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ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of Difelikefalin Compared to Standard Care for Treating Chronic Kidney Disease Associated Pruritus (CKD-aP) in People with Kidney Failure Receiving Haemodialysis

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Abstract

Background Chronic kidney disease-associated pruritus (CKD-aP) is associated with an increased risk of depression, poor sleep and reduced health-related quality of life. Two phase III studies (KALM-1 and KALM-2) of difelikefalin showed reduced CKD-aP severity and improved itch-related health-related quality of life in patients with moderate and severe CKD-aP receiving haemodialysis for kidney failure.

Objective We aimed to estimate the cost effectiveness of difelikefalin for patients with CKD-aP receiving haemodialysis for kidney failure compared to standard care from a UK National Health Service perspective.

Methods A cohort model was developed with four health states representing levels of pruritus intensity over time, based on the KALM trials augmented with longer term CKD-aP severity data from another haemodialysis trial (SHAREHD) for standard care. Utilities were estimated from a mapping study of 5-D Itch to EQ-5D-5L in 487 patients receiving haemodialysis, costs were estimated based on resource use alongside the SHAREHD and 2018 unit costs, and inflated to 2021 costs. Costs and quality-adjusted life-years were discounted at 3.5% per annum. A de novo economic model was developed in Microsoft Excel with scenario analyses performed using a range of assumptions.

Results In the base-case analysis over a time horizon of 64 weeks, using a placeholder cost of £75 per 28-days for difelikefalin, the incremental cost-effectiveness ratio of difelikefalin compared with standard care was £19,558/quality-adjusted life-year (QALY). Scenario analyses resulted in incremental cost-effectiveness ratios that ranged from £10,154/QALY (severe only) to £16,957/QALY (5-year horizon) for difelikefalin compared to standard care. Probabilistic sensitivity analyses suggested difelikefalin has a 48.6% probability of being cost effective at a threshold of £20,000/QALY and a 57.2% probability of being cost effective at a threshold of £30,000/QALY.

Conclusions The cost effectiveness of difelikefalin in a range of scenarios could make it an important pharmacotherapy to address the high burden of disease and unmet need for treatments associated with CKD-aP in the UK.

1 Introduction

Chronic kidney disease-associated pruritus (CKD-aP) affects 40–70% of patients undergoing haemodialysis for kidney failure and is associated with a generalised persistent and refractory itching [1, 2]. Patients experiencing CKD-aP are associated with an increased risk of depression, poor sleep and reduced health-related quality of life [1, 3]. Although it can improve, CKD-aP persists in about 70% of people who have moderate or worse severity when followed for up to 2 years [4]. This high prevalence and impact have led to repeated prioritisation by patients and healthcare professionals for new therapies for CKD-aP [5].

Although a number of existing topical and systemic therapies exist, issues such as poor adherence, undesirable side effects and varied efficacy result in a residual unmet need for patients with CKD-aP [6]. In response to this, difelikefalin, a peripherally restricted and selective agonist of kappa opioid receptors, was tested in two phase III studies (KALM-1 and KALM-2) [7, 8]. Both KALM studies were double blinded and placebo controlled for 12 weeks, after which placebo-treated patients switched to difelikefalin and both arms continued in an open-label extension up to 52 weeks. Difelikefalin significantly improved the primary endpoint of the Worst Itching Intensity Numerical Rating Scale, which was

Extended author information available on the last page of the article

Key Points for Decision Makers

Results from two phase III studies (KALM-1 and KALM-2) suggest that difelikefalin reduces chronic kidney disease-associated pruritus intensity and improved dermatological health-related quality of life; however, there are no studies examining the cost effectiveness of difelikefalin in patients with chronic kidney disease-associated pruritus.

This is the first study estimating the cost effectiveness of difelikefalin and our results suggest that the base-case incremental cost-effectiveness ratio of £19,558/quality-adjusted life-year is within the threshold range of £20,000–£30,000 per quality-adjusted life-year used by the National Institute for Health and Care Excellence.

Given the high prevalence of chronic kidney disease-associated pruritus in people with kidney failure, its impact on quality of life and the relative lack of effective treatments, our analyses support the inclusion of difelikefalin in routine clinical practice for patients receiving haemodialysis in England and Wales.

assessed in the initial 12-week double-blind treatment phase, and the 5-D Itch scale that combines severity with other patient-reported measures of the impact of itching during the subsequent 52-week open-label extension. Difelikefalin has been recently authorised for commercialisation in USA, the European Union, the UK, and other countries [9–11].

In addition to the importance to patients of new therapies for CKD-aP, and the clinical effectiveness of difelikefalin, the cost effectiveness needs to be understood. To our knowledge, there are no studies examining the cost effectiveness of difelikefalin in patients with CKD-aP. Data on the natural history of CKD-aP, utilities estimated from a mapping study and data from the pivotal trials were combined to estimate the cost effectiveness of difelikefalin in addition to current standard of care in patients with CKD-aP receiving haemodialysis for kidney failure from a UK National Health Service perspective.

2 Methods

2.1 Conceptual Modelling

The aim of conceptual modelling was to develop the model structure that can capture all the health states, relevant costs and utilities as well as identifying the modelling approach. First, a range of alternative model structure options were considered following review of the relevant literature including key studies in CKD-aP, the severity measures for CKD-aP and existing economic models in similar disease areas [1, 2, 6, 12–14]. Eight (four clinical and four health economic) experts met with the authors on two occasions to develop the conceptual model, explore assumptions and identify appropriate data sources.

After reviewing the model structures and horizons, the expert group suggested that a shorter term economic model is likely to be more appropriate, particularly because this could utilise data from the 12-week, double-blind, placebo-controlled, phase III clinical trials of difelikefalin and their 52-week open-label extension studies. As such, a cell-based cohort model structure using the proportions of patients in different health states sourced directly from the KALM studies was preferred (Fig. 1) over a more complex modelling approach (e.g. microsimulation). That is, rather than modelling the transitions between the different health states (such as in a Markov modelling approach), the cells containing the proportions of patients in the different health states are populated directly with the data from KALM trials.

Based on the similarity between the widely used Kidney Disease Quality of Life instrument [15], the 5-D Itch instrument [12] used in the KALM studies and the Verbal Rating Scale [16], the CKD-aP severity health states of none, mild, moderate and severe used in the model were based on the intensity question of the 5-D Itch instrument. The severe CKD-aP health state includes patients who reported severe or overwhelming in the intensity question of the 5-D Itch instrument. A 28-day cycle length and 64-week time horizon were used in the model to correspond to the follow-up points and length of follow-up in the KALM trials, respectively.

2.2 CKD-aP Severity in Patients Receiving Difelikefalin

The data used in the model for people receiving difelikefalin were based on trajectories observed for difelikefalin arms in the pivotal KALM trials [7, 17]. Identically structured patient-level clinical trial data from KALM-1 ($n = 378$) and KALM-2 ($n = 473$) were merged to generate a dataset with 851 patients to estimate a more precise measure of effectiveness. The degree domain of the 5-D Itch instrument was used to estimate the proportions of patients in the different severity states over 64 weeks in patients receiving difelikefalin (Fig. 2A) and for the first 12 weeks in standard care.

2.3 CKD-aP Severity in Patients Receiving Standard Care

The plausibility of what was observed in the published KALM trials in the placebo arm was compared to what was

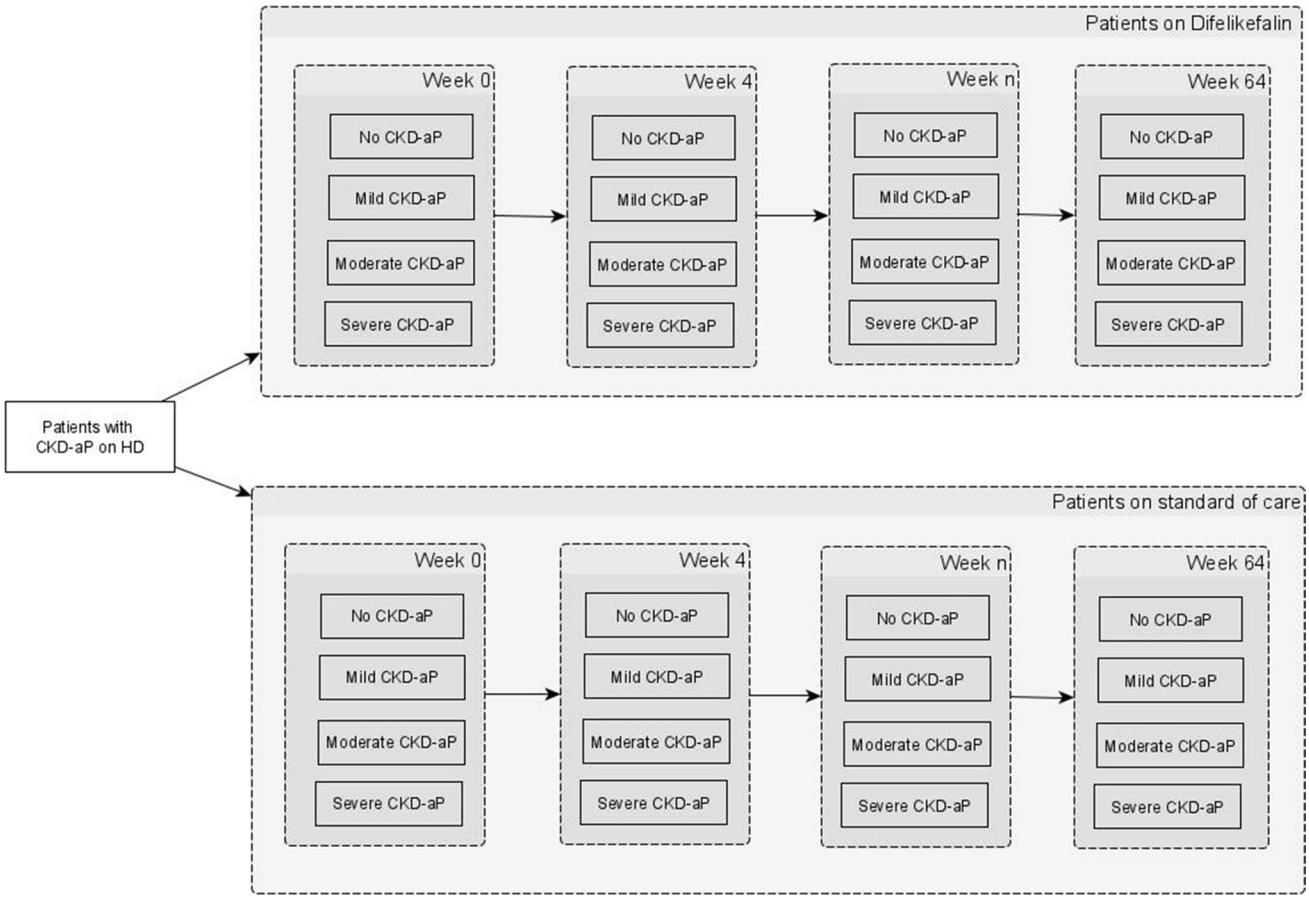

Fig. 1 Model structure of chronic kidney disease-associated pruritus (CKD-aP). *HD* haemodialysis

observed in patients with moderate or worse pruritus receiving standard care in the SHAREHD Stepped Wedge Cluster Randomised Trial (SWCRT) [18] [for details, see the Electronic Supplementary Material (ESM)]. SHAREHD SWCRT evaluated a quality improvement collaborative designed to support in-centre haemodialysis patients to dialyse more independently both at centres and at home, and data were collected for 24 months in 12 renal centres in England.

Data on the Verbal Rating Scale in haemodialysis patients receiving standard of care demonstrated a much more gradual decline in CKD-aP severity over time than that observed in the KALM trials. This suggested a significant placebo response in the placebo arm, resulting in improvements in pruritus severity at 12 weeks in the KALM trials of a size that took 18–24 months for participants in the SHAREHD SWCRT to achieve (Fig. 2 of the ESM).

As such, the prevalence of CKD-aP severity states at 64 weeks in the SHAREHD SWCRT were applied at 64 weeks in the model, with a linear trajectory between 12 weeks and 64 weeks (Fig. 2B). The rationale being that in receiving standard care outside a trial for a CKD-aP therapy the cohort with moderate or worse CKD-aP would have the severity distribution seen at 64 weeks in the SHAREHD SWCRT, with improvement beyond these levels being clinically implausible. Mixed-effects ordered Probit regression including age, sex, diabetes mellitus and polynomial terms for time was used to generate observations between the study sampling timepoints where values were needed for the model, and where patient responses in the study were missing. The methods for the pessimistic sensitivity analysis assumed standard care patients follow the difelikefalin trajectory from 12 weeks and are detailed in the ESM.

2.4 Costs of Difelikefalin

A placeholder value of £75 per 28-day cycle was used for difelikefalin costs, as the incremental cost-effectiveness ratio (ICER) was close to the National Institute for Health and Care Excellence (NICE) threshold of £20,000 per QALY at this price and could inform reimbursement decisions. Sensitivity analyses were conducted using arbitrary values of £50 and £150 per cycle.

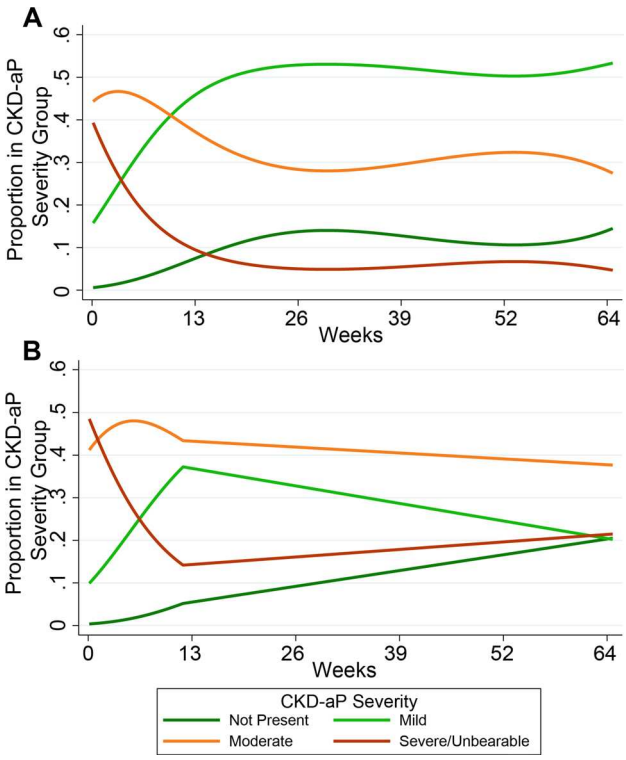

Fig. 2 Chronic kidney disease-associated pruritus (CKD-aP) severity trajectories for patients receiving **A** difelikefalin and **B** placebo (extrapolated from SHARE-HD data from 3 months)

2.5 Mapping Study and Utilities

A mapping study was conducted to estimate EQ-5D-3L from 5-D Itch scale data. EQ-5D-5L and 5-D Itch questionnaires were administered to 478 haemodialysis patients in five dialysis centres in the UK. The 5-D Itch scale is a multidimensional questionnaire developed to capture the course of pruritus. In line with NICE Health Technology Assessment (HTA) guidance [19], the mapping function developed by the NICE Decision Support Unit [20], using the 'EEPRU dataset' [21], was used to convert EQ-5D-5L into EQ-5D-3L. Mixture models using a range of latent classes were used to predict EQ-5D-3L using the 5-D Itch scale, adjusting for age, sex, having diabetes and time receiving dialysis (measured in years). Details of the mapping model are presented in the ESM. For utilities, the 5-D Itch scale values from both the placebo-controlled and open-label extension periods of the KALM-1 and KALM-2 studies were mapped to EQ-5D-3L to estimate the utility parameters for the different health states in the model, as shown in Table 1.

2.6 Healthcare Resource Use and Costs

Evidence on resource use was obtained from existing SHAREHD SWCRT data [18], the published literature [13, 22] and a primary data analysis from supplementary data items collected from the mapping study. These included antihistamines, gabapentinoids, oral steroids, topical steroids, antidepressants, sedatives and topical emollients, the selection of which were informed by a systematic review [6]. Uncertainties and assumptions were supplemented by clinical input. The healthcare resource use was combined with the average 2018 unit costs to estimate the costs used in the model, as shown below in Table 2. The costs were inflated to 2021 costs using the pay and prices National Health Service cost inflation indices reported by the Personal Social Services Research Unit [23].

2.7 Model Assumptions

The model includes 'responder' and 'non-responder' categories to capture differences in treatment duration (and hence treatment costs) between these two groups. Responders are defined as those who achieve an improvement in the health state and non-responders are those who stop treatment because of a lack of efficacy. In the base-case analysis, it was assumed that the patients in the 'severe' health state in the difelikefalin arm at three cycles, corresponding to the duration of the double-blind phase, would discontinue difelikefalin because of a lack of response, and hence do not accrue the costs of difelikefalin beyond this period. Being already in the worst health state, and based on the flattening of the extrapolation curves, no impact on utilities was foreseen.

In the moderate severity stopping rule, individuals who began with moderate severity CKD-aP and did

Table 1 Utilities of the different health states estimated from the mapping study

Health state	Utility value		
	Mean utility	95% confidence interval	Distribution used in the probabilistic analysis
No CKD-aP	0.6168	(0.5537, 0.6799)	Normal (0.6168, 0.0322)
Mild CKD-aP	0.5790	(0.5321, 0.6260)	Normal (0.5790, 0.0240)
Moderate CKD-aP	0.5143	(0.4681, 0.5605)	Normal (0.5143, 0.0236)
Severe CKD-aP	0.4293	(0.3627, 0.4959)	Normal (0.4293, 0.0340)

CKD-aP chronic kidney disease-associated pruritus

not experience an improvement in the CKD-aP severity health state at three cycles (or put more simply, those who did not transition into severity states mild or none) were assumed to stop difelikefalin treatment. Those who began in a severe health state but had transitioned into a moderate health state would remain receiving difelikefalin treatment. There is no adjustment for any improvement that difelikefalin may have had on CKD-aP severity in these non-responding individuals (e.g. moderate severity at baseline who without difelikefalin would have transitioned into severe); however, observational data of the natural history of this condition generally imply an initial improvement and then stabilisation in people receiving standard care. Worsening severity of CKD-aP appears to be difficult to demonstrate at a cohort level [4].

2.8 Model Analyses

The model estimated the incremental cost per QALY gained through use of difelikefalin compared to current practice for the UK, using the healthcare system perspective. A discount rate of 3.5% per annum was used for costs or QALYs (which was applied in the model as a discount rate of 0.26% per 28-day cycle, converted from the annual rate into the rate per cycle). The key input parameters were varied in one-way sensitivity analyses, the ranges were based on the confidence intervals whilst preserving the monotonicity in the direction of costs/utilities between different health states (e.g. ensuring that the utility of the 'mild CKD-aP' health state does not exceed that of the 'no CKD-aP' health state).

Scenario analyses were also performed assuming: (a) both moderate and severe health state patients stop treatment at three cycles, (b) data only from the KALM-1 trial (owing to a more pronounced "placebo effect" in KALM-2), (c) severe health state patients only at the start of the model using trajectories modelled specifically for them, (d) a 5-year time horizon including mortality and (e) the placebo patients follow difelikefalin trajectory in an extremely pessimistic scenario.

To account for non-linearities amongst the model inputs, probabilistic sensitivity analyses (PSAs) were undertaken using 1000 model runs, as the model results converged by this number of PSA runs. There was uncertainty in the short-term data, i.e. the proportions of patients in the different health states were modelled using Dirichlet distributions across the PSA runs, utility inputs were modelled using normal distributions estimated from the mapping study (as shown in Table 1) and the cost inputs were modelled as being within ± 20% of the mean values presented in Table 2.

2.9 Model Validation

We performed validation of the conceptual model, model inputs, model programming and the model results as outlined in the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool [26].

Table 2 Healthcare resource use, unit costs and the total costs for the different health states

Healthcare resource use (per 28-day cycle)	No CKD-aP	Mild CKD-aP	Moderate CKD-aP	Severe CKD-aP	Source (resource use)	Unit costs	Source (unit costs)
Medication use[a]	£1.98	£1.84	£1.84	£3.69	Mapping study		BNF [24]
ESA (units)	41354.19	41387.29	42059.02	44885.57	Ramakrishnan et al. 2013 [13]	£0.01	BNF [24]
Iron usage (mg)	185.18	182.77	180.48	187.40	Ramakrishnan et al. 2013 [13]	£0.10	BNF [24]
Hospital admissions[b]	0.09	0.10	0.09	0.10	SHAREHD study [18]	£3940.61	NHS reference costs 2018 [25]
Haemodialysis 28-day cost[b]	£1964	£1958	£1974	£2067	SHAREHD study [18]		NHS reference costs 2018 [25]
Emergency room visits[b]	0.11	0.11	0.11	0.12	SHAREHD study [18]	£194.06	NHS reference costs 2018 [25]
Total costs (2018)	£2552	£2584	£2624	£2802			
Total costs (inflated to 2021)	£2751	£2786	£2829	£3020			

BNF British National Formulary, *CKD-aP* chronic kidney disease-associated pruritus, *ESA* Erythropoiesis-stimulating agents, *NHS* National Health Service

[a]Medications excluding ESA and iron

[b]Unit costs are different by the health state, more details are provided in the ESM

3 Results

In the base-case analysis over a time horizon of 64 weeks, difelikefalin increased costs compared with standard care by £598 (i.e. from £44,717 in the usual care arm to £45,314 in the difelikefalin arm). The QALYs per patient for difelikefalin and standard care were 0.659 and 0.629, respectively, reflecting an increase of 0.030 QALY with difelikefalin. The resultant ICER, the ratio between incremental costs and the QALYs, was estimated at £19,558/QALY as shown in Table 3.

3.1 PSA

The results of the PSA displayed on a scatterplot (Fig. 3) show a cluster of results in the north-east and south-east quadrants suggesting that difelikefalin is always more clinically effective, consistent with the results of the KALM trials. Lines indicating willingness-to-pay (WTP) thresholds of ICERs of £20,000/QALY and £30,000/QALY have been drawn for reference; these lines represent the WTP thresholds below which NICE typically recommends a new treatment be made available to National Health Service patients. Almost half of the points on the scatterplot in Fig. 3 are below the £20,000/QALY line, and this is also observed in the cost-effectiveness acceptability curve in Fig. 4, which suggests a 48.6% probability of difelikefalin being cost effective at a WTP threshold of £20,000/QALY. Figure 3 also shows that the majority of the points in the scatterplot are below the £30,000/QALY line, as the probability of difelikefalin being cost effective at a WTP threshold of £30,000/QALY is 57.2%, as seen in Fig. 4.

3.2 Scenario Analysis

Scenario analyses were also performed using a range of model settings and assumptions as shown in Table 4. In the scenario assuming both moderate and severe health state patients stop treatment at three cycles, difelikefalin has an ICER of £14,737/QALY compared to standard care. In the

Table 3 Base-case cost-effectiveness results

	Difelikefalin costs	Healthcare costs (non-difelikefalin)	Total costs	QALYs	Cost/QALY gained
Difelikefalin	£1118	£44,197	£45,314	0.659	£19,558
Standard care	–	£44,717	£44,717	0.629	

QALY quality-adjusted life-year

Fig. 3 Cost-effectiveness scatter plot. *Lines indicate willingness-to-pay thresholds of incremental cost-effectiveness ratios of £20,000/quality-adjusted life-year (QALY) and £30,000/QALY

scenario analysis using data only from the KALM-1 trial (owing to a more pronounced "placebo effect" in KALM-2), difelikefalin has an ICER of £13,539/QALY compared to standard care. In the scenario analysis assuming severe health state patients only at the start of the model, difelikefalin has an ICER of £10,154/QALY compared to standard care. In the pessimistic scenario analysis, assuming standard care patients follow the difelikefalin trajectory resulted in an ICER of £74,700/QALY for difelikefalin compared to standard care. Performing the base-case analysis using a 5-year time horizon resulted in an ICER of £16,957/QALY for difelikefalin compared to standard care.

3.3 One-Way Sensitivity Analysis

Results of the one-way sensitivity analyses shown in Fig. 5 suggest that the key drivers of cost effectiveness are the costs of difelikefalin and the costs of mild, moderate and severe health states.

3.4 Model Validation

We performed validation of the conceptual model, model inputs, model programming and the model results as outlined in the AdViSHE tool. The conceptual model was

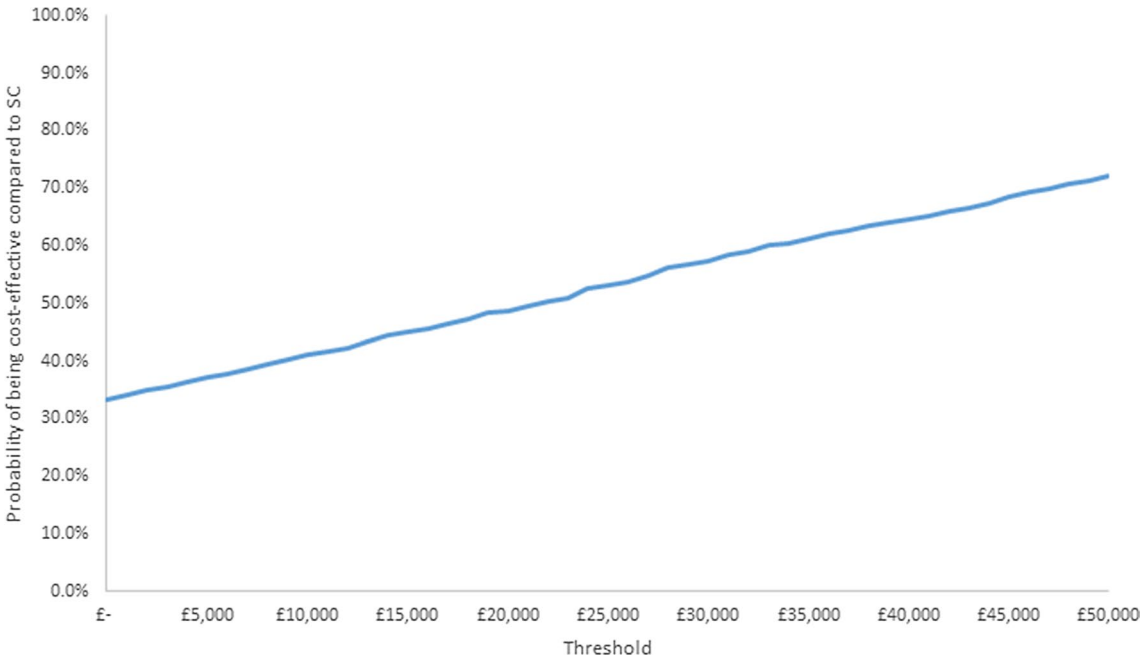

Fig. 4 Cost-effectiveness acceptability curve. *SC* standard care

Table 4 Results of the scenario analyses

	Scenario	Standard care		Difelikefalin		ICER
		QALYs	Costs	QALYs	Costs	
1	Base case	0.629	£44,717	0.659	£45,314	£19,558/QALY
2	Scenario assuming both moderate and severe as non-responders[a]	0.629	£44,717	0.659	£45,167	£14,737/QALY
3	Scenario using KALM-1 data only	0.627	£44,765	0.663	£45,255	£13,539/QALY
4	Scenario analysis using severe patients at model start	0.606	£45,167	0.642	£45,531	£10,154/QALY
5	Scenario analysis assuming standard care patients follow difelikefalin trajectory	0.647	£44,400	0.659	£45,314	£74,700/QALY
6	Base case analysis using a 5-year time horizon	1.980	£139,701	2.083	£141,439	£16,957/QALY

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

[a]The proportion remaining in moderate health state at the end of three model cycles in the KALM trials were considered non-responders and assumed to stop treatment

validated with an expert advisory group. The disease progression data for difelikefalin were based directly on KALM studies, as such, this already constitutes internal model validation. Similarly, the costs and the disease progression data for standard care were based on the SHAREHD data, and the utilities were based on a robust mapping study.

The model also underwent technical validation. Analysis were performed using extreme values (e.g. setting all utilities to 1, and comparing the life-years to QALYs; setting all utilities to zero, and checking that the QALYs are zero). Scenario analyses were also performed using different model inputs and the results were sense checked for face validity. Our model, as far as we know, is the first study estimating the cost effectiveness of difelikefalin so we cannot perform validation by comparing to the findings from other studies.

4 Discussion

The results of our cost-utility analysis suggest that difelikefalin could represent a cost-effective therapy to address the high burden of disease and unmet need for treatments associated with CKD-aP in the UK: the base-case ICER of £19,558/QALY is within the threshold range of £20,000–£30,000 per QALY used by NICE. The results of the scenario analyses suggest that the base-case analysis involves conservative assumptions as the ICERs for the majority of the scenario analyses were all lower than the base-case ICER.

Our model is the first study estimating the cost effectiveness of difelikefalin. As such, there is a lack of published cost-effectiveness models for therapies for CKD-aP on which to compare our work; however, the inputs and underlying assumptions informing our model are supported by the published literature on CKD-aP [6, 22]. A systematic review of the association between CKD-aP and health-related quality of life suggested that increased severity of CKD-aP resulted in lower health-related quality of life but was unable to estimate this relationship with utilities [3]. To address this issue, a mapping study was performed, and the utilities estimated in the mapping study are comparable to the range reported for people receiving haemodialysis in recent systematic reviews [27].

The trajectory of CKD-aP in people receiving standard care from SHAREHD SWCRT is comparable to other studies reporting patients over 12–24 months from European and international cohorts [4, 28]. Meanwhile, the placebo effect seen in the KALM-1 trial and more specifically the KALM-2 trial is in excess of those seen in other therapies for CKD-aP reported in a recent Cochrane review [29]. By limiting analyses to just the KALM-1 trial, the scenario analyses highlight the importance of estimating the real-world treatment effect of standard care without the associated placebo effect that would not be present outside of a trial. This is further supported by the trajectory of CKD-aP severity seen in other real-world studies including those informing our analysis [4]. Whilst the scenario analysis assuming standard care patients follow a difelikefalin trajectory suggested a high ICER, the clinical expert in the authorship group suggested that this scenario was pessimistic and not in line with the observational data for this population. The choice of a horizon of 5 years in the scenario analyses is informed by the short life expectancy of people receiving haemodialysis who are not eligible for a kidney transplant, a patient group that other authors reported similar mortality and resource use to people with non-metastatic cancers [30]. The relative severity of the condition of kidney failure may justify the use of different ICER thresholds such as the severity modifier introduced by NICE, and the holistic consideration of the technology and the disease it treats.

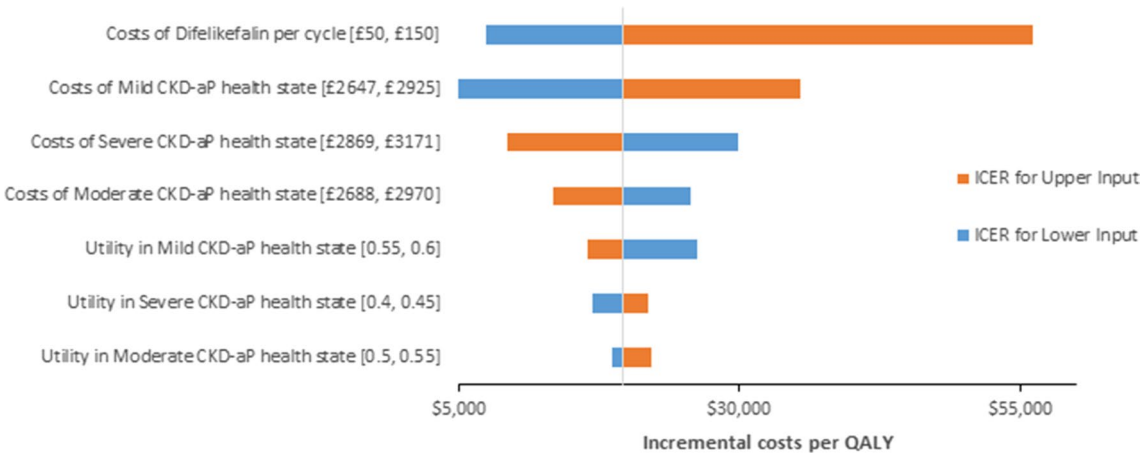

Fig. 5 Tornado diagram showing the results of one-way sensitivity analyses. *CKD-aP* chronic kidney disease-associated pruritus, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

Our economic model has a number of strengths, especially in terms of the robust data used to populate the model: the disease progression was based on a primary analysis of existing external trial data to model the severity of CKD-aP in patients receiving standard care, the utilities were estimated based on a mapping study of trial CKD-aP pruritus measures to generic preference-based measures (i.e. EQ-5D), evidence on resource use and costs was obtained from a primary data analysis of supplementary data collected in the mapping study, existing SHAREHD SWCRT data and published literature. All primary analyses were designed and conducted to achieve the wider goal of estimating the clinical and cost effectiveness of difelikefalin for treating this common and unpleasant condition prioritised by patients and healthcare professionals.

However, all models and modelling analyses have to make assumptions and simplify reality in some way, which leads to limitations. These include requiring external sources of data for some inputs, and the assumption that reductions in CKD-aP severity due to difelikefalin lead to reductions in the resource utilisation associated with CKD-aP severity (e.g. other CKD-aP therapies, delivered dialysis and hospitalisation), and the implementation of clinical practice around stopping rules in the real world. However, we have made conservative choices when defining the base case and we believe that the ICER is likely to be an overestimate. Additionally, whilst the disease progression data (and potentially utilities) could be applicable to similar settings (e.g. European Union/USA), the costs in other settings will be different to those used in the model. As such, we suggest caution in the generalisability of the model findings to different contexts. Access to longer term real-world data on longitudinal patient-reported outcomes in chronic diseases, combined with the linkage of these to administrative datasets that capture resource use and attendant costs would be of value to researchers, industry, reimbursement agencies and ultimately patients. This may explore the hypothesis that the higher medication use in patients with no CKD-aP is higher than those with mild or moderate CKD-aP because medications are indicated for other conditions. Further research into extrapolation methods for patient-reported outcome measures to inform health-economic modelling would be beneficial.

5 Conclusions

Given the high prevalence of CKD-aP in people with kidney failure, its impact on quality of life and the relative lack of effective treatments, the cost-effectiveness analysis of difelikefalin under a set of conservative base-case assumptions supports the inclusion of difelikefalin in routine clinical practice for patients receiving haemodialysis in England and Wales.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40273-022-01237-4.

Declarations

Funding This work was funded by VIFOR Pharma Intl.

Conflict of interest PT, PEHS, MH, AS and JF received an unconditional research grant by Vifor Pharma Intl. TS and MS are Vifor Pharma employees.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Researchers wishing to access the primary data from SHAREHD study are requested to follow the directions of the associated primary publication (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8291659/). The primary data for the mapping study are available from the corresponding author on reasonable request following approval from the study funder.

Code availability Not applicable.

Authors' contributions PT developed the economic model and drafted the outline in collaboration with JF. PEHS performed the analysis to estimate the resource use and costs for the model. JF analysed data from the KALM and SHAREHD studies. MH and AS performed the mapping study to estimate the utilities for the model. All authors contributed to the conceptualisation, writing, editing and finalising of the manuscript.

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