Difelikefalin for treating pruritus in people having haemodialysis

For public – contains redacted information

Technology appraisal committee B 08th February 2023

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Process: STA 2022

Key issues for discussion

Issue	ICER impact
Comparator - different to that in NICE scope	Unknown
Lack of anti-itch medication sub-grouping	Unknown
Generalisability - Differences in ethnicity between trials and UK target population	Unknown
Imputation and regression analysis - Unclear rationale for statistical analysis	Unknown
Methods used to pool trials were unclear	Unknown
Estimating transition probabilities	Medium
Lack of clarity on how multiple imputation was used	Unknown

Abbreviations: SLR, systematic literature review

Difelikefalin (Kapruvia, Vifor Pharma)

Marketing authorisation	• Indicated for treatment of moderate-to-severe pruritus associated with chronic kidney disease in adults on haemodialysis. It is restricted to in centre haemodialysis use only. • UK marketing authorisation granted by MHRA on 29th April 2022.
Mechanism of action	Difelikefalin is a selective kappa opioid receptor agonist with low central nervous system penetration
Administration	Administered three times a week by intravenous bolus injection into the venous line of the dialysis circuit at the end of haemodialysis treatment. Recommended dose is 0.5 micrograms/kg dry body It is restricted for in-centre haemodialysis use
Price	• List price per pack = £35.00 per 1mL vial (50µg/mL • Simple discount patient access scheme

Background on CKD-associated Pruritis (CKD-aP)

Causes

- CKD-aP is a systemic itch comorbidity that is common in kidney failure patients
    - occurs in dialysis-dependent and non-dialysis-dependent patients - more prevalent in dialysis-dependent
    - caused by immune system dysfunction and imbalances in the endogenous opioid system

Diagnosis and classification

- CKD is categorised into five stages dependent on kidney functionality
    - CKD-aP can be generalised affecting the entire skin or localised affecting specific areas (scalp, face, upper back, arms or buttocks)
    - Severity can change over time from sporadic discomfort to complete restlessness reducing quality of life

Symptoms and prognosis

- Skin manifestations include excoriations, prurigo nodularis, and scarring caused by scratching
- Higher rate of all-cause mortality in those extremely bothered than those who report not being at all bothered by itchy skin** and CKD-aP patients on HD had a higher mortality rate than those with CKD alone ***

Epidemiology

- Overall prevalence of moderate-to-extreme CKD-aP was 24%
    - moderately bothered by itchy skin ranged 26% (Germany) to 48% (UK), and
    - very much or extremely bothered by itchy skin* 13% (Germany) and 26% (UK)

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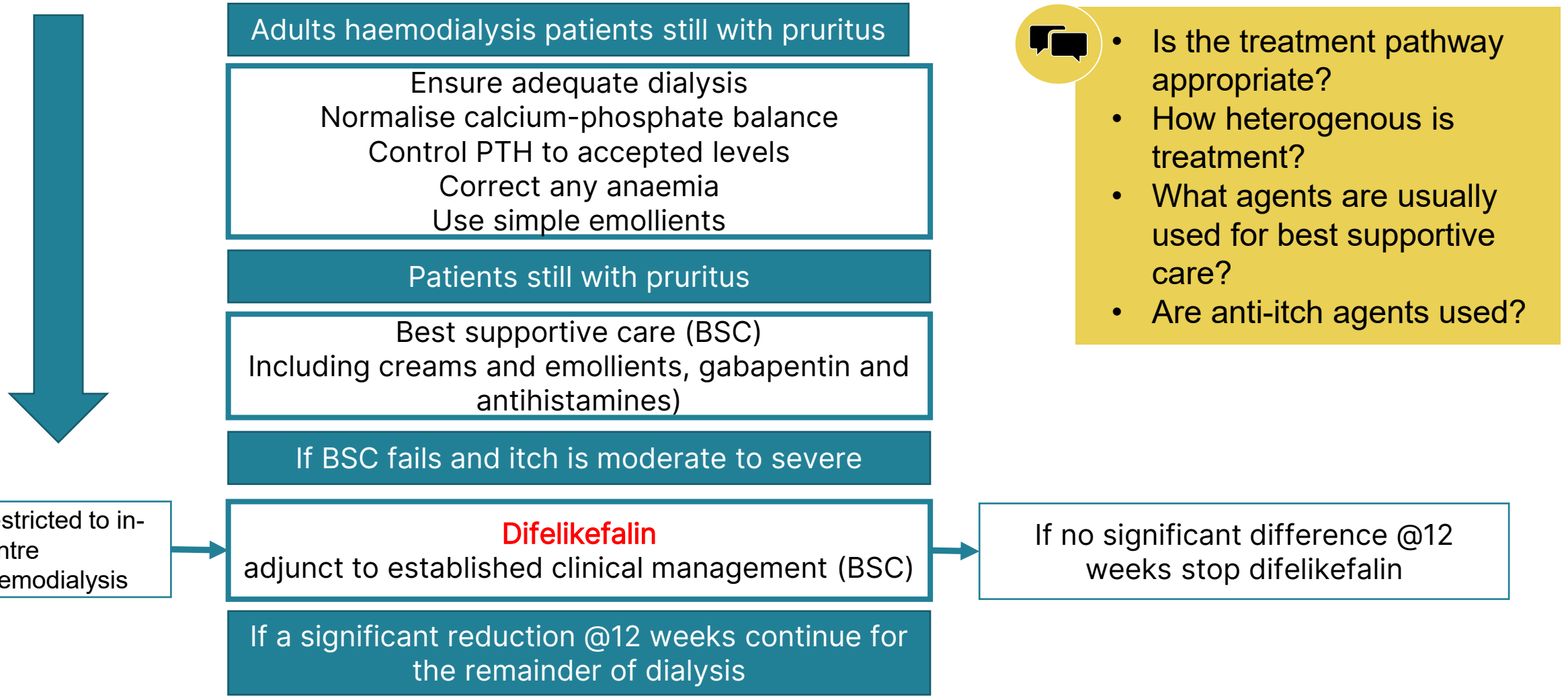
Abbreviations: CKD, chronic kidney disease; CKD-aP, CKD-associated pruritus
*Analysed using data from CKD Outcomes and Practice Patterns Study; ** based on analysis by Sukul et al, (2021);
*** based on analysis by Balaskas and Grapsa, (1995)

Treatment pathway for difelikefalin



- Is the treatment pathway appropriate?
- How heterogenous is treatment?
- What agents are usually used for best supportive care?
- Are anti-itch agents used?

Abbreviations: PTH; parathyroid hormones

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Patient perspectives

Submission from Kidney Research, UK *

- Pruritus can impact on a patient's day to day life physically, emotionally and socially
- It can cause disturbed sleep, limit social interaction and impact self-esteem
- Patients reported being given different advice to cope with the itching – from using certain emollients to changing their diet
- Some participants in the survey felt they were already taking too many medications. However, participants also pointed out limitations with topical products when the itch was in certain locations, like the centre of their back (especially if they lived alone) or on their head.
- Many patients under-report their experience of itch to healthcare professionals
- 18% of haemodialysis patients are very much or extremely troubled by itching, but up-to 18% receive no treatment for this symptom. 17% had not reported itching to a healthcare professional

"For me itch was a real pain, it felt as if my body was on fire and endless nights and some days of rigorous itching, using anything I could find or think of to relieve the itch"

"The main disadvantage (of current treatment) is that it did not relieve the burden of itch. I wasn't sleeping well and my general quality of life suffered as I couldn't do what I wanted to in the day as I had not slept in the night "

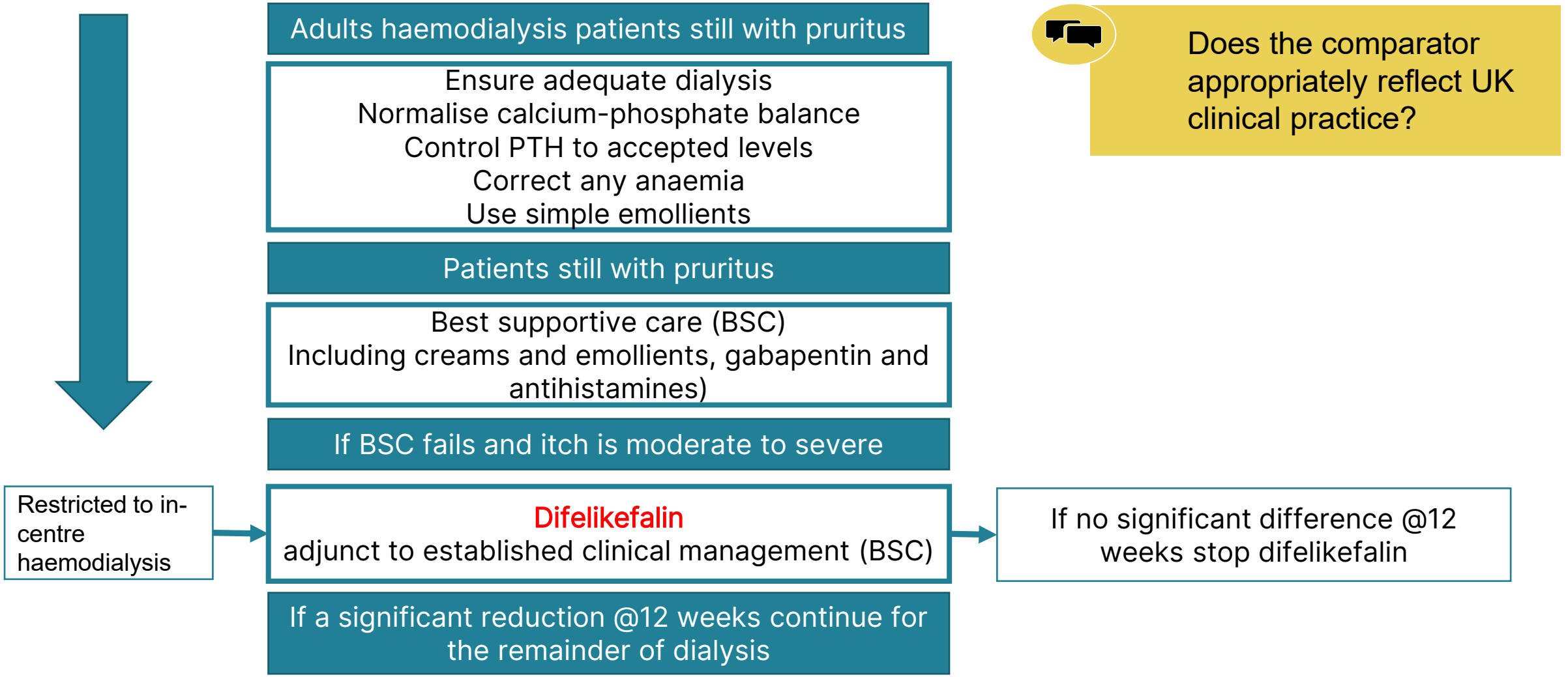
Source: *Sharma et al, interim findings 2023 - research funded by Kidney Research UK

Decision problem

	Final scope	Company	EAG comments
Population	Adults with moderate to severe pruritus receiving haemodialysis	restricted for ***in centre haemodialysis use only***	Limiting to in-centre use is sensible and is in line with the SmPC
Intervention	Difelikefalin	No change from scope	Intervention in trials is difelikefalin plus ECM compared with placebo plus ECM - Different to the scope. - If ECM in trials differs from target UK population this could create concerns about external validity.
Comparators	Established clinical management without difelikefalin, including gabapentin and pregabalin	No change from scope	KALM trials compare difelikefalin with placebo but this is likely to be difelikefalin plus ECM versus placebo plus ECM and is likely to have a more optimistic effect than comparison with ECM so cannot be used as a substitute
Outcomes	• Itching intensity • Adverse effects • Health related quality of life	No change from scope	No EAG comments

Abbreviations, CS, company submission; ECM, established clinical management, SmPC, Summary of Product Characteristics

Treatment pathway - reminder



Abbreviations: PTH; parathyroid hormones

Clinical effectiveness

NICE National Institute for Health and Care Excellence

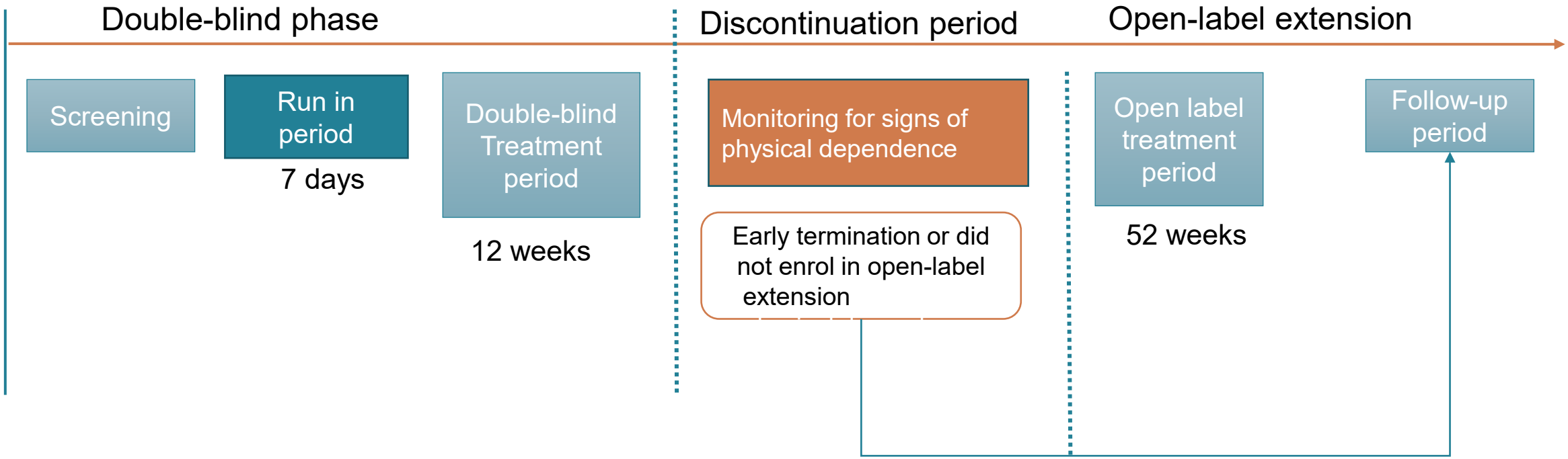
Key clinical trials

	CLIN3102 (KALM-1) (n=378)	CLIN3103 (KALM-2) (n=473)
Design	Phase 3 randomised, double-blind, placebo-controlled study	
Population	Adults* with ESRD on HD for at least 3 times per week for at least 3 months and moderate-to-severe CKD-aP **	
Intervention and comparator	Intervention: intravenous difelikefalin (0.5 mcg/kg) Comparator: Placebo	
Duration	12 weeks (open label extension** 52 weeks)	
Primary outcome	Proportion achieving at least 3-point reduction from baseline in weekly mean WI-NRS score (week 12)	Proportion achieving at least 3-point improvement from baseline in weekly mean of daily 24-hour WI-NRS score at week 12
Locations	57 centres in USA	93 centres in USA, Australia, Canada, Czech Republic, Germany, Hungary, South Korea, New Zealand, Poland, Taiwan, and UK
Used in model?	Yes	Yes

Notes: *Adults were aged 18 years or over; in KALM-1 and 18 to 85 years in KALM-2; **defined as weekly mean score >4 on WI-NRS
** Patients that had at least 30 doses of study drug during 12-Week study period and met other eligibility criteria were eligible for open-label difelikefalin for a further 52 weeks

Abbreviations: CKD-aP, chronic kidney disease associated pruritus; ESRD, end stage renal disease; HD, haemodialysis; WI-NRS, 24-hour Worst Itching Intensity Numerical Rating Scale

KALM-1 and KALM-2 study design



Discontinuation period is only applicable to KALM-1 and not KALM-2

Measuring itch-severity in KALM-1 and KALM-2

- Trials measured itch severity using 2 measures - the WI-NRS and 5-D itch scores

- **WI-NRS** - a single-item patient-reported - assesses intensity of the worst itching experienced in the past 24 hrs

Please indicate the intensity of the worst itching you experiences over the past 24 hours										
0 No itching	1	2	3	4	5	6	7	8	9	10 Worst itching imaginable

- Company considered the WI-NRS to be a reliable, reproducible, and a valid measure of itch intensity in moderate-to-severe CKD-aP patients, and therefore a reasonable choice

- **5-D Itch scale** - multidimensional questionnaire - assesses itch severity and itch-related QoL in previous 2 weeks.
  - **5 dimensions of itch**, scoring from 5 to 25 (higher scores suggested worse responses)
  - **Duration** of itch; **Direction** (improvement or worsening); **Degree** (intensity of itch); **Disability** (impact on activities); and **Distribution**(place of itch on the body)
- Company stated the 5-D itch scale had been validated in people with chronic pruritus, including haemodialysis patients and was appropriate to measure itch in people with CKD-aP

How appropriate are the WI-NRS and 5-D itch scales for measuring itch-intensity in CKD aP?

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Abbreviations: CKD, chronic kidney disease; aP, associated pruritus; WI-NRS, Worst Itching Intensity Numerical Rating Scale

KALM-1 and KALM-2 (Itching intensity)

	KALM-1		KALM-2	
Combined estimates at week 12	Placebo (n=189)	DFK (n=189)	Placebo (n=236)	DFK (n=237)
Observed at least 3-point NRS improvement n (%)				
Yes n (%)	51 (30.9)	82 (52.2)	77 (33.2)	95 (49.7)
No n (%)	114 (69.1)	75 (47.8)	130 (62.8)	96 (50.3)
Missing n(%)	24	32	29	46
LS means estimate of percent with improvement				
Percent (95% CI)	27.6 (20.2, 36.6)	51.0 (42.9, 58.9)	42.2 (32.5, 52.5)	54.0 (43.9, 63.9)
Odds ratio (95% CI)	2.72 (1.72, 4.30)		1.61 (1.08, 2.41)	
p-value	p<0.001		p=0.020	

- Mean percentage with at least a 3-point improvement from baseline in WI-NRS was higher for DFK compared with placebo.
- OR for at least 3-point improvement from baseline was statistically significantly higher for DFK compared with placebo

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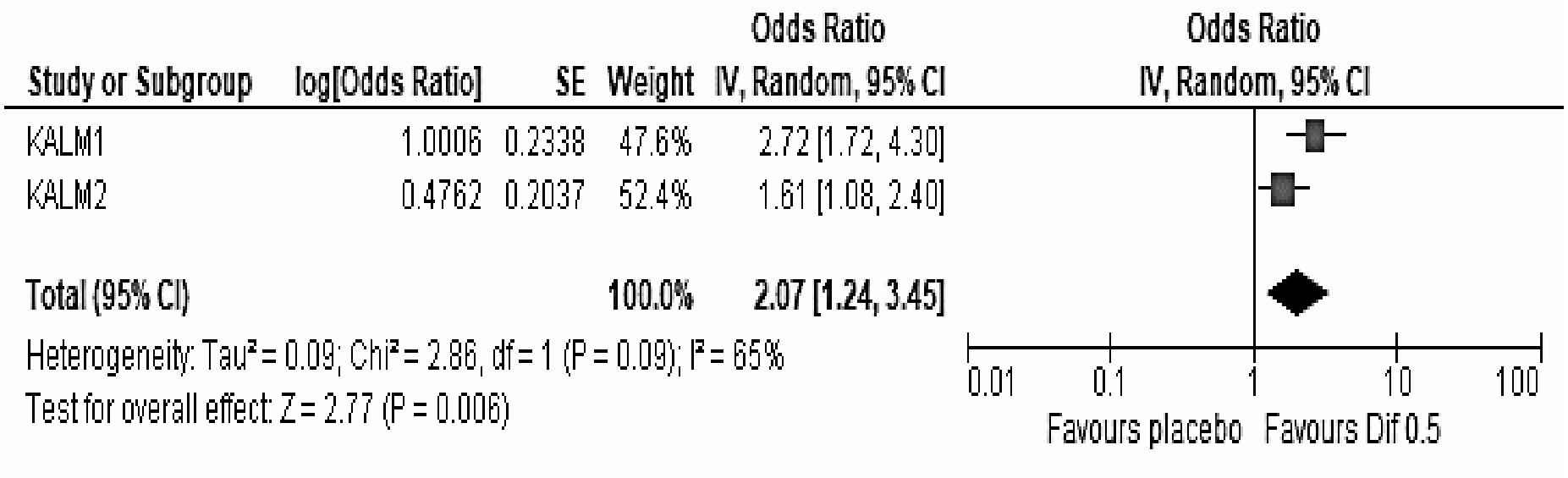
Abbreviations: CI, confidence interval; DFK, difelikefalin; LS, least squares; WI-NRS, 24-hour Worst Itching Intensity Numerical Rating Scale

Pooled analysis of KALM-1 and KALM-2

- The company provided further evidence on the efficacy of difelikefalin from a pooled analysis of results from the KALM trials (Topf et al, 2022).
    - OR of 1.93 (95% CI 1.44, 2.57) for achieving at least 3-point reduction in WI-NRS score at week 12
- The EAG had some concerns in the method used in the pooled analyses
    - The efficacy analyses was carried out in the intent-to-treat population from the pooled KALM-1 and KALM-2 studies, and consisted of all randomized participants.
    - This suggested the individual patient data from both trials was added together and a meta-analysis was not used.
    - This approach may lead to over-precise results and bias if any of the trials has unequal numbers in the two arms.
    - The EAG carried out its own meta-analysis of the results from the KALM studies

Abbreviations: CI, confidence interval; WI-NRS, 24-hour Worst Itching Intensity Numerical Rating Scale

Itching intensity: Meta-analysis of KALM-1 and KALM-2



- Based on a meta-analysis carried out by the EAG, in the pooled analysis, the odds of achieving at least a 3-point reduction in WI-NRS score at week 12 was 2.07 (95% CI 1.24 to 3.45)

Abbreviations: CI, confidence interval; DFK, difelikefalin; WI-NRS, 24-hour Worst Itching Intensity Numerical Rating Scale

Key issue: Comparison is different to that in NICE scope

Background

- **Trials**: difelikefalin plus ECM Vs placebo plus ECM; **Scope:** difelikefalin Vs ECM
- ECM can contain anti-itch agents.
  - EAG note ECM may increase potency of difelikefalin and have greater effects than for ECM on placebo

Company

- Accept comparison is different to scope and
  - Key clinical data in people with and without anti-itch medication is compared with placebo
- Presented analyses with and without anti-itch medication at baseline in the KALM trials - Cost effectiveness results are consistent

EAG comments

- Still consider comparison could lead to an effect of greater magnitude than comparison in NICE scope.
- If difelikefalin will only be given with ECM then it is unnecessary to compare difelikefalin alone to ECM

Stake holder comment: Renal Pharmacy group:

- Trial population are likely to have tried other treatments and benefits may not have been captured
- For some people difelikefalin might be a more appropriate than other ECM treatments (in elderly patients on dialysis it may be best to avoid gabapentin and pregabalin due to adverse effects)
- People that have good responses to difelikefalin will allow reduction of some pre-existing clinical management (pill burden is a problem in people on dialysis)

Does the comparator appropriately reflect UK clinical practice?
Is difelikefalin used in addition to other anti-itch medications in UK clinical practice?

Abbreviations: ECM, established clinical management

Key issue: Lack of anti-itch medication sub-grouping (1/2)

Background

- Participants in the KALM trials were allowed to continue using existing anti-itch medication during the trial
- Company did not provide information regarding the use of anti-itch medications in the UK population
    - Were the anti-itch medications allowed in the KALM trials is comparable standard UK care?

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Company

- No current standard of care for CKD-aP
    - No one medication is preferred over others
    - Large variation of medication used in KALM (small observations on each) therefore uncertain
        - Requested EAG analysis is unlikely to aid further evaluation of generalisability
    - Provided a sub-group analysis of anti-itch medications in original submission
- Company carried out a Delphi panel which shows generalisability of KALM trials to UK practice

Abbreviations: CKD, Chronic Kidney disease: aP; associated pruritis; ECM, established clinical management

Key issue: Lack of anti-itch medication sub-grouping (2/2)

EAG

- Company had provided data from KALM studies, sub-grouped by 5 key anti-itch medicines used in established clinical management.
  - Antihistamines, opioids or steroids can increase benefits of difelikefalin over placebo
  - Gabapentin or pregabalin would reduce benefits of difelikefalin over placebo
- Unclear about applicability of anti-itch medicines used in the KALM trials

Anti-itch medicines used in KALM-1 and KALM-2	Placebo (n=425)	Difelikefalin (n=426)
Any baseline use of an anti-itch medication	163 (38.4%)	159 (37.3%)
Most commonly used anti-itch medications at baseline (>2%)		
Diphenhydramine	100 (23%)	104 (24%)
Hydroxyzine	52 (12%)	42 (10%)
Hydrocortisone	16 (4%)	11 (3%)
Cetirizine	10 (2%)	7 (2%)
Clemastine	10 (2%)	7 (2%)

Renal Pharmacy Group

- Variation across the UK
  - Difficult to compare UK practice to ECM in the trials
- Topical therapies, antihistamines and pregabalin/gabapentin are likely to be the most common practice
- Effectiveness will be reviewed at 12 weeks, so if difelikefalin is not effective therapy will be ceased

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Which anti-itch medications are most frequently used in the UK?

Key issue: Differences in ethnicity between trials and UK target population (1/2)

Background

- Larger % of black participants in KALM than UK target population
  - EAG note the effect sizes from the trial may not be applicable to the UK target population.

Company

- Comparison of ethnicities is not appropriate
  - Black patients having HD are not more likely to experience CKD-aP
  - Black participants of KALM trials not expected to have a different relative treatment effect.
- Kidney Research UK states
  - *"Kidney disease disproportionally affects people from deprived communities and ethnic minority groups and people in these cohorts progress faster to end stage renal failure.*
  - *Evidence shows that fewer kidney patients from deprived communities are treated with peritoneal dialysis, with more treated with haemodialysis. There are therefore likely to be proportionally more people from these cohorts on haemodialysis, experiencing pruritus and likely to benefit from this treatment*".

Abbreviations: CKD-aP, Chronic Kidney disease-associated pruritis; ECM, established clinical management; ESRD; end stage renal disease; HD, haemodialysis

Key issue: Differences in ethnicity between the trials and UK target population (2/2)

	Ethnicity (Race)		
	White	Black	Asian/other
United Kingdom Renal Register Adults (ICHD)	67.6%	12.8%	19.6%
KALM pooled dataset	60.8%	29.2%	10.0%

Sub-grouping variable	KALM-1: At least 3 point improvement in WI-NRS from baseline to 12 weeks			KALM-2: At least 3 point improvement in WI-NRS from baseline to 12 weeks		
Race categories	White	Black	Other	White	Black	Other
Race OR (95% CI)	2.67 (1.39,5.12)	3.21 (1.60,6.42)	1.10 (0.23,5.20)	1.56 (0.99,2.47)	2.26 (0.89,5.70)	0.68 (0.19,2.50)

Renal Pharmacy Group:
- Concerned issue relating to health inequalities has been misinterpreted
- Fewer kidney patients from deprived communities are treated with PD, with more treated with HD
- Likely to be proportionally more people from these cohorts on HD having pruritus and likely to benefit from treatment. This is not equal to the treatment being more beneficial to those groups exclusively

Kidney Research UK: Benefit was across all ethnicities so this shouldn't limit difelikefalin across ethnic groups

NHS England: A therapy that may benefit ethnic minority groups should not be discounted based upon a population-wide evaluation

- Is ethnicity a treatment effect modifier that needs to be controlled for in the trials?
- Are the KALM trials generalisable to the UK target population?

Key issue: Unclear rationale for statistical analysis (1/2)

Background

- Company used multiple imputation (MI) to handle missing data in the KALM trials and logistic regression for the primary efficacy outcome - Rationale why it chose MI over other methods was not clear
  - Company clarified MI was suggested by FDA and provided details on methodology
  - EAG considered the rationale methodologically insufficient
    - Fer example, choice of specific covariates in the MI analysis - why these were chosen instead of other prognostic variables that correlated to the outcome of interest.
  - EAG also considered the company had not provided appropriate rationale and justification on the conceptualization of the logistic regression model

Company

- Chose multiple imputation because single imputation methods would underestimate the variability of results and not be adequate in the setting – consistent the Panel on Handling Missing Data in Clinical Trials
- Used a Missing at Random approach to impute missing weekly WI-NRS scores in KALM-1 and 2
  - Assumed people stopping treatment early would have similar scores to those with complete data

Abbreviations: CKD, Chronic Kidney disease: aP; associated pruritis; ECM, established clinical management; FDA, food and Drug Administration; MI, multiple imputation;

Key issue: Unclear rationale for statistical analysis (2/2)

	Multiple imputation	Logistic regression
Covariate/ variable	For KALM-1 and KALM-2 • Baseline WI-NRS score; • Randomisation stratification factors (use of anti-itch medication the week before randomisation and presence of specific medical conditions); • Non-missing NRS scores for each week For KALM-2 only • Region	• Trial group • Baseline WI-NRS score • Baseline use of antipruritic medication • History of prespecified medical conditions

EAG

- Lack of a justification on why specific covariates were used in the models and others were not considered or excluded
  - Company has not provided further evidence on this
- Company did not report the design and results of the logistic regression and key aspects were missing

- Are the company's covariates appropriate or should any other covariates be used?
- Has the statistical analyses been carried out appropriately?

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Abbreviations: WI-NRS; worst itching-numerical rating scale

Key issue: Methods used to pool trials were unclear

Background

- Pooled analysis of the KALM trials had been carried out and published (Topf, 2022).
- EAG considered publication suggested data was pooled without adjusting for differences between the trials.
  - Potential for bias – EAG suggested company reanalyse pooled data adjusting for differences

Company

- Clarified pooled patient data and mean count estimates were used in the model. Pooled analysis adjusted for region and study was carried out but not included as point estimates were not used in modelling
- Cost-effectiveness results are consistent when trial data are used individually and pooled.

EAG comments

- Company considered only 2 regions (USA and non-USA) but covariate should contain 4 levels (KALM-1 was carried out in 1 region and KALM-2 in 4 regions)
- Adjusting combined covariate for differences between studies and regions introduces errors
  - Multicollinearity when 2 covariates are known to highly correlate with each other
  - Company did not carry out sensitivity analysis to explore if study and region are equal covariates
- For consistency, MI should have been executed for the pooled studies using same parameters
- EAG maintains pooling data before statistical analysis is carried out may introduce systematic errors
- Maintains a proper critique of methods should apply and does not agree cost-effectiveness results are consistent when trial data are used individually and pooled

Would more detail on the methods used to pool trials assist decision-making?

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Abbreviations: MI, multiple imputation

Cost effectiveness

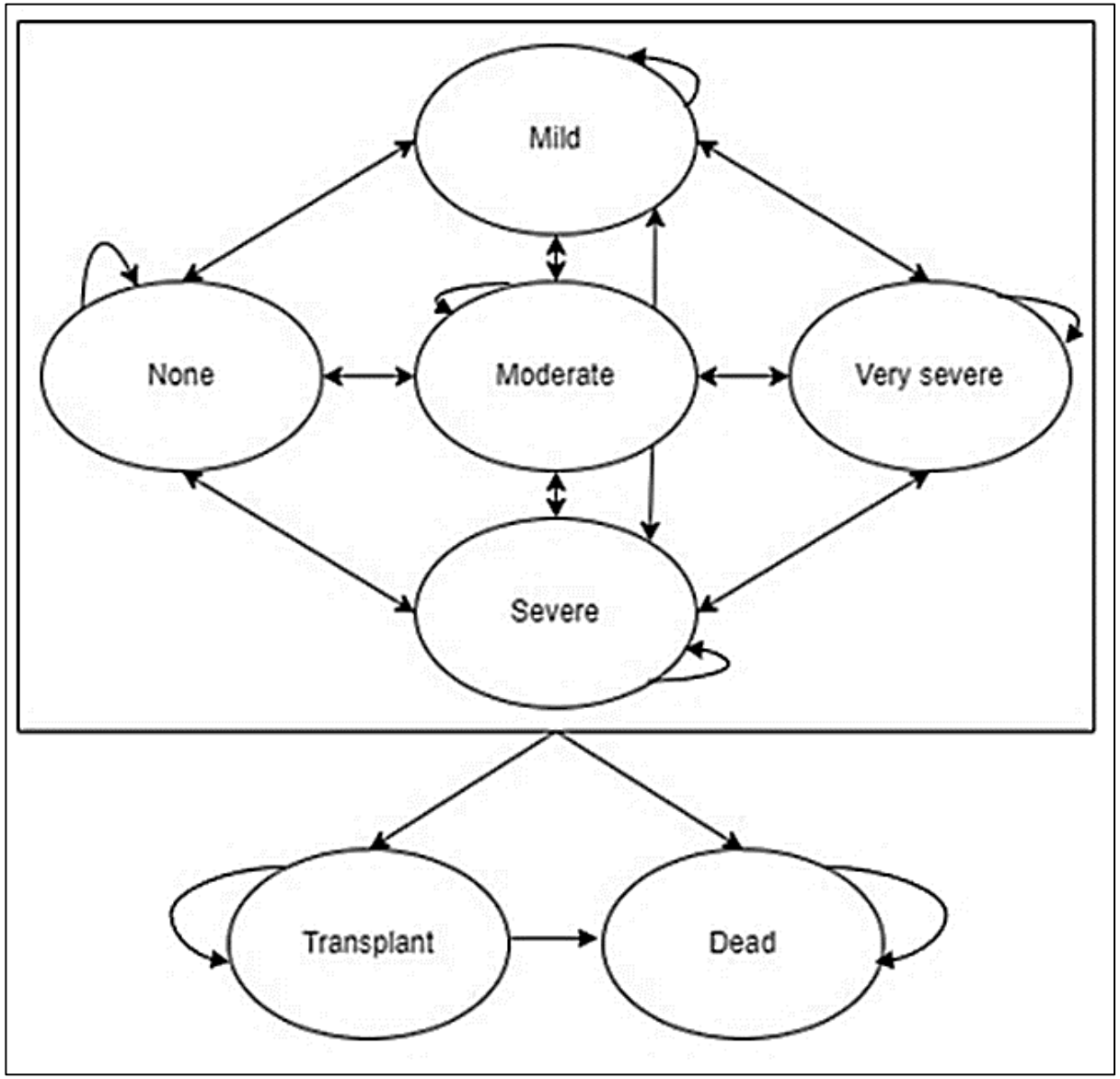
NICE National Institute for Health and Care Excellence

Key cost effectiveness issues for discussion

Issue	ICER impact
Estimating transition probabilities • What source of evidence should we use to estimate the transition probabilities?	Moderate
Lack of clarity on how multiple imputation was used • Is there anything the committee need to further consider relating to the imputation of missing data?	Unknown

Abbreviations: SLR, systematic literature review

Company's model overview



Model structure	Markov model based on level of itch severity
Perspective	UK NHS and PSS
Time horizon	42 years (mean age at baseline 58.3 years)
Cycle length	Cycle 0 to 3 = 4 weeks Cycle 4= 52 weeks
Discounting	3.5% per annum for costs and benefits

EAG consider model structure is appropriate

- Difelikefalin affects costs by increasing number in better health states and lowering costs of management of pruritus
- Difelikefalin affects QALYs by increasing number in better health states and improving HRQoL

Assumption with greatest effect on the ICER:

- How transition probabilities should be estimated from the clinical data

Abbreviations CKD, chronic kidney disease; aP, associated pruritus; PSS, Personal Social Services

How company incorporated evidence into model (1/2)

Input	Assumption and evidence source

Baseline characteristics	• Based on KALM trials population characteristics
	  • Average baseline age 58.3 years
	  • 58.7% male, 41.3% female
	  • Mean weight 84.4 kg
	  • Mean time on dialysis 4.78 years
	  • 55.28% (moderate), 34.17% (severe); 10.55% (very severe)

Intervention efficacy	• Difelikefalin IV bolus injection 0.5mcg/kg • 5D Itch score data from baseline, weeks 4, 8, 12 and 64
Comparator	• ECM including capsaicin cream, topical calcipotriol, or oral gabapentin and advises against sedative antihistamines and cetirizine
Utilities	• Company used a separate primary data collection study to map WI-NRS and 5-D Itch scale to EQ-5D-3L
Costs	• Drug acquisition and administration costs; disease management costs; adverse event costs

How company incorporated evidence into model (2/2)

- Difelikefalin is intended for people in *Moderate, Severe and Very severe* health states
  - *Severe & very severe* populations were merged in the mapping study due to small no.
  - Mapping study this was mostly comprised of people in the severe group
- EAG –
  - no reason for the model to distinguish between severe and very severe health states.
  - But it is likely the model was developed before the results of the mapping study were available

Health state utility inputs used in the model

Health state	Mean (SE)
None	[redacted]
Mild	[redacted]
Moderate	[redacted]
Severe	[redacted]
Very severe	[redacted]

Total weighted treatment costs by health state

Severity	ECM arm	DFK arm List price
None	£31.98	£5,424.64
Mild	£42.48	£5,435.14
Moderate	£42.48	£5,435.14
Severe	£75.65	£5,468.31
Very severe	£75.65	£5,468.31

Is it appropriate to include the very severe health state in the model?

Abbreviations: CKD-ap, chronic kidney disease-associated pruritus; ECM, established clinical management

Key issue: Estimating transition probabilities between CKD-aP severity categories (1/2)

Background

- Company assumed people could transition to a better or worse health state, independent of the current health state they were in. It used simulated data assuming individuals could improve or deteriorate up to 3 health states at a time. Based on this approach, patients would never switch to a worse health state.
- EAG noted that based on simulated data, patients always improved up to a maximum of 2 health states so it preferred to apply transition probabilities based upon direct observations

Company

- Maintains use of simulated data in base case is most appropriate for decision making.
- Estimating probabilities of moving from one state to others could lead to unrealistic outcomes due to small observation for each probability value
- EAG probabilistic results were much higher than EAGs deterministic base case results
- Although transition rates from more severe to less severe states may be underestimated and from less severe to more severe states overestimated, this had little impact on overall movement across health states

EAG comments

- Noted company assumption suggests response to treatment is averaged across the population
- The EAG probabilistic outcomes from observed data reflect uncertainty in estimates
- Transitions based on observed data allow patients to move to a maximum improvement/deterioration of 3 health states compared to simulated data allowing for a maximum improvement of 2 health states
- Moving one state down does not depend on the current health state, is not supported by the data
- Transition probabilities estimated from direct observations is preferable to aggregate data

Abbreviations: CKD-ap, chronic kidney disease-associated pruritus

Key issue: Estimating transition probabilities between CKD-aP severity categories (2/2)

Transition probability matrices between severity levels of itching used in base case and estimated from simulated data

Baseline itch score	Baseline health state	Score distribution week 0	Change in itch score week 4	Week 4 itch score	Week 4 health state	Change in state
12	Moderate	4.5%	-2.9	9.1	Mild	-1
13	Moderate	8.0%	-2.9	10.1	Mild	-1
14	Moderate	9.4%	-2.9	11.1	Mild	-1
15	Moderate	11.3%	-2.9	12.1	Moderate	0
16	Moderate	10.9%	-2.9	13.1	Moderate	0
17	Moderate	11.1%	-2.9	14.1	Moderate	0
18	Severe	10.8%	-5.1	12.9	Moderate	-1
19	Severe	8.5%	-5.1	13.9	Moderate	-1
20	Severe	7.2%	-5.1	14.9	Moderate	-1
21	Severe	7.7%	-5.1	15.9	Moderate	-1
22	Very severe	5.0%	-6.1	15.9	Moderate	-2
23	Very severe	1.9%	-6.1	16.9	Moderate	-2
24	Very severe	2.6%	-6.1	17.9	Severe	-1
25	Very severe	1.0%	-6.1	18.9	Severe	-1

Should transition probabilities be estimated from simulated data or directly observed data?

Abbreviations: CKD-aP, chronic kidney disease-associated pruritus

Key issue: Concern with how variability was captured in the multiple imputation

Background

- EAG noted concern with the way the company managed missing data - observations from trials
- Company used multiple imputation (MI) to account for missing data in its estimation of transition probabilities for 279 observations in KALM data
- EAG were unclear how all transition matrices were derived or how analyses were combined to find final estimates, or how uncertainty was estimated and requested information on this

Company

- Clarified it used MI to estimate missing values in Itch score for KALM data based on patient demographics
- Missing values were generated through predictive mean matching. Mean predictions were matched to the closest observation from the data. This ensured imputed values were consistent with the observed data
- Carried out scenario analyses without MI to account for missing data

EAG comments

- Company explanation focuses methods of imputing missing data
- Have not addressed the unknown within-dataset variation compared with between-dataset variation in the estimation of the overall uncertainty
- Company scenario analysis showed that estimating transition probabilities using non-imputed data increases the EAG ICER slightly whereas the revised company base case ICER would remain the same

- Is the company's use of multiple imputation appropriate?
- Should more detail be provided to ensure transition probabilities are estimated appropriately?

Abbreviations: ICER, incremental cost-effectiveness ratio; MI, multiple imputation;

Company and EAG preferred base case assumptions

Only remaining difference between the company and EAG base cases is the approach to estimating transition probabilities

Base case preferred assumptions	Company	EAG
Transition probabilities	Estimated based on simulated data	Estimated based on observed data
Waning effect for established clinical management	10% probability of deteriorating per year	
Elevated risk of death for patients in moderate, severe and very severe health states	No increased risk of death	
Cost of haemodialysis	Costs of haemodialysis included	

Abbreviations: TA, technology appraisal; TE, technical engagement

Company base case results

Deterministic	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
DFK plus ECM	[redacted]	[redacted]			
ECM	[redacted]	[redacted]	[redacted]	[redacted]	£24,552

Probabilistic	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
DFK plus ECM	[redacted]	[redacted]			
ECM	[redacted]	[redacted]	[redacted]	[redacted]	£24,299

- As the ICER for a technology increases in the range of £20,000 to £30,000 per QALY gained, the committee's decisions about the acceptability of the technology as an effective use of NHS resources will make explicit reference and will specifically consider the following factors
  - The degree of certainty and uncertainty around the ICER
  - Aspects that relate to uncaptured benefits and non-health factors

(NICE Health Technology Evaluations- the manual, 6.3.5 and 6.3.7)

Abbreviations: DFK, Difelikefalin; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LYG, life-year gains; QALY,

EAG base case results

Deterministic	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
DFK plus ECM	[redacted]	[redacted]			
ECM	[redacted]	[redacted]	[redacted]	[redacted]	£26,646

Probabilistic	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
DFK plus ECM	[redacted]	[redacted]			
ECM	[redacted]	[redacted]	[redacted]	[redacted]	£29,121

Abbreviations: DFK, Difelikefalin; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; LYG, life-year gains; QALY, quality-adjusted life-year

Company and EAG scenario analysis (deterministic)

	Company			EAG		
Subgroup/Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
Revised Base cases after technical engagement	[redacted]	[redacted]	£24,552	[redacted]	[redacted]	£26,646
Subgroup anti-inch medication at baseline	[redacted]	[redacted]	£25,339*	[redacted]	[redacted]	£26,461
Subgroup no anti-itch medication at baseline	[redacted]	[redacted]	£26,956*	[redacted]	[redacted]	£27,455
Subgroup KALM-1 only	[redacted]	[redacted]	£30,389	-	-	-**
Subgroup KALM-2 only	[redacted]	[redacted]	£23,115	-	-	-**
No MI for missing data	[redacted]	[redacted]	£24,516	[redacted]	[redacted]	£28,366
ECM waning effect applied to match baseline at year 5	[redacted]	[redacted]	£18,613	[redacted]	[redacted]	£19,248
ECM waning effect applied to match baseline at year 10	[redacted]	[redacted]	£20,668	[redacted]	[redacted]	£21,625

Notes: * EAG could not reproduce company estimates, ** EAG did not have transition matrices to perform subgroup analyses
Abbreviations: ECM, established clinical management; ICER, incremental cost-effectiveness ratio; MI, multiple imputation; QALY, quality-adjusted life year

Other considerations

Equality considerations

- Company submission noted several groups of people that are at greater risk of developing CKD-aP and having symptoms for longer while on dialysis. These include:
  - People in lower socio-economic groups who are more likely to develop chronic kidney disease, progress towards kidney failure, and die earlier with CKD;
  - People with Black, Asian and minority ethnic family backgrounds who are more likely to progress to kidney failure faster and less likely to receive a transplant;
  - Women who are more likely to be diagnosed with CKD, but less likely to start dialysis and older people with CKD who are less likely to have a kidney transplant compared to younger people.
  - Company note difelikefalin is restricted for in-centre haemodialysis use, which may be considered a barrier for people that find in-centre haemodialysis less accessible.

Severity

- Company consider difelikefalin is not expected to meet the criteria for a severity weight

Innovation

- No additional benefits not captured in the modelling

Abbreviations: CKD, chronic kidney disease; CKD-aP, CKD-associated pruritus

NICE National Institute for Health and Care Excellence

Thank you.