ESTIMATING THE IMPACT OF TREATING CHRONIC KIDNEY DISEASE-ASSOCIATED PRURITUS ON QUALITY OF LIFE IN THE ABSENCE OF DIRECT UTILITY MEASURES

Schaufler T [1], Ramirez de Arellano Serna A [1], Munera C [2], Menzaghi F [2]

[1] Vifor Pharma, Glattbrugg, ZH, Switzerland; [2] Cara Therapeutics, Inc., Stamford, CT, USA

Background and Objectives:

Chronic kidney disease-associated pruritus (CKD-aP) is a debilitating itching condition, significantly impacting health-related quality of life (HRQoL) of patients with progressive kidney disease. It is associated with depression, poor sleep quality and increased mortality. Epidemiologic data from several studies demonstrate that at least 30-40% of patients with end-stage renal disease suffer from moderate-to-severe pruritus. At the same time, data shows that CKD-aP is underdiagnosed by nephrologists and underreported by patients. There is currently no approved pharmaceutical treatment option in Europe or the US for the treatment of CKD-aP. [i]

In the absence of utility data directly measuring the impact of CKD-aP on patients HRQoL, we used available patient-reported outcomes (PRO) instruments to simulate EQ-5D-5L health profiles.

Methods:

Difelikefalin (DFK) is a first-in-class, highly selective kappa opioid receptor (KOR) agonist that targets KOR located on peripheral sensory neurons and immune cells , which is currently in clinical development to treat CKD-aP in patients on hemodialysis (HD). It has demonstrated significant improvements of itch intensity and HRQoL as measured by the Skindex-10 (Sk-10) and 5-D Itch scale in HD patients with moderate-to-severe CKD-aP in a recently completed double blind placebo-controlled phase-3-study (CR845-CLIN3102, KALM-1). [ii]

For this study, we used data collected in a phase-2-study in 174 CKD-aP patients treated with either DFK 0.5, 1.0, and 1.5 mcg/kg or placebo that assessed itch intensity, Sk-10 and 5D-Itch Scale, but no EQ-5D data to simulate EQ-5D-5L health profiles and estimate utility changes over the course of the 8 week study period. This posters reports results for patients receiving 0.5mcg/kg DFK (or placebo) at the end of each dialysis session, the dosing schedule studied in phase 3.

We assessed different approaches to map individual questions and their rating from Sk-10 and 5-D Itch to the five dimensions of the EQ-5D (cf. Table 1). EQ-5D-5L tariffs from United Kingdom (UK) and United States (US) were used to extrapolate utilities.

Table 1: Mapping of Sk-10 and 5D Itch questions to EQ-5D Domains

EQ-5D Domain	Mobility	Self-care	Usual Activities	Pain/ Discomfort	Anxiety/ Depression
Model 1	5D Itch Disability questions on (c) housework/errands, (d) work/school	None	5D Itch Disability questions on (a) sleep, (b) leisure/social, (c) housework/errands, (d) work/school	5D Itch question Duration of itch (hours per day)	Skindex Q6: Feeling depressed about your itching
Model 2	5D Itch Disability questions on (c) housework/errands, (d) work/school (constant baseline value)	Skindex Q4: Frustration about your itching	Skindex Q10: Effect of itching making it hard to work or do what you enjoy	5D Itch question Degree (intensity) of itch	Skindex Q6: Feeling depressed about your itching
Model 3	5D Itch Disability questions on (c) housework/errands, (d) work/school (constant baseline value)	Skindex Q4: Frustration about your itching	Skindex Q10: Effect of itching making it hard to work or do what you enjoy	Skindex Q1: Degree of being bothered by itching	Skindex Q6: Feeling depressed about your itching
Model 4	5D Itch Disability questions on (c) housework/errands, (d) work/school (constant baseline value)	Skindex Q4: Frustration about your itching	Skindex Q8: Effects of itching on interactions with others	Skindex Q1: Degree of being bothered by itching	Skindex Q6: Feeling depressed about your itching

The 5 point scale of 5D Itch was directly mapped to EQ-5D. The 7 point Sk-10 scale the following assumptions were used: 0 – no problems; 1, 2 – slight problems; 3, 4 some problems; 5 – severe problems; 6 – extreme problems

For the *Anxiety / Depression* domain of the EQ-5D questionnaire, we found that question 6 of Sk-10 was a logical fit: “Feeling depressed about your itching”. For other domains, the impact of the itch was less clear and we tested several assumptions. For example, one can question whether the presence or severity of the itch has any impact on the S*elf-care* domain. Therefore, we tested models assigning (1) all patients a value of 3, therefore assuming no impact from the treatment and (2-4) using question 4 of Sk-10 (“frustration about your itching”) as an alternative indicator.

A similar approach was taken for the *Mobility* domain, where we used two questions on disability from 5-D Itch (“In the past 2 weeks rate the impact of your itching on (c) housework/errands, (d) work/school”), but kept the baseline value constant in models 2 – 4, as improving the itch might not translate into improved mobility in CKD-aP patients on hemodialysis.

For the EQ-5D domains *Usual Activities* and *Pain/Discomfort* the challenge was in identifying the question with the best match from the two PRO questionnaires with available data and we therefore tested different options in the four models.

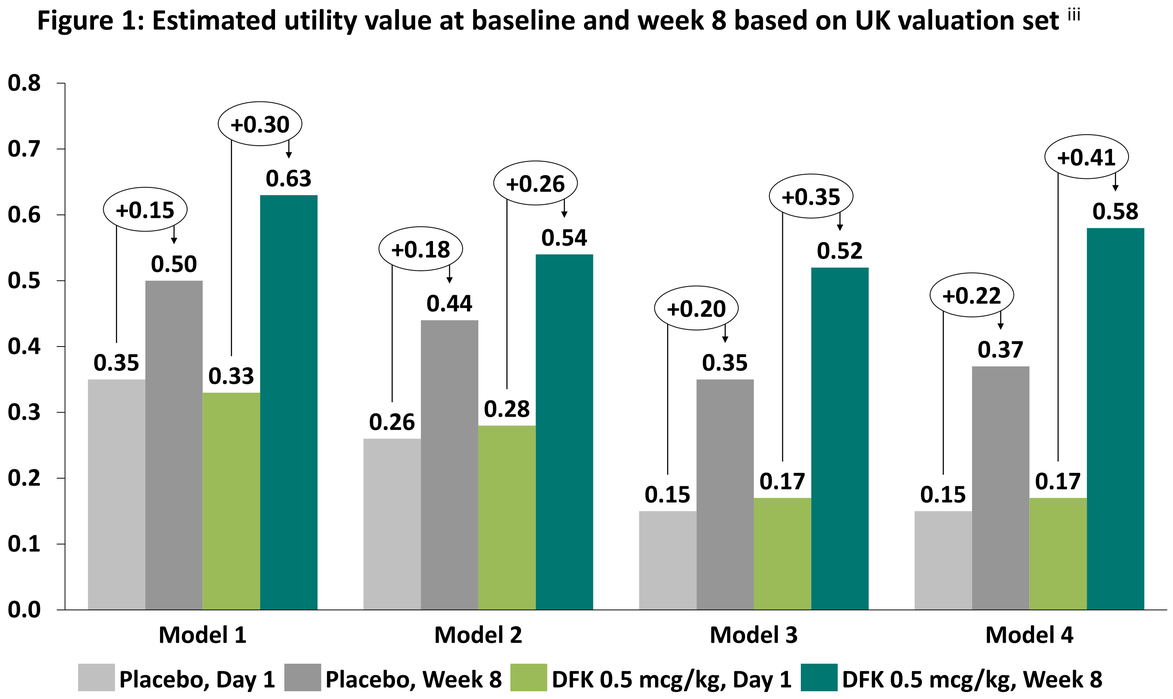
Results:

Using the UK tariff, patients with moderate-to-severe CKD-aP showed substantial utility impairment (baseline scores in both study arms between 0.15 and 0.35 depending on mapping used, cf. Figure 1). Applying the US tariff (cf. Figure 2) resulted in a higher baseline of 0.39 – 0.53, reflecting different valuations in diverse populations.

Patients treated with 0.5 mcg/kg DFK **significantly improved their utility** to 0.52 – 0.63 (UK tariff) or 0.64 to 0.71 (US tariff) respectively (all $p < 0.05$). Main driver of the improvements were lower severity of reported problems in the EQ-5D *Self-Care* and *Pain / Discomfort* domains. Patients receiving placebo registered a lower improvement to 0.35 – 0.5 (UK) or 0.54 – 0.64 (US).

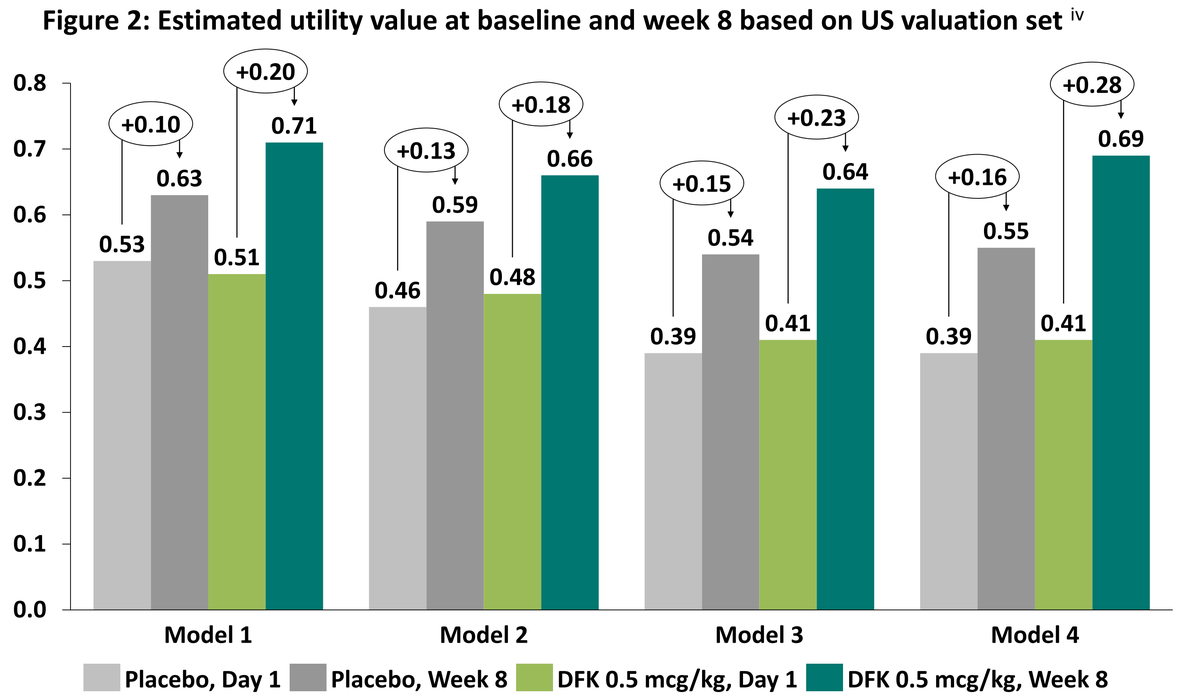
These results reflect the negative impact on patients’ HRQoL from untreated moderate-to-severe CKD-aP and **are in line with the statistically significant improvement over time and relative to placebo measured with both Sk-10 and 5-D Itch** in the clinical study.

Figure 1: Estimated utility value at baseline and week 8 based on UK valuation set [iii]



Placebo N=42, Difelikefalin 0.5 mcg/kg N=39

Figure 2: Estimated utility value at baseline and week 8 based on US valuation set [iv]



Placebo N=42, Difelikefalin 0.5 mcg/kg N=39

Conclusion:

While absolute values vary between countries, data from this study suggests that **HD patients with moderate-to-severe CKD-aP have lower HRQoL than HD patients in general**. Treatment that improves itch-related HRQoL (as shown by improvements of patient-reported itch intensity as well as on Sk-10, 5-D Itch PROs) results in higher utility values. While the methodological limitations of this extrapolation preclude any conclusions on the exact magnitude of the utility improvement, the fact that **DFK-treated patients reach values close to those previously measured in HD patients** in other studies give us confidence in the directionality of the results.

i) Rayner et al., *Clinical Journal of the American Society of Nephrology*, 2017; Pisoni et al., *Nephrol Dial Transplant Journal,* 2006; Fishbane et al., *NDT Journal*, 2001; ii) Cara Therapeutics, press release, May 2019; iii) Devlin et al., *Health Economics*, 2017; iv) Pickard et al., *Value Health,* 2019;