UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 OR 15(d) of The Securities Exchange Act of 1934

Date of Report (Date of earliest event reported) **April 29, 2021**

CARA THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-36279**	**75-3175693**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

4 Stamford Plaza **107 Elm Street, 9th Floor** **Stamford, Connecticut**	**06902**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code **(203) 406-3700**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2.):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, par value $0.001 per share	CARA	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐.

Item 7.01. Regulation FD Disclosure.

On April 29, 2021, Cara Therapeutics, Inc. (the "Company") issued a press release (the "Press Release") announcing topline results from its KARE Phase 2 dose-ranging clinical trial of Oral KORSUVA™ (difelikefalin tablets) for the treatment of moderate-to-severe pruritus in mild-to-severe atopic dermatitis ("AD") patients. The Company will hold a conference call to discuss the results at 8:00 a.m. ET on April 29, 2021. A copy of the Press Release and the presentation to be discussed on the conference call are furnished as Exhibit 99.1 and Exhibit 99.2, respectively, to this Current Report on Form 8-K and incorporated herein by reference.

The information furnished under this Item 7.01, including Exhibit 99.1 and Exhibit 99.2, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or subject to the liabilities of that section. The information shall not be deemed incorporated by reference into any other filing with the Securities and Exchange Commission made by the Company, regardless of any general incorporation language in such filing.

Item 8.01. Other Information.

On April 29, 2021, the Company issued the Press Release announcing topline results from its KARE Phase 2 dose-ranging clinical trial of Oral KORSUVA™ (difelikefalin tablets) for the treatment of moderate-to-severe pruritus in mild-to-severe AD patients.

The KARE Phase 2 trial was a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of Oral KORSUVA for moderate-to-severe pruritus in 401 adult subjects with AD. Patients were stratified across treatment groups by disease severity. KARE enrolled 64% of patients characterized as mild-to-moderate (BSA<10%) and 36% falling into the moderate-to-severe category (BSA>10%). Subjects were randomized to three tablet strengths of Oral KORSUVA: 0.25 mg, 0.5 mg and 1 mg taken twice daily (BID) versus placebo for 12 weeks followed by 4 weeks of an active extension phase. A prespecified interim conditional power assessment was conducted after approximately 50% of the originally targeted patient number completed the designated 12-week treatment period. Based on the Independent Data Monitoring Committee's recommendation, the sample size for the 0.5 mg dose and placebo groups was increased by approximately 60%, respectively.

Primary Efficacy Endpoint

- KARE's primary efficacy endpoint was change from baseline in the weekly mean of the daily 24-hour Itch numerical rating scale ("NRS") score at week 12 of the treatment period. Although no dose group met this endpoint, a statistically significant improvement from baseline was evident as early as week 1 for the 1 mg dose group, which was sustained through 75% of the treatment period.

- In a prespecified analysis, a statistically significant change in the primary efficacy endpoint was observed in the mild-to-moderate (BSA<10%) patient population (p=0.036, All doses versus placebo) which was evident at week 1 and sustained through the treatment period.

Key Secondary Endpoint

- The key secondary endpoint for KARE was the assessment of the proportion of patients achieving an improvement from baseline of ≥4 points with respect to the weekly mean of the daily 24-hour Itch NRS score at week 12 (4-point Responder Analysis). No dose group met this endpoint for the ITT population.

- Prespecified analysis by disease severity indicated a statistically significant improvement in the 4-point Responder Analysis in the mild-to-moderate (BSA<10%) patient population with 32% of KORSUVA-treated patients achieving a ≥4 point reduction in NRS at Week 12 versus 19% in the placebo group (p=0.033, All doses versus placebo). A statistically significant improvement was also achieved for the 0.5 mg dose (p=0.046, 0.5 mg versus placebo).

Safety and Tolerability

- Oral KORSUVA was generally well-tolerated across all doses. Overall, the incidence of treatment-emergent adverse events ("AEs") was generally similar across KORSUVA and placebo groups. The most common treatment-emergent AEs reported in >5% of patients in any KORSUVA group and greater than placebo were abdominal pain, nausea, dry mouth, headache, dizziness and hypertension (5/77 patients in 1 mg dose group; 4/5 of patients had documented prior history of hypertension at enrollment).

Item 9.01. **Financial Statements and Exhibits.**

(d) Exhibits

Exhibit No.	**Description**
99.1	Press Release, dated April 29, 2021
99.2	Presentation, dated April 29, 2021
104	Cover page interactive data file (formatted as Inline XBRL)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

CARA THERAPEUTICS, INC.

By: **/s/ THOMAS REILLY**
Thomas Reilly
Chief Financial Officer
(Principal Financial and Accounting Officer)

Date: April 29, 2021

Exhibit 99.1

Cara Therapeutics Announces Topline Results From KARE Phase 2 Dose-Ranging Trial of Oral KORSUVA™ in Atopic Dermatitis Patients with Moderate-to-Severe Pruritus

– Study did not meet Primary Endpoint of worst-itch NRS change from baseline at week 12 or Secondary Endpoint of 4-point responder analysis in the ITT patient population

– Study achieved Primary Endpoint of worst-itch NRS change and Secondary Endpoint of 4-point responder analysis in pre-specified analyses of mild-to-moderate AD patients (64% of ITT patient population)

– Statistically significant improvement in 4-point responder analysis in mild-to-moderate (BSA <10%) AD patients with 32% of KORSUVA-treated patients achieving a $\geq$ 4-point reduction vs. 19% in placebo group (p=0.03)

– KORSUVA was well tolerated at all dose levels

– Company to host conference call today at 8:00 a.m. ET

STAMFORD, Conn., April 29, 2021 – Cara Therapeutics, Inc. (Nasdaq: CARA), a biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pruritus by selectively targeting peripheral kappa opioid receptors, or KORs, today announced topline results from its KARE Phase 2 dose-ranging clinical trial of Oral KORSUVA™ (difelikefalin tablets) for the treatment of moderate-to-severe pruritus in mild-to-severe atopic dermatitis (AD) patients. The trial enrolled 401 patients at multiple clinical sites across the United States

“We are encouraged to have met the expected Phase 3 registration endpoint of a 4-point responder analysis in the mild-to-moderate AD group,” said Joana Goncalves, M.D., Chief Medical Officer at Cara Therapeutics. “We now have a defined patient group and active dose range for Oral KORUSVA in which to design a registration program that we expect to discuss with the FDA in the coming months .”

“The KARE Phase 2 trial demonstrates the unique anti-itch effects of KORSUVA in atopic dermatitis, a highly inflammatory skin disease,” said Dr. Brian Kim, M.D., MTR, FAAD, Co-Director, Center For The Study of Itch And Sensory Disorders, Washington University School of Medicine. “This is novel and promising for a future in which we can treat the central symptom of AD, especially for patients with mild-to-moderate AD who experience severe itch.”

KARE Phase 2 Trial Design and Results

The KARE Phase 2 trial was a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of Oral KORSUVA for moderate-to-severe pruritus in 401 adult subjects with atopic dermatitis. Patients were stratified across treatment groups by disease severity. KARE enrolled 64% of patients characterized as mild-to-moderate (BSA<10%) and 36% falling into the moderate-to-severe category (BSA>10%). Subjects were randomized to three tablet strengths of Oral KORSUVA: 0.25 mg, 0.5 mg and 1 mg taken twice daily (BID) versus placebo for 12 weeks followed by 4 weeks of an active extension phase. A prespecified interim conditional power assessment was conducted after approximately 50% of the originally targeted patient number completed the designated 12-week treatment period. Based on the Independent Data Monitoring Committee's (IDMC) recommendation, the sample size for the 0.5 mg dose and placebo groups was increased by approx. 60% respectively.

Primary Efficacy Endpoint

- KARE's primary efficacy endpoint was change from baseline in the weekly mean of the daily 24-hour Itch NRS score at week 12 of the treatment period. Although no dose group met this endpoint, a statistically significant improvement from baseline was evident as early as week 1 for the 1 mg dose group which was sustained through 75% of the treatment period.
- In a prespecified analysis, a statistically significant change in the primary efficacy endpoint was observed in the mild-to-moderate (BSA<10%) patient population (p=0.036, All doses vs placebo) which was evident at week 1 and sustained through the treatment period.

Key Secondary Endpoint

- The key secondary endpoint for KARE was the assessment of the proportion of patients achieving an improvement from baseline of ≥4 points with respect to the weekly mean of the daily 24-hour Itch NRS score at week 12 (4-point Responder Analysis). No dose group met this endpoint for the ITT population.
- Prespecified analysis by disease severity indicated a statistically significant improvement in the 4-point Responder Analysis in the mild-to-moderate (BSA<10%) patient population with 32% of KORSUVA-treated patients achieving a ≥4 point reduction in NRS at Week 12 versus 19% in the placebo group (p=0.033, All doses vs placebo). A statistically significant improvement was also achieved for the 0.5 mg dose (p=0.046, 0.5 mg vs placebo).

Oral KORSUVA was generally well-tolerated across all doses. Overall, the incidence of treatment-emergent adverse events (AEs) was generally similar across KORSUVA and placebo groups. The most common treatment-emergent AEs reported in >5% of patients in any KORSUVA group and greater than placebo were abdominal pain, nausea dry mouth, headache, dizziness and hypertension (5/77 patients in 1 mg dose group; 4/5 of patients had documented prior history of hypertension at enrollment).

About Atopic Dermatitis

AD is a chronic, pruritic inflammatory dermatosis that affects up to 25% of children and 2-5% of adults (Eichenfeld et al 2015, Barbarot 2018). Pruritus is an integral part of AD and can aggravate the disease due to scratching. Itch is so common in AD that AD is often described as the itch that rashes (Boguniewicz M (2005). Pruritus prevalence in AD patients is greater than 80% and greatly impairs the quality of life of AD patients by causing sleep and psychological disturbance. (Mochizuki H, Schut 2005; Farmer WS, 2017) Both quality of life and psychosocial well-being are known to negatively correlate with itch severity.(Yosipovitch G, 2008)

The cause of AD is multifactorial, including genetic predisposition, impaired skin barrier, environmental triggers, and immune dysregulation (Bieber T. 2010; Thyssen JP, Kezic S; 2014). The sensation of itch in AD is similarly complex. Chronic itch in AD is mediated by a complex interplay between keratinocytes, cutaneous nerve fibers, pruritogenic molecules, and the peripheral and central nervous system (Pavlis J, Yosipovitch G 2018). An imbalance in the epidermal opioid system has also been described as potentially playing a role in the modulation of pruritus in AD (Tominaga et al 2007).

Available systemic immunosuppressants have shown to reduce pruritus, however several factors may limit their use e.g., these agents are generally reserved for patients with only moderate to severe AD, safety concerns exist with regards to long term therapy, there is limited efficacy with some of the treatments and certain routes of administration (e.g., an injectable route of administration) may be problematic in some patients.

Despite the treatments available to manage pruritus in AD, there remain limitations in the current modalities for use in the mild-to-moderate AD population. As ~80% of the AD population falls within the mild-to-moderate category this remains the most significant opportunity in the AD market for the development of effective systemic anti-pruritic agents.

References

1. Boguniewicz M. Atopic dermatitis: beyond the itch that rashes. Immunol Allergy Clin N Am. 2005;25(2):333–51
2. Dawn A, Papoiu AD, Chan YH, Rapp SR, Rassette N, Yosipovitch G.Itch characteristics in atopic dermatitis: results of a web-based questionnaire.Br J Derm.2009;160(3):642–4.
3. Eichenfeld L et al *Am Acad Dermatol*. 2014 February ; 70(2): 338–351.
4. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, Margolis DJ, de Bruin-Weller M, Eckert L, Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy. 2018 Jun;73(6):1284-1293
5. Mochizuki H, Schut C, Nattkemper LA, Yosipovitch G. Brain mechanism of itch in atopic dermatitis and its possible alteration through non-invasive treatments. *Allergology international : official journal of the Japanese Society of Allergology.* 2017;66(1):14-21.
6. Farmer WS, Marathe KS. Atopic Dermatitis: Managing the Itch. *Advances in experimental medicine and biology.* 2017;1027:161-177.
7. Yosipovitch G, Papoiu AD. What causes itch in atopic dermatitis? *Current allergy and asthma reports.* 2008;8(4):306-311.
8. Bieber T.Atopic dermatitis. Ann Dermatol. 2010;22(2):125–37. 7.
9. Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. J Allergy Clin Immunol. 2014;134(4):792–9
10. Janelle Pavlis' Gil Yosipovitch, Management of Itch in Atopic Dermatitis; Am J Clin Dermatol (2018) 19:319–332
11. Tominaga M, Ogawa H, Takamori K. Possible roles of epidermal opioid systems in pruritus of atopic dermatitis. J Invest Dermatol. 2007;127(9):2228-2235

Conference Call

Cara management will host a conference call today at 8:00 a.m. ET to discuss the results of the study.

To participate in the conference call, please dial (800) 708-4539 (domestic) or (847) 619-6396 (international) and refer to conference ID 50157934. A live webcast of the call can be accessed under "Events & Presentations" in the News & Investors section of the Company's website at www.CaraTherapeutics.com.

An archived webcast recording will be available on the Cara website beginning approximately two hours after the call.

About Cara Therapeutics

Cara Therapeutics is a clinical-stage biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pruritus by selectively targeting peripheral kappa opioid receptors, or KORs. Cara is developing a novel and proprietary class of product candidates, led by KORSUVA™ (CR845/difelikefalin), a first-in-class KOR agonist that targets the body's peripheral nervous system, as well as certain immune cells. In two Phase 3 trials, KORSUVA Injection has demonstrated statistically significant reductions in itch intensity and concomitant improvement in quality of life measures in hemodialysis patients with moderate-to-severe chronic kidney disease-associated pruritus (CKD-aP). The U.S. Food and Drug Administration (FDA) has accepted and granted Priority Review for the New Drug Application (NDA) for KORSUVA™ (difelikefalin) solution for injection for the treatment of moderate-to-severe pruritus in hemodialysis patients. The PDUFA target action date for KORSUVA is August 23, 2021. Oral KORSUVA™ has completed Phase 2 trials for the treatment of pruritus in patients with CKD and AD and is currently in Phase 2 trials in primary biliary cholangitis and notalgia paresthetica patients with moderate-to-severe pruritus.

The FDA has conditionally accepted KORSUVA™ as the trade name for difelikefalin injection. CR845/difelikefalin is an investigational drug product and its safety and efficacy have not been fully evaluated by any regulatory authority.

Forward-looking Statements

Statements contained in this press release 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 ongoing clinical trials, the future development of Oral KORSUVA for pruritus in patients with mild-to-moderate atopic dermatitis, the plans for meeting with the FDA regarding the potential registrational program for Oral KORSUVA for mild-to-moderate AD and the timing of such discussions, and the potential for Oral KORSUVA to treat these patients. 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's filings with the Securities and Exchange Commission, including the "Risk Factors" section of Cara Therapeutics's Annual Report on Form 10-K for the year ended December 31, 2020 and its other documents subsequently filed with or furnished to the Securities and Exchange Commission. All forward-looking statements contained in this press release speak only as of the date on which they were made. Except to the extent required by law, 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.

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Exhibit 99.2

KARE Phase 2 Topline Data:

Oral KORSUVA™ for Pruritus in Atopic Dermatitis

APRIL 2021

KARE Phase 2 study evaluated the efficacy and safety of oral difelikefalin for moderate to severe pruritus in adult subjects with atopic dermatitis (AD). The FDA has conditionally accepted KORSUVA™ as the trade name for difelikefalin injection. Difelikefalin injection is an investigational drug product and its safety and efficacy have not been fully evaluated by any regulatory authority.

CARA™ THERAPEUTICS

Disclaimers

This presentation is confidential and is being provided subject to the terms of the Confidentiality Agreement between Cara Therapeutics and the recipient.

This presentation contains certain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. In some cases, you can identify forward-looking statements by the words "anticipate," "believe," "continue," "estimate," "expect," "objective," "ongoing," "plan," "propose," "potential," "projected", or "up-coming" and/or the negative of these terms, or other comparable terminology intended to identify statements about the future. Examples of these forward-looking statements in this presentation include, among other things, statements concerning plans, strategies and expectations for the future, including statements regarding the expected timing of our planned clinical trials and regulatory submissions; the potential results of ongoing and planned clinical trials; future regulatory and development milestones for the Company's product candidates; the size of the potential markets that are potentially addressable for the Company's product candidates, including the pruritus market and the potential commercialization of Korsuva™.

These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that these statements are based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain. Factors that may cause actual results to differ materially from any future results expressed or implied by any forward-looking statements include the risks described in the "Risk Factors" section of the Company's Annual Report on Form 10-K for the year ended December 31, 2020, as well as those set forth from time to time in the Company's other SEC filings, available at http://www.sec.gov. Any forward-looking statements speak only as of the date of this presentation.

The Company undertakes no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise except as required by law.

CARA THERAPEUTICS

Cara Therapeutics Pipeline

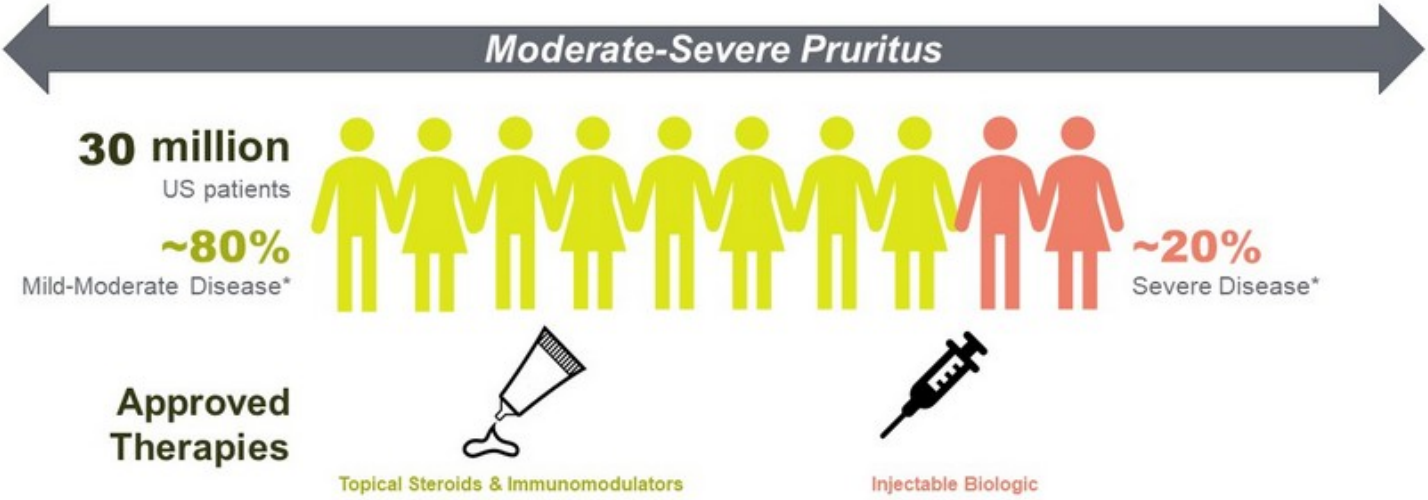
Program	Indication*	STAGE OF DEVELOPMENT: Phase I / Phase II / Phase III / NDA Review	Commercialization Rights† (ex-Japan and S. Korea)‡
KORSUVA™ Injection	Pruritus CKD-HD§	FDA Priority Review	US-Vifor EU / Other-VFMCRP‖
Oral KORSUVA™	Pruritus NDD-CKD		Cara
Oral KORSUVA™	Pruritus AD		Cara
Oral KORSUVA™	Pruritus PBC		Cara
Oral KORSUVA™	Pruritus NP		Cara

**Cara Therapeutics has investigated KORSUVA™ for post-operative pain.*
†Vifor has commercial rights in Non-US Fresenius Medical Care dialysis clinics under a profit-share arrangement.
‡Commercialization rights to KORSUVA™ in defined indications—Japan: Maruishi Pharma; South Korea: CKD Pharma.
§PDUFA date is August 23, 2021.
‖VFMCRP and Cara have rights to promote in Fresenius clinics in the US under a profit-share agreement.
CKD-HD: Chronic Kidney Disease-Hemodialysis; NDD—CKD: Non-Dialysis Dependent-Chronic Kidney Disease; AD: Atopic Dermatitis; PBC: Primary Biliary Cholangitis; NP: Notalgia Paresthetica.

 The FDA has conditionally accepted KORSUVA™ as the trade name for difelikefalin injection. Difelikefalin injection is an investigational drug product and its safety and efficacy have not been fully evaluated by any regulatory authority.

CARA THERAPEUTICS

Oral KORSUVA™ (Difelikefalin) For Atopic Dermatitis-Associated Pruritus



*Silverberg JI. Public Health Burden and Epidemiology of Atopic Dermatitis. Dermatol Clin. 2017;35(3):283-289. Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. J Invest Dermatol. 2019;139(3):583-590. Barbarot S et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy 2018; 1284-1293. Chovatiya R et al. Clinical phenotyping of atopic dermatitis using combined itch and lesional severity: A prospective observational study. Annals of Allergy, Asthma Immunology 2021.The FDA has conditionally accepted KORSUVA™ as the trade name for difelikefalin injection. Difelikefalin injection is an investigational drug product and its safety and efficacy have not been fully evaluated by any regulatory authority.

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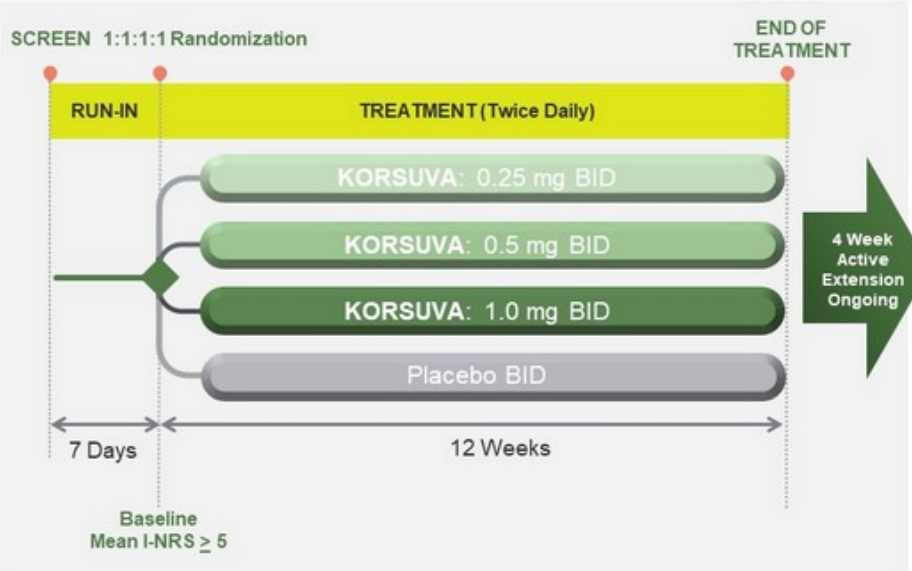
KARE: Phase 2 Study Design



Primary Endpoint

- Change from baseline in the weekly mean of the daily 24-hr Itch-Numeric Rating Scale (I-NRS) at Week 12

Key Secondary Endpoint

- Proportion of subjects achieving ≥4-point improvement in I-NRS at Week 12

 The FDA has conditionally accepted KORSUVA™ as the trade name for difelikefalin injection. Difelikefalin injection is an investigational drug product and its safety and efficacy have not been fully evaluated by any regulatory authority.

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KARE: Patient Disposition

Total Randomized
(N=401)

	Placebo (N=123*)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124*)	DFK 1.0 mg (N=77)
Completed	97 (79%)	63 (82%)	102 (82%)	61 (79%)
Discontinued	26 (21%)	14 (18%)	22 (18%)	16 (21%)
Adverse event	4	3	1	9
Subject withdrew consent	5	3	8	4
Subject non-compliance	6	2	7	0
Lost to follow-up	5	2	1	2
Lack of therapeutic efficacy	3	1	2	0
Other	3	3	3	1
Use of Rescue Medication	2 (1.6%)	4 (5.2%)	1 (0.8%)	1 (1.3%)

 *The sample size for DFK 0.5 mg and placebo was increased based on the results of the Interim Assessment for sample size re-estimation

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KARE: Patient Demographics

	Placebo (N=123)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124)	DFK 1.0 mg (N=77)
Female, n (%)	80 (65)	54 (70)	83 (67)	53 (69)
Age - Mean (SD)	40 (15.6)	43 (16.2)	42 (15.4)	41 (14.0)
Race, n (%)				
White	71 (58)	44 (57)	74 (60)	40 (52)
Black	42 (34)	31 (40)	40 (32)	33 (43)
Asian	5 (4)	1 (1)	5 (4)	2 (3)
BMI – Mean (SD)	29 (7)	30 (8)	32 (9)	31 (8)

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KARE: Baseline Disease Characteristics

	Placebo (N=123)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124)	DFK 1.0 mg (N=77)
Duration of AD (yrs) – Mean (SD)	20 (16)	25 (14)	21 (15)	23 (16)
Baseline BSA (%) – Mean (SD)	8.4 (6.9)	8.3 (6.0)	8.4 (6.4)	9.5 (6.9)
Baseline BSA Group – n (%)				
< 10 %	79 (64)	50 (65)	82 (66)	46 (60)
≥ 10 %	44 (36)	27 (35)	42 (34)	31 (40)
Baseline EASI – Mean (SD)	5.9 (4.9)	6.9 (5.4)	5.9 (4.3)	6.5 (4.5)
Baseline IGA				
2	56 (46)	33 (43)	57 (46)	33 (43)
3	64 (52)	40 (52)	64 (52)	43 (56)
4	3 (2)	4 (5)	3 (2)	1 (1)
Baseline I-NRS – Mean (SD)	7.7 (1.3)	7.8 (1.3)	7.8 (1.2)	7.9 (1.2)

 BSA=Body Surface Area & <10% is mild/moderate AD; EASI scores ranges from 0 to 72; IGA scores range from 0 to 4; I-NRS: Worst Itching Numeric Rating Scale (0 to 10) where 0 = no itch and 10 = worst itching imaginable.

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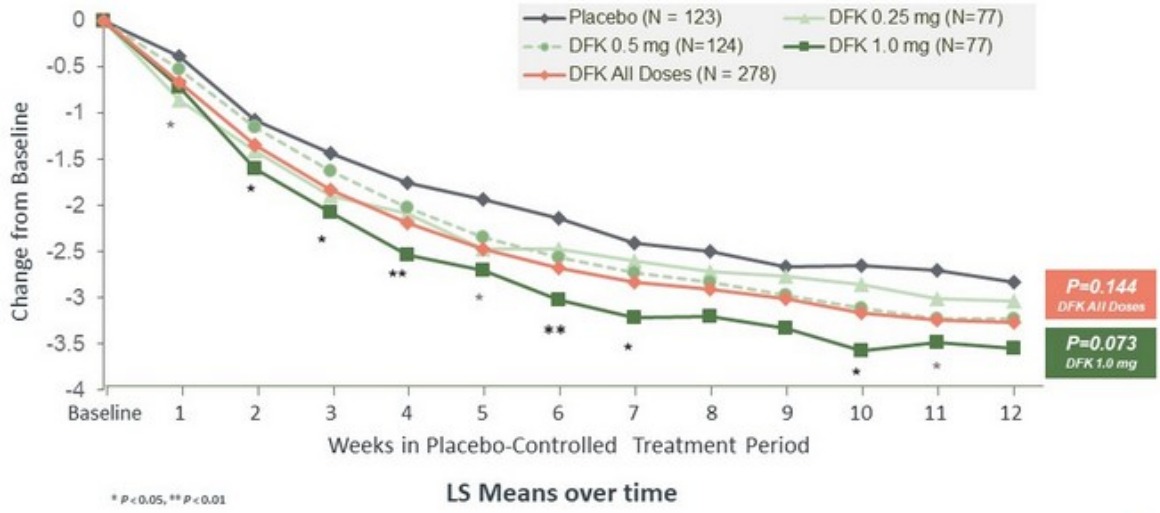
Primary Endpoint:
Change from Baseline in Daily I-NRS at Week 12 (ITT)

Significant improvement observed in 1.0 mg DFK vs placebo in majority of timepoints, starting at week 1



* $P < 0.05$, ** $P < 0.01$

LS Means over time

LS Means from MMRM with terms for treatment, week, week by treatment interaction, baseline score, and AD severity. Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption. I-NRS scores after use of rescue are set to missing and then imputed with MI

CARA THERAPEUTICS

Key Secondary Endpoint: ≥ 4-point Improvement in I-NRS at Week 12 (ITT)

	Placebo (N=123)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124)	DFK 1.0 mg (N=77)
Estimated Percent Responder	29%	38%	32%	33%
Odds Ratio		1.5	1.2	1.2
P-value		p=0.18	p=0.55	p=0.59

Estimated percentage & P-value based on a logistic regression model with terms for treatment group, baseline I-NRS score, and AD disease severity
Patients who d/c early or have missing data in a specific week are included as "non-responders"

CARA THERAPEUTICS

KARE Trial Patient Population

~64%

Mild-Moderate Disease
BSA < 10%
(N=257)

~36%

Moderate-Severe Disease
BSA ≥ 10%
(N=144)

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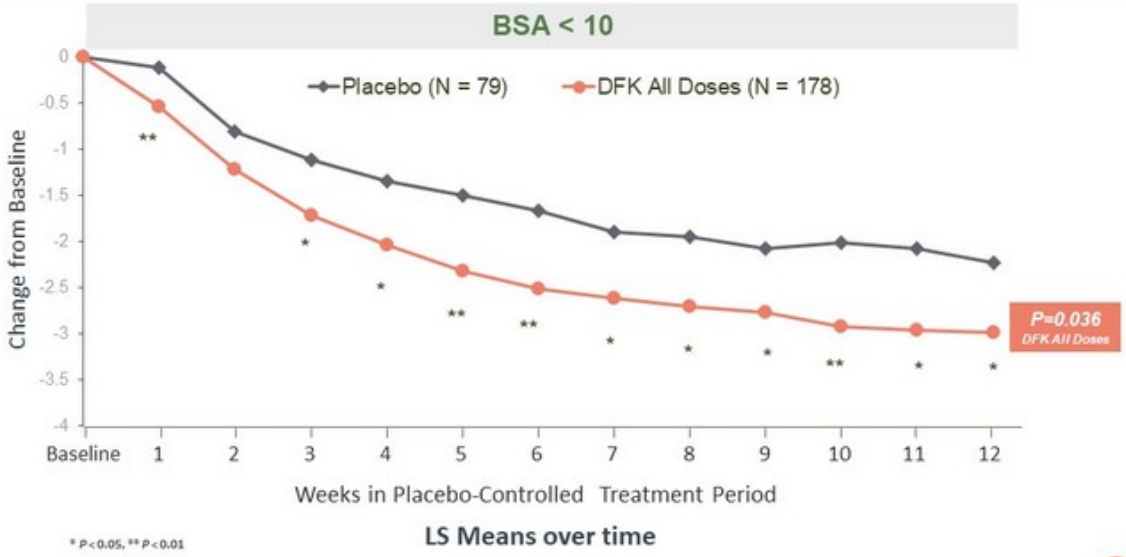
Mild to Moderate AD
Change from Baseline in Daily I-NRS Through Week 12

Significant anti-pruritic effect of DFK observed beginning Week 1 and sustained through Week 12



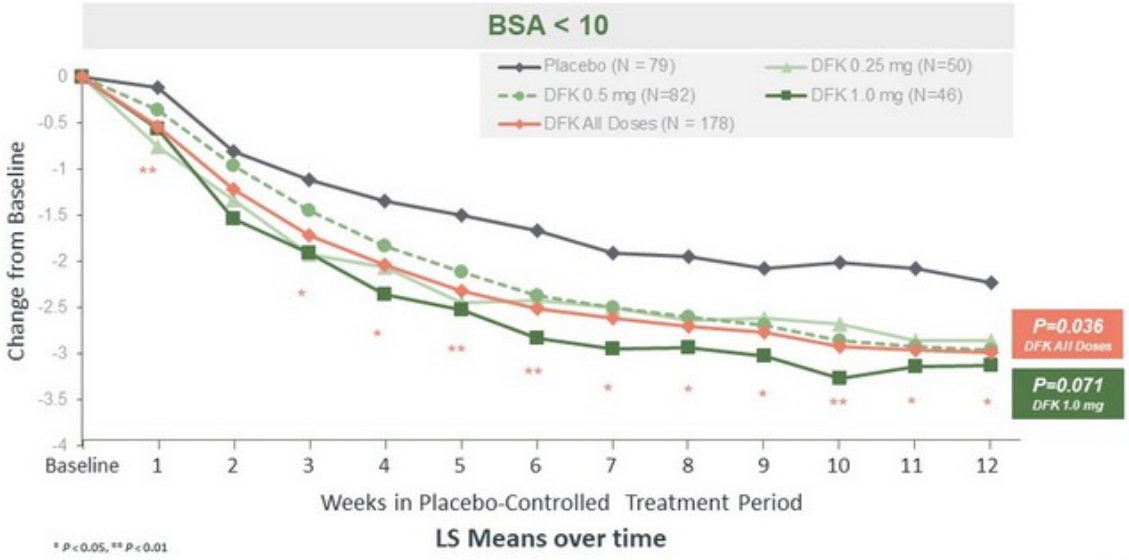
LS Means over time

* $P<0.05$, ** $P<0.01$

LS Means from MMRM with terms for treatment, week, week by treatment interaction, baseline score, and AD severity. Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption. I-NRS scores after use of rescue are set to missing and then imputed with MI

CARA THERAPEUTICS

Mild to Moderate AD
Change from Baseline in Daily I-NRS through Week 12

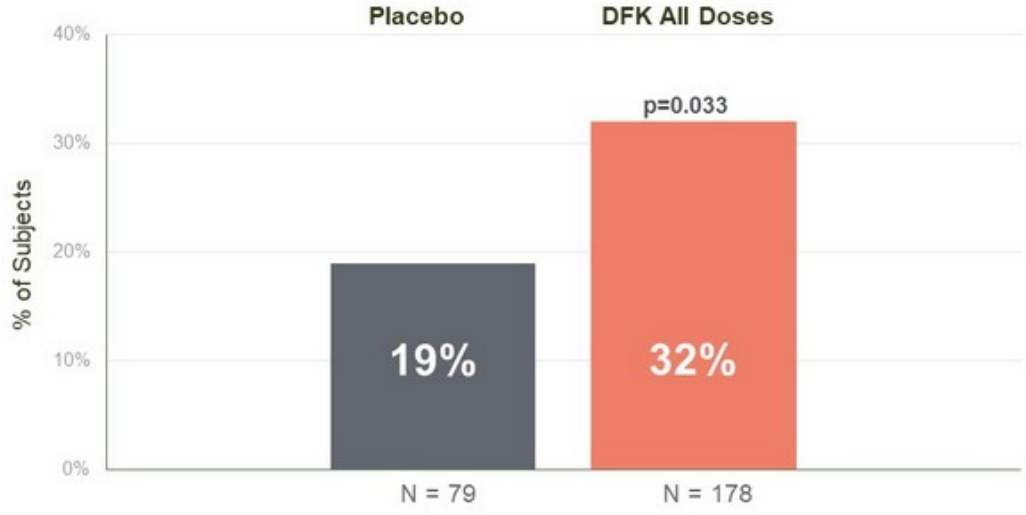


13 | *LS Means from MMRM with terms for treatment, week, week by treatment interaction, baseline score, and AD severity. Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption. I-NRS scores after use of rescue are set to missing and then imputed with MI*

CARA THERAPEUTICS

Mild to Moderate AD
Subjects with ≥ 4-point Improvement in I-NRS at Week 12

A significantly greater proportion of patients on DFK achieved 4-point improvement in I-NRS



14 | *Estimated percentage & P-value based on a logistic regression model with terms for treatment group and baseline I-NRS score. Patients who d/c early or have missing data in a specific week are included as "non-responders"*

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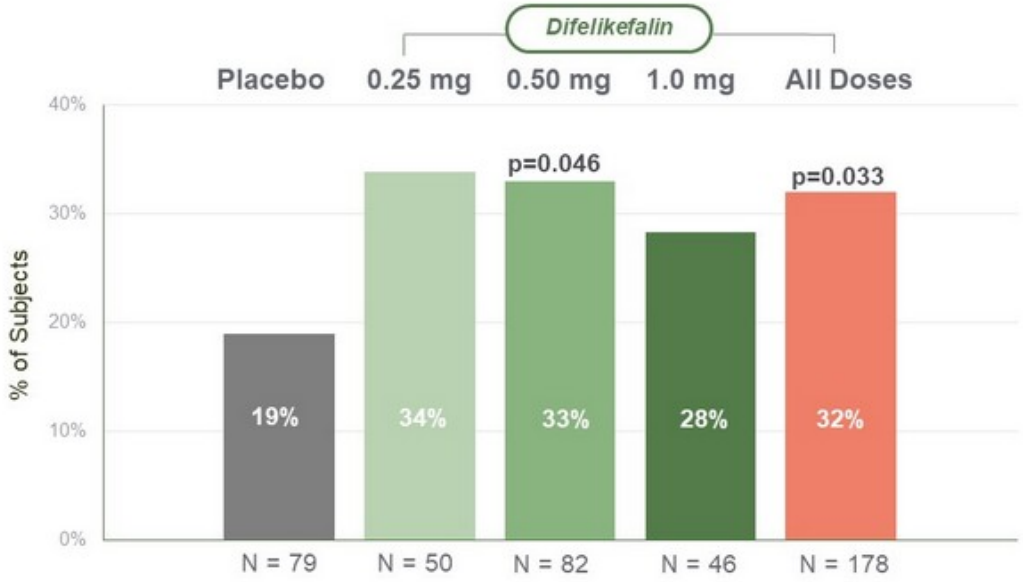
Mild to Moderate AD
Subjects with ≥ 4-point Improvement in I-NRS at Week 12



15 | *Estimated percentage & P-value based on a logistic regression model with terms for treatment group, baseline I-NRS score, and AD disease severity. Patients who d/c early or have missing data in a specific week are included as "non-responders"*

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Summary of Adverse Events

	Placebo (N=123)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124)	DFK 1.0 mg (N=77)
Subjects with at least one TEAE, n (%)	54 (43.9%)	36 (46.8%)	49 (39.5%)	42 (54.5%)
Subjects with at least one serious TEAE, n (%)	0	1 (1.3%)	1 (0.8%)	2 (2.6%)
Subjects with TEAE resulting in treatment discontinuation, n (%)	4 (3.3%)	3 (3.9%)	1 (0.8%)	9 (11.7%)

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Most Commonly Reported TEAEs

Treatment-emergent Adverse Events at ≥5% frequency; n (%)	Placebo (N=123)	DFK 0.25 mg (N=77)	DFK 0.50 mg (N=124)	DFK 1.0 mg (N=77)
Abdominal pain*	13 (10.6%)	4 (5.2%)	11 (8.9%)	14 (18.2%)
Nausea	11 (8.9%)	1 (1.3%)	6 (4.8%)	5 (6.5%)
Dry Mouth	0	2 (2.6%)	2 (1.6%)	6 (7.8%)
Headache	5 (4.1%)	5 (6.5%)	3 (2.4%)	2 (2.6%)
Dizziness	2 (1.6%)	4 (5.2%)	3 (2.4%)	2 (2.6%)
Hypertension	1 (0.8%)	1 (1.3%)	1 (0.8%)	5 (6.5%)

 Safety analyses performed in the safety population, defined as all randomized patients who received ≥1 dose of study drug based on actual treatment received.
**includes PTs abdominal pain, abdominal pain upper, abdominal discomfort*

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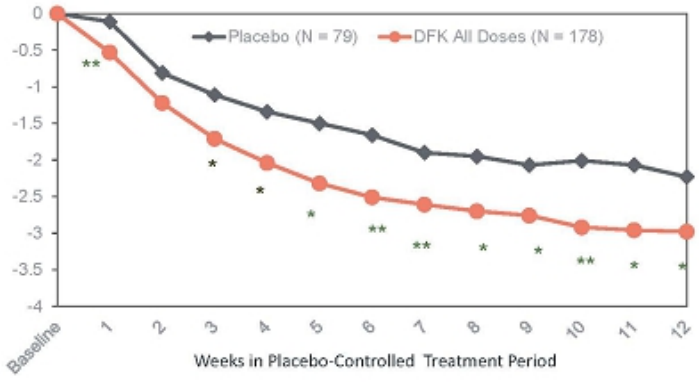
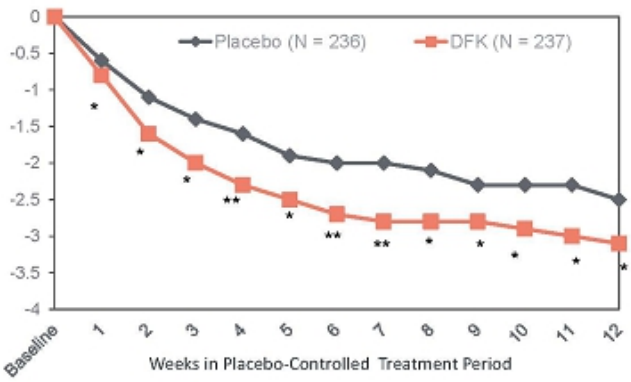
KORSUVA™ Profiles: Mild to Moderate AD-aP & CKD-aP

Similar anti-pruritic effects were observed in KARE and KALM-2 trials

Mild to Moderate Atopic Dermatitis-aD: KARE



CKD-aP: Phase 3/KALM-2 Hemodialysis Patients



LS Means over time

* $P < 0.05$, ** $P < 0.01$

 The FDA has conditionally accepted KORSUVA™ as the trade name for difelikefalin injection. Difelikefalin injection is an investigational drug product and its safety and efficacy have not been fully evaluated by any regulatory authority.

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Conclusions

- Oral KORSUVA™ did not meet Primary Endpoint of I-NRS change from baseline at week 12 in ITT population
  - However, statistically significant improvement was observed in mild-to-moderate subjects throughout Week 12
- Oral KORSUVA™ resulted in statistically significant improvement in the registration endpoint 4-point responder analysis in subjects with mild to moderate AD at Week 12
- Oral KORSUVA™ was generally well tolerated across all doses

Efficacy and safety data support further development of KORSUVA in mild-to-moderate AD patients –
EOP2 FDA meeting target for 2H, 2021

 The FDA has conditionally accepted KORSUVA™ as the trade name for difelikefalin injection. Difelikefalin injection is an investigational drug product and its safety and efficacy have not been fully evaluated by any regulatory authority.

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