Cost-Effectiveness of Difelikefalin Compared to Best Supportive Care for Treatment of Chronic Kidney Disease-Associated Pruritus in Australia

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D. JACKSON[1], M. RATKOVIC[1], D. TILDEN[1], M. SORO[2], T. SCHAUFLER[2], A. GRAVA[2], S. HARSLEY[3], S. BRYDON[3]

[1]THEMA Consulting Pty Ltd, Milsons Point, NSW, Australia, [2]CSL Vifor, Glattbrugg, ZH, Switzerland, [3]CSL Seqirus, Melbourne, VIC, Australia

INTRODUCTION

- Chronic kidney disease-associated pruritus (CKD-aP) is a chronic, unremitting, debilitating condition in patients with chronic kidney disease, particularly those undergoing haemodialysis (HD).
- Patients are at increased risk of morbidities associated with infection (e.g., cellulitis, sepsis, bacteraemia, and infections of the dialysis access) and have a greater (>15%) mortality risk than HD patients without CKD-aP.[1,2,3]
- Difelikefalin (DFK) is a novel, highly specific agonist at kappa opioid receptors specifically indicated for the treatment of moderate to severe CKD-aP in adult patients on HD.
- The use of DFK as a treatment for CKD-aP in HD patients is well supported by clinical evidence from two high quality 12-week, Phase III double blinded, randomised, placebo-controlled clinical trials (KALM-1[4]; KALM-2[5]), with associated 52-week open label extension (OLE) studies supporting longer-term effectiveness.
- KALM-1[4] and KALM-2[5] demonstrated that DFK with best supportive care (BSC) is superior in terms of efficacy relative to BSC alone.

OBJECTIVE

- To assess the comparative costs and outcomes with and without the use of DFK for HD patients with moderate to severe CKD-aP on the basis of the two KALM studies.

METHODS

Model structure

- A cost-utility analysis was conducted using a Markov cohort model to estimate the incremental cost per QALY gained of DFK plus BSC relative to BSC alone in Australia among patients with moderate to severe CKD-aP.
- Health states of the Markov model were defined based on 5-D Itch Scale total score categories (5-8, 9-11, 12-17, and 18-25) and treatment received (DFK and BSC). All patients at baseline started in the 12-17 and 18-25 health states, corresponding to moderate to severe CKD-aP.
- The 5-D Itch Scale is a multi-dimensional scale used to assess pruritic severity over five dimensions: duration, degree, direction, disability, and distribution. Each dimension is scored from 1 to 5, with total scores ranging between 5 (best) and 25 (worst). The 5-D Itch scale was included as a secondary outcome measure in the pivotal trial evidence for DFK (KALM-1[4] and KALM-2[5]).
- The 5-D Itch total score categories used in the economic evaluation were based on thresholds proposed in the literature[6], where five categories: 5-8, 9-11, 12-17,18-21, 22-25 were shown to correlate the best with Numerical Rating Scale (NRS) categories of NRS=0, mild, moderate, severe, and very severe pruritus. For this economic evaluation, 18-25 was chosen as the worst 5-D Itch Scale total score category corresponding to severe to very severe pruritus on the NRS instrument.
- Pooled individual patient data from the 12-week KALM-1 and KALM-2 studies, along with their 52-week OLE studies (for DFK only) were used to derive transition probabilities between 5-D Itch defined health states over time up until week 64 in DFK treated patients and week 12 in BSC treated patients for use in the Markov model (See Figure 1 for model structure).

Model inputs

- Assumptions concerning treatment waning (or placebo effect attenuation) were used to extrapolate health state membership beyond the trial/OLE duration to a 10-year model horizon. This involved assuming a treatment waning rate of 5% per annum in DFK treated patients and 10% per annum in BSC treated patients (i.e., placebo effect attenuation). These values mimic the treatment scenario accepted by NICE in their HTA guidance of DFK in 2023[7].
- Implementation of a stopping rule was modelled at week 12, which limited continued DFK treatment to patients achieving a ≥5-point improvement from baseline in total 5-D Itch score. An analysis of the data collected from the supportive Phase 2 study (CLIN2101) demonstrated that a ≥5-point reduction in total 5-D Itch Scale score from baseline represents a clinically meaningful improvement for this patient population[8]. Upon discontinuation, DFK patients transitioned to BSC and received transition probabilities consistent with the BSC arm of the economic model.
- Utility values for health states in the economic model were estimated from a mapping study between 5-D Itch total scores and EQ-5D-3L conducted by the School of Health And Related Research at the University of Sheffield. Utility values of 0.6328, 0.5800, 0.5203 and 0.4420 were estimated for the 5-8, 9-11, 12-17, and 18-25 health states, respectively.
- Health state costs were calculated from the perspective of the Australian healthcare system and were based on hospitalisation rates (cardiovascular, infection, skin-related and mental status change/ confusion) defined by severity of itch[3]. Derived health state costs (per 28 days) by 5-D Itch Scale score health state were A$135.27 for 5-8, A$137.79 for 9-11, A$145.75 for 12-17, and A$152.92 for 18-25.
- Background mortality in the economic evaluation was reflective of CKD patients receiving HD. An elevated mortality risk was applicable (HR 1.24) for patients in the 18-25 5-D Itch score category[3]. Adverse events (AEs) associated with DFK treatment were captured in the model using trial-reported net rates of cardiac failure and respiratory failure, while treatment costs[9] and utility decrements[10] were taken from the literature. In total, whilst on DFK treatment, an AE disutility of 0.00039 and an AE treatment cost of A$3.71 were applied.

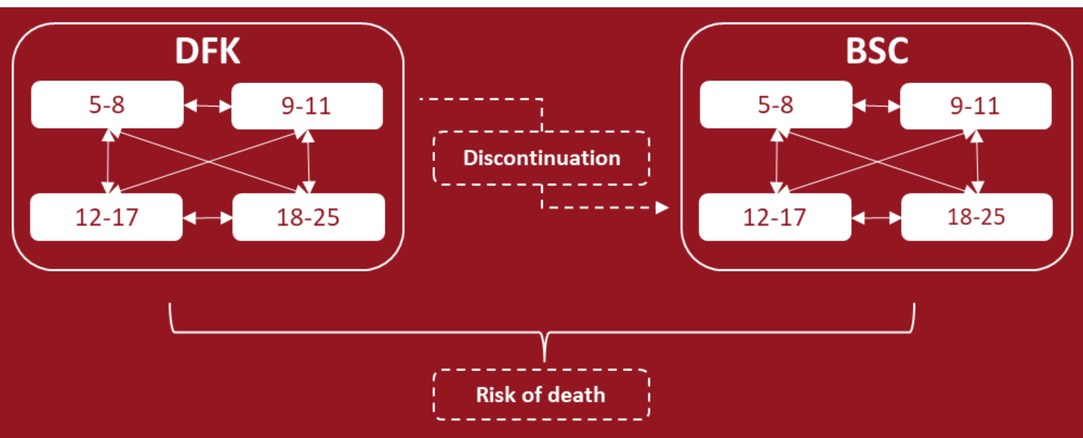

Figure 1: Simplified model schematic

***Health state categories based on disease severity were informed by the 5-D Itch scale (whereby scores range from 5 to 25 with higher scores indicating more severe itch).**

RESULTS

- The DFK treatment arm was associated with greater QALYs than the BSC treatment arm (2.95 vs 2.78) however was more costly (A$19,112 vs A$10,161), as seen in Table 1.
- The incremental cost per QALY of DFK compared to BSC was A$51,312 which is considered within an acceptable range in Australia.
- Figure 2 presents the estimated change in 5-D Itch Scale Total Score by treatment arm over the 10-year time horizon.
- Sensitivity analyses demonstrated the main sources of uncertainty in the economic model were utility values and extrapolation assumptions, where Table 2 below demonstrates that these have a low/moderate effect on the ICER.

Table 1: Base case results: Incremental cost-effectiveness (A$)

	Difelikefalin	Best supportive care	Incremental
Cost	A$19,112	A$10,161	A$8,951
QALY	2.95	2.78	0.17
ICER			A$51,312/QALY

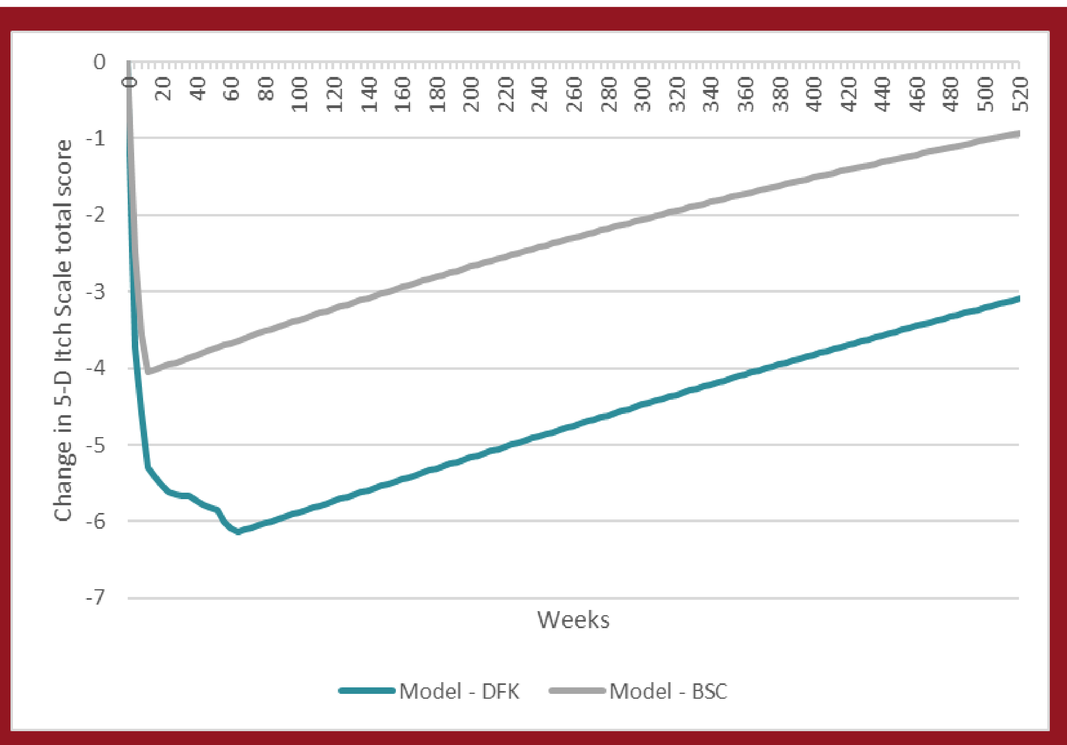

Figure 2: Change in 5-D Itch Scale Total Score over time (10-year horizon) from baseline

Table 2: Sensitivity results: Incremental cost-effectiveness (A$/QALY)

	Discount rate (3%)	Model horizon (5 years)	Utilities (Lower; 5 to 8: 0.6168 9 to 11: 0.579 12 to 17: 0.5143 18 to 25: 0.4293)	Placebo effect attenuation (0% for both DFK and BSC)
ICER	A$49,043	A$75,290	A$67,616	A$55,784

CONCLUSIONS

- DFK for treatment of CKD-aP in HD patients is an effective and cost-effective intervention relative to current clinical practice in Australia.
- The model relies on assumptions which may limit its generalisability, including the treatment waning effect assumed in the absence of long-term data (particularly for the BSC cohort), and the utility values based on mapping of the 5-D Itch scale in the absence of EQ-5D-3L data in the two KALM trials.
- Overall, these assumptions are considered conservative and robust as shown from the conducted sensitivity analysis.
- The model returned a generally acceptable ICER of A$51,312 per QALY, supporting the routine use of DFK in patients with CKD-aP undergoing HD in Australia.

References

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Contact information

Scott Brydon, CSL Seqirus, Melbourne, VIC, Australia; Email: Scott.Brydon@seqirus.com

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Abbreviations: AE, adverse event; BSC, best supportive care; CKD-aP, chronic kidney disease-associated pruritus; DFK, difelikefalin; HD, haemodialysis; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NRS, numerical rating scale; OLE, open-label extension; QALY, quality adjusted life years.