias including AF in patients on HD with a medical history of AF

Dialysis-dependent ESRD is a serious illness with high disease burden, poor QoL and an increased all-cause mortality relative to the general population. The most common comorbidity in patients undergoing HD is CV disease, occurring in up to 70% of patients, with the most prevalent (> 20%) CV conditions being heart failure, coronary artery disease, peripheral arterial disease, and AF. There are no approved drugs in the US (other than difelikefalin) or in EU that exhibit the KOR selectivity of difelikefalin, so the effects on cardiac outcomes for this class of drugs is not known. However, nonclinical studies suggest that peripheral KOR agonists may have cardioprotective and antiarrhythmic effects (Beck et al, 2019; Maslov et al, 2016; Tong et al, 2016). In Japan, postmarketing surveillance of nalfurafine (a mixed KOR agonist, mu opioid receptor / delta opioid receptor partial agonist) in 3762 HD patients with intractable itch over a 1-year observation period showed a low frequency of ADRs in the Cardiac Disorder SOC (n = 17 (0.45%)); there were no ADRs of AF reported, and 1 (0.03%) ADR reported each of cardiac failure, cardiac failure acute and

cardiac failure congestive (Kozono et al, 2018). Overall, this would suggest that selective activation of KORs should not adversely alter cardiac function.

The clinical safety profile for difelikefalin was based on 18 clinical studies as described in Part II: Module SIII. The presentation of the clinical exposure data in this RMP is primarily focusing on the following 2 pools of the ISS datasets from the following clinical trials:

- The ISS Primary Safety Pool (consisting of the 2 pivotal, 12-week, placebo-controlled, double-blinded phase 3 clinical trials CR845-CLIN3102 and CR845-CLIN3103), where 424 subjects received difelikefalin (0.5 µg/kg) and 424 subjects received at least 1 dose of their assigned treatment in the placebo group (see Part II: Module SIII); the median duration of treatment (and cumulative exposure) was 85.0 days for both treatment groups.

- The ISS Difelikefalin Exposure Safety Pool (consisting of the phase 3 clinical trials: CR845-CLIN3101 (open-label safety study up to 52 weeks), CR845-CLIN3102 (12-week double–blinded study and up to 52-week open-label extension study), CR845-CLIN3103 (12-week double-blinded study and up to 52 weeks open-label extension study) and CR845-CLIN3105 (12-week open-label safety study) where 1306 subjects were exposed to difelikefalin; the median duration of continuous exposure was 6.9 months (range 0 to 17 months) and the median duration of cumulative exposure was 6.7 months (range 0 to 16 months).

Primary safety pool population

In the Primary Safety Pool population, the incidence of TEAEs in the Cardiac Disorders SOC (PT for ≥ 2 patients) was similar between the pooled difelikefalin group (7.8%), and the pooled placebo group (6.4%).

The incidence of nonfatal serious TEAEs in the Cardiac Disorders SOC was low in the 2 groups, 4.5% in the pooled difelikefalin group and 1.9% in the pooled placebo group. The IR showed no increase in the Difelikefalin Exposure Safety Pool (IR 176.3 / 1000 patient-years) compared to the IR in the Primary Safety Pool (244.8 / 1000 patient-years). The rates of events in the difelikefalin group in both the Primary Safety Pool and the Difelikefalin Exposure Safety Pool are aligned with the rate of hospitalisations for cardiac events reported for the patient population undergoing HD, ie, 460 events per 1000 patient-years (United States Renal Data System, 2018).

The pooled difelikefalin and pooled placebo groups showed a low and similar incidence of TEAEs in the cardiac arrythmias Standardised MedDRA Query (SMQ); however, there was a higher incidence observed for serious TEAEs in the difelikefalin group (2.4%) than the placebo group (1.4%). The most commonly reported TEAE in the difelikefalin group in the cardiac arrythmias SMQ was AF: 6 (1.4%) in the difelikefalin group versus 2 (0.5%) in the placebo group. Three (0.7%) subjects in the difelikefalin group versus 1 (0.2%) subject in the placebo group had serious TEAEs of AF, of which 3 subjects had a new onset of AF (2 subjects on difelikefalin and 1 subject on placebo). The IR of serious TEAEs of AF in the Difelikefalin Exposure Safety Pool, 13.6 / 1000 patient-years, did not increase over the rate (30.6 / 1000 patient-years) observed in the Primary Safety Pool.

The incidence of experiencing at least 1 major adverse CV event (MACE) was low in both the pooled difelikefalin and pooled placebo groups of the Primary Safety Pool:16 subjects (3.8%) and 10 subjects (2.4%), respectively. The most commonly reported (≥ 0.5%) MACEs from the 12-week Primary Safety Pool are presented in Table SVII.1.2-1. All other PTs of MACEs in the pooled difelikefalin group and pooled placebo group were reported in 1 subject (0.2%) each.

Table SVII.1.2-1: Most Commonly Reported (≥ 0.5%) Major Adverse Cardiovascular Events in the 12-week Primary Safety Pool

MACE	Placebo Group (Pooled; 424 Patients) N Events (%)	Difelikefalin Group (Pooled; 424 Patients) N Events (%)
Cardiac failure congestive	3 (0.7%)	3 (0.7%)
Acute coronary syndrome	0 (0.0%)	2 (0.5%)
Acute myocardial infarction / myocardial infarction[a]	2 (0.5%)	2 (0.5%)
Cardiac failure / cardiac failure acute[b]	0 (0.0%)	3 (0.7%)
Troponin increased	3 (0.7)	0
Cardiac arrest	2 (0.5)	1

MACE = major adverse cardiovascular event; TEAE = treatment-emergent adverse event

[a] One subject on placebo had a TEAE of myocardial infarction.

[b] One subject on difelikefalin had a TEAE of cardiac failure acute.

A total of 119 subjects (9.1%) in the pooled difelikefalin group of the Difelikefalin Exposure Safety Pool reported at least 1 MACE. The most common (≥ 0.5% of subjects) PTs were Acute myocardial infarction (2.3%), Cardiac failure congestive (1.6%), Cardiac arrest (1.5%), Troponin increased (1.1%), Pulmonary oedema (0.9%) and Cerebrovascular accident (0.5%).

An additional PT synonymous with acute myocardial infarction, Myocardial infarction (0.3%), was reported, as was another PT synonymous with pulmonary oedema, ie, Acute pulmonary oedema (0.3%). Other PTs synonymous with cardiac failure congestive included Cardiac failure (0.2%) and Cardiac failure acute (0.2%). The IR for any MACE in the pooled difelikefalin group of the Difelikefalin Exposure Safety Pool was 199.7 events per 1000 patient-years, showing no notable increase over the rate of 193.8 events per 1000 patient-years in the pooled difelikefalin group of the Primary Safety Pool.

Additionally, electrocardiogram (ECG) findings for the Primary Safety Pool showed no effects of difelikefalin on QTc or other interval duration measurements (heart rate, PR, and QRS). New ECG morphologic findings, which are very common in patients undergoing HD, were generally evenly distributed between the pooled difelikefalin and pooled placebo treatment groups. Slight imbalances in the number of subjects with ECG evidence of a new myocardial infarction (more in the pooled placebo group) and with new T wave inversion (more in the difelikefalin group) were observed. The clinical significance of these imbalances is unclear, as the target population (CKD subjects undergoing chronic HD) shows a high prevalence of pre-existing CV disease and CV risk factors, and patients undergoing HD frequently have ST and T wave abnormalities on ECGs related to fluid and electrolyte shifts (eg, hypokalaemia, hypocalcaemia and hypomagnesaemia). In the thorough QT / QTc study (CR845-100201), difelikefalin showed no signal of any clinically significant effects on heart rate, atrioventricular conduction as measured by the PR interval or cardiac depolarisation as measured by the QRS duration or other electrocardiographic parameters. There were no new clinically relevant morphological changes. In addition, there was no signal of clinically significant effect of difelikefalin on cardiac repolarisation as evidenced by the results of the time-averaged, time-matched, outlier and pharmacokinetic (PK) / pharmacodynamic analyses.

Additional analyses in subjects with or without a known medical history of AF (using the MedDRA PTs of AF and atrial flutter) have been conducted in the Primary Safety Pool (placebo-controlled phase 3 studies CR845-CLIN3102-DB and CR845-CLIN3103-DB); the results are shown in Table SVII.1.2-2 and Table SVII.1.2-3, and are discussed below.

Table SVII.1.2-2 shows the incidence and the relative risk (RR) with difelikefalin versus placebo of serious TEAEs in the MedDRA SOC of Cardiac Disorders for subjects with a medical history of AF: While the RRs of serious cardiac events were numerically higher in subjects with a medical history of AF (2.54), the 95% CIs of their risk ratios were large and

overlapping, suggesting that patient numbers in each group (61 and 47 in the placebo and difelikefalin groups, respectively) were insufficient to draw definitive conclusions regarding this event.

Table SVII.1.2-2: Incidence of Serious Treatment-emergent Adverse Events in the Cardiac Disorders System Organ Class (Primary Safety Pool)

		Placebo		Difelikefalin		Risk Ratio Difelikefalin / Placebo (95% CI)[a]	Relative Risk[b]
		N	n (%) with Cardiac TEAE	N	n (%) with Cardiac TEAE	Risk Ratio Difelikefalin / Placebo (95% CI)[a]	Relative Risk[b]
MH of atrial fibrillation	No	363	8 (2.2)	377	17 (4.5)	2.05 (0.89, 4.68)	-
	Yes	61	1 (1.6)	47	4 (8.5)	5.19 (0.60, 44.93)	2.54

CI = confidence interval; MH = medical history; N = number; TEAE = treatment-emergent adverse event

[a] Risk ratio is defined as the observed incidence of a cardiac disorder serious TEAE in a subgroup for the difelikefalin group divided by the similar incidence in the placebo group. Wald 95% CIs are displayed.

[b] Relative risk is defined as the risk ratio for a subgroup with specific medical history divided by the risk ratio of the reference group (no medical history).

The incidence and the RR with difelikefalin versus placebo of all (ie, nonserious and serious) TEAEs in the MedDRA SOC of Cardiac Disorders are shown in Table SVII.1.2-3. The RRs of all cardiac events were numerically higher in subjects with a medical history of AF (1.90). However, as for the serious TEAEs, the 95% CIs of the risk ratios were large and overlapping, suggesting that patient numbers in each group (61 and 47 with AF in the placebo and difelikefalin groups, respectively) were insufficient to draw definitive conclusions.

Table SVII.1.2-3: Incidence of Treatment-emergent Adverse Events in the Cardiac Disorders System Organ Class (Primary Safety Pool)

		Placebo		Difelikefalin		Risk Ratio Difelikefalin / Placebo (95% CI)[a]	Relative Risk[b]
		N	n (%) with Cardiac TEAE	N	n (%) with Cardiac TEAE	Risk Ratio Difelikefalin / Placebo (95% CI)[a]	Relative Risk[b]
MH of atrial fibrillation	No	363	22 (6.1)	377	25 (6.6)	1.09 (0.63, 1.91)	-
	Yes	61	5 (8.2)	47	8 (17.0)	2.08 (0.73, 5.94)	1.90

CI = confidence interval; MH = medical history; TEAE = treatment-emergent adverse event
[a] Risk ratio is defined as the observed incidence of a cardiac disorder serious TEAE in a subgroup for the difelikefalin group divided by the similar incidence in the placebo group. Wald 95% CIs are displayed.
[b] Relative risk is defined as the risk ratio for a subgroup with specific medical history divided by the risk ratio of the reference group (no medical history).

An analysis of all cardiac events in subjects with a medical history of AF from the Primary Safety Pool is presented below.

A medical history of AF was present in 108 subjects. Among these subjects, 1 out of 61 (1.6%) in the placebo group and 4 out of 47 (8.5%) in the difelikefalin group developed a serious TEAE in the MedDRA Cardiac Disorders SOC. The proportion of subjects in the difelikefalin arm who developed serious cardiac events was numerically higher in the group with a medical history of AF (8.5%; 4 / 47) compared to subjects without a history of AF (4.5%; 17 / 377). The placebo arm showed a higher proportion of subjects without a medical history of AF developing serious cardiac events (2.2%; 8 / 363) as compared to the subjects with a medical history of AF (1.6%; 1 / 61), resulting in an RR of 2.54. However, due to the small number of subjects who had a medical history of AF and developed serious events under the MedDRA Cardiac Disorders SOC, there was a high variability in the estimates, with large CIs overlapping 1.00, as shown in Table SVII.1.2-2. This limits the interpretation of the findings.

The serious events in the Cardiac Disorders SOC in subjects in the difelikefalin arm with a known medical history of AF were: AF in a subject who missed HD and carvedilol doses before the onset of the event; angina associated with pneumonia in a subject who discontinued plavix and aspirin 3 months prior to the event; cardiac failure in a subject with severe anaemia; and bradycardia twice in a subject with multiple high-risk conditions for cardiac morbidity. The subject on placebo experienced a serious TEAE of congestive cardiac failure. All these events were considered as unrelated to the study drug by the Investigator and occurred with varying time of onset, ranging from 40 to 80 days.

Five out of 61 (8.2%) subjects in the placebo group and 8 out of 47 (17%) subjects in the difelikefalin group developed any TEAE (nonserious or serious) in the MedDRA Cardiac Disorders SOC. The proportion of subjects in the difelikefalin arm who developed a cardiac TEAE was numerically higher in the group with a medical history of AF (17%; 8 / 47) compared to subjects without a medical history of AF (6.6%; 25 / 377). The placebo arm showed a similar pattern; subjects with a known medical history of AF had a higher incidence of TEAEs (8.2%; 5 / 61) than subjects without a known medical history of AF (6.1%; 22 / 363), resulting in an RR of 1.9. These numbers, however, were small, with high

variability and large CIs overlapping 1.00, as shown in Table SVII.1.2-3, limiting the interpretation of the findings.

Overall, there were 8 TEAEs in the Cardiac Disorders SOC in subjects with a medical history of AF in the difelikefalin arm, of which 4 were serious (as described above) and 4 were nonserious. There were also 4 nonserious events in subjects on placebo. Of the 8 subjects in the difelikefalin arm, 2 developed AF and 2 developed tachycardia; the events were mild-to-moderate in severity and assessed as unrelated to the study drug. Of the 4 subjects in the placebo arm, 2 developed congestive cardiac failure and 1 developed AF and tachycardia. All the subjects had a predisposing or concomitant condition for the mild-to-moderate TEAEs, which were all considered unrelated to the study drug. The events in the difelikefalin and the placebo groups were similar in nature.

Based on a quantitative analysis, there was a numerically increased RR (difelikefalin versus placebo) of TEAEs in the MedDRA Cardiac Disorders SOC in subjects with a medical history of AF or hyperkalaemia. However, the nature, severity and time to onset of these cardiac TEAEs were not noticeably different from those occurring in subjects on placebo, with all subjects having significant cardiac comorbidities, which is characteristic for a patient population with HD-dependent CKD (United States Renal Data System, 2018).

Furthermore, the analyses of subjects with a known medical history of heart failure and hypertension does not demonstrate increased RRs. In order to inform healthcare professionals and provide appropriate guidance, the Applicant proposes additional wording for SmPC Section 4.4 (Special Warnings and Precautions for Use). Difelikefalin has not been studied in patients with New York Heart Association Class IV heart failure. In the pivotal clinical studies, a small numerical imbalance of cardiac failure and AF events was observed in the difelikefalin treated patients compared to placebo, in particular among patients with a medical history of AF who discontinued or missed their AF treatment. No causal relationship was established.

According to the published nonclinical and clinical data of KOR agonists, the selective activation of KORs is not expected to adversely alter cardiac function in CKD-aP subjects.

In line with all the available experience with KOR agonists, including the nonclinical data of difelikefalin, neither the thorough analysis of all cases with cardiac TEAEs overall and with heart failure in particular in the difelikefalin phase 3 clinical trials nor the review of all

cardiac events in the supportive studies revealed any trends or signals that would confirm an association of difelikefalin with such events.

When interpreting cardiac safety, the population studied needs to be taken into consideration. The population included in the presented studies is characterised by an abundance of underlying cardiac disorders, other comorbidities and in particular long-term HD therapy due to kidney failure. Overall, based on the data observed, there were no clear trends in timing, age, dosage or background, which suggests that treatment with difelikefalin increases cardiac disorder risks in chronic heart failure patients, and there was no apparent causal relationship to the study drug.

While HD-dependent CKD is itself an important CV risk factor, the majority (60-80%) of all subjects in the difelikefalin phase 3 studies, and in particular most (80-100%) of the subjects who had cardiac events in these studies, suffered from pre-existing cardiac conditions. Given the large number of CV risk factors and intercurrent events in HD-dependent CKD subjects, their interaction during the study may cause important random effects. However, no significant relation of the cardiac events with difelikefalin emerged, neither in CKD-aP subjects overall nor in any specific patient subgroup.

While the causes of cardiac events in the difelikefalin clinical trials cannot be determined with certainty, most CKD-aP patients present with multiple CV risk factors and / or cardiac conditions. Disease progression, intercurrent events (eg, volume overload, changes in salt intake, infections or mineral bone disorder resulting in vascular calcification in HD-dependent CKD subjects) or the culmination of several factors and events during the study frequently causes cardiac TEAEs in this population.

In the 4 difelikefalin phase 3 trials, the majority of subjects (61.8%, 63.3%, 82.9%, and 73.0%, respectively, in Studies CR845-CLIN3102, CR845-CLIN3103, CR845-CLIN3101 and CR845-CLIN3105) had a pre-existing cardiac condition and the remaining subjects had a medical history of concomitant diseases, including hypertension and / or diabetes, in addition to HD-dependent CKD, which are CV risk factors and potentially contributing factors for a cardiac event. Overall, all the TEAEs of the SOC Cardiac Disorders in these studies were confounded by cardiac pre-existing conditions or comorbidities, such as hypertension and diabetes, that may have caused or contributed to the cardiac event.

Difelikefalin was planned to be assessed in several phase 3 trials of oral difelikefalin in other indications (CR845-310301, CR845-310302 and CR845-310501), including pruritus

associated with atopic dermatitis (AD) and pruritus associated with earlier stages of CKD not dependent on dialysis. These trials would collect additional safety data in non-HD populations, thus addressing the concern that underlying CV morbidity and mortality is so high in the HD-dependent CKD population that any outcome would be severely confounded. While avoiding the high background incidence of cardiac events and the multiple confounding factors of the HD-population this data will be helpful to further understand the cardiac safety profile of difelikefalin. Accordingly, safety data from these supportive phase 3 trials of oral difelikefalin in those other indications, would be monitored, analysed, assessed and presented as part of ongoing routine pharmacovigilance activities. Upon available new study data from those supportive trials, this RMP and all relevant sections would be revised accordingly. Any potential signals from those trials in the non-HD populations would be properly analysed and appropriate actions impacting the benefit-risk profile of the IV difelikefalin formulation in the targeted population in patients on HD with CKD-aP will be taken, as required (eg, informing the health authorities as per regulatory required timelines).

From the analysis of safety data from those 3 clinical studies of oral difelikefalin (CR845-310301, CR845-310302 and CR845-310501), the incidence of TEAEs within the Cardiac Failure (Narrow) and Cardiac Arrhythmias (Broad) SMQs with particular attention to subjects with a history of AF was low. Notably:

- In the CKD studies (CR845-310301 and CR845-310302), the overall incidence of cardiac SMQ events was 7.7% and 4.8%, respectively, with the majority of events occurring in non-HD subjects. No clinically meaningful differences were observed between treatment groups, and AF was reported more frequently in placebo-treated subjects than in those receiving difelikefalin.

- In the AD study (CR845-310501), only 2 subjects experienced nonserious cardiac SMQ events, which were considered unrelated to the study drug and had plausible alternative aetiologies. No cases of AF were reported.

- Furthermore, ECG evaluations across all 3 studies revealed no safety signals or adverse cardiac trends related to difelikefalin treatment. The incidence of new-onset clinically important ECG findings was low and comparable between treatment groups, with no ECG-related TEAEs reported.

- In all 3 studies, the incidence of TEAEs in the Cardiac SMQ categories evaluated was low and none of the events were considered related to difelikefalin, and the majority

of all subjects with CKD who experienced Cardiac Failure and Cardiac Arrythmias SMQ events had cardiac-related conditions in their medical history.

- These findings provide reassuring evidence that oral difelikefalin is not associated with an increased risk of cardiac failure or arrhythmias, including AF, in non-HD populations. The absence of a treatment-related signal across diverse patient groups—including those with underlying cardiac comorbidities—supports the conclusion that the cardiac safety profile of oral difelikefalin is acceptable and consistent with the known background risk in CKD and AD populations.

Given the cumulative evidence from both IV and oral formulations, the important potential risk of cardiac failure and arrhythmias—including AF—remains relevant for HD patients with a medical history of AF. However, the additional data from non-HD populations reinforce the absence of a causal relationship and support continued monitoring via routine pharmacovigilance, including the use of a Targeted Questionnaire. This Targeted Questionnaire will continue to be used to collect enhanced data (ie, medical history, concomitant medications, duration of treatment, time-to-onset of new events; cardiac disease / event description) from postmarketing reporting sources to further characterise cardiac failure and arrhythmias including AF in HD patients with a medical history of AF in the treated patient population. Besides the legal status (prescription only medicine), the Applicant believes that routine risk minimisation activities are warranted in the product information and proposes to add a wording in the SmPC Section 4.4 (Special Warning and Precautions for Use).

Missing information: Use in pregnant and lactating women

Use in pregnancy

Risk-benefit impact: There are no or limited amount of data from the use of difelikefalin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of difelikefalin during pregnancy.

Use in lactating women

Risk-benefit impact: It is unknown whether difelikefalin is excreted in human breast milk. Animal studies have shown excretion of difelikefalin in breast milk, but no difelikefalin was

detected in the plasma of nursing pups. A risk to the newborns / infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue / abstain from difelikefalin therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Missing information: Use in patients with impaired blood-brain barrier

Risk-benefit impact: The BBB integrity is important for minimising difelikefalin uptake into the CNS. No specific investigations have been performed to detect or quantify BBB disruptions in the clinical trials. Patients with clinically important disruptions to the BBB (eg, primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis, advanced Alzheimer's disease) may be at risk for difelikefalin entry into the CNS. Difelikefalin should be prescribed with caution in such patients taking into account their individual benefit-risk balance with observation for potential CNS effects.

Missing information: Use in patients with severe hepatic impairment

Risk-benefit impact: Insufficient PK data are available for HD subjects with severe hepatic impairment; PK and any dose adjustments in this patient population could not be assessed or predicted. Treatment with difelikefalin in patients with severe hepatic impairment is not recommended.

SVII.2 New safety concerns and reclassification with a submission of an updated risk management plan

Removal of safety concern:

Important potential risk: cardiac failure and arrhythmias including AF in HD patients with a medical history of AF

With the submission of RMP Version 3.1, the risk 'Cardiac Failure and Arrhythmias Including Atrial Fibrillation (AF) in Hemodialysis (HD) Patients with a Medical History of AF' previously classified as an important potential risk has been removed from the list of identified safety concerns.

Reasons for the removal from the list of safety concerns:

On 28 November 2025, CSL Vifor submitted a Type II Variation (Procedure No. EMA/VR/0000316094) to the Agency. This submission included clinical study reports and an updated Kapruvia RMP (Version 3.0), incorporating safety data from three completed studies: CR845-310301, CR845-310302, and CR845-310501. These studies were previously categorized in the RMP as Category 3 PASS studies for characterizing the cardiac safety profile of difelikefalin.

The Agency further noted that since no additional pharmacovigilance activities are ongoing, the risk 'Cardiac Failure and Arrhythmias Including Atrial Fibrillation (AF) in Hemodialysis (HD) Patients with a Medical History of AF' may be removed as an important potential risk from the Kapruvia EU RMP. However, the Agency requested that this topic continue to be monitored in the upcoming Kapruvia Periodic Safety Update Reports (PSURs). In the next PSUR, the MAH should provide a comprehensive summary of 'cardiac failure and arrhythmias events including atrial fibrillation (AF) observed with Kapruvia within the reporting interval'.

The Agency also confirmed the current wording in section 4.4 of the Kapruvia SmPC;

'In the pivotal clinical studies, a small numerical imbalance of cardiac failure and atrial fibrillation events was observed in the difelikefalin treated patients compared to placebo, in particular among patients with a medical history of atrial fibrillation who discontinued or missed their atrial fibrillation treatment. No causal relationship was established.'

CSL Vifor acknowledges the Pharmacovigilance Risk Assessment Committee assessment and, in accordance with the guidance in Good Pharmacovigilance Practices module V (Rev. 2), confirms that, since no additional pharmacovigilance activities are ongoing, 'Cardiac Failure and Arrhythmias Including Atrial Fibrillation (AF) in Hemodialysis (HD) Patients with a Medical History of AF' has been removed as an important potential risk from the list of safety concerns. This topic will continue to be monitored via routine pharmacovigilance and routine risk minimisation activities.

CSL Vifor will continue to provide a comprehensive summary of cardiac failure and arrhythmias events including AF associated with Kapruvia within the reporting interval in the PSURs until further notice.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risks: Important identified risks are currently not defined for difelikefalin.

Important Potential Risk: Important potential risks are currently not defined for difelikefalin.

SVII.3.2 Presentation of the missing information

Missing Information: Use in Pregnant and Lactating Women

Missing Information	What Is Known
Use in pregnant and lactating women	Pregnant women: There are no or limited amount of data from the use of difelikefalin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of difelikefalin during pregnancy. Lactating women: It is unknown whether difelikefalin is excreted in human breast milk. Animal studies have shown excretion of difelikefalin in breast milk, but no detectable difelikefalin was detected in the plasma of nursing pups. A risk to the newborns / infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue / abstain from difelikefalin therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Missing Information: Use in Patients with Impaired Blood-Brain Barrier

Missing Information	What Is Known
Use in patients with impaired BBB	Difelikefalin is a peripherally acting KOR agonist with restricted access to the CNS. The BBB integrity is important for minimising difelikefalin uptake into the CNS. No specific investigations have been performed to detect or quantify BBB disruptions in the clinical trials. Patients with clinically important disruptions to the BBB (eg, primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis, advanced Alzheimer's disease) may be at risk for difelikefalin entry into the CNS. Difelikefalin should be prescribed with caution

Missing Information	What Is Known
	in such patients taking into account their individual benefit-risk balance with observation for potential CNS effects.

BBB = blood-brain barrier; CNS = central nervous system; KOR = kappa opioid receptor

Missing Information: Use in Patients with Severe Hepatic Impairment

Missing Information	What Is Known
Use in patients with severe hepatic impairment	The influence of mild-to-moderate hepatic impairment on the PK of difelikefalin was evaluated in a population PK analysis, which concluded that no dose adjustments were needed. Because insufficient PK data are available for HD subjects with severe hepatic impairment, PK and any dose adjustments in this patient population could not be assessed or predicted. Treatment with difelikefalin in patients with severe hepatic impairment is not recommended.

HD = haemodialysis; PK = pharmacokinetic

Part II: Module SVIII - Summary of the safety concerns

Table SVIII-1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• N/A
Important potential risks	• None
Missing information	• Use in pregnant and lactating women • Use in patients with impaired blood-brain barrier • Use in patients with severe hepatic impairment

N/A = not applicable

Part III: Pharmacovigilance plan (including postauthorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for use in pregnant women**:

The pregnancy follow-up form has been incorporated into routine follow-up and is presented in this RMP in Annex 4 (Report on Exposure to Medicines During Pregnancy). All pregnancy cases will be carefully followed up and a thorough assessment will be made.

- **Specific adverse reaction follow-up questionnaire for Cardiac Failure and Arrhythmias Including Atrial Fibrillation in Patients on HD with a Medical History of Atrial Fibrillation**

The follow-up Targeted Questionnaire specific for evaluating events of cardiac failure and arrhythmias including AF in patients on HD with a medical history of AF has been incorporated into routine follow-up and is presented in this RMP in Annex 4 (Kapruvia (difelikefalin) HD PM Targeted Questionnaire healthcare professional). All cardiac failure and cardiac arrhythmia cases (from SMQ cardiac failure and SMQ cardiac arrhythmias) will be carefully followed up and a thorough assessment will be made, in particular, among patients with a medical history of AF, who discontinued or missed their AF treatment.

There are no other specific adverse reaction follow-up questionnaires for the other safety concerns listed in this RMP in Table SVIII-1.

- **Other forms of routine pharmacovigilance activities:**

There are no other forms of routine pharmacovigilance activities for the safety concerns listed in this RMP in Table SVIII-1.

III.2 Additional pharmacovigilance activities

There are no additional pharmacovigilance activities.

As a part of the global clinical development programme, difelikefalin was initially developed under the code CR845 by Cara. Difelikefalin was initially planned to be assessed in 3 phase 3 trials (CR845-310501, CR845-310301, and CR845-310302) of oral difelikefalin in other indications, including pruritus associated with AD and pruritus associated with earlier stages of CKD not dependent on dialysis. These trials were expected to collect additional safety data in non-HD populations, thereby avoiding the high background incidence of cardiac events and multiple confounding factors present in the HD population. This data would have been valuable in further characterising the cardiac safety profile of difelikefalin.

On 18 December 2023, Cara announced that oral difelikefalin as adjunct to topical corticosteroids did not demonstrate meaningful clinical benefit compared to topical corticosteroids alone. As a result, Cara discontinued its clinical programme in pruritus associated with AD. On 22 January 2024, Cara announced that the oral development

programme of difelikefalin in pruritus associated with CKD was terminated. At that time, ongoing studies were closed down. Despite early termination of these studies for strategic reasons, the available data demonstrate a low incidence of cardiac-related TEAEs, no treatment-related safety signals and comparable ECG findings across treatment groups. These findings strengthen the evidence base and support the conclusion that oral difelikefalin is not associated with increased cardiac risk in non-HD populations. On 14 June 2024, Cara announced that all clinical development would be discontinued and the company would pursue strategic alternatives. The development programme was not discontinued for any safety reasons. On 15 April 2025, CSL Vifor acquired the global rights for difelikefalin from Cara. An overview of these studies is presented in Annex 2.

III.3 Summary table of additional pharmacovigilance activities

Table Part III.3-1: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Milestones (Required by Regulators)	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)					
N/A	N/A	N/A	N/A	N/A	N/A
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances					
N/A	N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities (by the competent authority)					
N/A	N/A	N/A	N/A	N/A	N/A

N/A = not applicable

Part IV: Plans for postauthorisation efficacy studies

No postauthorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations are planned.

Table Part IV-1: Planned and Ongoing Postauthorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
N/A	N/A	N/A	N/A	N/A
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A

N/A = not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk minimisation plan

V.1 Routine risk minimisation measures

Table Part V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Use in pregnant and lactating women	
Routine risk communication	SmPC Section 4.6. PIL Section 2
Routine risk minimisation activities recommending specific clinical measures to address the risk	Not applicable - No clinical measures in place
Other routine risk minimisation measures beyond the Product Information	Legal status: Prescription only medicine
Use in patients with impaired blood-brain barrier	
Routine risk communication	SmPC Section 4.4. PIL Section 2
Routine risk minimisation activities recommending specific clinical measures to address the risk	Not applicable - No clinical measures in place

Safety Concern	Routine Risk Minimisation Activities
Other routine risk minimisation measures beyond the Product Information	Legal status: Prescription only medicine
Use in patients with severe hepatic impairment	
Routine risk communication	SmPC Section 4.2.
Routine risk minimisation activities recommending specific clinical measures to address the risk	PIL Section 3 Not applicable - No clinical measures in place
Other routine risk minimisation measures beyond the Product Information	Legal status: Prescription only medicine

PIL = patient information leaflet; SmPC = Summary of Product Characteristics

V.2 Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are deemed sufficient to manage the safety concerns of difelikefalin.

V.3 Summary of risk minimisation measures

Table Part V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnant and lactating women	Routine risk minimisation measures: SmPC Section 4.6 PIL Section 2 Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for use in pregnant women (Report on Exposure to Medicines During Pregnancy) Additional pharmacovigilance activities: None
Use in patients with impaired blood-brain barrier	Routine risk minimisation measures: SmPC Section 4.4 PIL Section 2 Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 PIL Section 3 Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

PIL = patient information leaflet; SmPC = Summary of Product Characteristics

Part VI: Summary of the risk management plan

Summary of risk management plan for Kapruvia (Difelikefalin)

This is a summary of the RMP for Kapruvia. The RMP details important risks of Kapruvia, how these risks can be minimised and how more information will be obtained about Kapruvia's risks and uncertainties (missing information).

Kapruvia's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Kapruvia should be used.

This summary of the RMP for Kapruvia should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of Kapruvia's RMP.

I. The medicine and what it is used for

Kapruvia is authorised for the treatment of moderate-to-severe pruritus associated with CKD in adult patients on HD (see SmPC for the full indication). It contains difelikefalin as the active substance and it is given as 50 µg/ml solution for injection.

Further information about the evaluation of Kapruvia's benefits can be found in Kapruvia's European Public Assessment Report, including in its plain language summary, available on the European Medicines Agency website, under the webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/kapruvia

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Kapruvia, together with measures to minimise such risks and the proposed studies for learning more about Kapruvia's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that can affect the safe use of Kapruvia is not yet available, it is listed under missing information below.

II.A List of important risks and missing information

Important risks of Kapruvia are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kapruvia. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• N/A
Important potential risks	• None
Missing information	• Use in pregnant and lactating women • Use in patients with impaired blood-brain barrier • Use in patients with severe hepatic impairment

N/A = not applicable

II.B Summary of important risks

Missing Information: Use in pregnant and lactating women	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6, PL Section 2 • Legal status: Prescription only medicine Additional risk minimisation measures: None

SmPC = Summary of Product Characteristics; PL = Package Leaflet

Missing Information: Use in patients with impaired blood-brain barrier	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4; PL Section 2 • Legal status: Prescription only medicine Additional risk minimisation measures: None

SmPC = Summary of Product Characteristics; PL = Package Leaflet

Missing Information: Use in patients with severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, PL Section 3 • Legal status: Prescription only medicine Additional risk minimisation measures: None

SmPC = Summary of Product Characteristics; PL = Package Leaflet

II.C Postauthorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or a specific obligation for Kapruvia.

II.C.2 Other studies in postauthorisation development plan

There are no studies required for Kapruvia.

Part VII: Annexes

Table of contents

Annex 4 Specific adverse drug reaction follow-up forms

REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 1

Name of Vifor Drug (Trade name / IMP):

Patients Initials / No: Country: Local Reference No:

Details of Mother and Pregnancy

Date / Year of Birth: / / (dd/mmm/yyyy) Age: Occupation:

Previous Pregnancy

Yes ☐ No ☐ Total no. of pregnancies: Normal Deliveries:

Abortions (Spontaneous): Abortions (performed):

Relevant Medical History:
(including pregnancy risk factors, Pre-eclampsia, eclampsia, smoking, alcohol, environmental & occupational exposures etc.)

Relevant Family History:
(hereditary diseases e.g. hypertension, diabetes)

Current Pregnancy

First day of Last Menstruation: / / (dd/mmm/yyyy) Expected Delivery Date: / / (dd/mmm/yyyy)

Gestational age of foetus (specify at time of exposure / time of reporting) :

Ultrasound performed? Yes ☐ No ☐ If yes, findings if any:

Any complications, infections or illnesses during pregnancy? Yes ☐ No ☐

If yes, elaborate:

Drug Exposure during Pregnancy

Mother /Father Exposure	**Suspect Drug/ Concomitant medication**	**Product Name** (Trade / IMP) **Batch no.**	**Total Daily Dose** (Units)	**Therapy Start date**	**Therapy Stop date**	**Indication for use**	**Route of application (oral, infusion, injection)**

Reporting Physician: Name: Profession:

Privacy Notification:

The personal data that you provide, such as your name and contact details, will be handled and stored by Vifor Pharma. You can read in detail what information we save and how the information will be handled in our Privacy Notices on the Vifor Pharma website (www.viforpharma.com/dataprivacy) where you also find contact details if you have questions.

NOTE: The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule specifically permits covered entities (such as pharmacists, physicians or hospitals) to use and disclose health information without authorization in order to report adverse events and other information related to the quality, effectiveness and safety of FDA-regulated products both to the manufacturers and directly to FDA. Please submit only that health information which is reasonably necessary to achieve the purpose of the report.

REPORT ON EXPOSURE TO MEDICINES DURING PREGNANCY Part 2

Information on Outcome of Pregnancy

Name of Vifor Drug (Trade name/IMP)**:**

Patients Initials / No: Country: Local Reference No:

Outcome of Pregnancy

☐ Full Term Normal delivery or Caesarean:

☐ Premature Birth If premature birth, gestational age: weeks

☐ Spontaneous Miscarriage

☐ Elective termination Medical Reason? ☐ Yes ☐ No

If yes, specify:

Details / Comments (if any):

☐ Healthy Baby ☐ Multiple Births

☐ Sick Baby (e.g. Birth trauma, infection etc.) ☐ Congenital anomaly or Birth defect ☐ Still Birth

Date of Birth / / (dd/mmm/yyyy) Sex ☐ Male ☐ Female

Size: Weight: APGAR scores, if provided (Birth/5/10 mins.)

Details / Comments (if any):

Please comment on any abnormal condition or occurrence regarding outcome of pregnancy and/or birth/delivery.

Is there a suspicion that adverse outcome of pregnancy is related to exposure to Product?

☐ Yes ☐ No

Please elaborate:

Reporting Physician: Name: Profession:

Please provide all available information and send to completed form. Attach any applicable supporting documentation if applicable. (such as pictures, autopsy report, hospital discharge summary, laboratory values)

Privacy Notification:

The personal data that you provide, such as your name and contact details, will be handled and stored by CSL Vifor. You can read in detail what information we save and how the information will be handled in our Privacy Notices on the CSL Vifor website (https://privacy.csl.com/cslviforpv) where you also find contact details if you have questions.

***NOTE**:* The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule specifically permits covered entities (such as pharmacists, physicians or hospitals) to use and disclose health information without authorization in order to report adverse events and other information related to the quality, effectiveness and safety of FDA-regulated products both to the manufacturers and directly to FDA. Please submit only that health information which is reasonably necessary to achieve the purpose of the report.

Please always send both, Part I and Part II of the form to safety@viforpharma.com or fax to: +41 58851 8659

KAPRUVIA (difelikefalin) HD PM TARGETED QUESTIONNAIRE_HCP

To be completed if data has not previously been provided.
Use additional pages to provide additional information

Please Email or Fax this report toVifor Pharma Ltd.:
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MCN #:	Date (dd-mm-yy):

I. Healthcare Professional Information

Name:	E-mail address:	Postal Address:	Country:

II. Patient Information

Patient's Initials:	Year of Birth:	Sex: ☐M ☐F	BMI:	Weight (kg/ lb): _____ Height (inch/ cm):

Patient's Ethnicity:	☐ Aboriginal	☐ Asian	☐ Black	☐ White	☐ Torres Strait Islander	☐ Other:

III. Adverse Event Information (attach additional pages if reporting more than 3 adverse events)

Event Term	Onset Date	Resolution Date	Outcome	Seriousness Criteria	Additional Event Outcome	Event Severity
Kindly Enter One Adverse Event Term Per Line	DD-MM-YY	DD-MM-YY	1) Recovered/ Resolved 2) Recovered/ Resolved With Sequelae 3) Not recovered/ Not resolved 4) Recovering/Resolving 5) Unknown 6) Fatal	1) Death 2) Immediately Life-Threatening 3) Requires/ Prolongs Hospitalization 4) Persistent/ Significant Disability/ Incapacity 5) Congenital Anomaly /Birth Defect 6) Important Medical Event	1. Non-Serious Medical Intervention 2. Surgical Intervention 3. Pharmacological Intervention 4. ER Visit 5. Clinician Visit 6. No Intervention Required 7. Intervention Not Provided 8. Specialty Consultation Specialist)	1) Mild 2) Moderate 3) Severe
1.						
2.						
3.						

IV. Hospital Admission & Death Information (if applicable)

Hospital Admission Date:	Hospital Discharge Date:	Date of Death:
_____ dd-mm-yy or ☐ N/A	_____ dd-mm-yy or ☐ N/A	_____ dd-mm-yy or ☐ N/A

Autopsy Performed? ☐ Yes ☐ No ☐ N/A If Yes, Report Attached? ☐ Y ☐ N
Cause of Death:

V. Concise Narrative Description of the course of event(s): Kindly provide a concise description of the course of the serious adverse event(s) with dates and results of relevant labs, diagnostic tests and procedure(s), vital signs, fluid status, relevant medical/ surgical and family history, relevant concomitant medications, drug and non-drug treatment(s) of the event(s), as well as outcome of the event(s), follow-up plans (if applicable) and HCP assessment including rationale for causality for the events. Please attach discharge summary and/or summary of post-mortem exam, if applicable.

VI. KAPRUVIA Drug Information

Indication:

Dose	Batch No.	Date of First Dose	Date of Last Dose Prior to this Event	Action Taken
1.				
2.				

KAPRUVIA De-Challenge: Was KAPRUVIA discontinued due to the event? ☐ YES DATE:_____ ☐ NO ☐ N/A OR
Was KAPRUVIA dose reduced due to the event? ☐ YES DATE:_____ ☐ NO ☐ N/A
IF YES, did the reported adverse event resolve after de-challenge with KAPRUVIA? ☐YES ☐NO ☐ N/A
IF 'NO' OR 'N/A', skip "KAPRUVIA Re-challenge" below

KAPRUVIA Re-Challenge: Was KAPRUVIA re-started after the de-challenge? ☐YES DATE:_____ ☐ NO ☐ N/A
IF YES, did the reported adverse event re-occur after Re-challenge with KAPRUVIA? ☐ YES ☐ NO ☐ N/A

KAPRUVIA (difelikefalin) HD PM TARGETED QUESTIONNAIRE_HCP

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VII. Centrally Acting Depressant Drug Information (attach additional pages if reporting more than 1 Centrally Acting Depressants)

Was the patient receiving one or more Centrally Acting Depressants prior to or during treatment with **KAPRUVIA**? ☐ **YES** ☐ **NO**

Name of Drug/Product:			**Dosage Form:**
Indication:			
Dose	**Date of First Dose**	**Date of Last Dose Prior to this Event**	**Action Taken**
1.			
2.			

Centrally Acting Depressant De-challenge: Was the Depressant discontinued due to the event? ☐ **YES** ☐ **NO** ☐ **N/A OR**
Was the Depressant dose reduced due to the event? ☐ **YES** **DATE:**_____ ☐ **NO** ☐ **N/A**
IF YES, did the reported adverse event resolve after de-challenge with the Depressant? ☐ **YES** ☐ **NO** ☐ **N/A**
IF 'NO' OR 'N/A', skip "Centrally Acting Depressant Re-challenge" below

Centrally Acting Depressant Re Challenge: Was the Depressant re started after the de challenge? ☐ **YES** **DATE:**_____ ☐ **NO** ☐ **N/A**
IF YES, did the reported adverse event re-occur after Re-challenge with the Depressant? ☐ **YES** ☐ **NO** ☐ **N/A**

VIII. Pro-arrhythmic Drug Information (attach additional pages if reporting more than 1 Pro-arrhythmic drugs)

Name of Drug/Product:			**Dosage Form:**

Was the patient receiving one or more Pro-arrhythmic drugs prior to or during treatment with **KAPRUVIA**? ☐ **YES** ☐ **NO**

Indication:			
Dose	**Date of First Dose**	**Date of Last Dose Prior to this Event**	**Action Taken**
1.			
2.			

Pro-arrhythmic Drug De-challenge: Was the Pro-arrhythmic discontinued due to the event? ☐ **YES** ☐ **NO** ☐ **N/A OR**
Was the Pro-arrhythmic dose reduced due to the event? ☐ **YES** **DATE:**_____ ☐ **NO** ☐ **N/A**
IF YES, did the reported adverse event resolve after the de-challenge with the Pro-arrhythmic? ☐ **YES** ☐ **NO** ☐ **N/A**
IF 'NO' OR 'N/A', skip "Pro-arrhythmic Drug Re-challenge" below

Pro-arrhythmic Drug Re-Challenge: Was the Pro-arrhythmic re-started after the de-challenge? ☐ **YES** **DATE:**_____ ☐ **NO** ☐ **N/A**
IF YES, did the reported adverse event re-occurred after the Re-challenge with the Pro-arrhythmic? ☐ **YES** ☐ **NO** ☐ **N/A**

IX. Herbal Preparation Use Information (attach additional pages if reporting use of more than 1 Herbal Preparations)

Was the patient consuming one or more Herbal Preparations prior to or during treatment with **KAPRUVIA**? ☐ **YES** ☐ **NO**

Name of Preparation/Product:			**Dosage Form:**
Indication:			
Dose	**Date of First Dose**	**Date of Last Dose Prior to this Event**	**Action Taken**
1.			
2.			

Herbal Preparation De-challenge: Was the Herbal Preparation discontinued due to the event? ☐ **YES** ☐ **NO** ☐ **N/A OR**
Was the Herbal Preparation dose reduced due to the event? ☐ **YES** **DATE:**_____ ☐ **NO** ☐ **N/A**
IF YES, did the reported adverse event resolve after the de-challenge with the Herbal Preparation? ☐ **YES** ☐ **NO** ☐ **N/A**
IF 'NO' OR 'N/A', skip "Herbal Preparation Re-challenge" below

Herbal Preparation Re-Challenge: Was the Pro-arrhythmic re-started after the de-challenge? ☐ **YES** **DATE:**_____ ☐ **NO** ☐ **N/A**
IF YES, did the reported adverse event re-occurred after the Re-challenge with the Pro-arrhythmic? ☐ **YES** ☐ **NO** ☐ **N/A**

X. Illicit Substance Use Information (attach additional pages if reporting use of more than 1 Illicit Substances)

Was the patient using one or more Illicit Substances prior to or during treatment with **KAPRUVIA**? ☐ **YES** ☐ **NO**

Name of Substance/Product:			**Dosage Form:**
Indication:			
Dose	**Date of First Dose**	**Date of Last Dose Prior to this Event**	**Action Taken**
1.			
2.			

Illicit Substance De-challenge: Was the Illicit Substance discontinued due to the event? ☐ **YES** ☐ **NO** ☐ **N/A OR**
Was the Illicit Substance dose reduced due to the event? ☐ **YES** **DATE:**_____ ☐ **NO** ☐ **N/A**
IF YES, did the reported adverse event resolve after the de-challenge with the Illicit Substance? ☐ **YES** ☐ **NO** ☐ **N/A**
IF 'NO' OR 'N/A', skip "Illicit Substance Re-challenge" below

Illicit Substance Re-Challenge: Was the Illicit Substance re-started after the de-challenge? ☐ **YES** **DATE:**_____ ☐ **NO** ☐ **N/A**
IF YES, did the reported adverse event re-occurred after the Re-challenge with the Illicit Substance? ☐ **YES** ☐ **NO** ☐ **N/A**

KAPRUVIA (difelikefalin) HD PM TARGETED QUESTIONNAIRE_HCP

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XI: Other Concomitant Medications, Products and Preparations List of concomitant medications received within 30 days of the event onset, including pain medications (prescription and Over-the-Counter).

Name of Product/ Drug	Indication(s)	Dose and Dosage Form	Date of First Dose	Date of Last Dose

XII. Laboratory & Diagnostic Tests (Provide relevant diagnostic tests and laboratory values for the reported event)

Test Name	Date	Result	Comment
Serum Potassium			
Serum Sodium			
Serum Magnesium			
Serum Calcium			
Troponin			
BNP			
NT-pro BNP			
Creatine Kinase			
Haemoglobin			
Oxygen Saturation			
Blood Pressure			
ECG			
Chest X-Ray			
CT Scan			
Echocardiogram			
Stress Test			
Other Relevant Lab & Test Results (Please list below)			

KAPRUVIA (difelikefalin) HD PM TARGETED QUESTIONNAIRE_HCP

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XIII. Medical and Family History

Haemodialysis (HD) History	Date of First HD	Frequency	Date of Last HD Prior to AE	Comments

	YES	NO	UNK	COMMENTS
New York Heart Association (NYHA class I-IV heart failure)				
Class I	☐	☐	☐	
Class II	☐	☐	☐	
Class III	☐	☐	☐	
Class IV	☐	☐	☐	
NO NYHA Class listed or unable to determine if known	☐	☐	☐	
Does Patient have a **Family history** of sudden death?	☐	☐	☐	Relationship & age at onset
Does Patient have a history of cardiomyopathy?	☐	☐	☐	
Does Patient have a **Family history** of cardiomyopathy?	☐	☐	☐	Relationship & age at onset
Does Patient have a history of Myocardial Infarction?	☐	☐	☐	
Does Patient have a **Family history** of Myocardial Infarction?	☐	☐	☐	Relationship & age at onset
Does Patient have a history of Coronary Artery Disease?	☐	☐	☐	
Does Patient have a **Family history** of Coronary Artery Disease?	☐	☐	☐	Relationship & age at onset
Does Patient have a history of Cardiovascular Disease (such as valvular heart disease)?	☐	☐	☐	
Does Patient have a **Family history** of Cardiovascular Disease (such as valvular heart disease)?	☐	☐	☐	Relationship & age at onset
Does Patient have a history of other cardiac disorders?	☐	☐	☐	Please provide details with date(s).
Does Patient have a **Family history** of other cardiac disorders? (Please specify)	☐	☐	☐	
Does Patient have a history of Atrial Fibrillation (AF.)?	☐	☐	☐	
If patient received treatment for AF, please specify if Patient has a history of missed doses or discontinuation of medications to treat AF prior to onset of the cardiac AE	☐	☐	☐	Please specify and provide details with date(s).
Does Patient have a history of Hypertension?	☐	☐	☐	
Does Patient have a history of Angina?	☐	☐	☐	
Does Patient have a history of Diabetes Mellitus?	☐	☐	☐	
Does Patient have a history of Sleep apnoea? (Please specify use of sleep aid including apnoea machine)	☐	☐	☐	
Does Patient have a history of Pulmonary disease, such as COPD (e.g. Asthma, Emphysema), Pneumonia, or Pulmonary oedema?	☐	☐	☐	Please specify and provide details with date(s).
Does Patient have a history of Thyroid disease?	☐	☐	☐	
Does Patient have a history of Anaemia?	☐	☐	☐	

XIV. Risk Factors

Smoking (current or past, duration in years, in amount per day/week)	❑ Yes ❑ No ❑ Unknown ❑ If yes, ongoing? Please describe below:
Alcohol or substance abuse (e.g., cocaine, illicit drug use - current or past; in drinks per day/week)	❑ Yes ❑ No ❑ Unknown ❑ If yes, ongoing? Please describe below:
Toxic exposure (e.g., chemotherapy, radiation, etc.)	❑ Yes ❑ No ❑ Unknown ❑ If yes, ongoing? Please describe below:

XV. Endorsement: Please provide signature of the reporting Healthcare Professional (with Title) and date.

Signature Date (dd-mmm-yyyy)

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable

Annex 7 Other supporting data (including referenced material)

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