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HEALTH TECHNOLOGY BRIEFING
OCTOBER 2020

Difelikefalin for pruritus associated with chronic kidney disease

NIHRIO ID	11414	**NICE ID**	10181
Developer/Company	Vifor Pharma UK Ltd	**UKPS ID**	657666

Licensing and market availability plans	Currently in phase III/II clinical trials.

SUMMARY

Difelikefalin is intended to treat adult haemodialysis patients with moderate to severe chronic kidney disease-associated pruritus (CKD-aP) (uraemic pruritus). Uraemic pruritus can be very unpleasant; about half of affected individuals become agitated or depressed. Uraemic pruritus in haemodialysis patients is associated with a 17% increase in mortality. Currently there are no approved treatments specifically for this condition.

Difelikefalin is a potent kappa opioid receptor agonist that is an itch and inflammation suppressant. Difelikefalin intravenous injection acts as an itch and inflammation suppressant without the undesirable side-effects typical of a centrally-acting opioid medicine such as hallucinations or opioid addiction. If licensed, difelikefalin will offer an additional treatment option for adult haemodialysis patients with moderate to severe CKD-aP who currently have few effective therapies available.

PROPOSED INDICATION

Adult haemodialysis patients with chronic kidney disease-associated pruritus (CKD-aP) (uraemic pruritus).[a]

TECHNOLOGY

DESCRIPTION

Difelikefalin (Korsuva, DIFELIKEFALIN) is a potent kappa opioid receptor agonist that is itch and inflammation suppressant.[1] Stimulation of the kappa opioid receptors by difelikefalin results in the initiation of an intracellular cascade that leads to the inhibition of ion channels necessary for peripheral nerve activity and culminates in reduced afferent nerve activity. Activation of kappa receptors on immune cells results in reduced release of nerve-sensitizing pro-inflammatory molecules.[2]

Difelikefalin is currently in development for the treatment of pruritus associated with chronic kidney disease in patients that require haemodialysis. In the phase III clinical trials (NCT03636269 and NCT03422653) difelikefalin 0.5mcg/kg intravenous (IV) injection is administered after each dialysis session (3 times/week).[3,4]

INNOVATION AND/OR ADVANTAGES

According to company, difelikefalin injection "is a first-in-class, innovative investigational medicine for treating a highly debilitating disease".[1]

Difelikefalin is a potent and selective itch and inflammation suppressant that does not activate mu or delta opioid receptors. It's a synthetic drug that mimics endogenous dynorphin. Its key attribute is that it does not cross the blood/brain barrier, so it does not pose a risk for adverse events caused by activation of central opioid receptors such as hallucination or opioid addiction.[1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Difelikefalin does not currently have Marketing Authorisation in the EU/UK for any indication.

Oral difelikefalin is currently under evaluation in phase II clinical trials for the treatment in subjects with:[5]

- pruritus related to atopic dermatitis
- pruritus related to primary biliary cholangitis
- pain relief in osteoarthritis of the hip or knee (on hold)

[a] Information provided by Vifor Pharma UK Ltd on UK PharmaScan

Intravenous difelikefalin has been evaluated in a phase II/III clinical trial for pain relief in patients undergoing abdominal surgery.[6]

PATIENT GROUP

DISEASE BACKGROUND

Chronic kidney disease associated pruritus (CKD-aP) is also called uraemic pruritus. Uraemia refers to excessive urea in the blood, and occurs when both kidneys stop working (renal failure). Pruritus, or itch, is a common problem for patients with chronic renal failure or end stage renal disease.[7] Uraemia causes severe episodes of pruritus, especially during the summer or at night. Although pruritus sometimes improves at the start of dialysis some patients experience itch, during or soon after treatment, usually beginning within 6 months of the onset of dialysis.[8]

Uraemic pruritus is thought to be due to a combination of factors including: dry skin, reduced sweating, abnormal metabolism of calcium and phosphorus / raised parathyroid hormone, accumulation of toxins, sprouting of new nerves, systemic inflammation, co-existing medical problems, particularly diabetes and liver disease.[7] Several situations have been known to worsen CKD-aP including extreme hot or cold, stress, physical activity and showering.[9]
The distribution of itching in CKD-aP is often symmetrical but can be localized or generalized. When localized, it often occurs in the back, face, and shunt arm. Also, CKD-aP can occur without any skin manifestations, can coexist with xerosis (dry skin) in between 50% and 85% of patients, or can occur with superimposed complications of excoriation including impetigo, linear crusts, papules, ulcerations, and prurigo nodularis.[10]

The effect of pruritus on quality of life in dialysis patients is readily apparent. These patients often appear unable to find a comfortable position and can scratch to the point of causing skin excoriations. When pruritus is severe and unrelenting despite treatment, sleep and social functioning can be affected. Finally, if left untreated long enough, these patients can develop depression. [10]

CLINICAL NEED AND BURDEN OF DISEASE

Data from an international study, where the UK was included, undertaken between 1996 and 1999 suggests that CKD-aP occurs with an incidence of 45% in haemodialysis patients worldwide.[11]

Data collected from 8 EU countries (incl. UK), Canada, Japan, New Zealand and the USA in 2002-2003 reported 42% of patients undergoing haemodialysis with moderate to severe pruritus. The same study reported a prevalence of 50% in moderate to extreme pruritus haemodialysis patients in the UK.[11]

According to the NHS OPCS-4 classification system for renal units code X40.1 for renal dialysis, between 2018-19 the Hospital Episodes Statistics (HES) for England recorded a total of 775 finished consultant episodes (FCE) for this procedure, and for haemodialysis NEC (X40.3) - 38,078 episodes.[12] For the same time period, the HES data for all diagnoses

admissions recorded a total of 1,467,528 FCE for chronic kidney disease of which 58,850 were main diagnoses.[13] Uraemic pruritus can be very unpleasant; about half of affected individuals become agitated or depressed. Uraemic pruritus in haemodialysis patients is associated with a 17% increase in mortality.[7]

The latest UK Renal Registry report for 2017 estimates a prevalence of in-centre haemodialysis for England of 20,574, 37.6% of the 54,773 prevalent patients on renal replacement therapy (RRT).[14]

The company, using the data from the UK Renal Registry, has reported that 24,218 adult patients were receiving in-centre haemodialysis (ICHD) for end stage renal disease (ESRD) in the UK on December 2017, which represented 37.3% of the (Renal Replacement Therapy) RRT population. Extrapolated estimates for 2019, would be 25,581 adult patients receiving ICHD (UK Renal Registry) ~40% of UK HD patients have a reported prevalence of moderate to severe CKD-aP that would equate to 10,232 patients in the UK.[b]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The first step in treatment of uraemic pruritus is optimising dialysis efficacy. It is also important to attempt to reduce serum parathyroid hormone to normalise calcium/phosphorus.[7]

CURRENT TREATMENT OPTIONS

- Topical emollients [15]
- Antihistamines [15]
- Gabapentin or pregabalin [15,16]
- Sertraline [16]

Some of the medicines above are not licensed for use for itching.[16]

PLACE OF TECHNOLOGY

if licensed, difelikefalin will provide a new treatment option for adult haemodialysis patients.

CLINICAL TRIAL INFORMATION

Trial	**NCT03281538, An Open-Label, Multicenter, Extension Study to Evaluate the Long Term Safety of Intravenous CR845 in Hemodialysis Patients With Chronic Kidney Disease-Associated Pruritus** **Trial phase: III** **Locations: USA and Puerto Rico**

[b] Information provided by Vifor Pharma UK Ltd on UK PharmaScan

	Study completion date: February 11, 2020
Trial design	Open-label, multicenter, long-term extension safety study
Population	N=288; Female or male subjects ⩾ 18 years or older, currently on haemodialysis for end-stage renal disease and has been categorized as experiencing moderate to severe uremic pruritus.
Intervention(s)	IV difelikefalin 0.5 mcg/kg administered after each dialysis session (3 times/week)
Comparator(s)	No comparator
Outcome(s)	Safety of IV difelikefalin based on physical examination; adverse events, vital signs and changes in laboratory tests. [Time Frame: Up to 52 weeks]
Results (efficacy)	-
Results (safety)	-

Trial	**NCT03636269, A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenous DIFELIKEFALIN in Hemodialysis Patients With Moderate-to-Severe Pruritus, With a 52-Week Open Label Extension KALM-2** **Trial phase: III** **Locations: EU (incl UK), USA, Canada and other countries** **Study completion date: March 30, 2020**
Trial design	Randomized, parallel assignment, triple blind
Population	N=474; Female or male subjects ≥ 18 years or older, has end-stage renal disease (ESRD) and has been on haemodialysis 3 times per week for at least 3 months prior to the start of screening
Intervention(s)	IV difelikefalin 0.5 mcg/kg administered after each dialysis session (3 times/week)
Comparator(s)	Matched placebo
Outcome(s)	Reduction of itch intensity as assessed by the proportion of patients achieving an improvement from baseline ≥3 points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity Numerical Rating Scale (NRS) score at Week 12 [Time Frame: Week 12] See trial record for full list of other outcomes
Results (efficacy)	• Primary Endpoint: The proportion of patients on 0.5 mcg/kg of difelikefalin Injection achieving a three-point or greater improvement from baseline in the weekly mean of the daily 24 hour Worst Itching Intensity Numeric Rating Scale (WI-NRS) score at week 12 was 54% versus 42% for patients on placebo (p= 0.02). [17]

	• Key Secondary Endpoint: The proportion of patients on 0.5 mcg/kg of difelikefalin Injection achieving a four-point or greater improvement from baseline in the weekly mean of the daily 24 hour WI-NRS score at week 12 was 41% versus 28% for patients on placebo (p= 0.01). [17] • Itch-Related Quality of Life Measures: Patients on difelikefalin Injection experienced a 12% and 29% improvement over placebo in the change from baseline for the Skindex-10 and total 5-D Itch scores respectively, which did not meet statistical significance. [17]
Results (safety)	Difelikefalin Injection was generally well-tolerated with a safety profile consistent with that seen in KALM-1 and the difelikefalin clinical program in patients with CKD-aP. Overall, the incidence of adverse events (AEs) and serious AEs were similar across both difelikefalin and placebo groups. The most common treatment-emergent AEs reported in >5% of patients were diarrhea (8.1% difelikefalin versus 5.5% placebo), falling (6.8% difelikefalin versus 5.1% placebo), vomiting (6.4% difelikefalin versus 5.9% placebo), nausea (6.4% difelikefalin versus 4.2% placebo) and dizziness (5.5% difelikefalin versus 5.1 % placebo). [17]

Trial	**NCT03422653, A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenous DIFELIKEFALIN in Hemodialysis Patients With Moderate-to-Severe Pruritus, With a 52-Week Open Label Extension KALM-1** **Trial phase: III** **Location: USA** **Study completion date: March 26, 2020**
Trial design	Randomized, parallel assignment, double blind
Population	N=378; Female or male subjects ≥ 18 years or older, has end-stage renal disease (ESRD) and has been on haemodialysis 3 times per week for at least 3 months prior to the start of screening
Intervention(s)	IV difelikefalin 0.5 mcg/kg administered after each dialysis session (3 times/week)
Comparator(s)	Matched placebo
Outcome(s)	Reduction of itch intensity as assessed by the proportion of patients achieving an improvement from baseline ≥3 points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity Numerical Rating Scale (NRS) score at Week 12 [Time Frame: Week 12]

Results (efficacy)	A total of 378 patients underwent randomization. A total of 82 of 158 patients (51.9%) in the difelikefalin group had a decrease of at least 3 points in the WI-NRS score (primary outcome), as compared with 51 of 165 (30.9%) in the placebo group. The imputed percentage of patients with a decrease of at least 3 points in the WI-NRS score was 49.1% in the difelikefalin group, as compared with 27.9% in the placebo group (P<0.001). Difelikefalin also resulted in a significant improvement from baseline to week 12 in itch-related quality of life as measured by the 5-D itch scale and the Skindex-10 scale. The imputed percentage of patients with a decrease of at least 4 points in the WI-NRS score at week 12 was significantly greater in the difelikefalin group than in the placebo group (37.1% [observed data: 64 of 158 patients] vs. 17.9% [observed data: 35 of 165 patients], P<0.001).[18]
Results (safety)	Diarrhoea, dizziness, and vomiting were more common in the difelikefalin group than in the placebo group.[18]

Trial	**NCT02858726, A Two-Part, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Intravenous DIFELIKEFALIN in Hemodialysis Patients With Moderate-to-Severe Pruritus** **Trial phase: II/III** **Location: USA** **Study completion date: March 14, 2017**
Trial design	Randomized, parallel assignment, double blind
Population	N=175; Female or male subjects ≥ 18 years or older, has end-stage renal disease (ESRD) and has been on haemodialysis 3 times per week for at least 3 months prior to the start of screening
Intervention(s)	• IV difelikefalin 0.5 mcg/kg administered after each dialysis session (3 times/week) • IV difelikefalin 1 mcg/kg administered after each dialysis session (3 times/week) • IV difelikefalin 1.5 mcg/kg administered after each dialysis session (3 times/week)
Comparator(s)	Matched placebo
Outcome(s)	Change from baseline in the weekly mean of the daily 24-hour Worst Itching Intensity NRS Score during week 8 [Time Frame: Baseline, Week 8]
Results (efficacy)	A significant reduction from baseline in itch intensity scores at week 8 favored all difelikefalin doses combined versus placebo (P ¼ 0.002). Difelikefalin also showed improvement over placebo in Skindex-10, 5-D itch, and sleep disturbance scores (P<0.005).[19]

Results (safety)	Overall, 78% of patients receiving difelikefalin reported treatment-emergent adverse events versus 42% of patients given placebo, with diarrohea, dizziness, nausea, somnolence, and fall being the most frequent (≥5%).[19]

Trial	**NCT02229929, A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Pharmacokinetics of Intravenous DIFELIKEFALIN in Hemodialysis Patients, and Its Safety and Efficacy in Hemodialysis Patients With Uremic Pruritus** **Trial phase: II** **Location: USA** **Study completion date: July 2015**
Trial design	Randomized, parallel assignment, double blind
Population	N=89; Female or male subjects ≥ 18 years or older, end stage renal disease (ESRD) patients who have been on haemodialysis for at least three months and are currently on haemodialysis: At least three times per week (Part A) Three times per week (Part B)
Intervention(s)	• Part A: difelikefalin 0.5 mcg/kg administered after each dialysis session over a 1 week treatment period (3 times per week) • Part A: difelikefalin 1.0 mcg/kg administered after each dialysis session over a 1 week treatment period (3 times per week) • Part A: difelikefalin 2.5 mcg/kg administered after each dialysis session over a 1 week treatment period (3 times per week) • Part B: difelikefalin, 1.0 mcg/kg administered after each dialysis session over a 2 week treatment period (3 times per week)
Comparator(s)	Matched placebo for both parts
Outcome(s)	Part A: Determine the Pharmacokinetics of Repeated Doses of difelikefalin in Haemodialysis Patients (half-life, Cmax, Tmax, AUC, Vd) [Time Frame: 1 week] Part B: Change in Worst Itching Intensity using a 100-mm Visual Analog Scale [Time Frame: 2 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**NCT03998163, 2018-004572-35 An Open-Label, Multicenter Study to Evaluate the Safety and**

	Effectiveness of Intravenous DIFELIKEFALIN in Hemodialysis Patients With Moderate-to-Severe Pruritus **Trial phase: III** **Location: USA, Czechia, Hungary, Poland** **Study completion date: March 6, 2020**
Trial design	Single group assignment, open label
Population	N=223; Female or male subjects 18 to 85 years old, has end-stage renal disease (ESRD) and has been on haemodialysis 3 times per week for at least 3 months prior to the start of screening
Intervention(s)	IV difelikefalin 0.5 mcg/kg administered three times/week
Comparator(s)	No comparator
Outcome(s)	Safety Endpoints • Adverse events [Time Frame: Up to Follow-Up Visit (Week 13-14)] • ECG [Time Frame: Baseline, Up to End of Treatment Visit (Week 13)] • Vital signs [Time Frame: Baseline, Up to Follow-Up Visit (Week 13-14)] • Clinical laboratory values [Time Frame: Baseline, Up to Follow-Up Visit (Week 13-14)] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Cost of difelikefalin was confidential at the time of producing this briefing.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- Commissioning Policy: Dialysis Away from Base. A06/p/a. February 2016.
- In Centre Haemodialysis (ICHD): Main and Satellite Units. Service Specifications. A06/S/a

OTHER GUIDANCE

British Association of Dermatologists' guidelines for the investigation and management of generalized pruritus in adults without an underlying dermatosis. 2018. [8]

ADDITIONAL INFORMATION

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