# Cara Therapeutics

## CORPORATE PRESENTATION

MAY 2022

CARA™ THERAPEUTICS

# Forward Looking Statements

Statements contained in this presentation regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of these forward-looking statements include statements concerning the Company's ability to successfully commercialize KORSUVA injection and Kapruvia, planned future regulatory submissions and potential future regulatory approvals, the Company's ability to obtain and maintain coverage and adequate reimbursement for KORSUVA injection, the performance of our commercial partners, including Vifor Pharma, expected timing of the initiation, enrollment and data readouts from the Company's planned and ongoing clinical trials, the potential results of ongoing clinical trials, timing of future regulatory and development milestones for the Company's product candidates, the potential for the Company's product candidates to be alternatives in the therapeutic areas investigated, the size and growth of the potential markets for pruritus management, the Company's expected cash reach, and the potential impact of COVID-19 on the Company's clinical development and regulatory timelines and plans. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Risks are described more fully in Cara Therapeutics' filings with the Securities and Exchange Commission, including the "Risk Factors" section of the Company's Annual Report on Form 10-K for the year ending December 31, 2021 and its other documents subsequently filed with or furnished to the Securities and Exchange Commission. All forward-looking statements contained in this presentation speak only as of the date on which they were made. Cara Therapeutics undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

CARA™ THERAPEUTICS

# OUR MISSION:

**Transform the way pruritus is treated to bring quality to the lives of those who suffer.**

# Millions of US patients could benefit from a chronic pruritus therapy

| | | Estimated US Addressable Pruritis Population |
|---|---|---|
| SYSTEMIC | HD-Dependent Chronic Kidney Disease (CKD)[1-2] | 200K |
| | Non-Dialysis Dependent CKD (Stage 4-5)[3-7] | 300K |
| | Chronic Liver Disease[8-12] | 3M |
| DERMATOLOGICAL | Atopic Dermatitis[13-15] | 12M |
| NEUROLOGICAL | Notalgia Paresthetica[16] | 1M |

1..National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease. 2. Pisoni et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrology Dialysis Transplantation (2006); 21(12): 3495-3505. 3. Centers for Disease Control and Prevention https://nccd.cdc.gov/ckd/detail.aspx?Qnum=Q372. 4. DataMonitor 5. States Renal Data System https://adr.usrds.org/2020/chronic-kidney-disease/1-ckd-in-the-general-population. 6. Wong SJY et al. Decisions about Renal Replacement Therapy in Patients with Advanced Kidney Disease in the US Department of Veterans Affairs, 2000–2011. Clin Journal of Am Soc Neprol. 2016. 11(10): 1825-1833. 7. Sukul N et al. Pruritus and patient reported outcomes in non-dialysis CKD. Clin J Am Soc Neprhol 2019. 673-681. 8.Centers for Disease Control and Prevention https://www.cdc.gov/nchs/fastats/liver-disease.htm 9. Odea S et al. Prevalence of pruritus in patients with chronic liver disease: A multicenter study. Hepatology Research. 2018. 28(3): E252-E262. 10. Fujino H et al. Pruritus in patients with chronic liver disease and serum autotaxin levels in patients with primary biliary cholangitis. BMC Gastroenterology. 2019. 19:169. 11. Yoshikawa et al. Pruritus is common in patients with chronic liver disease and is improved by nalfurafine hydrochloride. Scientific Reports. 2021. 11:3015. 12. Data on file. 13. National Eczema Assocaition. https://nationaleczema.org/eczema/types-of-eczema/atopic-dermatitis/ 14. DRG Analysis. 15. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? Clin Rev Allergy Immunol. (2016) 51:263–92. 16. Data on file.



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# Cara is well positioned to seize the opportunity and drive significant immediate and future growth

**First-and-only FDA-approved treatment for CKD-aP in HD**

**Robust R&D engine with multiple pipeline indications**

**Significant market opportunity & strong financial foundation to deliver growth strategy**



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# KORSUVA Injection is poised for rapid uptake

NOW APPROVED
& COMING SOON

KORSUVA™
(difelikefalin) Injection

**FIRST-AND-ONLY PRODUCT APPROVED FOR CKD-aP in HD**

**STRONG COMMERCIAL POSITIONING & PARTNERSHIP**

**FIRST INNOVATIVE PRODUCT TO RECEIVE TDAPA**

 Korsuva is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease (CKD-aP) in adults undergoing hemodialysis (HD). Limitations of Use Korsuva has not been studied in patients on peritoneal dialysis and is not recommended for use in this population

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# KORSUVA Injection addresses significant unmet need in US CKD-aP hemodialysis market

**~500K**

**Patients on hemodialysis[1-2]**

**40%**

**With moderate-severe pruritus[2]**

**~200K**

**Addressable Market**


1. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease.
2. URSDS. https://adr.usrds.org/2021/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities
3. Pisoni et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrology Dialysis Transplantation (2006); 21(12): 3495-3505.




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# Concentrated dialysis market dynamics can facilitate rapid uptake

## 2 Key Providers

- **Fresenius Medical Care and DaVita have a combined market share of ~75%[1]**

FRESENIUS MEDICAL CARE

DaVita® Kidney Care

## 1 Major Payer

- **Medicare covers ~80% of CKD-HD patients[2]**
- **2nd drug in TDAPA**
  - 1st drug Parsabiv - $1.4B revenue in 3-yr period[3]

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

Medicare

1. https://healthcareappraisers.com/2020-outlook-dialysis-clinics-and-esrd/
2. https://adr.usrds.org/2020/end-stage-renal-disease/9-healthcare-expenditures-for-persons-with-esrd
3. Amgen Annual Report 2018, 2019, 2020



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# Partnership with Vifor Pharma can maximize launch potential

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VIFOR PHARMA

- Leading commercial nephrology organization with turnkey infrastructure, including 100+ sales FTEs
- Strong relationships with US nephrology offices and dialysis centers, including joint venture with Fresenius Medical Care
- Contractual economics bring near term profitability for KORSUVA Injection

# KORSUVA injection launch commenced in April 2022 and is progressing well

**KORSUVA injection is available to order at all dialysis organizations nationwide**

**Healthcare Providers and Patients are being educated and activated**

**Product reimbursement via TDAPA is in place**



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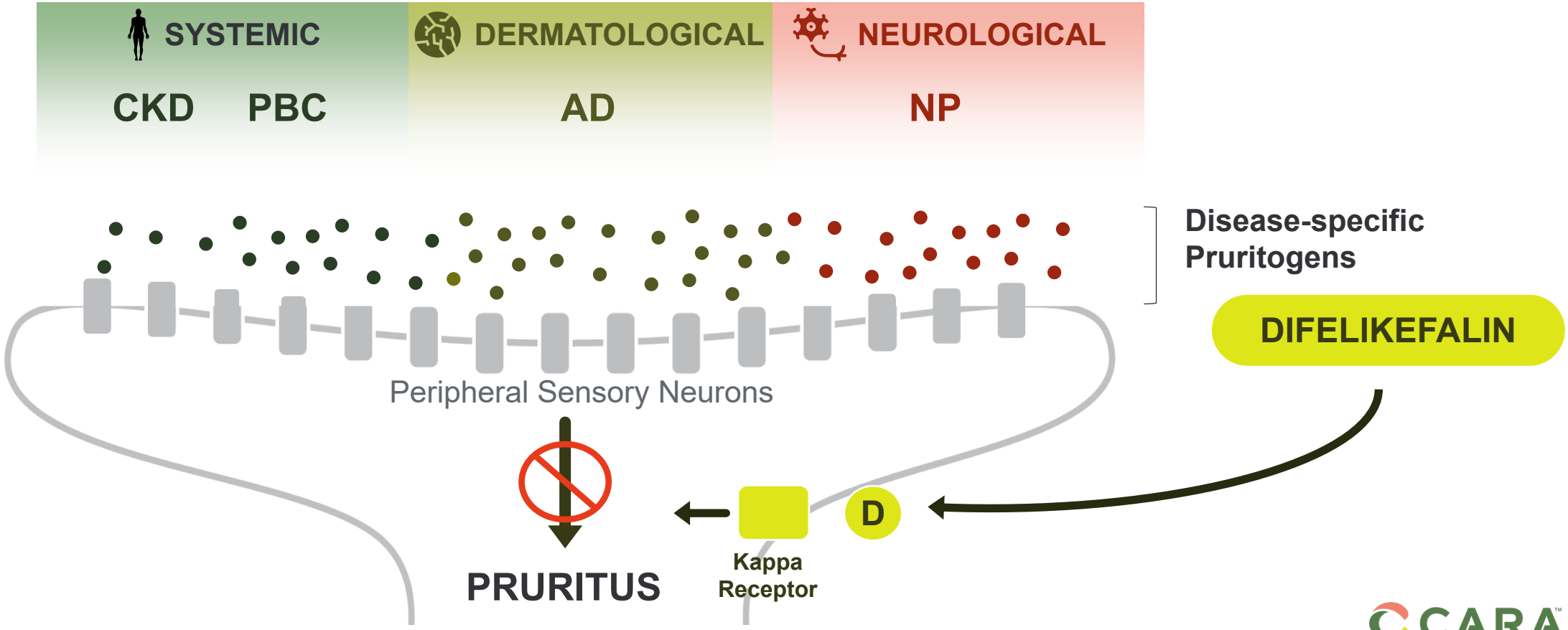
# Difelikefalin MOA has potentially broad application

## Difelikefalin blocks itch response agnostic of itch trigger




 | Adapted from Pflugers Arch . 2013 December ; 465(12): doi:10.1007/s00424-013-1284-2.

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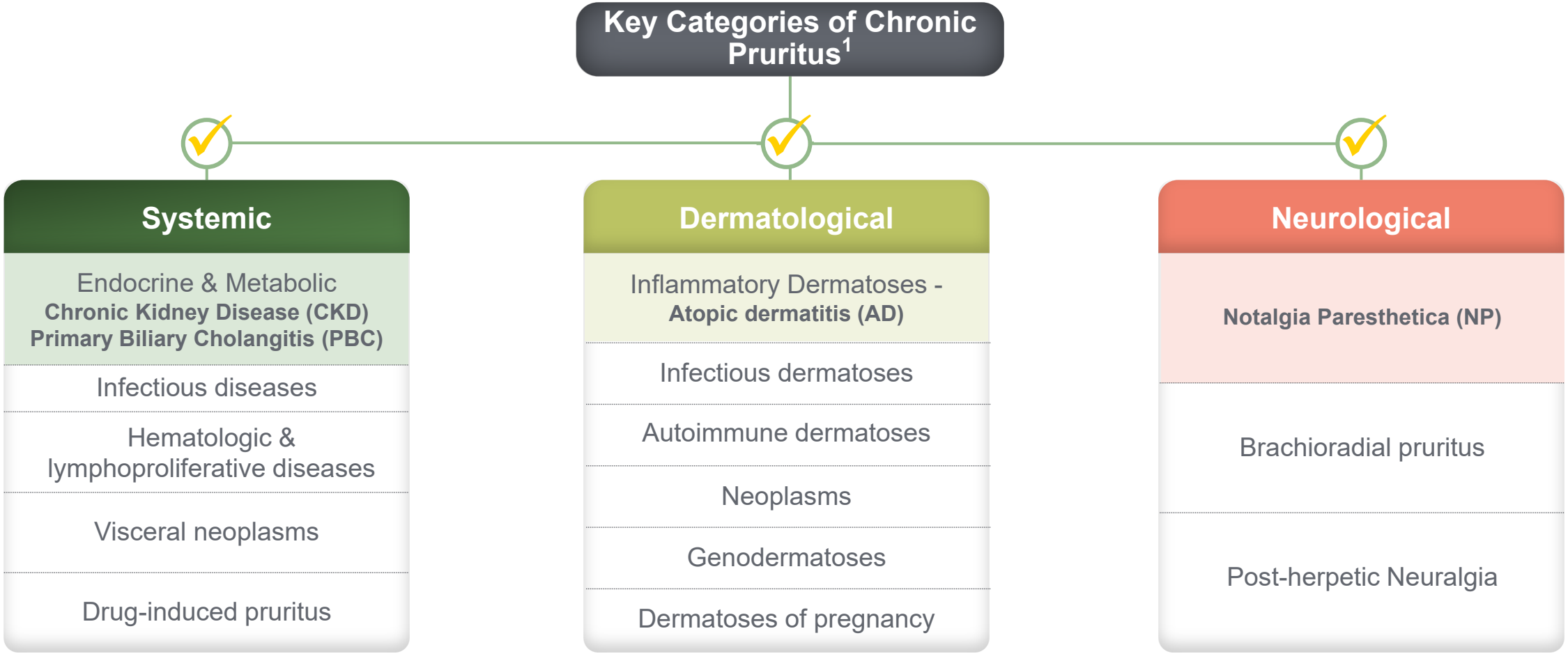
# Oral difelikefalin has potential for long-term growth






1. Matterne U. et al. Prevalence, correlates and characteristics of chronic pruritus: a population-based crosssectional study. Acta Derm Venereol. 2011;91(6):674-9.2. Matterne U et al. Incidence and determinants of chronic pruritus: a population-based cohort study. Acta Derm Venereol. 2013;93(5):532-7. 3. Adapted from: Stander S. et al. Clinical classification of itch: a position paper of the international forum for the study of itch. Acta Derm Venereol 2007. 87: 291-294.

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# Advancing our late-stage pipeline in multiple indications

| Program | Indication | STAGE OF DEVELOPMENT | | | | Commercial Rights (ex-Japan and S. Korea)^ |
|---|---|---|---|---|---|---|
| | | Phase 1 | Phase 2 | Phase 3 | Approved | |
| **KORSUVA™ Injection** | Pruritus HD-CKD | | | | | US- Vifor* EU/Other- VFMCRP# |
| **Oral difelikefalin** | Pruritus NDD-CKD (stages IV-V) | | | | | Cara |
| **Oral difelikefalin** | Pruritus in Atopic Dermatitis | | | | | Cara |
| **Oral difelikefalin** | Pruritus in NP | | | | | Cara |
| **Oral difelikefalin** | Pruritus PBC | | | | | Cara |



^ Commercialization rights to difelikefalin in defined indications - Japan: Maruishi Pharmaceutical Co, LTD; South Korea: Chong Kun Dang Pharmaceuticals. # Vifor Fresenius Medical Care Renal Pharma (VFMCRP) and Cara have rights to promote in Fresenius Medical Care dialysis clinics in the US under a profit share agreement. * Vifor has commercial rights in Non-US Fresenius clinics under a profit-share arrangement. HD CKD-aP: Hemodialysis Chronic Kidney Disease-associated Pruritus; NDD-CKD-aP: Non-Dialysis Dependent Chronic Kidney Disease associated Pruritus

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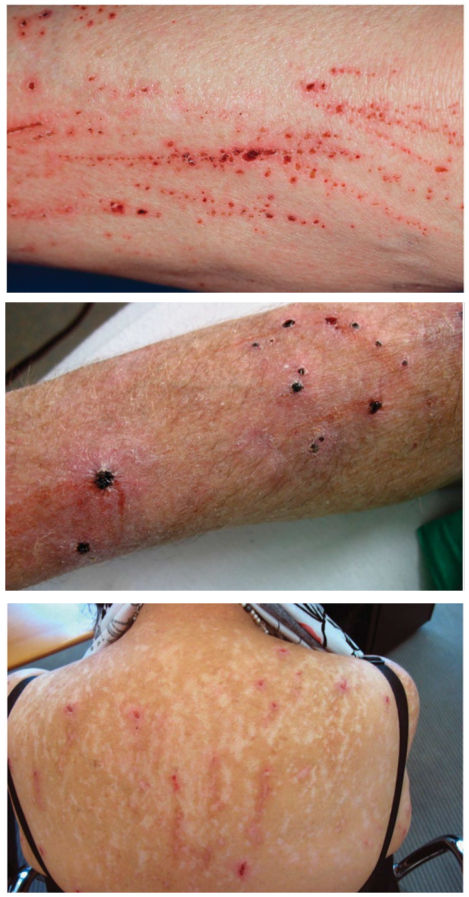
# Oral difelikefalin: expanding reach in non-dialysis CKD market

NDD-CKD



**Pruritis control is a significant unmet need among non-dialysis CKD patients[1]**

**There are no FDA-approved therapies and current anti-pruritic approaches are inadequate[1]**

**Approximately 1.2 million US patients have advanced (stage 4-5) non-dialysis CKD[2-5]**

**~30% advanced non-dialysis CKD patients experience moderate to severe pruritus[6]**



1. Makar M et al. Chronic kidney disease associated pruritus: a review. Kidney Blood Press Res 2021. 46:659-669. 2. Centers for Disease Control and Prevention https://nccd.cdc.gov/ckd/detail.aspx?Qnum=Q372. 3. DataMonitor 4. States Renal Data System https://adr.usrds.org/2020/chronic-kidney-disease/1-ckd-in-the-general-population. 5. Wong SJY et al. Decisions about Renal Replacement Therapy in Patients with Advanced Kidney Disease in the US Department of Veterans Affairs, 2000–2011. Clin Journal of Am Soc Neprol. 2016. 11(10): 1825-1833. 6. Sukul N et al. Pruritus and patient reported outcomes in non-dialysis CKD. Clin J Am Soc Neprhol 2019. 673-681. 7. Mettang T and Kremer AE. Uremic Pruritus. Kidney International. 2015. 87:685-691

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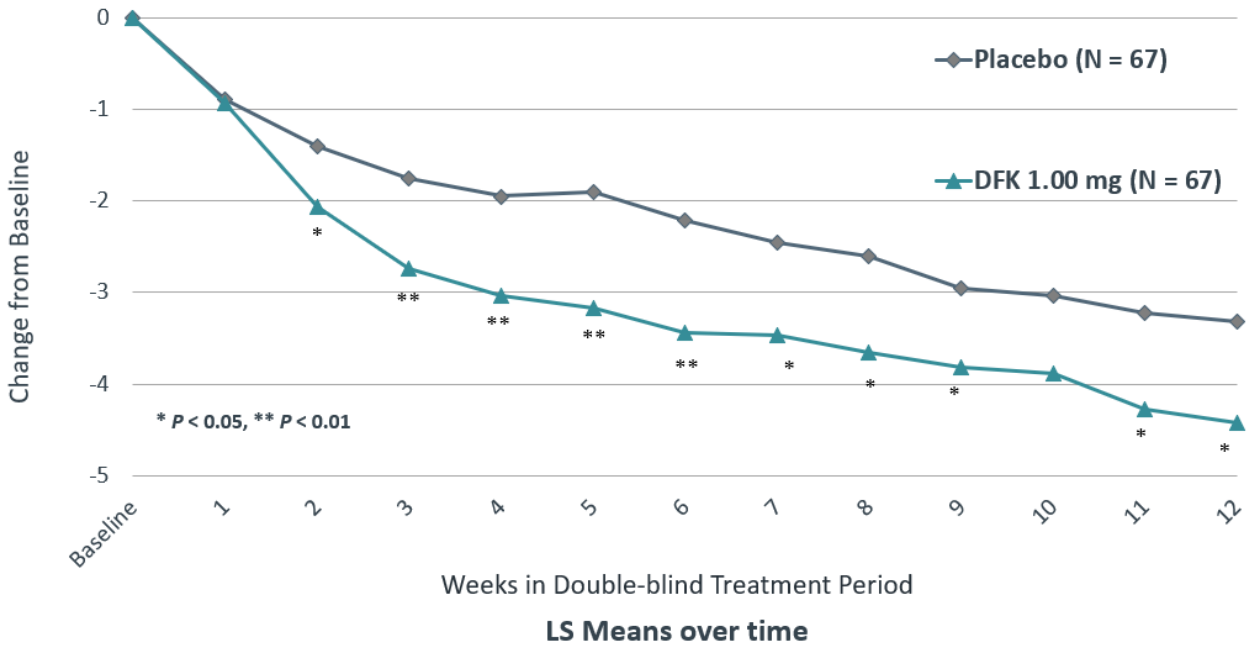
# Phase 2 data in provides path forward into Phase 3 NDD-CKD

NDD-CKD

Primary Endpoint
Change From Baseline in WI-NRS Over Time




- ✓ **Significant difference achieved between 1mg oral difelikefalin and placebo in WI-NRS score at Week 12**
- ✓ **Generally well-tolerated with safety profile consistent with clinical development program**
- ✓ **Phase 2 findings and EOP2 discussion with FDA established dose and patient population in Advanced CKD for Phase 3 trial**



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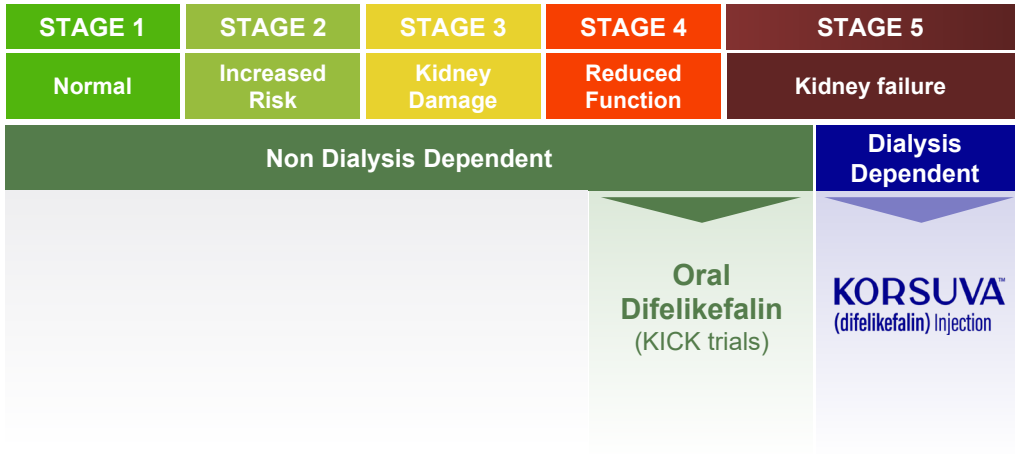
NDD-CKD

# KICK 1 & KICK 2: Patient Population

## STUDY PATIENT POPULATION

- Adults with advanced stage 4 and 5 CKD
- Chronic Pruritus for at least 6 months prior to screening
- Moderate to Severe Pruritus at Baseline (WI-NRS ≥ 5)
- Allowed to be on stable treatment for itch including antihistamines and gabapentinoids



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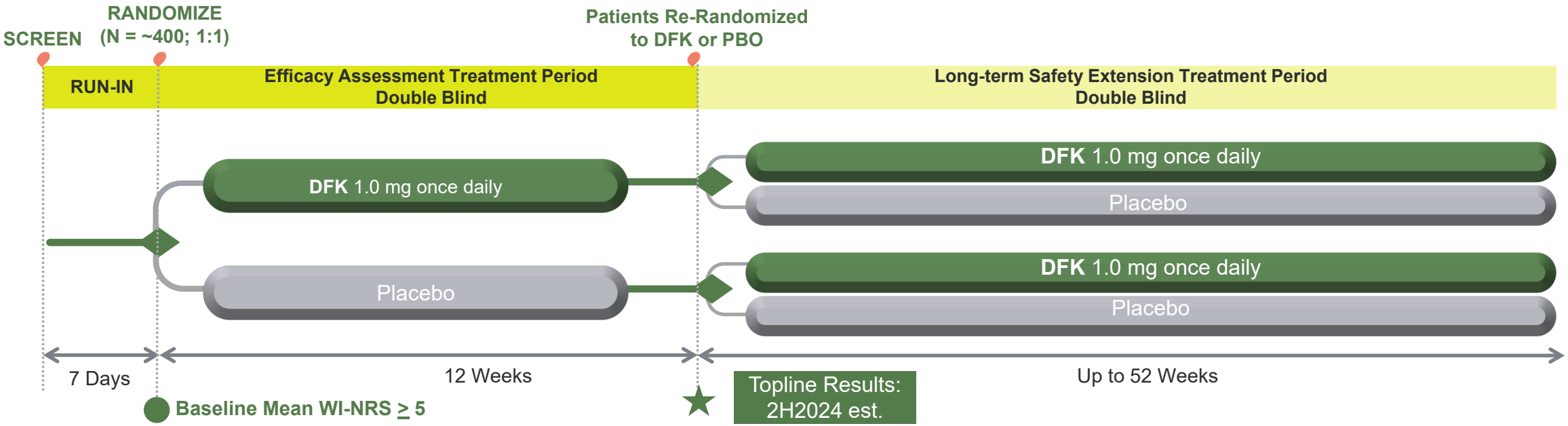
NDD-CKD

# KICK 1 & KICK 2: Study Design




**PRIMARY ENDPOINT**

- **% of subjects with ≥4-point improvement from baseline in WI-NRS score at Week 12**

**ADDITIONAL ENDPOINTS**

- Quality of life including sleep
- Safety assessments

 *KICK1 US sites only, KICK 2 US and ex-US sites*

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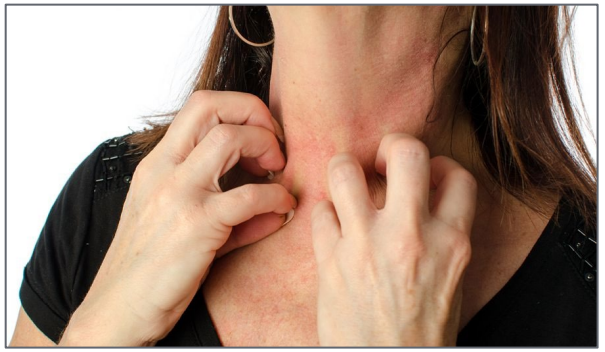
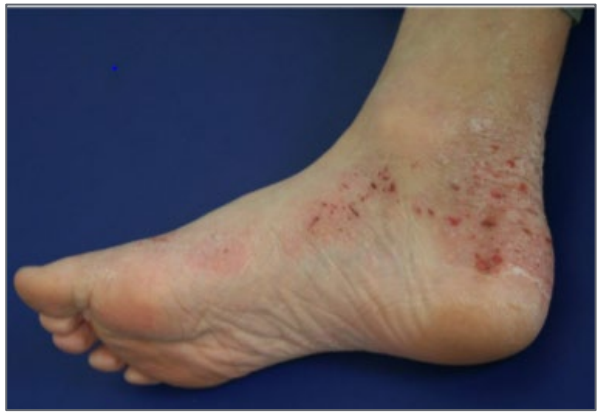
# Oral difelikefalin: potential to address significant need for an oral antipruritic in atopic dermatitis (AD)

AD





**Pruritus is a hallmark of AD, often called “the itch that rashes”[1]**

**Itch is considered the most burdensome AD symptom by patients,[2] strongly and negatively impacts quality of life[3]**

**~12M diagnosed patients that experience chronic pruritus[4-6]**

**Targeting pruritus in AD remains unmet need**



1. Correale CE et al. Atopic dermatitis: a review of diagnosis and treatment. Am Fam Physician. 1999. 60(4):1191-1198 2. Silverberg JI et al. Patient burden and quality of life in atopic dermatitis in US adults. Annals of Allergy, Asthma, and Immunology (2018). 121(3): 340-347 3. Legat FJ. Itch in atopic dermatitis – what is new? Front Med (Lausanne) 2021. 8:644760. 4. National Eczema Assocaition. https://nationaleczema.org/eczema/types-of-eczema/atopic-dermatitis/ 5. DRG Analysis. 6. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? *Clin Rev Allergy Immunol.* (2016) 51:263–92. 7. Lipman et al. Current clinical options for the management of itch in atopic dermatitis. Clin Cosmet Investig Dermatol. 2021. 14:959-969 8. Kapur S et al. Atopic dermatitis. Allergy Asthma and Clin Immunol. 2018. 14(Suppl2):52.

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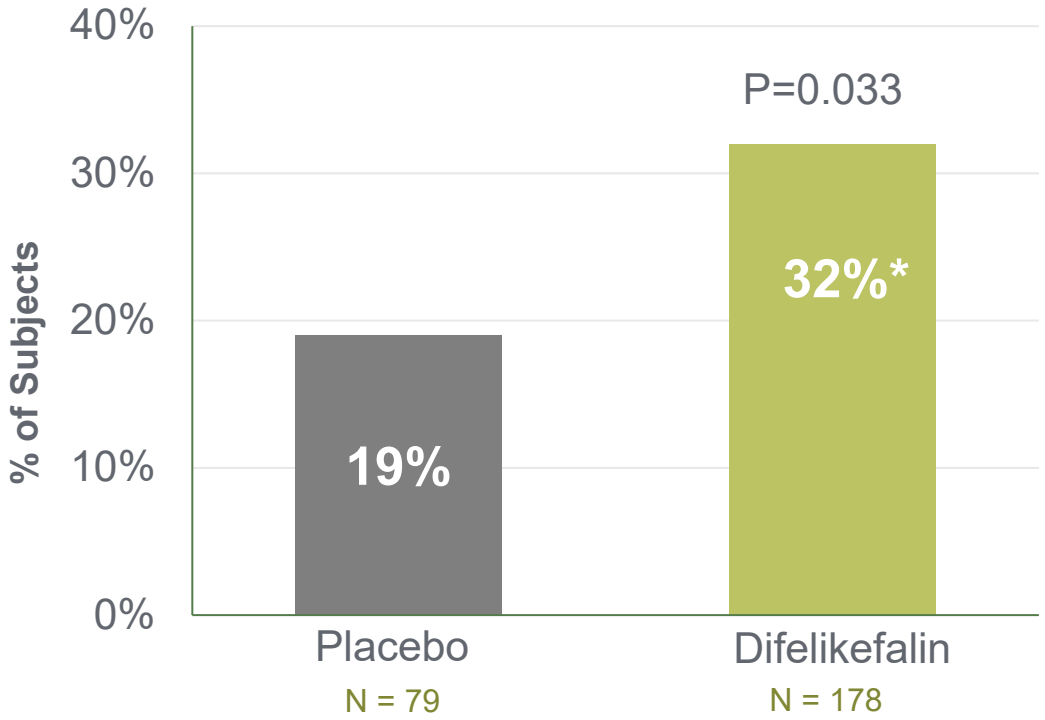
# KARE STUDY: Phase 2 data in Atopic Dermatitis (AD)

**Population: Mild to Moderate AD** (BSA <10)
4-point Responder Analysis at Week 12




- All doses performed similarly (.25mg, .50mg, 1.0mg) versus PBO

- ✓ **Anti-pruritic effect started at week 1 and was sustained through week 12**
- ✓ **Statistical significance achieved for the registration endpoint (4-point responder) in mild-to-moderate AD population**
- ✓ **The drug was generally well tolerated**

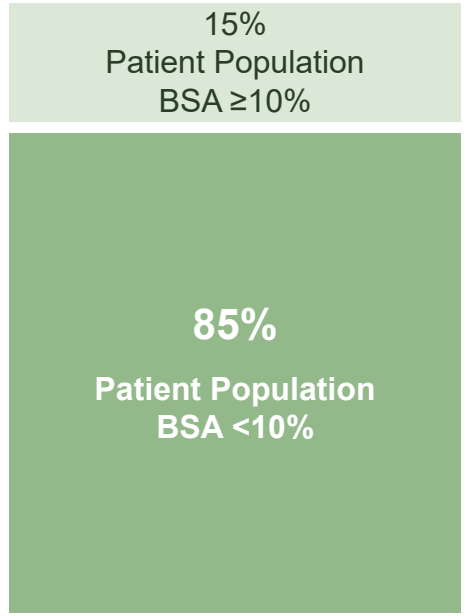
AD

# KIND 1 & KIND 2: Patient Population

## STUDY PATIENT POPULATION

- Adults with AD-related pruritus not adequately controlled by topical therapy alone
- Chronic AD-related Pruritus ≥6 weeks
- Moderate to Severe Pruritus at Baseline (I-NRS ≥ 5)
- Mild to severe Atopic Dermatitis:
  - IGA ≥ 2, BSA ≤20%
- Patients need to be washed out of any medication that may impact itch and/or AD prior to screening
- Stratification to BSA <10% and ≥10%

## Target Enrollment



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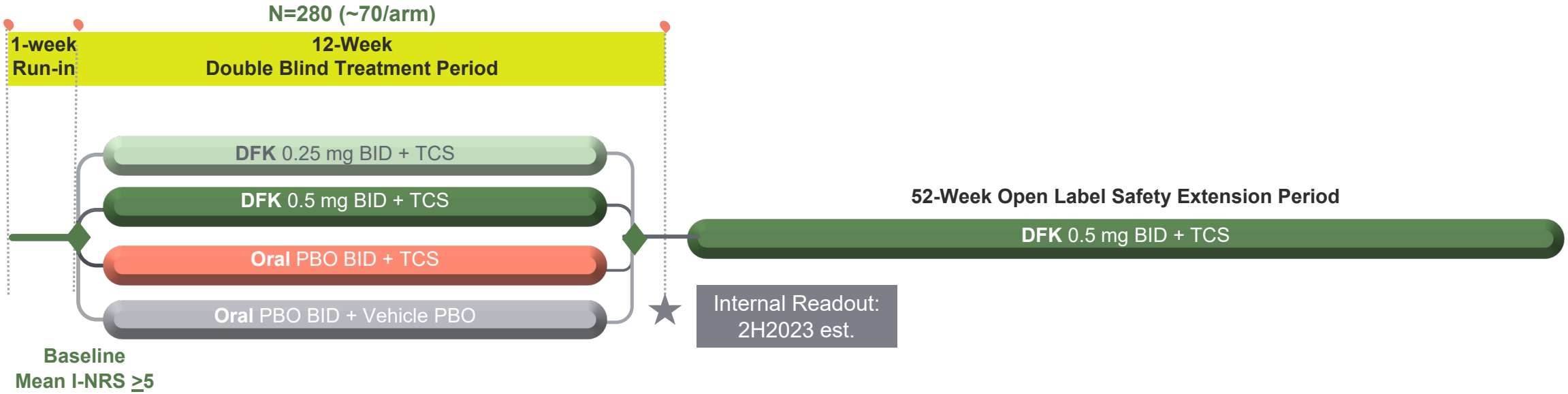
AD

# KIND 1 Part A: Study Design




**CRITERIA**

- % of subjects with ≥4-point improvement from baseline in WI-NRS score at Week 12
- Safety assessments

**INFORMATION**

- Dose
- Sample size

 *KIND 1 Part A will include sites in North America only*

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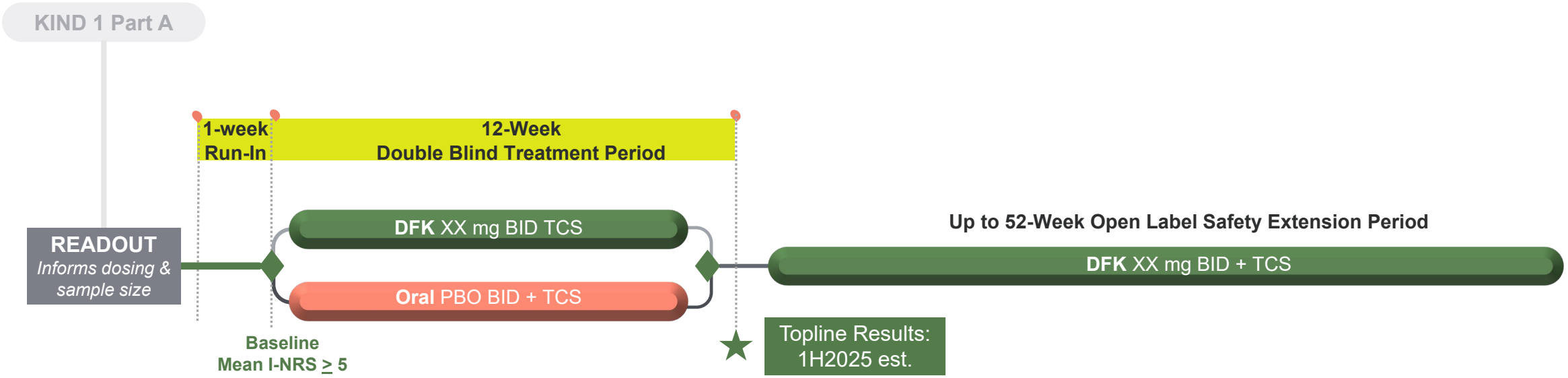
AD

# KIND 1 Part B & KIND 2: Study Design




**PRIMARY ENDPOINT**

- **% of subjects with ≥4-point improvement from baseline in WI-NRS score at Week 12**

**ADDITIONAL ENDPOINTS**

- Quality of life including sleep
- Skin assessment
- Safety assessments



*KIND 1 Part B will include sites in North America only, while KIND 2 will include sites in North America and outside of North America*

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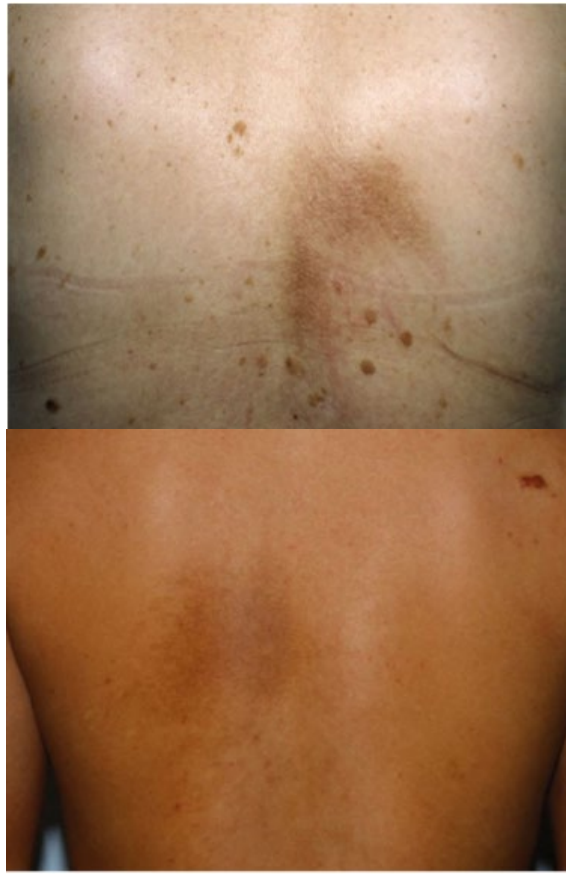
# Oral difelikefalin: potential to address significant need in Notalgia Paresthetica (NP)

NP



**NP is a sensory neuropathic syndrome characterized by chronic pruritus**

**Pruritus is burdensome decreasing quality of life[1]**

**Estimated that 1M patients suffer from NP[2]**

**No FDA-approved treatments**

**Phase 2 Readout Anticipated Q2 2022**



1. Howard M et al. Notalgia paresthetica: a review for dermatologists. Int J of Derm. 2017. 388-392. 2. Data on file.

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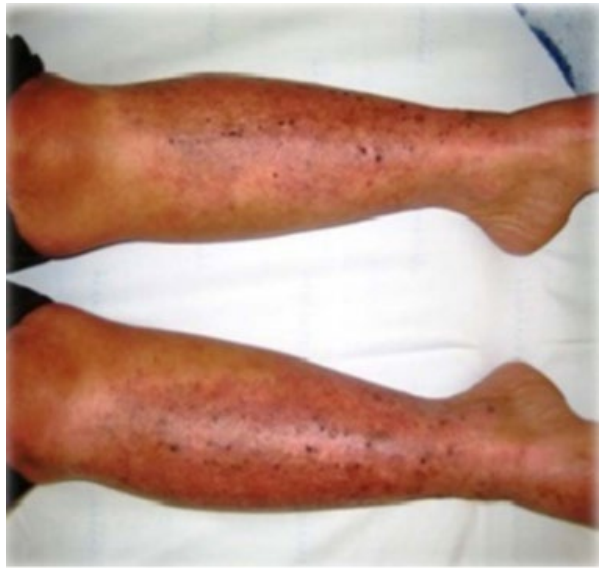
# Oral difelikefalin: potential in pruritus with Primary Biliary Cholangitis (PBC)

PBC



**Pruritus is hallmark symptom of PBC and may be persistent and debilitating[1]**

**Associated with severe fatigue, sleep disturbance, and mental health issues[2]**

**Addressable patient population of ~50K[3-4], with opportunity to establish efficacy in other chronic liver diseases**

**No FDA-approved treatments**

**Phase 2 Readout Anticipated 2H 2022**



1. Carrion AF et al. Understanding and treating pruritus in primary biliary cholangitis. Clin Liver Dis 2018. 22:517-532. 2. Pinheiro NC et al. Refractory pruritus in primary biliary cirrhosis. BMJ Case Rep. 2013. doi:10.1136/bcr-2013-200634 3. Lu M et al. Factors Associated with Prevalence and Treatment of Primary Biliary Cholangitis in United States Health Systems. Clin Gastroenterol Hepatol (2018 Aug);16(8):1333-1341.e6. 4. Trivedi HD et al. Management of Pruritus in Primary Biliary Cholangitis: A Narrative Review. The American Journal of Medicine (2017) 130, 744e1-744e7

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# Strong financial foundation to advance pipeline, enable long-term growth

## Cash runway into 1st half 2024

- Runway does not include potential near term income from KORSUVA Injection profit split or commercial milestones
- Contractual economics bring near term profitability on KORSUVA Injection

## $210M cash position Mar 31, 2022

- 54M shares outstanding and no debt
- We do not expect to incur commercial costs related to KORSUVA Injection

## Continued pipeline growth

- We have the resources to continue development of the oral difelikefalin program



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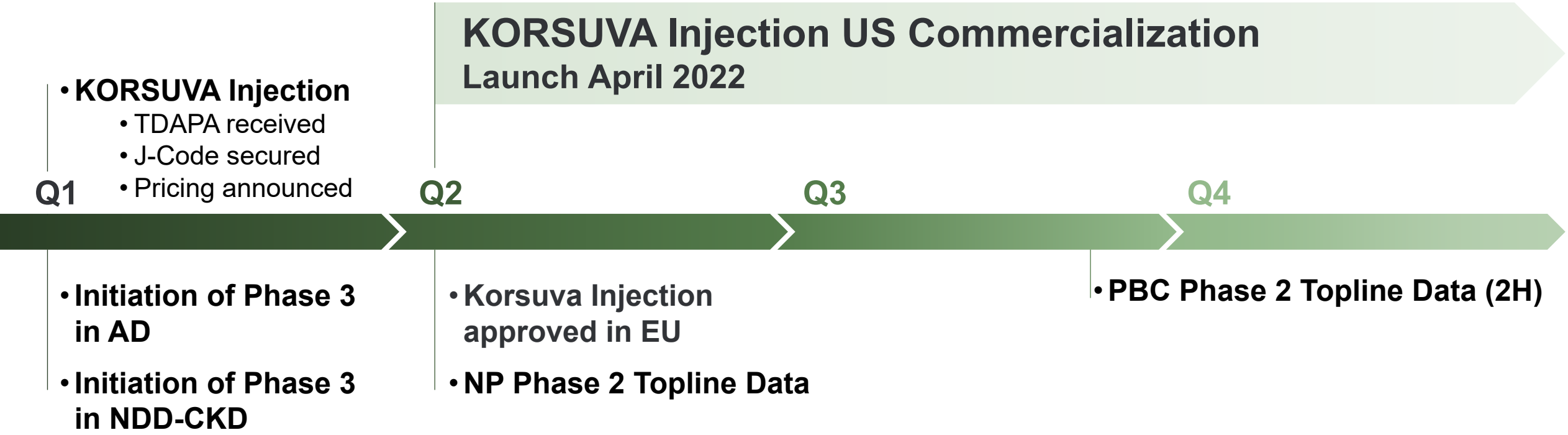
# 2022 Value Catalysts to Drive Long-term Growth*




*Anticipated Timelines



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# THANK YOU