Scratching the Surface of CKD-Associated Pruritus

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Disclosure

- This talk is sponsored by **CSL Vifor** to support medical education.
- I serve as a consultant for **CSL Vifor** and have participated in advisory board meetings.
- I have received an honorarium from **CSL Vifor** for delivering this presentation.
- The content of this presentation reflects my professional expertise and interpretation of the scientific evidence and is not dictated by the sponsor.

Chronic pruritus is a debilitating condition with a variety of underlying causes

Chronic pruritus can be defined as an ***unpleasant sensation*** of the skin leading to the ***desire to scratch***, with symptoms present for more than 6 weeks

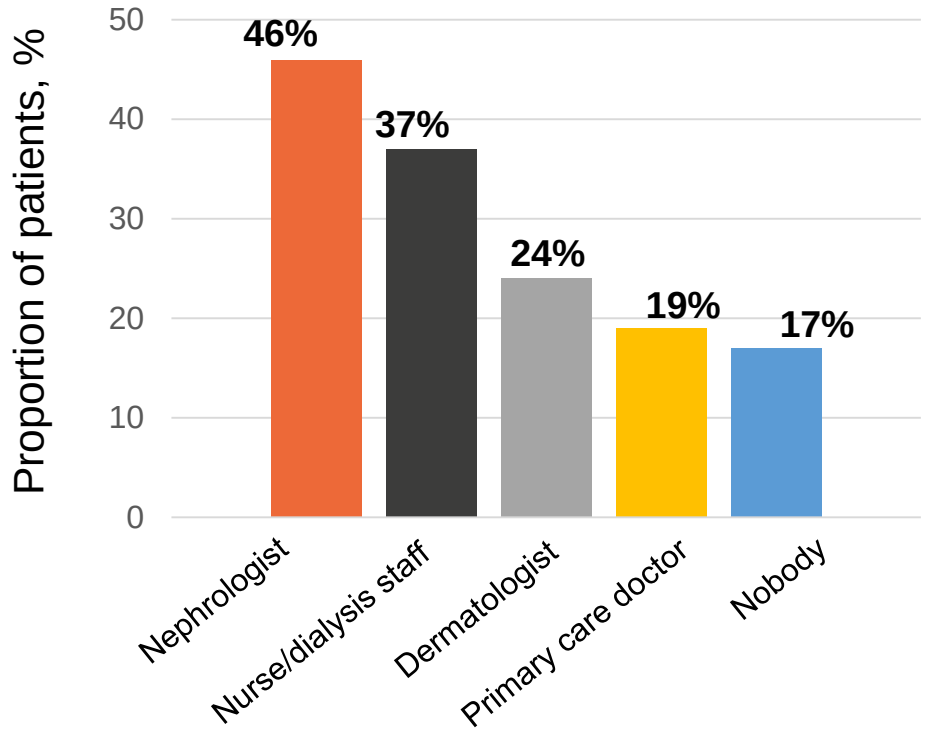
Causes	Presentation	Examples
Dermatologic	Primary skin lesions	Atopic dermatitis, psoriasis, prurigo nodularis, xerosis, scabies, insect bites, unknown origin
Systemic	No primary skin lesions	**Chronic kidney disease (CKD)** Primary biliary cholangitis (PBC), HIV infection, hyperthyroidism
Neuropathic		Postherpetic itch, brachioradial pruritus (spinal-nerve impingement), notalgia paraesthetica
Psychogenic		Obsessive-compulsive disorder, substance abuse, delusions of parasitosis

Ständer S, et al. Acta Derm Venereol 2007;87:291–4; Weisshaar E, et al. Acta Dermatol Venereol 2019;99:469–506; Yosipovitch G, Bernhard J. N Engl J Med 2013;368:1625–34.

The relationship between CKD and pruritus is often not well understood by patients, and many patients fail to report it to their healthcare providers

- **Reasons for patients failing to report symptoms:[1]**
- Unaware that itch is a symptom associated with CKD
- Lack of awareness around treatment options
- Acceptance of itch as inevitable
- Lack of prompting by healthcare professionals
- Time with nephrologist is too limited, and other health issues are prioritised
- Perceived trivialisation of itch by nephrologists
- History of unsuccessful treatments
- Fear of additional medications

Who do patients report their symptoms to?
(among patients nearly always or always bothered by itchy skin)[2]
N=999



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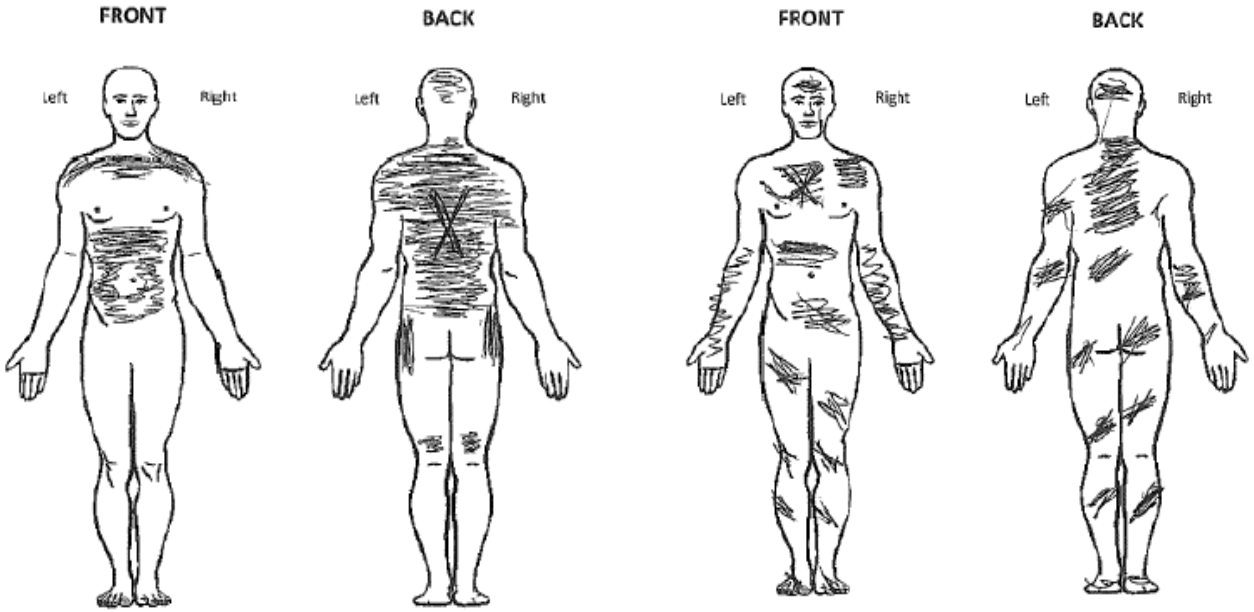
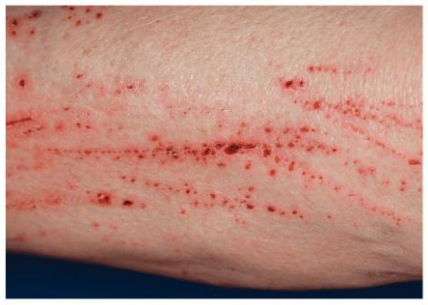
CKD-associated Pruritus is a condition with intense symptoms that markedly impair the QoL of patients with CKD undergoing HD

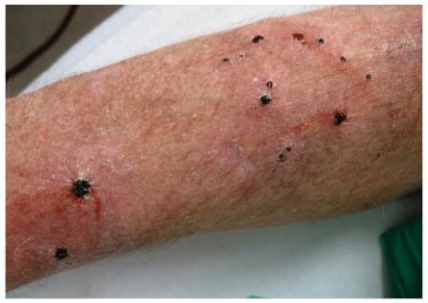
CKD-associated Pruritus is often bilaterally symmetrical, and can be localised or generalised[1,2]



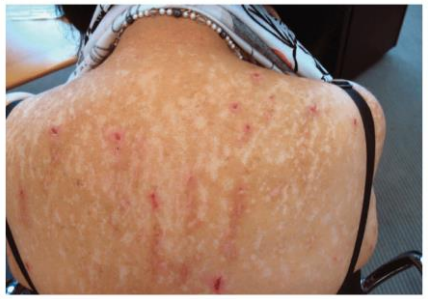
CKD-associated Pruritus is associated with visible skin lesions[3]



Scratch marks with excoriations at the lower leg



Prurigo nodularis located on the forearm



Deep scars and prurigo nodules at shoulders and back

- HD, haemodialysis; QoL, quality of life.

1. Mathur VS, et al. Clin J Am Soc Nephrol 2010;5:1410–19;
2. Shirazian S, et al. Int J Nephrol Renovasc Dis 2017;10:11–26; 3. Mettang T, Kremer AE. Kidney Int 2015;87:685–91.

The pathogenesis of CKD-associated Pruritus is multifactorial

KOR, Kappa opioid receptor; MOR, Mu opioid receptor.

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4. Kuypers DR. Nat Clin Pract Nephrol 2009;5:157–70; 5. Patel TS, et al. Am J Kidney Dis 2007;50:11–20; 6. Zakrzewska-Pniewska B, et al. Neurophysiol Clin 2001;31:181–93;
7. Phan NQ, et al. Acta Derm Venereol 2012;92:555–60; 8. Kimmel M, et al. Nephrol Dial Transplant 2006;21:749–55.

The pathogenesis of CKD-associated Pruritus is multifactorial

Implicated toxins[1–5]

Vitamin A, aluminium, calcium, phosphorus, magnesium

Alterations related to uraemia

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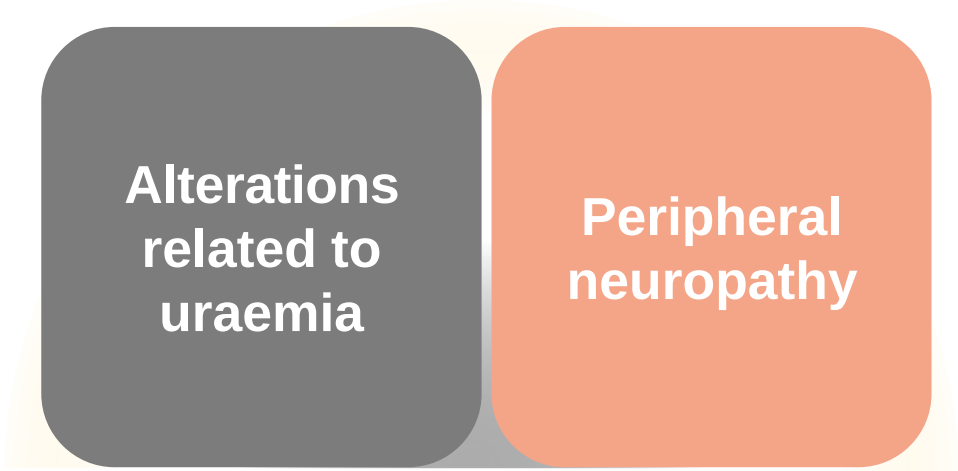

Altered nerve conduction[1,3,5,6]

Pattern of cutaneous innervation

Nerve conduction studies

KOR, Kappa opioid receptor; MOR, Mu opioid receptor.

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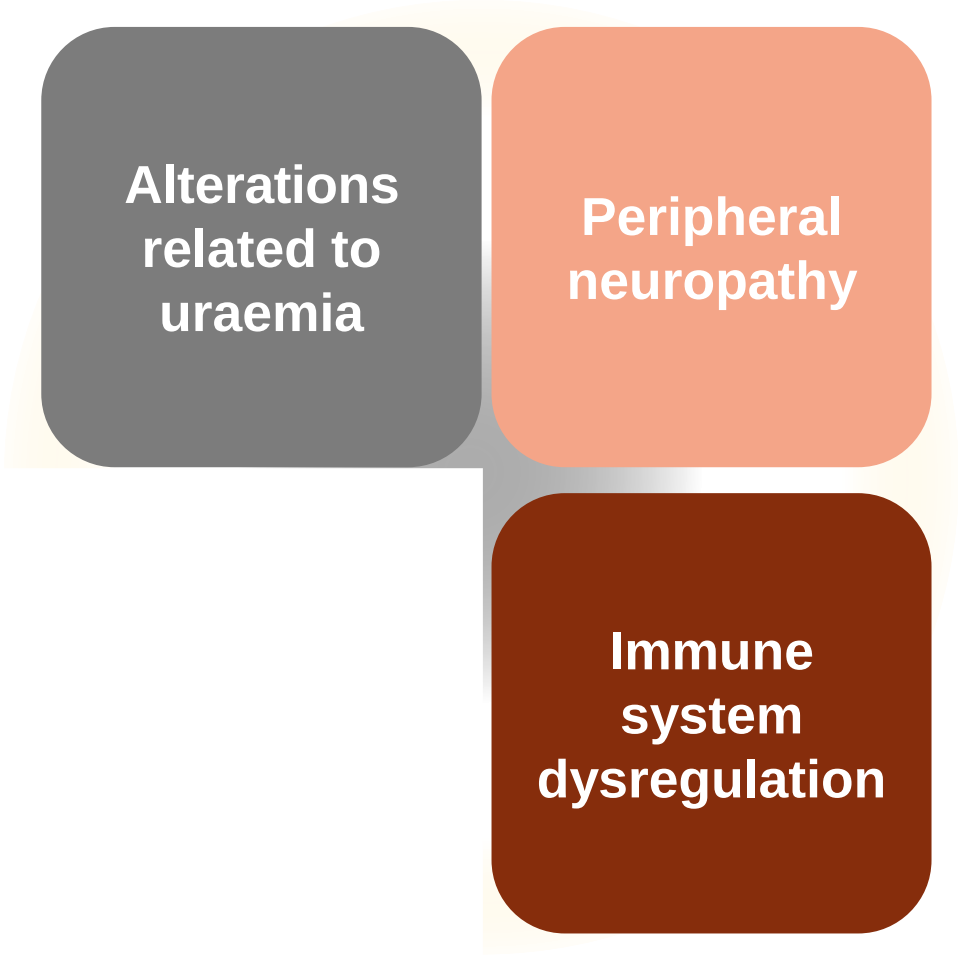

Altered nerve conduction[1,3,5,6]

Pattern of cutaneous innervation
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Pro-inflammatory state[1–5, 8]

↑ T-helper 1 cells, C-reactive protein, interleukin (IL)-6, IL-2

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The pathogenesis of CKD-associated Pruritus is multifactorial

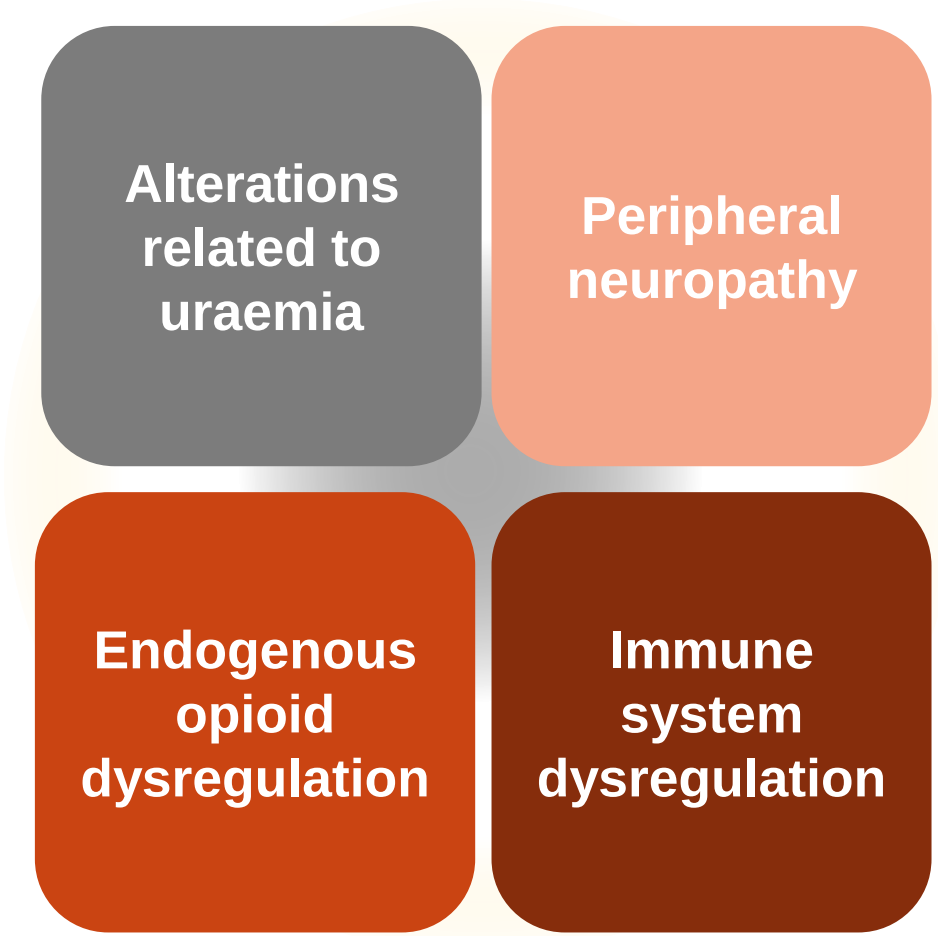
Implicated toxins[1–5]

Vitamin A, aluminium, calcium, phosphorus, magnesium

Imbalanced MOR and KOR activity[1–5, 7]

↑ endorphins (MOR agonist)

↓ dynorphins (KOR agonist)



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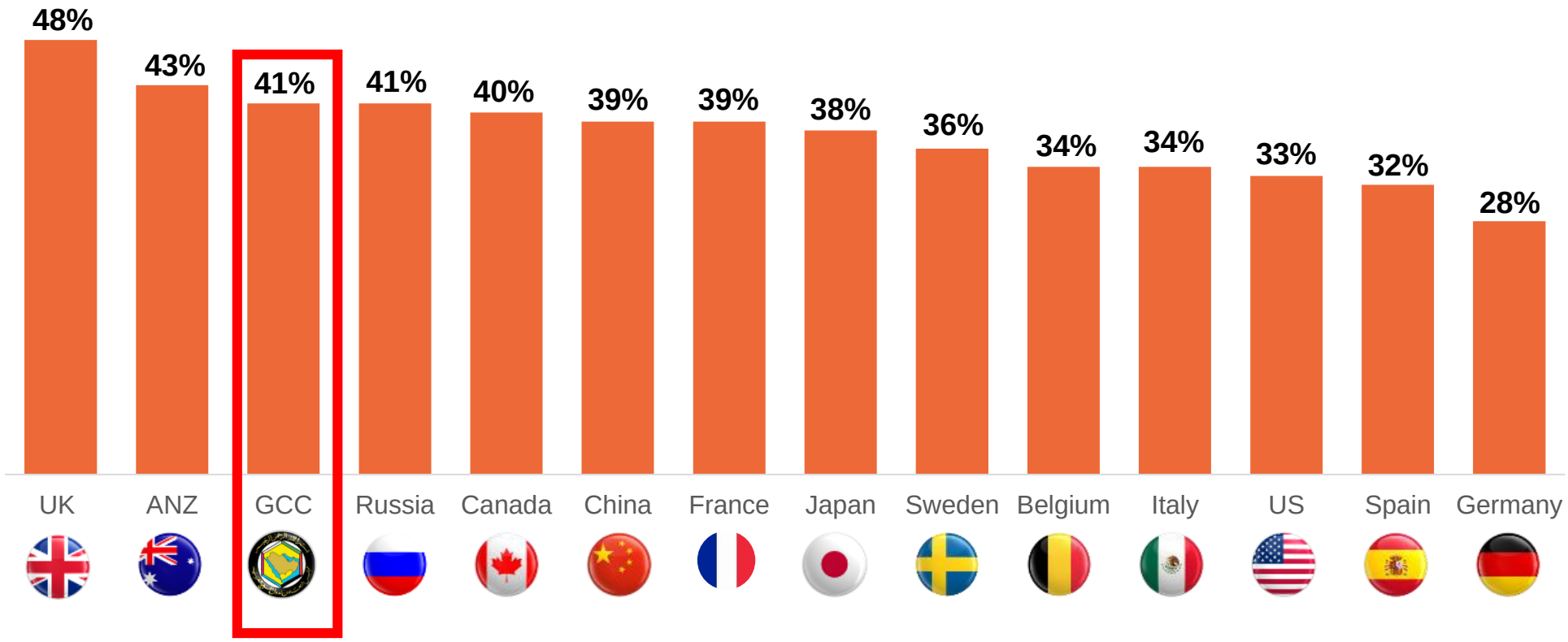
Across countries, pruritus symptoms were reported as moderate-to-severe in ~40% of patients undergoing HD

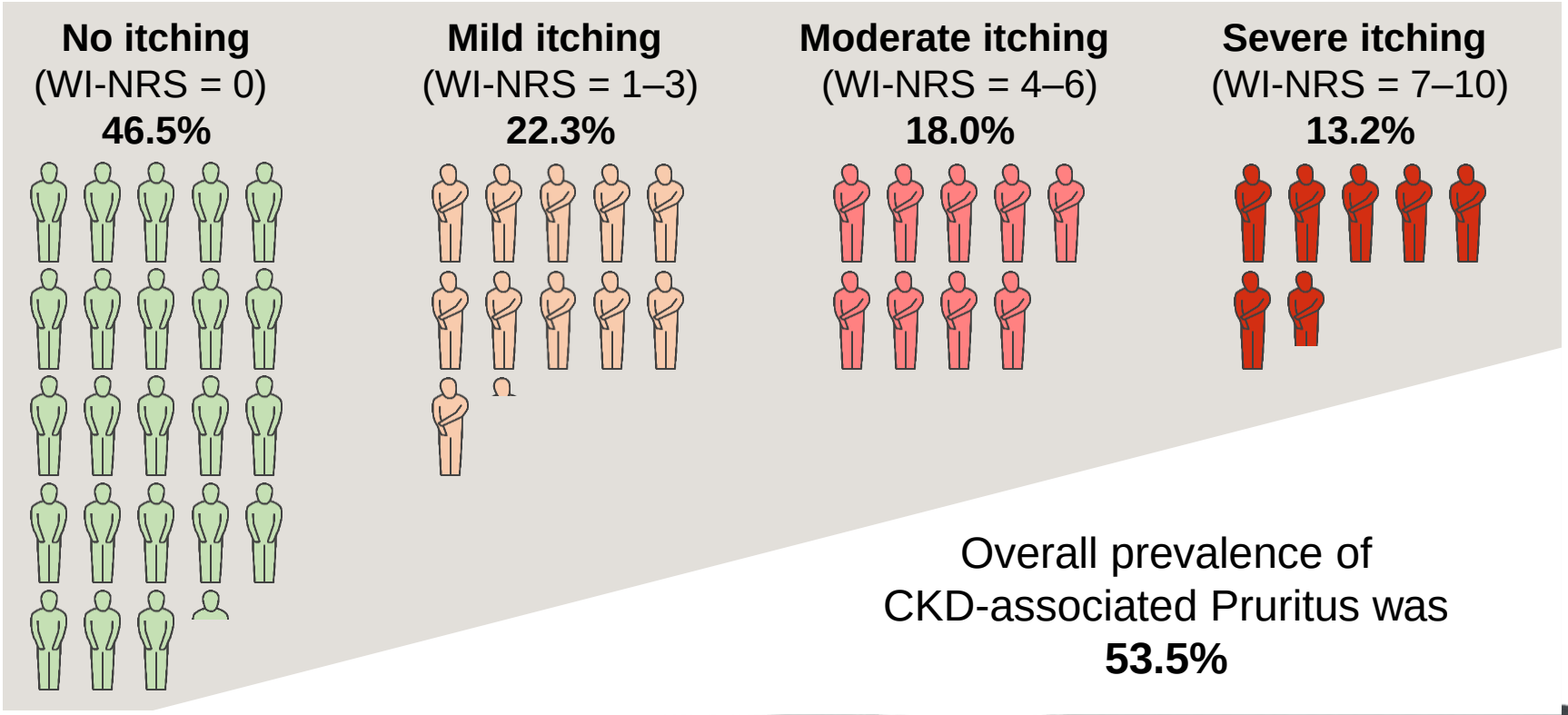
% of HD patients with a pruritus severity of moderate-to-severe by country (DOPPS 2006–2018)



ANZ, Australia and New Zealand; GCC, Gulf Cooperation Council; HD, haemodialysis..
Sukul N, et al. Kidney Med 2020;3:42–53.e1.

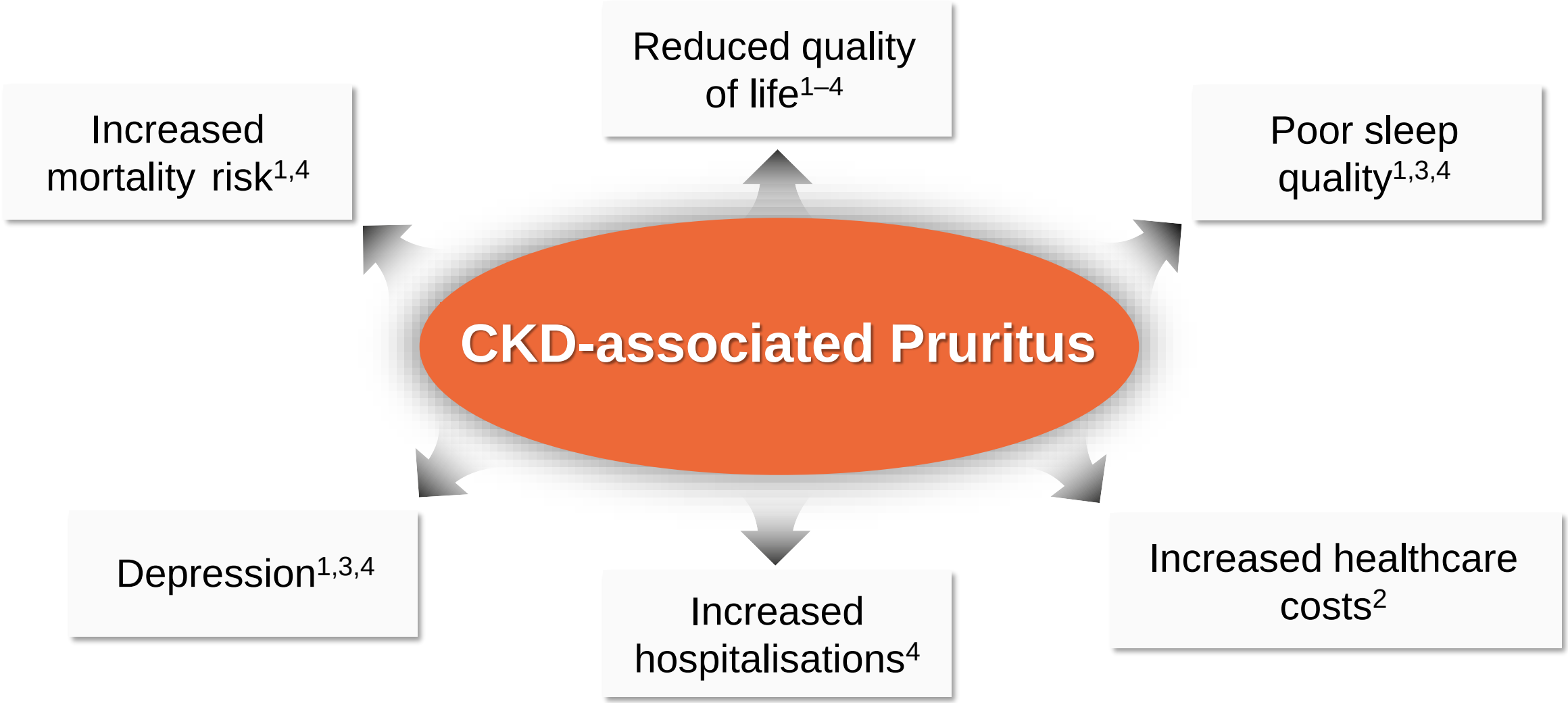
NEW DATA: CENSUS-EU: CKD-associated Pruritus is highly prevalent

- Patients (n=2963) from seven European countries completed WI-NRS to assess the prevalence and severity of CKD-associated Pruritus
- ~50% of patients on HD experience CKD-associated Pruritus with nearly one-third experiencing moderate or severe pruritus



HD, haemodialysis; WI-NRS, worst-itch numerical rating scale.
Burton J, et al. ASN 2024. Poster #FR-PO1144.

CKD-associated Pruritus is associated with adverse outcomes



1. Pisoni RL, et al. Nephrol Dial Transplant 2006;21:3495–505; 2. Ramakrishnan K, et al. Int J Nephrol Renovasc Dis 2013;19:1–12; 3. Mathur VS, et al. Clin J Am Soc Nephrol 2010;5:1410–9; 4. Sukul N, et al. Kidney Med 2020;3:42–53.e1.

CKD-ASSOCIATED PRURITUS IS ASSOCIATED WITH IMPACTS ON QOL, HEALTHCARE RESOURCE UTILISATION AND MORTALITY[1-3]

CKD-associated Pruritus is associated with:

Reduced physical and mental health-related QoL[2–5]

including depression, poor sleep, and avoidance of social interactions[1–5]

CKD, chronic kidney disease; **CV**, cardiovascular; **QoL**, quality-of-life.
*all cause, CV-related, and infection-related hospitalisations

1. Rayner HC, *et al*. *Clin J Am Soc Nephrol*. 2017;12:2000–2007. **2.** Silverberg JI, *et al. Am J Clin Dermatol*. 2018;19(5):759–769. **3.** Pisoni RL, *et al. Nephrol Dial Transplant*. 2006;21:3495–3505. **4.** Sukul N, *et al. Kidney Medicine*. 2021;3(1):42-53. **5.** Ibrahim MK, *et al. J Clin Diagn Res*. 2016;10(3):WC01–WC05. **6.** Ramakrishnan K, *et al. Int J Nephrol Renovasc Dis*. 2013;7:1–12. **7.** Narita I, *et al. Kidney Int*. 2006;69(9): 1626–1632.

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Increased healthcare resource utilisation[4,6]

Higher chance of hospitalisation* for patients extremely bothered by itch than those not at all bothered[4]

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Increased mortality in the most severe cases[4,7]

Severe CKD-associated Pruritus is an independent predictive factor for death[7]

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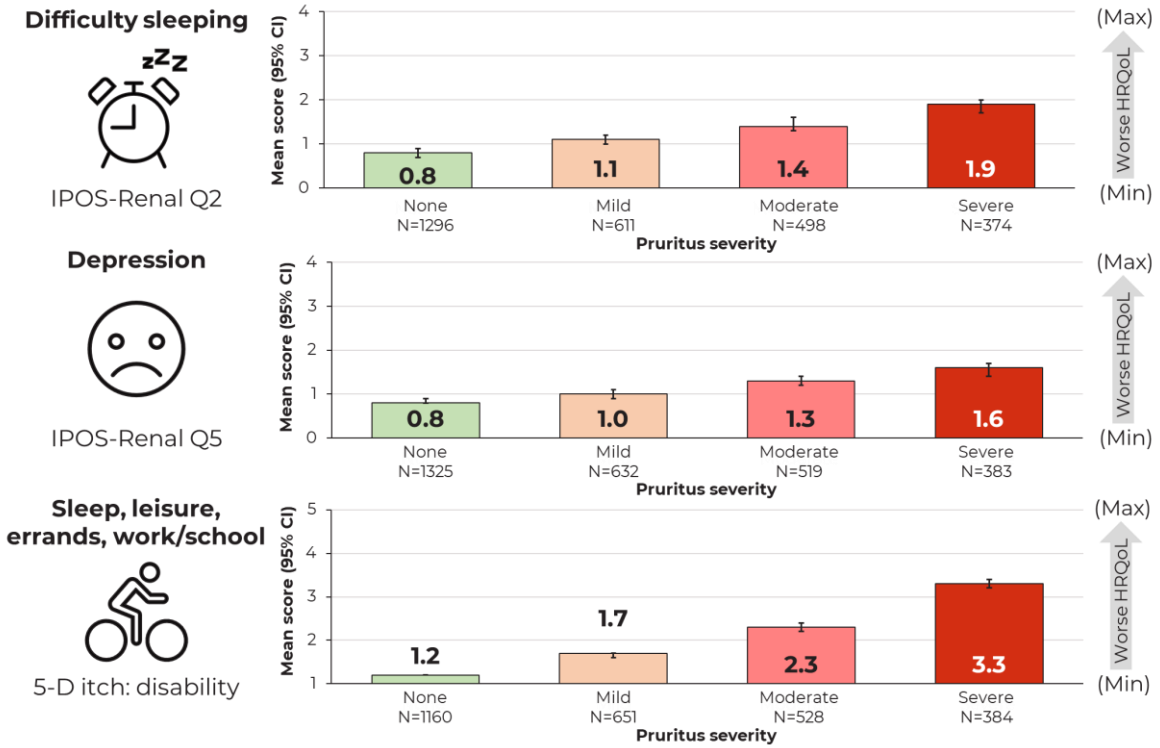
CENSUS-EU: CKD-associated Pruritus severity negatively impacts HRQoL measures

- Patients (n=2963) from seven European countries completed the WI-NRS, 5-D itch scale, IPOS-Renal and a management and communication survey
- Medical records were used to gather information on treatment patterns and healthcare resource utilisation

Impact of CKD-associated Pruritus severity on HRQoL measures*



Impact of CKD-associated Pruritus severity on healthcare resource use

Use of ≥1 ongoing anti-pruritic treatment increased with pruritus severity, but **remained low** in all subgroups (18.3%, 25.3%, and 39.9% for mild, moderate, and severe pruritus, respectively).

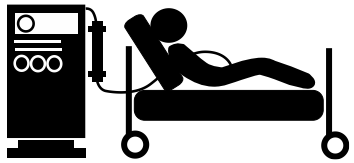
Mean **hospitalisations/year/patient** were 1.9, 1.8, 2.0, and 2.1 for no itching, mild, moderate and severe itching, respectively

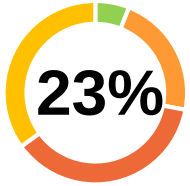
Pruritus severity may have a substantial impact on patients' daily lives, HRQoL, and healthcare resource use

*Data were analysed by pruritus severity based on WI-NRS Score (0: no pruritus; 1–3: mild; 4–6: moderate; 7–10: severe).
CI, confidence interval; HRQoL, health-related quality of life; IPOS-Renal, Integrated Palliative Care Outcome Scale symptom list for end-stage renal disease; Q, question; WI-NRS, worst-itch numerical rating scale.
Burton J, et al. ASN 2024. Poster #FR-PO1144.

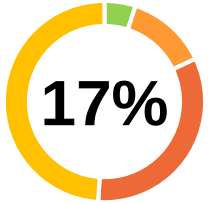
CKD-associated Pruritus
Disruptive of dialysis treatment and worse itch severity is associated with poorer quality of life

Impact on HD





reported **shortening HD sessions** because of itch (higher among patients with severe itch; 37%)



reported **missing HD sessions** because of itch (higher among patients with severe itch; 33%)

In bivariate analysis, patients with more severe itch reported significantly worse KDQoL-SF scores

Kidney disease score

Cognitive function

Quality of social interaction

Sleep

Sexual function

$P < 0.001$

$P < 0.05$

CI, confidence interval; CV, cardiovascular; PROM, patient-reported outcome measure.
Sukul N, et al. Am J Kidney Dis 2023;82:666–76.

CKD-ASSOCIATED PRURITUS IS UNDER-RECOGNISED AND UNDER-REPORTED[1,2]

According to DOPPS*

UNDER-RECOGNISED

69%

of medical units underestimated CKD-associated Pruritus[2]

CKD, chronic kidney disease; **DOPPS**, dialysis outcomes and practice patterns study; **HD**, haemodialysis; **KDQOL**, Kidney Disease Quality-of-Life; **QoL**, quality-of-life.

*DOPPS Phases 1–5 was prospective cohort study of 51,062 HD patients from up to 17 countries between 1996–2015. Pruritus data were collected from 35,452 of these HD patients. Analyses were adjusted for age, sex, dialysis vintage, 13 summary comorbidity measures, and country and facility clustering effects.

†DOPPS Phases 4-6 was a prospective cohort study of 23,264 HD patients from 21 countries between 2009–2018. The study analysed associations between itch-severity and several outcomes, including time to all-cause mortality; dialysis-related outcomes including withdrawal from dialysis and missed haemodialysis sessions; patient-reported outcomes including measure of health-related QoL, depression and sleep quality.

‡Severity of itch was established using the question from the KDQOL-36 questionnaire: During the past 4 weeks to what extent were you bothered by itchy skin? Answers: not at all, somewhat, moderately, very much, extremely.

§In total, 37% of patients were moderately to extremely bothered by itch. This figure can be broken down into patients moderately bothered (18%), very much bothered (12%), and extremely bothered (7%) by itch.

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UNDER-RECOGNISED

69%

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UNDER-REPORTED

25%

of patients with CKD-associated Pruritus who were bothered by itch did not report it to their clinician[2,3]

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The relationship between CKD and pruritus is often not well understood by patients, and many patients fail to report it to their healthcare providers

- **Reasons for patients failing to report symptoms:[1]**
- Unaware that itch is a symptom associated with CKD
- Lack of awareness around treatment options
- Acceptance of itch as inevitable
- Lack of prompting by healthcare professionals
- Time with nephrologist is too limited, and other health issues are prioritised
- Perceived trivialisation of itch by nephrologists
- History of unsuccessful treatments
- Fear of additional medications

Who do patients report their symptoms to?
(among patients nearly always or always bothered by itchy skin)[2]
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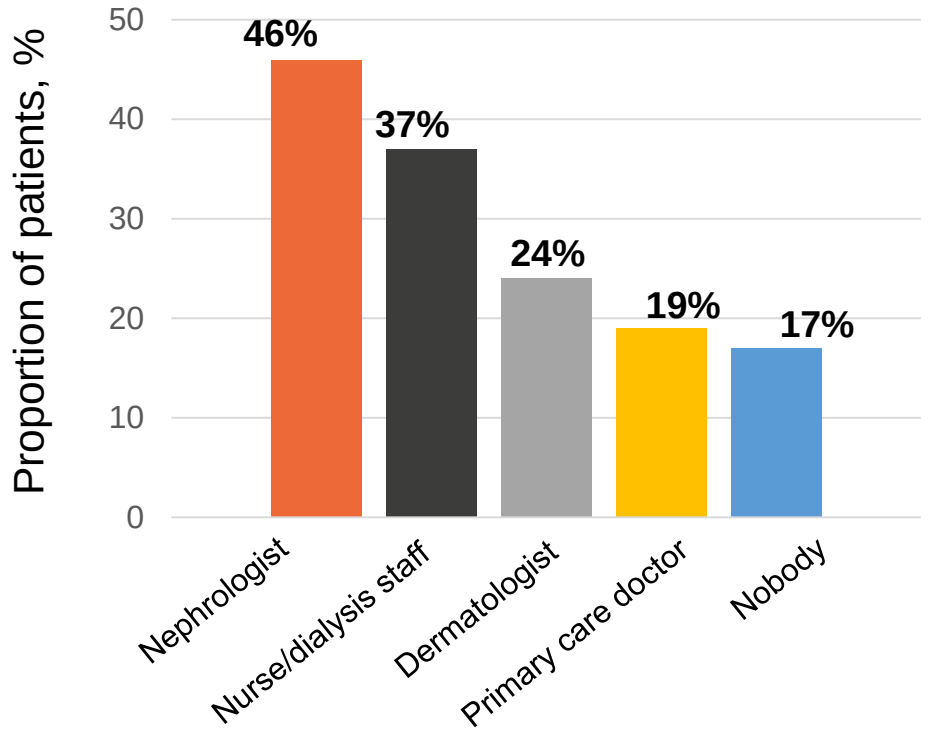

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WI-NRS should be part of the routine care

Nephrologists and nurses are asking patients the WI-NRS question

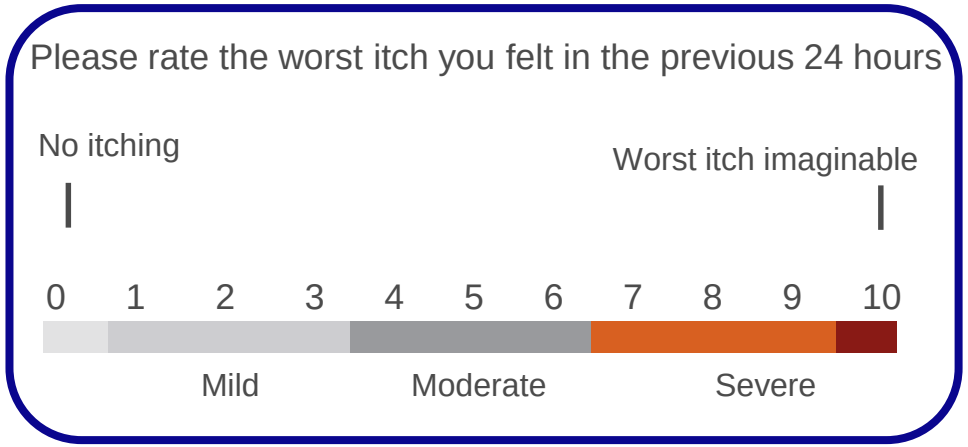
As per KDIGO's suggestion, the assessment of itch intensity should be implemented as part of the dialysis patient's medical record

WI-NRS, worst-itch numerical rating scale.
Speaker's own opinion.

ASSESSING THE IMPACT OF CKD-ASSOCIATED PRURITUS IN HAEMODIALYSIS PATIENTS

Two useful assessment scales have been developed to help measure itch severity and impact of itch on quality of life in patients with CKD-associated Pruritus, the Worst Itch Intensity - Numerical Rating Scale (WI-NRS) and the Self-Assessed Disease Severity (SADS) scale.

WI-NRS ASSESSES ITCH INTENSITY*[1,2]



In trials, a reduction of **≥3 points in WI-NRS** signified a **clinically meaningful improvement in itch** severity for patients with moderate-to-severe CKD-associated Pruritus[3]

CKD, chronic kidney disease; **HD**, haemodialysis; **QoL**, quality-of-life; **SADS**, Self-Assessed Disease Severity; **WI-NRS**, Worst Itch Intensity - Numerical Rating Scale.

*WI-NRS is a validated 11-point scale ranging from 0–10 where 0 represents 'no itching' and 10 'worst itch imaginable'.[1,2] The WI-NRS is based on a similar scale also validated for the measurement of pain.[2]

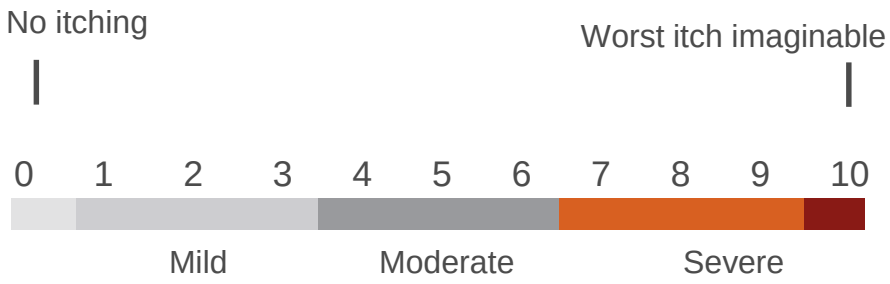
1. Mathur VS, *et al. Clin J Am Soc Nephrol*. 2010;5:1410–19. **2.** Phan NC, *et al. Acta Derm Venereol*. 2012;92:502–7. **3.** Vernon M, *et al. J Am Acad Dermatol*. 2021;84(4):1132–1134.

ASSESSING THE IMPACT OF CKD-ASSOCIATED PRURITUS IN HAEMODIALYSIS PATIENTS

Two useful assessment scales have been developed to help measure itch severity and impact of itch on quality of life in patients with CKD-associated Pruritus, the Worst Itch Intensity - Numerical Rating Scale (WI-NRS) and the Self-Assessed Disease Severity (SADS) scale.

WI-NRS ASSESSES ITCH INTENSITY*[1,2]

Please rate the worst itch you felt in the previous 24 hours



In trials, a reduction of **≥3 points in WI-NRS** signified a **clinically meaningful improvement in itch** severity for patients with moderate-to-severe CKD-associated Pruritus[3]

SADS ASSESSES ITCH-RELATED QoL[1]

Which of these patients are you most like?

PATIENT A (MILD)
- I do not generally have scratch marks on my skin
- I do not generally have a problem sleeping because of itching
- My itching does not generally make me feel agitated or sad

PATIENT B (MODERATE):
- I sometimes have scratch marks on my skin
- I sometimes have problems sleeping because of itching
- My itching can sometimes make me feel agitated or sad

PATIENT C (SEVERE):
- I often have scratch marks on my skin that may or may not bleed or get infected
- I often have a problem sleeping because of itching
- My itching often makes me feel agitated or sad

CKD, chronic kidney disease; **HD**, haemodialysis; **QoL**, quality-of-life; **SADS**, Self-Assessed Disease Severity; **WI-NRS**, Worst Itch Intensity - Numerical Rating Scale.

*WI-NRS is a validated 11-point scale ranging from 0–10 where 0 represents 'no itching' and 10 'worst itch imaginable'.[1,2] The WI-NRS is based on a similar scale also validated for the measurement of pain.[2]

1. Mathur VS, *et al. Clin J Am Soc Nephrol*. 2010;5:1410–19. **2.** Phan NC, *et al. Acta Derm Venereol*. 2012;92:502–7. **3.** Vernon M, *et al. J Am Acad Dermatol*. 2021;84(4):1132–1134.

Translated into local language.

Arabic versions:

ASSESSING THE IMPACT OF ITCH IN CKD-associated
Pruritus in HAEMODIALYSIS PATIENTS

تقييـم تأثـير الحكة المصاحبة لداء الكلى المزمن في المرضى اللذين يخضعون للغسيل الكلوي

أولاً: تقييم شدة الحكة عن طريق مقياس التقييم العددي لأسوأ حكة
(Worst Itch Numerical Rating Scale: WI-NRS)

يرجى اختيار شدة أسوأ حكة شعرت بها خلال ال ٢٤ ساعة الماضية

ثانياً: تأثير الحكة على جودة الحياة عن طريق مقياس درجة شدة المرض ذاتية التقييم

Self-assessed disease severity (SADS) Score

أي من هؤلاء المرضى يمثلك أكثر؟

المريض أ

ليس لدي بشكل عام علامات خدش على جلدي
ليس لدي بشكل عام مشكلة في النوم بسبب الحكة
لا تؤدي الحكة بشكل عام إلى شعوري بالاضطراب أو بالحزن

المريض ب

أحيانًا ألاحظ علامات خدش على جلدي
أحيانًا أعاني من مشاكل في النوم بسبب الحكة
أحيانًا قد أشعر بالاضطراب أو بالحزن بسبب الحكة

المريض ج

غالبًا ما أعاني من خدوش على جلدي التي قد تنزف وأحيانًا تصاب بالعدوى
غالبًا ما أعاني من مشكلة في النوم بسبب الحكة
غالبًا ما تجعلني الحكة أشعر بالاضطراب أو بالحزن

(هذا ويمثل "المريض أ" الحكة الطفيفة ؛ و"المريض ب" الحكة المتوسطة الشدة ؛ و"المريض ج" الحكة الشديدة)

Current CKD-associated Pruritus treatment landscape

Emollients and moisturisers for CKD-associated Pruritus

Skin care:[1]

- Moisturise skin daily to twice daily, especially after showers/baths
- Apply emollients, especially at night
  - Creams/lotions/gels

- The term '**moisturiser**' covers emollients, humectants and occlusives[2]
  - **Emollients** – improve skin barrier function, membrane fluidity and cell signalling, resulting in overall improvement of skin texture and appearance
  - **Humectants** – attract water into the stratum corneum
  - **Occlusives** – form a layer on the skin surface to physically block water evaporation from the skin
- Moisturiser and emollient are often used interchangeably; however, moisturisers often contain humectants in order to hydrate the stratum corneum of the skin[2,3]

1. Weisshaar E, et al. Acta Derm Venereol 2019;99:469–506; 2. Purnamawati S, et al. Clin Med Res 2017;15:75–87; 3. Lodén M. Am J Clin Dermatol 2003;4:771–88.

How has CKD-aP been treated so far?

	1: Chronic use, 1st line therapy	2: Chronic use, 2nd line therapy	3: Chronic use, 3rd line therapy	4: Acute use only (i.e., prescribe for 1 month or less)	5: I never prescribe for pruritus	N MDs
Topical antihistamines	23%	9%	7%	24%	36%	249
Oral antihistamines (over the counter)	32%	13%	3%	21%	31%	238
Oral antihistamines (prescription)	46%	24%	5%	19%	7%	259
IV antihistamines	2%	6%	9%	35%	48%	254
Topical corticosteroids	9%	11%	12%	39%	29%	256
Oral corticosteroids	2%	2%	4%	26%	66%	253
IV corticosteroids	1%	1%	1%	18%	79%	249
Gabapentin	5%	19%	21%	4%	52%	198
Antidepressants	2%	8%	21%	8%	60%	252
Anti-anxiolytics/sedatives	2%	6%	20%	19%	53%	251
Opioids	1%	5%	9%	6%	79%	249

International Comparisons of Prevalence, Awareness, and Treatment of Pruritus in People on Hemodialysis

Hugh C. Rayner, Maria Larkina, Mia Wang, Matthew Graham-Brown, Sabine N. van der Veer, Tevfik Ecder, Takeshi Hasegawa, Werner Kleophas, Brian A. Bieber, Francesca Tentori, Bruce M. Robinson, and Ronald L. Pisoni

Clin J Am Soc Nephrol 12: 2000–2007, 2017.

CKD-associated Pruritus is often inadequately treated

354 patients with CKD-associated Pruritus included in the survey:

- 22% had mild itch
- 49% had moderate itch
- 30% had severe itch

Most common treatments were:

- **75%** lotions/moisturisers → **38%**
- **48%** corticosteroids creams → **34%**
- **20%** oral prescriptions → **17%**

…were not satisfied with their current treatment

68%
reported symptoms to HCPs

55%
Received treatment recommendation

- CI, confidence interval; CV, cardiovascular; PROM, patient-reported outcome measure.
  Sukul N, et al. Am J Kidney Dis 2023;82:666–76.
- HCP, healthcare professional; HD, haemodialysis; KDQoL-SF; Kidney Disease Quality of Life Instrument

The only approved treatment for moderate-severe CKD-aP

DIFELIKEFALIN

*(*KURSOVA)*

Difelikefalin regulatory approvals

FDA

AUGUST 2021

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

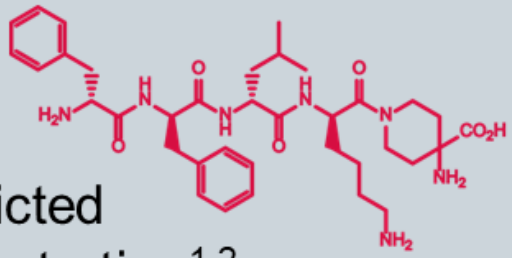
APRIL 2022

NICE
National Institute for Health and Care Excellence

MAY 2023

Difelikefalin (DFK)

DFK
is a synthetic small peptide designed to be peripherally restricted and to limit CNS penetration[1,2]



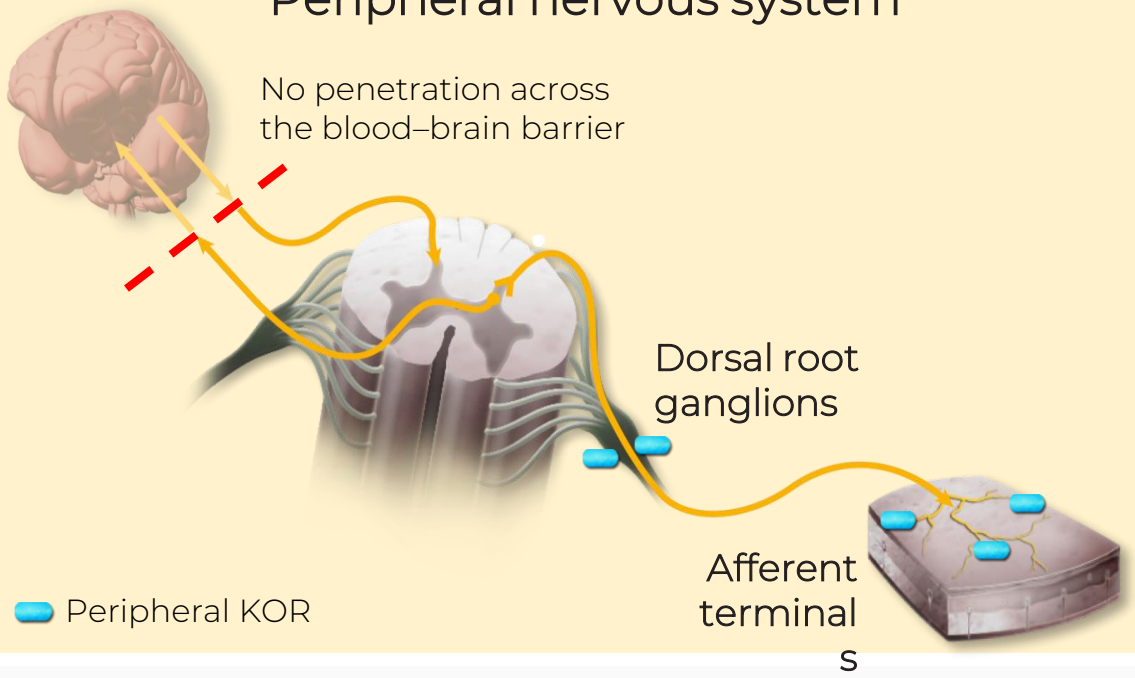
DFK
is a selective and full agonist at KORs with no identified off-target activity[1–3]

CNS, central nervous system; DFK, difelikefalin; MoA, mode of action.
1. Cara Therapeutics Difelikefalin Investigators' Brochure; 2. Cara Therapeutics Request for Breakthrough Therapy Designation Document;

Difelikefalin treats CKD-associated Pruritus by activating KORs on peripheral sensory neurons and immune cells

Peripheral KOR agonists are involved in the inhibition of the perception of itch

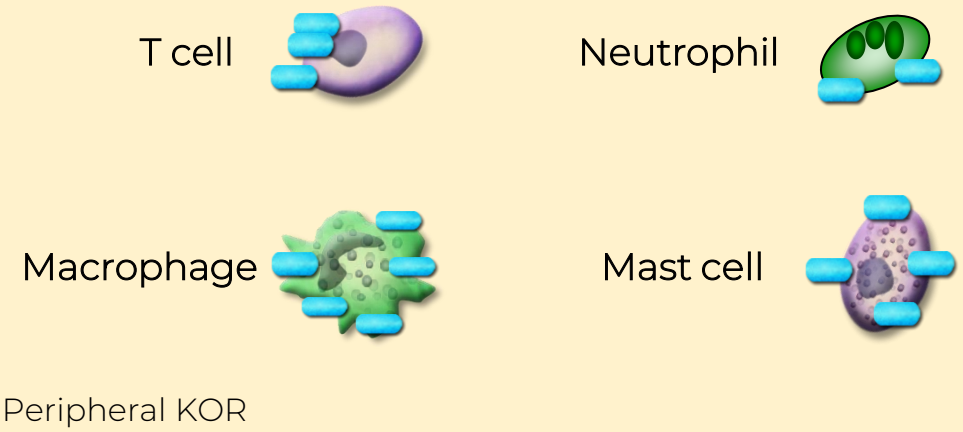
Peripheral nervous system



KOR activation:

- Leads to direct pruritic signal suppression
- Is also thought to regulate the response of C-fibres to pruritogens

Immune cells



Difelikefalin reduced secretion of:

- Pro-inflammatory cytokines TNF-α, IL-1β, IL-6, IL-8, and G-CSF following stimulation of primary human macrophages
- Pro-inflammatory cytokines TNF-α, IL-1β, IL-2, IL-12, and MIP-1β induced by LPS in mice

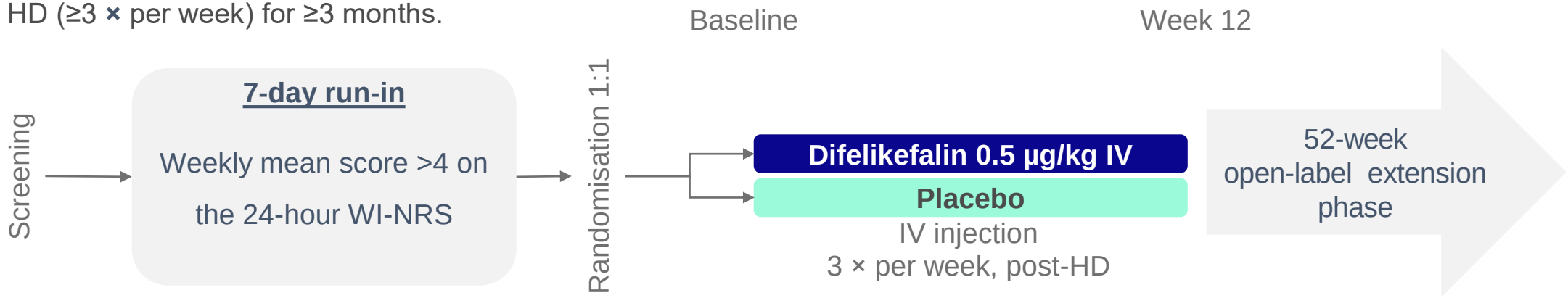
G-CSF, granulocyte-colony stimulating factor; IL, interleukin; KOR, kappa opioid receptors; LPS, lipopolysaccharide; MIP, macrophage inflammatory protein; TNF, tumour necrosis factor.

Spencer RH, et al. IASP 2010; Abstract PH-251 and poster presentation; Albert-Vartanian A, et al. J Clin Pharmacol Ther 2016:371–82;
Cara Therapeutics Difelikefalin Investigator's Brochure.

STUDY DESIGN: KALM-1 AND KALM-2 PIVOTAL PHASE 3 STUDIES

Patients ≥18 years of age with ESRD and moderate-to-severe pruritus.

On HD (≥3 × per week) for ≥3 months.



KALM-1[1]
US multicentre study
Difelikefalin (n=189) vs placebo (n=188)*
Completion date: April 2020

KALM-2[2]
Global multicentre study
Difelikefalin (n=237) vs placebo (n=236)
Completion date: March 2020

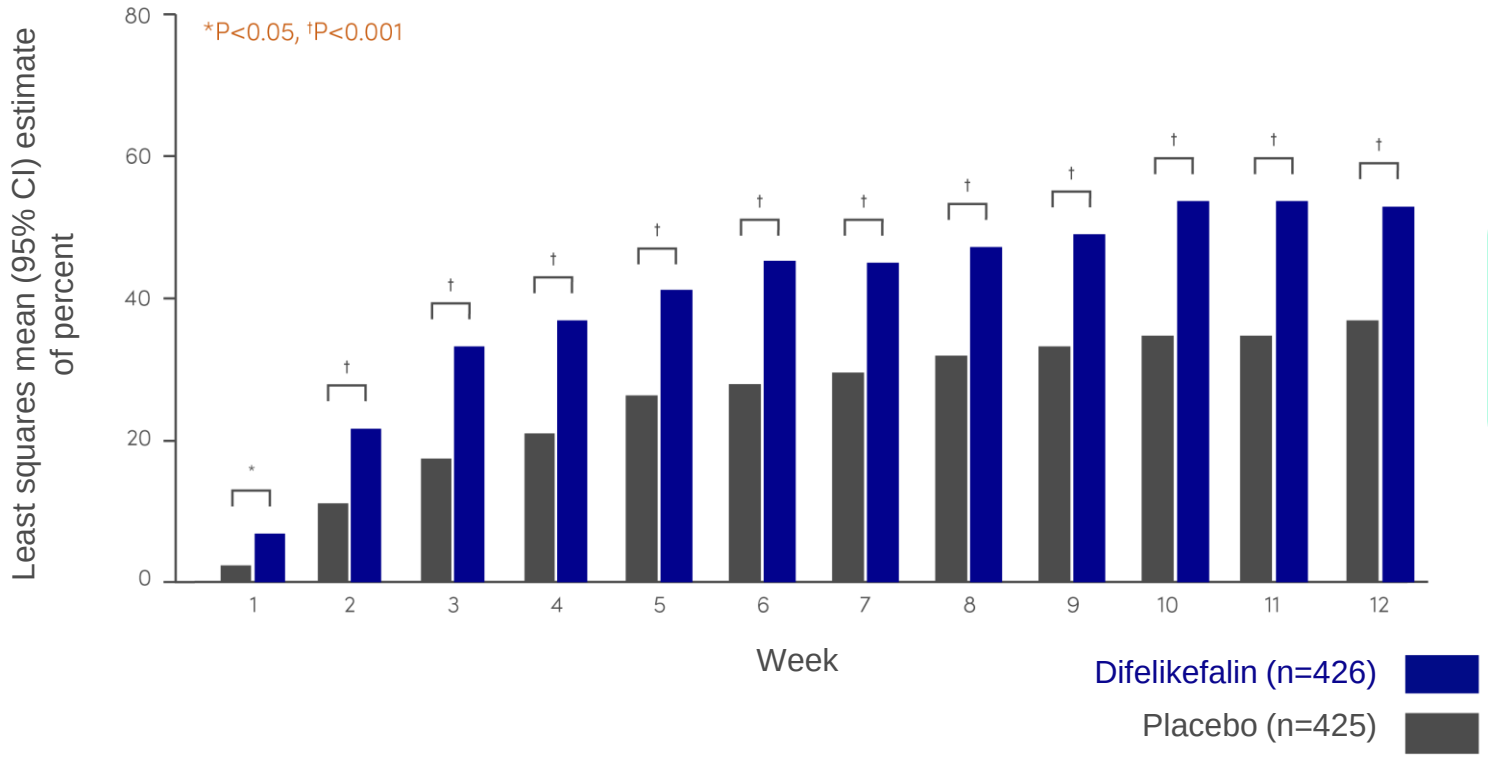
- *1 patient withdrew post-randomisation and before first dose of placebo.

ESRD, end-stage renal disease; **HD**, haemodialysis; **IV**, intravenous; **WI-NRS**, Worst Itch Intensity Numerical Rating Scale.

1. Fishbane S, *et al. N Engl J Med.* 2020;382:222–32; **2.** Wooldridge T, *et al.* ASN 2020; Abstract FR-OR24.

IN HD PATIENTS WITH CKD-ASSOCIATED PRURITUS, DIFELIKEFALIN PROVIDED CLINICALLY MEANINGFUL REDUCTION IN ITCH INTENSITY WHEN COMPARED TO PLACEBO

Proportion of patients with CKD-associated Pruritus achieving ≥3-point improvement in WI-RNS score until Week 12 (pooled KALM-1 and KALM-2)[1]



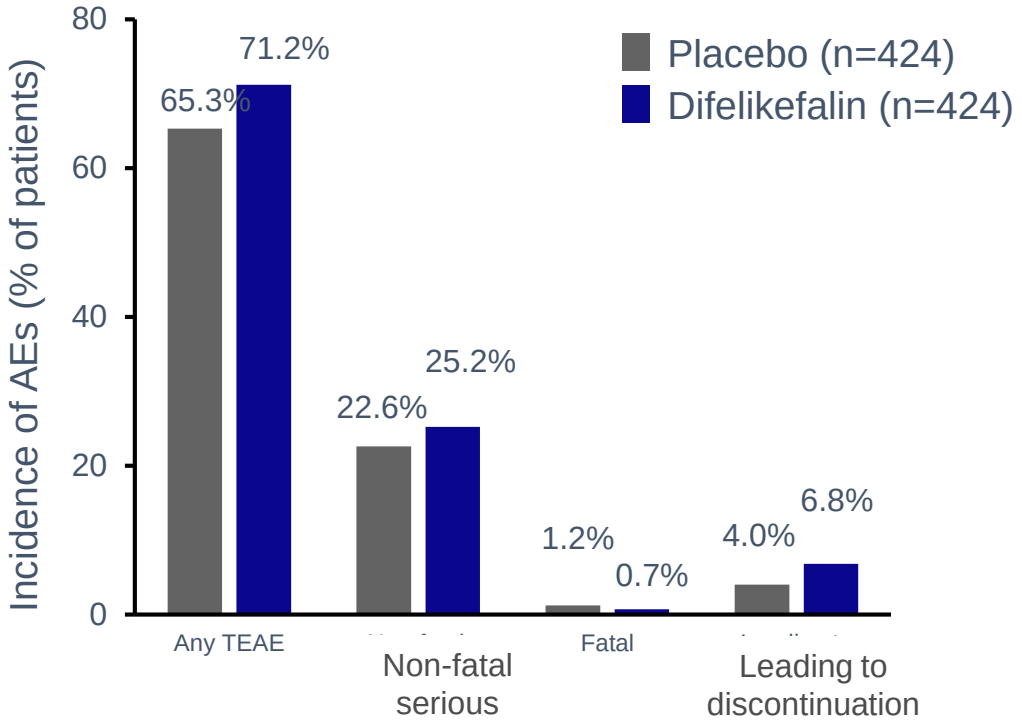
Difelikefalin **reduced itch intensity, sustaining it** at all time points up to **Week 12 when compared with placebo**[1]

CKD, chronic kidney disease; **CI**, confidence interval; **HD**, haemodialysis; **WI-NRS**, Worst Itch Intensity Numerical Rating Scale.

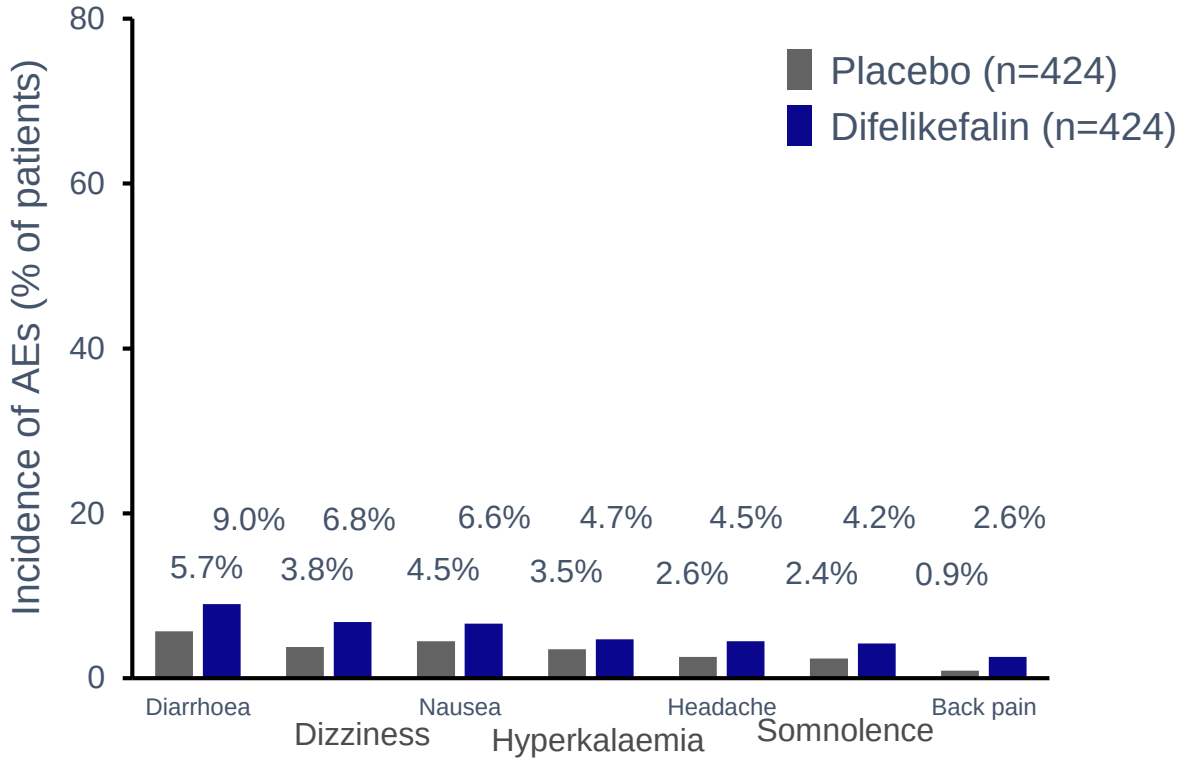
1. Topf J, *et al. Kidney Medicine*. 2022. doi: https://doi.org/10.1016/j.xkme.2022.100512.

TEAES WERE GENERALLY MILD-TO-MODERATE IN THE 12-WEEK PLACEBO-CONTROLLED PHASE (POOLED SAFETY DATA FROM KALM-1 AND KALM-2)

Safety overview



Most common AEs



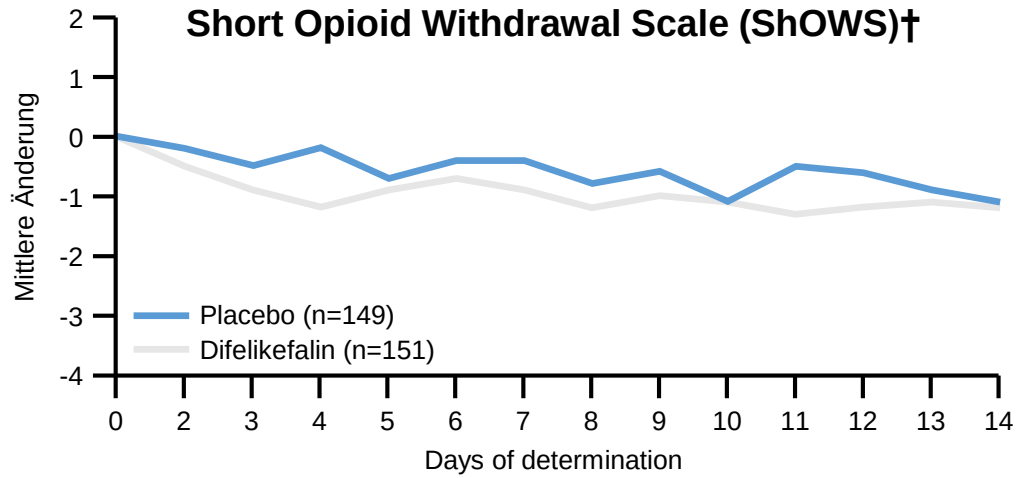
AE, adverse event; **TEAE**, treatment-emergent adverse event.

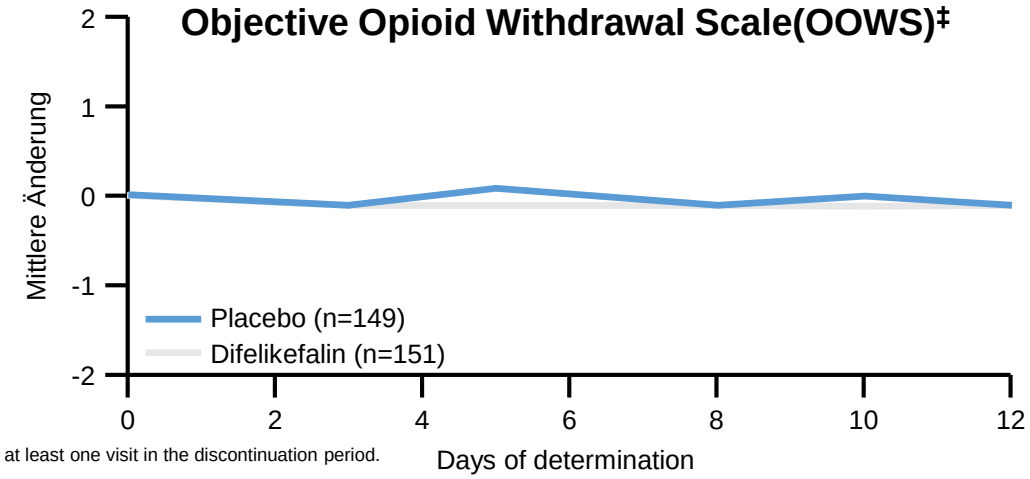
Adapted from Fishbane S, *et al.* Kidney Medicine. 2022. Doi: https://doi.org/10.1016/j.xkme.2022.100513.

Studies of difelikefalin demonstrated no abuse potential and no signs of physical dependence

- No AEs of euphoria, hallucinations or dysphoria were observed in the Phase 3 (KALM-1) and Phase 2 (CLIN2101) studies of difelikefalin in HD patients with moderate-to-severe pruritus [1,2]

- No signs of potential physical dependence* (as measured using ShOWS and OOWS scores) or AEs related to withdrawal were observed in the Phase 3 (KALM-1) study of difelikefalin in HD patients with moderate-to-severe pruritus [1]

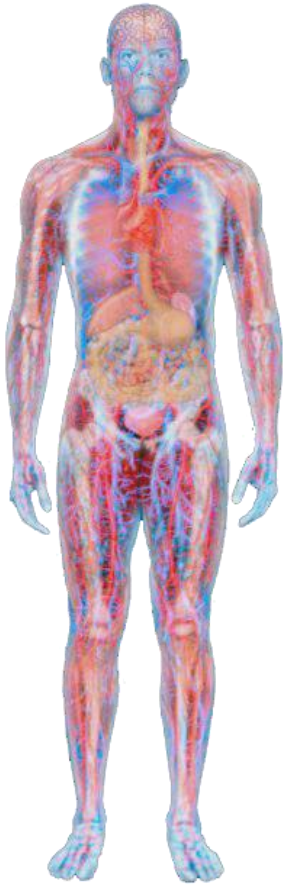




*Among patients who completed 12 weeks of treatment, received at least six doses of study drug in the last 2 weeks of the treatment period, and had at least one visit in the discontinuation period.
AE, adverse events; HD, haemodialysis; IV, intravenous; OOWS, Objective Opioid Withdrawal Scale; ShOWS, Short Opioid Withdrawal Scale; VAS, visual analogue scale.

1. Fishbane S, et al. N Engl J Med 2020;382:222–32; 2. Fishbane S, et al. Kidney Int Rep 2020;5:600–10; 3. Shram MJ, et al. Clin Transl Sci 2022 ;15:535–47.

MOR agonists display important side-effects such as euphoria, physical dependence and respiratory depression, whereas KOR agonists do not



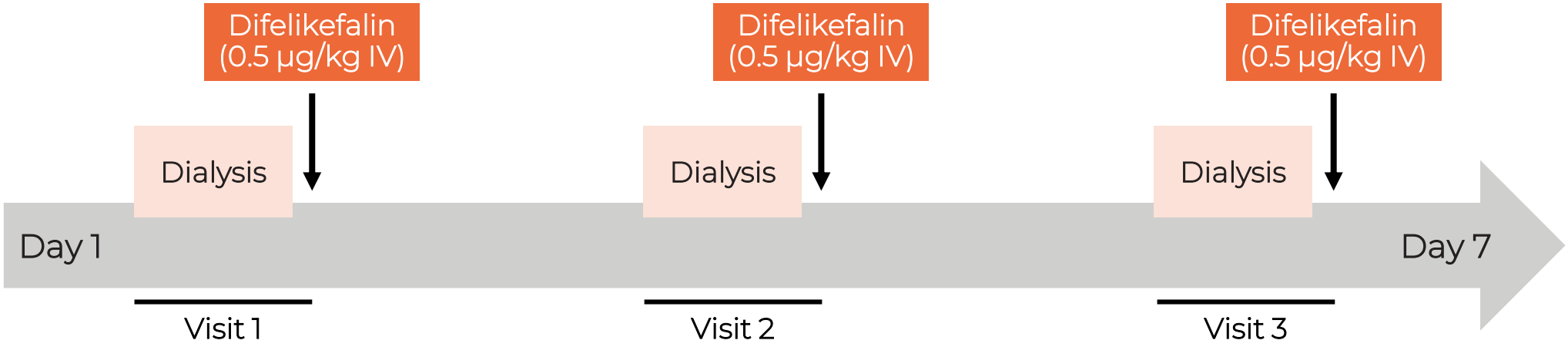
Pharmacological/physiological effects of MOR vs KOR agonists

Clinical effects	MOR	KOR
Analgesia	✓	✓
Itch	✓	Anti-itch
Constipation	✓	
Nausea/vomiting	✓	
Sedation/somnolence	✓	✓
Euphoria	✓	
Physical dependence	✓	
Respiratory depression	✓	
Dysphoria/hallucination		✓
Aquaresis*		✓

*The excretion of water loss without electrolyte loss.
KOR, kapa opioid receptor; MOR, mu opioid receptor.
Albert-Vartanian A, et al. J Clin Pharmacol Ther 2016:371–82; Umeuchi H, et al. Eur J Pharmacol 2003;477:29–35.

Difelikefalin is available as an IV formulation that can be administered at the end of each HD session

- Difelikefalin is administered as an IV bolus into the venous port of the dialysis circuit after each HD session[1–3]
  - Ensures high treatment adherence
  - Minimal additional burden to patients and healthcare resources
  - Plasma concentrations of difelikefalin were reduced by 70–80% at the end of the next dialysis treatment as difelikefalin is water soluble



HD, haemodialysis; IV, intravenous.

1. Fishbane S, et al. N Engl J Med 2020;382:222–32; 2. FDA. Prescribing information: Korsuva (difelikefalin) injection, for intravenous use;
3. EMA. Summary of product characteristics: Kapruvia (difelikefalin) injection, for intravenous use.

Contraindication

The use of Korsuva® is contraindicated in case of:

- hypersensitivity
  to its active substance or any of the excipients

Real world data

Received: 23 January 2023 | Accepted: 27 March 2023

DOI: 10.1111/jdv.19105

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

LETTER TO THE EDITOR

The first real-world experience of IV difelikefalin to treat chronic kidney disease-associated pruritus in haemodialysis patients

Leonie Kraft[1]
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Severin Schricker[1]
Markus Ketteler[1]
Gert Mayer[2]
Guy Rostoker[3]
Lucio Manenti[4]
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Joerg Latus[1]

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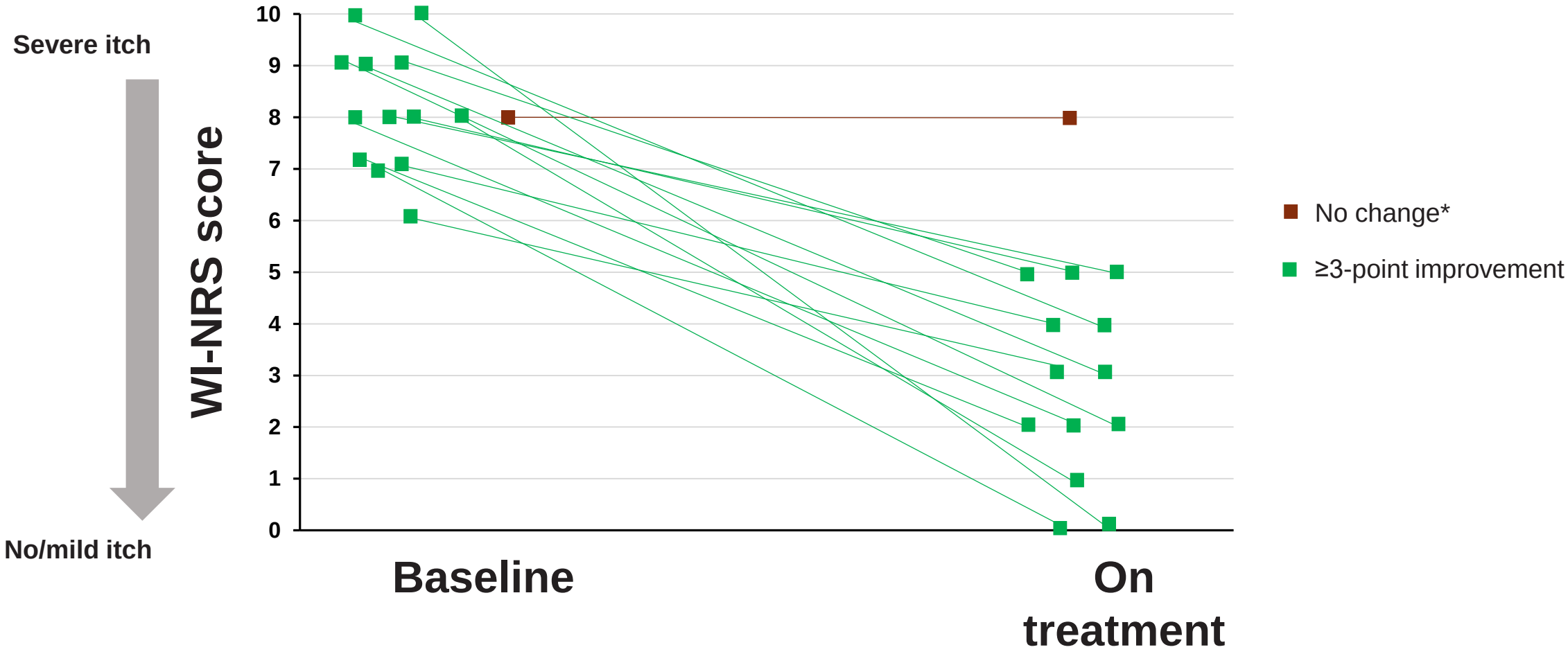
[3]*Department of Nephrology and Dialysis, Hôpital Privé Claude Galien, Ramsay Santé, Quincy-sous-Sénart, France*

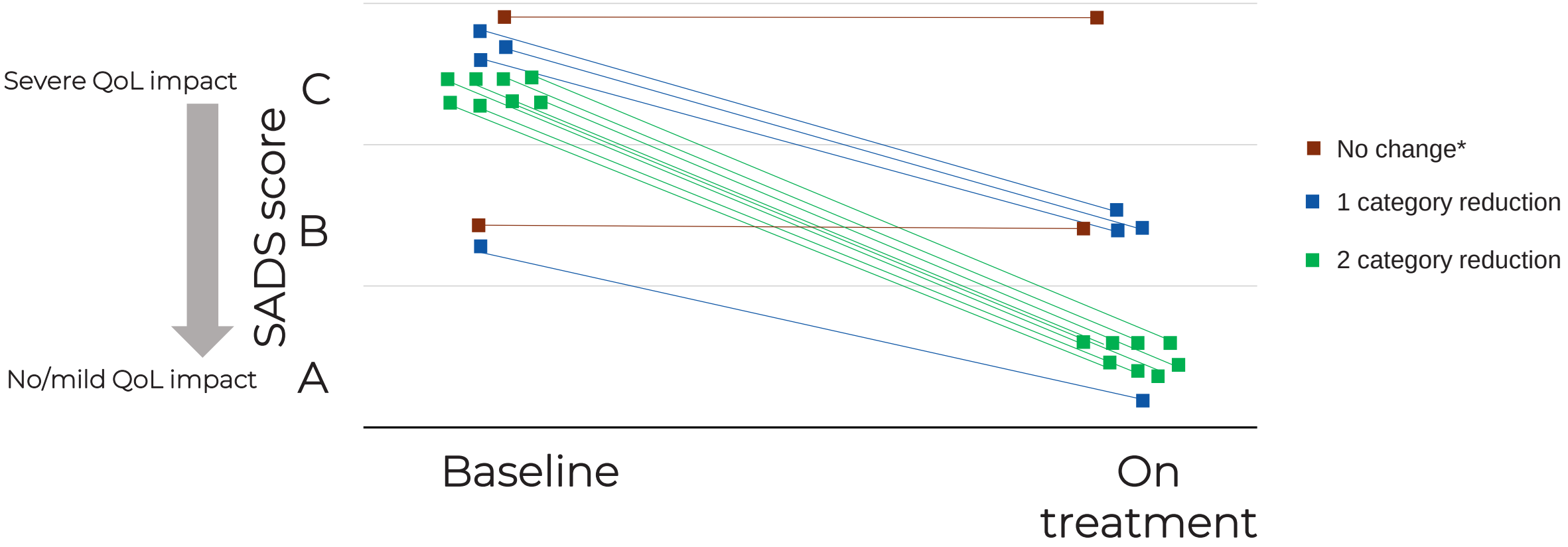
Change in itch (WI-NRS)



13 of 14 patients† (93%) experienced a ≥3-point improvement in WI-NRS score with DFK

*Patient 14 experienced no WI-NRS response after 4 weeks on treatment. †No WI-NRS data available for Patient 7.
DFK, difelikefalin; WI-NRS, Worst-Itch Numerical Rating Scale.

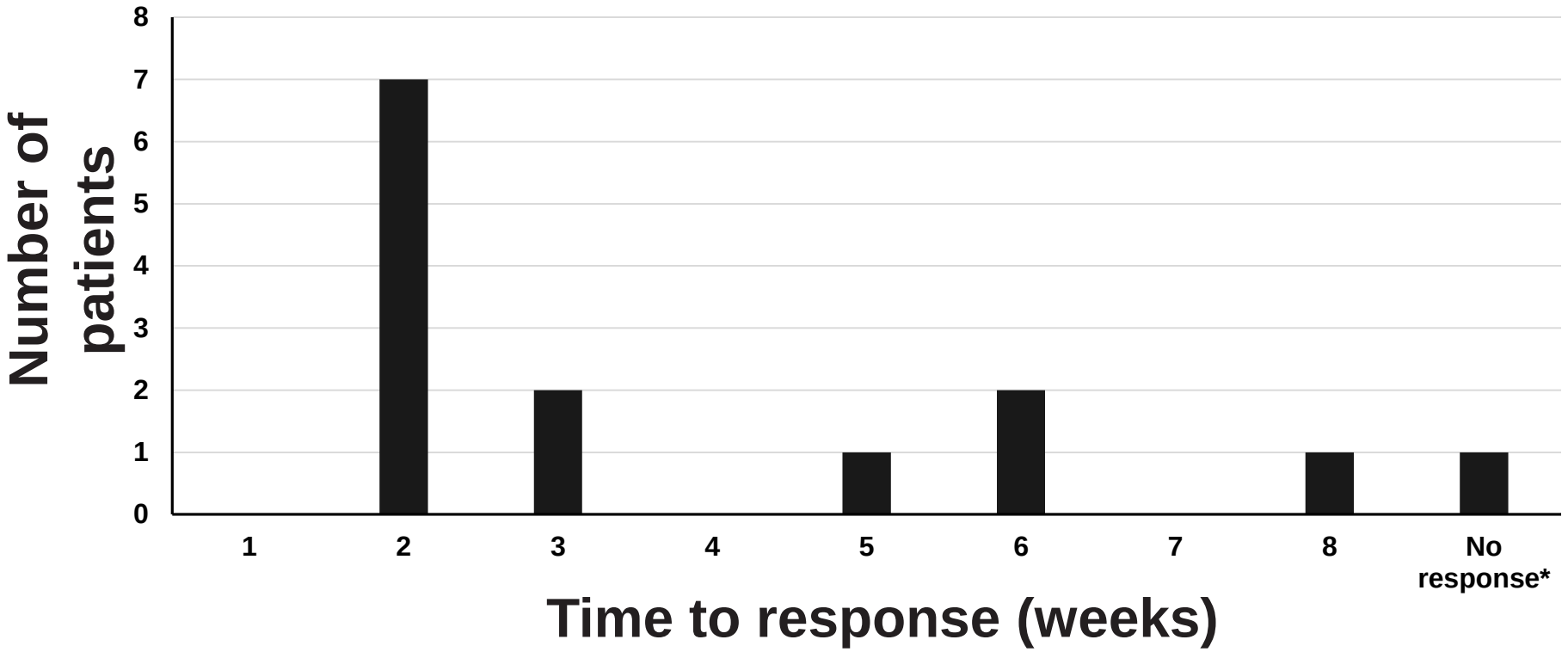
Change in QoL (SADS)



8 of 14 patients† (57%) experienced an improvement in QoL from SADS C to SADS A with DFK treatment

*Patients 6 and 14 experienced no SADS response after 6 and 4 weeks on treatment, respectively. †No SADS data available for Patient 7.
DFK, difelikefalin; QoL, quality of life; SADS, Self-Assessed Disease Severity.

Time to response



- 9 of 14 patients† (64%) responded to DFK within 2–3 weeks

*Patient 14 experienced no response after 4 weeks on treatment. †No data available for Patient 7.
DFK, difelikefalin.

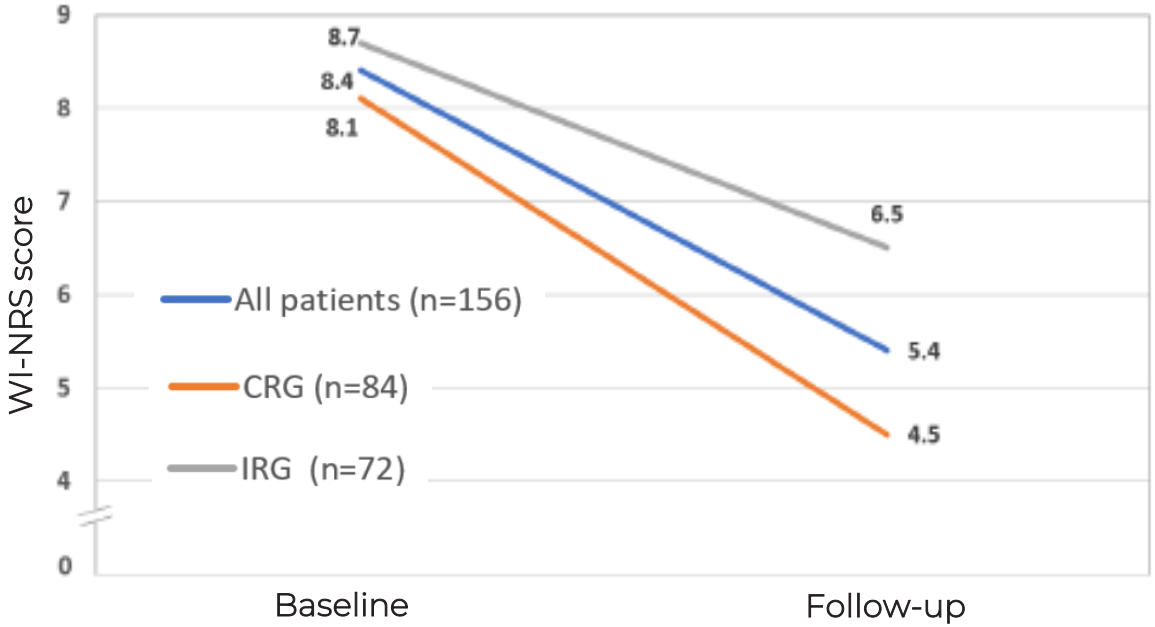
AEs reported during DFK treatment

Patient	AEs
1	None
2	None
3	Severe diarrhoea, dizziness
4	None
5	Death (lung cancer)
6	Death (sepsis)
7	Severe headache (migraine)
8	None
9	Headache, dizziness
10	None
11	None
12	None
13	None
14	None
15	Fatigue

AE, adverse event; DFK, difelikefalin.

Difelikefalin reduced WI-NRS scores in a real-world study of a US cohort

Change in WI-NRS by group*



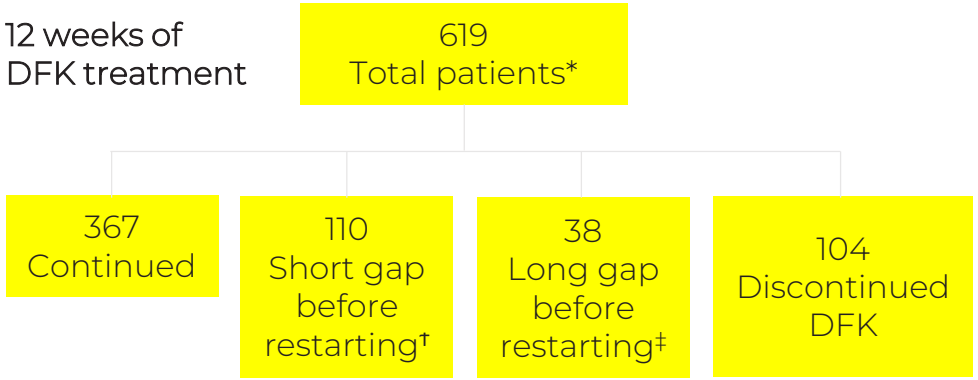
Occurrence of AEs among all patients before and after difelikefalin administration

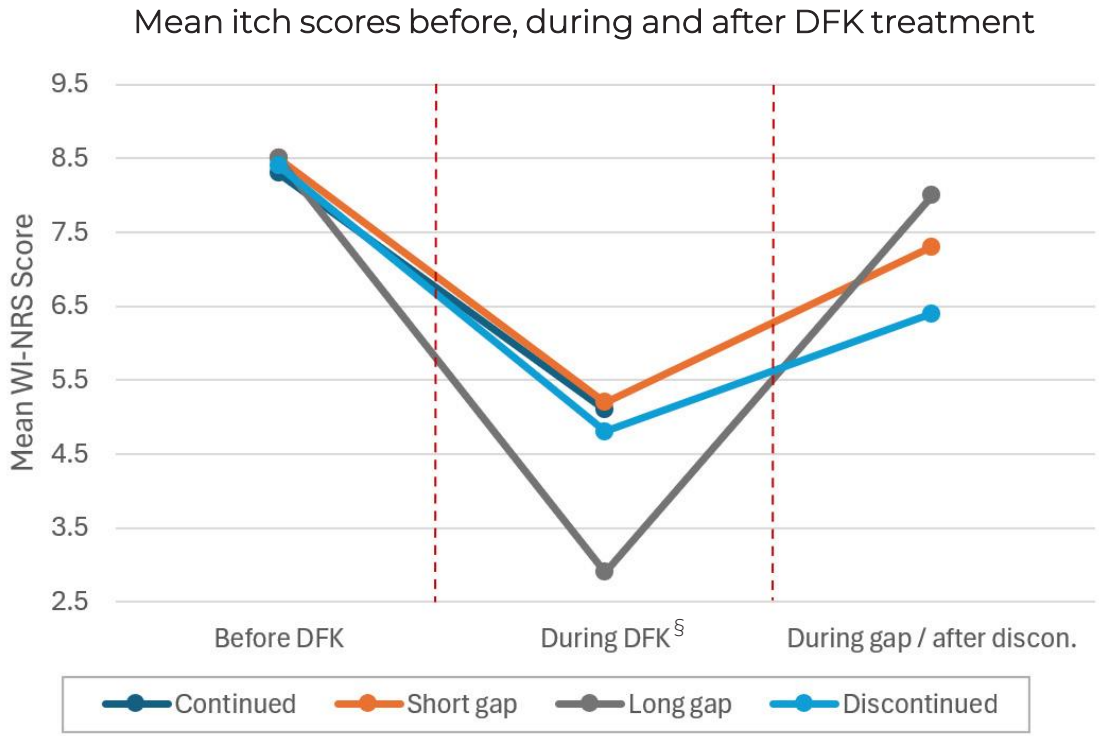
AEs	All patients (n=715)		
	Before DKF (n treatments=27,705)	After DKF (n treatments=225,141)	P value
Nausea	234 (0.8%)	215 (0.9%)	0.8486
Diarrhoea	157 (0.6%)	162 (0.6%)	0.2297
Vomiting	25 (0.09%)	34 (0.1%)	0.1168
Headache	51 (0.2%)	54 (0.2%)	0.4122
Dizziness	26 (0.09%)	48 (0.2%)	0.0027
Trouble walking	0 (0%)	0 (0%)	-
Hyperkalaemia	558 (2.0%)	650 (02.6%)	0.0001

- Experience of difelikefalin in a large dialysis organisation in the USA is consistent with experience in Europe and in clinical trials
- At 12 weeks, there was a significant improvement in WI-NRS scores (P<0.0001) and the rates of documented AEs overall were very low
- The CRG experienced a greater reduction in WI-NRS score with difelikefalin than the IRG

*Patients who received 30+ difelikfalin administrations within 74–84 days were classified as the CRG, while patients with fewer administrations were the IRG.
AE, adverse event; CRG, complete regimen group; IRG, incomplete regiment group; USA, United States of America; WI-NRS, worst-itch numerical rating scale.
Ruessmann D, et al. ASN 2023; Abstract and poster FR-PO425.

Reduction in itch while receiving Difelikefalin: long-term experience from a large dialysis organization in the USA



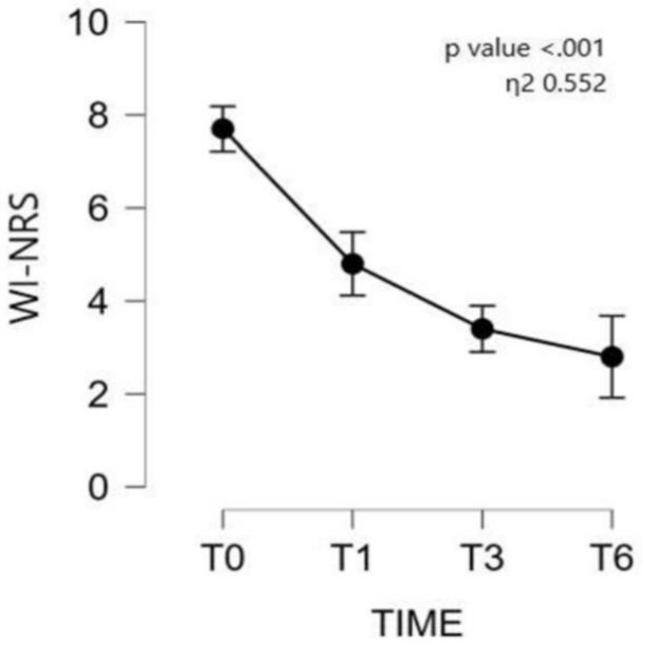


All groups experienced itch reduction while receiving difelikefalin, however itch scores increased in all groups after pausing or discontinuing difelikefalin

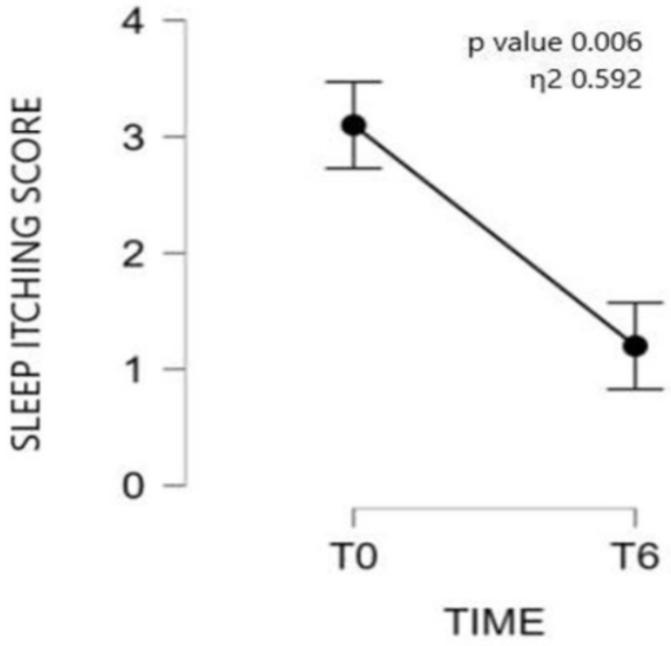
*Haemodialysis patients completed ≥1 WI-NRS assessment during the 90 days before DFK treatment start and one during treatment and received ≥30 doses of DFK during the first 12 weeks; †Paused treatment for 14–44 days then restarted DFK; ‡Paused treatment for >44 days then restarted DFK; §Patients must have received DFK for at least 7 days and up to discontinuation + 7 days to be considered "during DFK".
DFK, difelikefalin; WI-NRS, worst-itch numerical rating scale.
Lasky RA, et al. ASN 2024; Poster #TH-PO1191.

Experience from Italy indicates that Difelikefalin significantly reduces the intensity of itch

Itching trend during DFK treatment (n=19)



Scale of itching discomfort during sleep (n=19)



A significant decrease (P<0.001, η2 0.552) in the intensity of itching, most noticeable in the first month, was recorded .
A significant and lasting positive effect of difelikefalin on sleep quality (P=0.006, η2 0.592) was demonstrated

Di Giovanni M, et al. ERA 2024; Poster #2153.

Guideline recommendations Difelikefalin

DFK
Guideline / treatment recommendation overview

Drug	Society	Geography	Date	comment
DFK	AWMF	Germany	05/13/2022	S2-guidelines (are currently beeing updated)
	Algorithm Agrawal et.al	US	2022	
	Canadian J of kidney Health Rigato et al, endorsed by Canadian society of nephrology	Canada	2024	
	Local sponsored publication, no DGFN endorsement yet	Germany	2023	
	CKD-aP working group, endorsed by the Spanish society of nephrology	Spain	2024	
	Algorithm by the Austria Society of nephrology	Austria	13.07.23	
	CKD-aP working group, endorsed by the spanish society of nephrology	France		
	KDIGO		• 2023 R Mehrotra et al.: Dialysis symptom burden: a KDIGO conference report • Recognizing and adressing symptom burden in dialysis • ANNA Sept 27th 2022 submitted • PRO summit Dec 2024 submitted	We engaged with a KDIGO KoL and a nursing workshops in US and EU to point out the importance on symptoms in dialysis patients, two publications were issued , a third one is in progress, however KDIGO does not issue dialysis guidelines as to yet

In conclusion

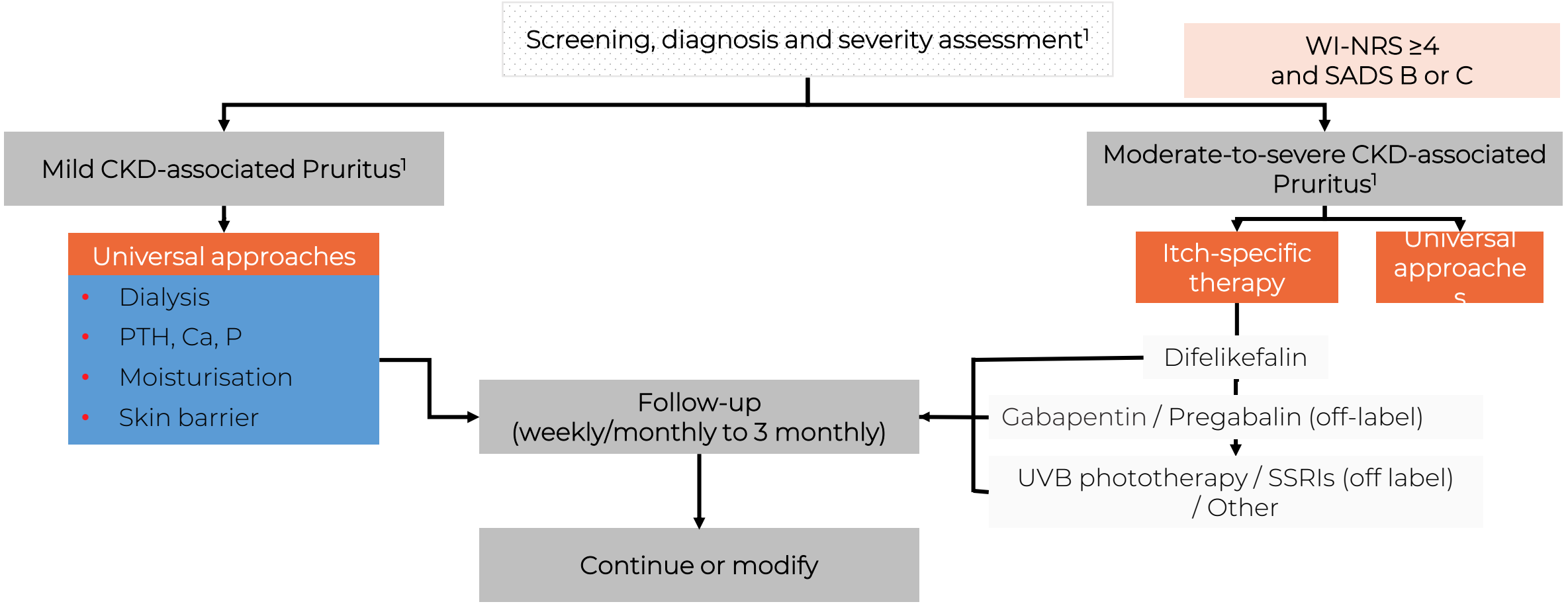
Alleviating the burden of CKD-associated Pruritus requires proactive identification of patients who suffer from it

Proactive assessment: 3 pillars

1	Identification of **pruritus**	• **Do you itch?** (every 3 months) • Exclusion of potential alternative causes
2	Assessment of **pruritus intensity**	• Use of a **single question:** ➢ ***Worst-Itch Numerical Rating Scale (WI-NRS)***
3	Understanding impact on patient **quality of life**	• Assess impact on sleep, work & social life, mood ➢ ***Self-assessed disease severity (SADS)***

- Sukul N, et al. Kidney Med 2020;42–53; Davison SN, et al. Kidney Int 2015;88:447–59; Phan NC, et al. Acta Derm Venereol 2012;92:502–7; Agarwal R, et al. Clin Kidney J 2023;16:30–40.

Treatment Algorithm for CKD-AP



Therapeutic approach should consider patient goals and promote 'life participation'[2]

Ca, calcium; P, phosphorous; PTH, parathyroid hormone; SADS, self-assessed disease severity; SSRI, selective serotonin reuptake inhibitor; UVB, ultraviolet B; WI-NRS, worst itch numerical rating scale

Take home msg

- CKD-associated Pruritus is **a condition with intense symptoms that markedly impair the QoL** of patients with CKD undergoing HD that can persist for several **years** in many patients
- Patients with severe pruritus have **worse medical outcomes**, including increased risk of **mortality**
- CKD-aP is **under-recognised** by HCPs and **under-reported** by patients

Take home msg

- A range of agents are used to manage CKD-aP, however, there are no widely approved therapies.
- Antihistamines **did not** demonstrate effectiveness in CKD-aP
- **Gabapentinoids** may be used to treat Pruritus but have significant **side effects** in HD patients
- **Difelikefalin**, a KOR agonist, has been **approved** for the treatment of CKD-aP
- Other new treatments for CKD-aP are in development

THANK YOU

Questions?