Oral KORSUVA™ for CKD-associated Pruritus: Phase 2 Topline Results

A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Oral KORSUVA™ (CR845, Difelikefalin) in Chronic Kidney Disease Patients with Moderate-to-Severe Pruritus

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Forward-Looking Statements

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; the potential results of ongoing and planned clinical trials; future regulatory and development milestones for the Company's product candidates; and the size of the potential markets that are potentially addressable for the Company’s product candidates, including the pruritus market

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, 2018, 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.

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US Market Opportunity in CKD-aP: Non-Dialysis

~7.3 million
diagnosed with CKD (IQVIA est)

33%
receive pruritus tx

Per NKF, CKD is a big under-recognized US public health issue

- ~30 million people affected (causes more deaths than breast/ prostate cancer)

No FDA approved therapies – large unmet medical need

- Commonly used medications: anti-histamines, corticosteroids, gabapentin, anti-depressants etc.

Oral KORSUVA™, if approved for pre-dialysis patients, would not fall under ESRD bundle payment system

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Executive Summary

- CR845-210301 Phase 2 study of Oral KORSUVA™ met the primary endpoint*
- A positive dose-related trend was observed for all secondary endpoints.
- Oral KORSUVA was generally well tolerated with the safety profile consistent with prior studies.
- Oral KORSUVA 1mg was identified as the appropriate dose to be studied in Phase 3.

** The primary endpoint was defined as the Change from baseline in weekly mean of daily Worst Itching Intensity NRS (WI-NRS) score and the study would be considered positive if at least one dose achieved statistical significance versus placebo in the primary endpoint and exhibited a favorable safety profile*

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Oral KORSUVA™ for CKD-aP

- Phase 2 dose ranging study to assess safety and efficacy of 3 dose levels of oral KORSUVA on itch severity and itch-related QoL compared to placebo across diverse CKD population
- Enrolled Stage 3 to 5 CKD patients (non-dialysis and dialysis) with chronic moderate to severe pruritus
- Stratified to treatment based on renal disease status:
  - Stage 3 CKD non-dialysis
  - Stage 4 or 5 CKD non-dialysis
  - Stage 4 or 5 CKD on hemodialysis (20% enrollment cap)
- The study to be considered positive if at least one dose is identified that achieves statistical significance versus placebo in the primary endpoint and exhibits a favorable safety profile.

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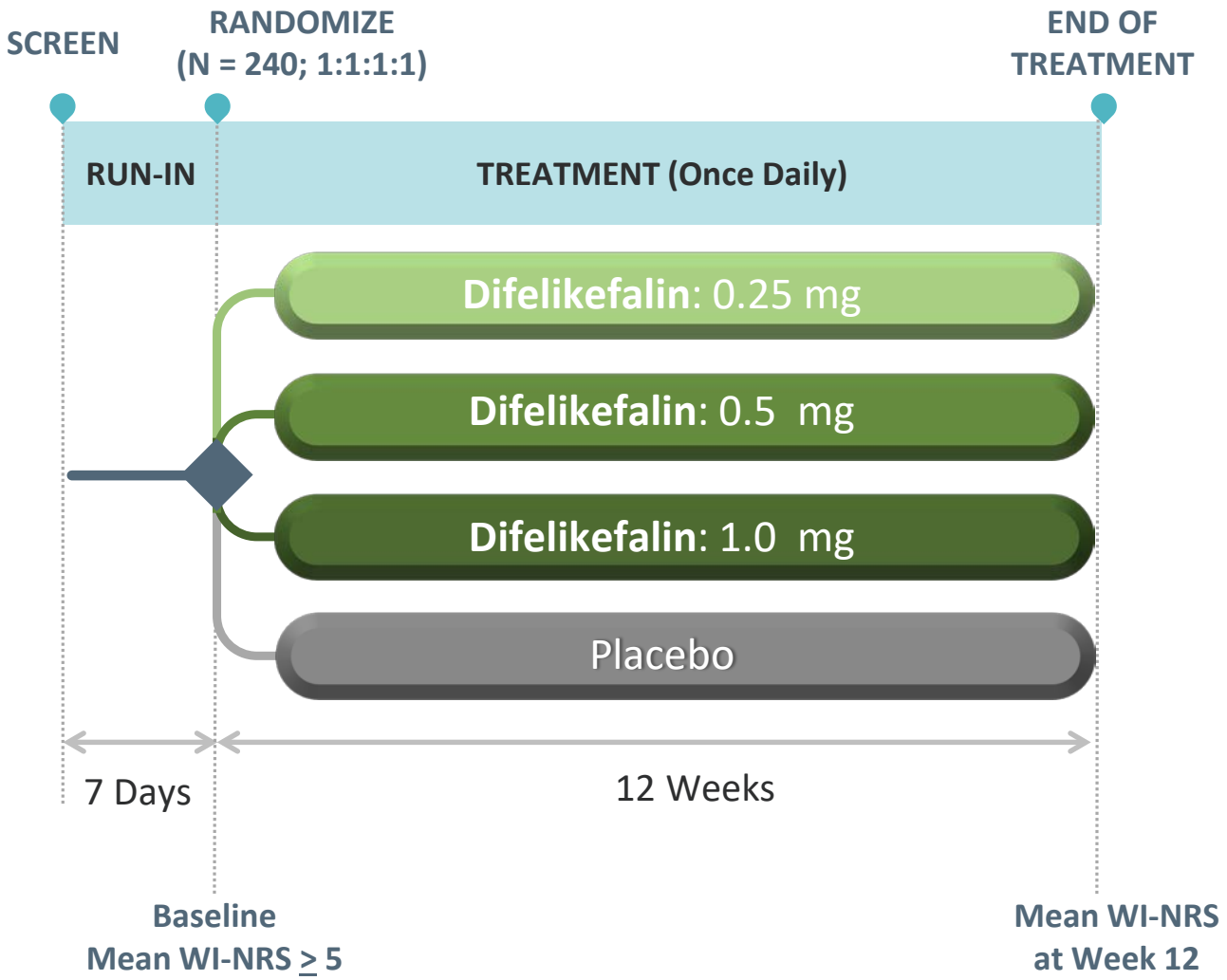
Oral KORSUVA™ for CKD-aP: Ph 2 Trial Design



Endpoints: Week 12

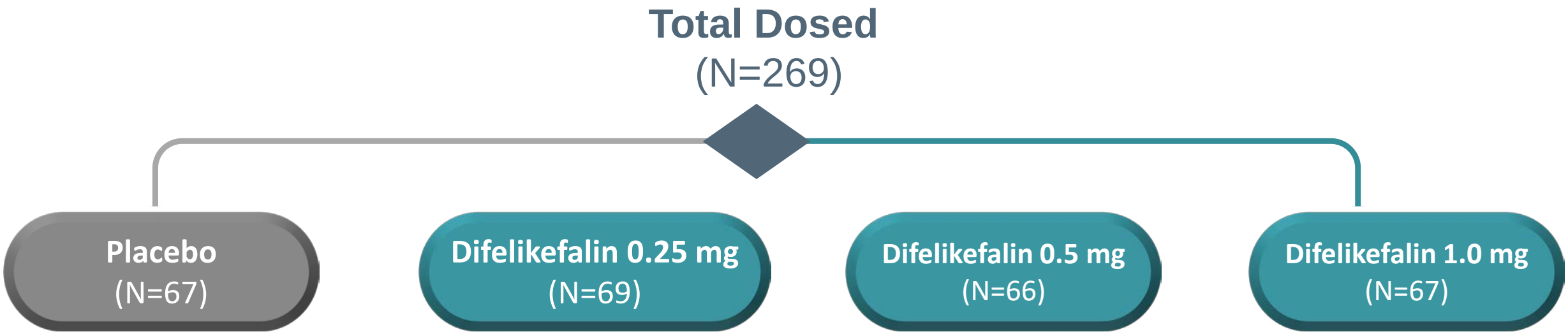
Primary

- Change from baseline in weekly mean of daily Worst Itching Intensity NRS (WI-NRS) score

Secondary

- Change from baseline in itch-related QoL
  - ✓ Skindex-10
  - ✓ 5-D Itch
- Proportion of subjects achieving >3 points improvement from baseline in weekly mean of daily WI-NRS score

Oral KORSUVA™ for CKD-aP: Patient Disposition



	Placebo (N=67)	Difelikefalin 0.25 mg (N=69)	Difelikefalin 0.5 mg (N=66)	Difelikefalin 1.0 mg (N=67)
Completed	**57** (85%)	**60** (87%)	**57** (86%)	**54** (81%)
Discontinued	**10** (15%)	**9** (13%)	**9** (14%)	**13** (19%)
Adverse event	4	3	6	8
Subject withdrew consent	3	2	2	3
Subject non-compliance	0	2	0	0
Eligibility	0	0	0	0
Lost to follow-up	0	2	0	0
Other	3	0	1	2

Oral KORSUVA™ for CKD-aP: Demographics

Demographic Characteristic	Placebo	Difelikefalin		
N (%)	N = 67	0.25 mg N = 69	0.5 mg N = 66	1.0 mg N = 67
Males	37 (55)	34 (49)	33 (50)	35 (52)
Age - Mean (SD)	66 (12)	66 (11)	69 (12)	68 (11)
Hispanic or Latino	34 (51)	30 (44)	31 (47)	33 (49)
White	47 (70)	49 (71)	49 (74)	48 (72)
Black	17 (25)	17 (25)	12 (18)	15 (22)
Asian	2 (3)	1 (1)	5 (8)	4 (6)

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Oral KORSUVA™ for CKD-aP: Baseline Disease Characteristics

Baseline Characteristics	Placebo	Difelikefalin		
N (%)	N = 67	0.25 mg N = 69	0.5 mg N = 66	1.0 mg N = 67
Stage 3 CKD Non-Dialysis (30 ≤ eGFR <60mL/min/1.73m^2)	40 (60)	41 (59)	38 (58)	40 (60)
Stage 4 or 5 CKD Non-Dialysis (eGFR <30 mL/min/1.73m^2)	15 (22)	16 (23)	16 (24)	15 (22)
Stage 4 or 5 CKD on Hemodialysis (eGFR <30 mL/min/1.73m^2)	12 (18)	12 (17)	12 (18)	12 (18)
History of Diabetes	51 (76)	46 (67)	45 (68)	48 (72)
History of Hypertension	66 (99)	63 (91)	61 (92)	61 (91)

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Oral KORSUVA™ for CKD-aP: Baseline Itch Characteristics

Baseline Itch Characteristics	Placebo	Difelikefalin		
Mean (SD)	N = 67	0.25 mg N = 69	0.5 mg N = 66	1.0 mg N = 67
Baseline Worst Itching Intensity NRS	6.98 (1.10)	7.24 (1.17)	7.04 (1.20)	7.04 (1.27)
Baseline Skindex-10 Total Score	34.9 (14.3)	36.5 (13.3)	33.1(14.3)	35.7(13.9)
Baseline 5-D Itch Total Score	16.8 (3.1)	16.2 (3.6)	16.2 (3.1)	16.4 (2.7)

NRS: Numeric Rating Scale (0 to 10) where 0 = no itch and 10 = worst itching imaginable
5-D Itch score ranges from 5 to 25 (lower scores indicate better QoL and reduced itch symptoms)
Skindex-10 scale ranges from 0 to 60 (lower scores indicate better QoL)

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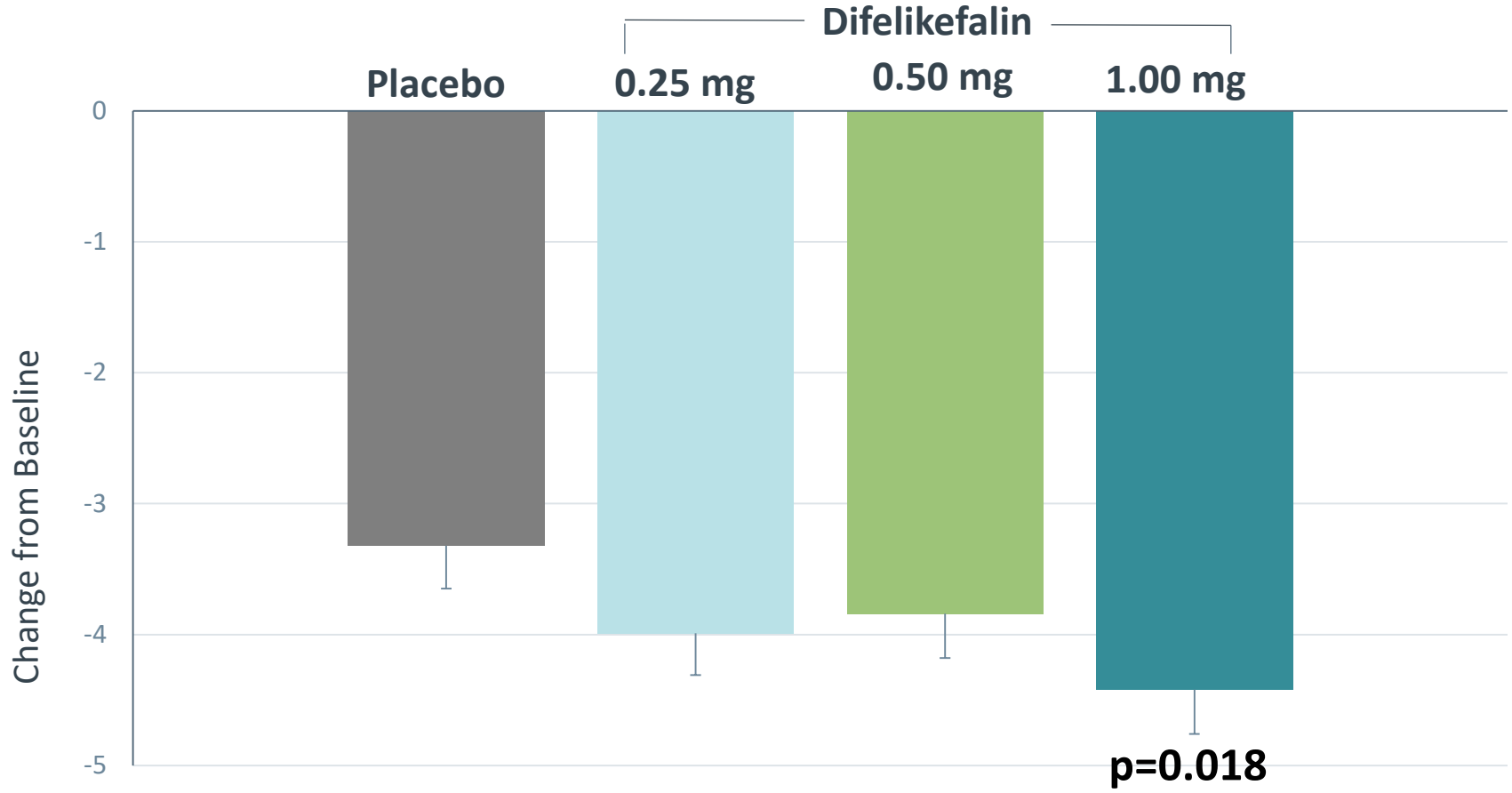
Primary Endpoint: Change from Baseline to Week 12 for WI-NRS

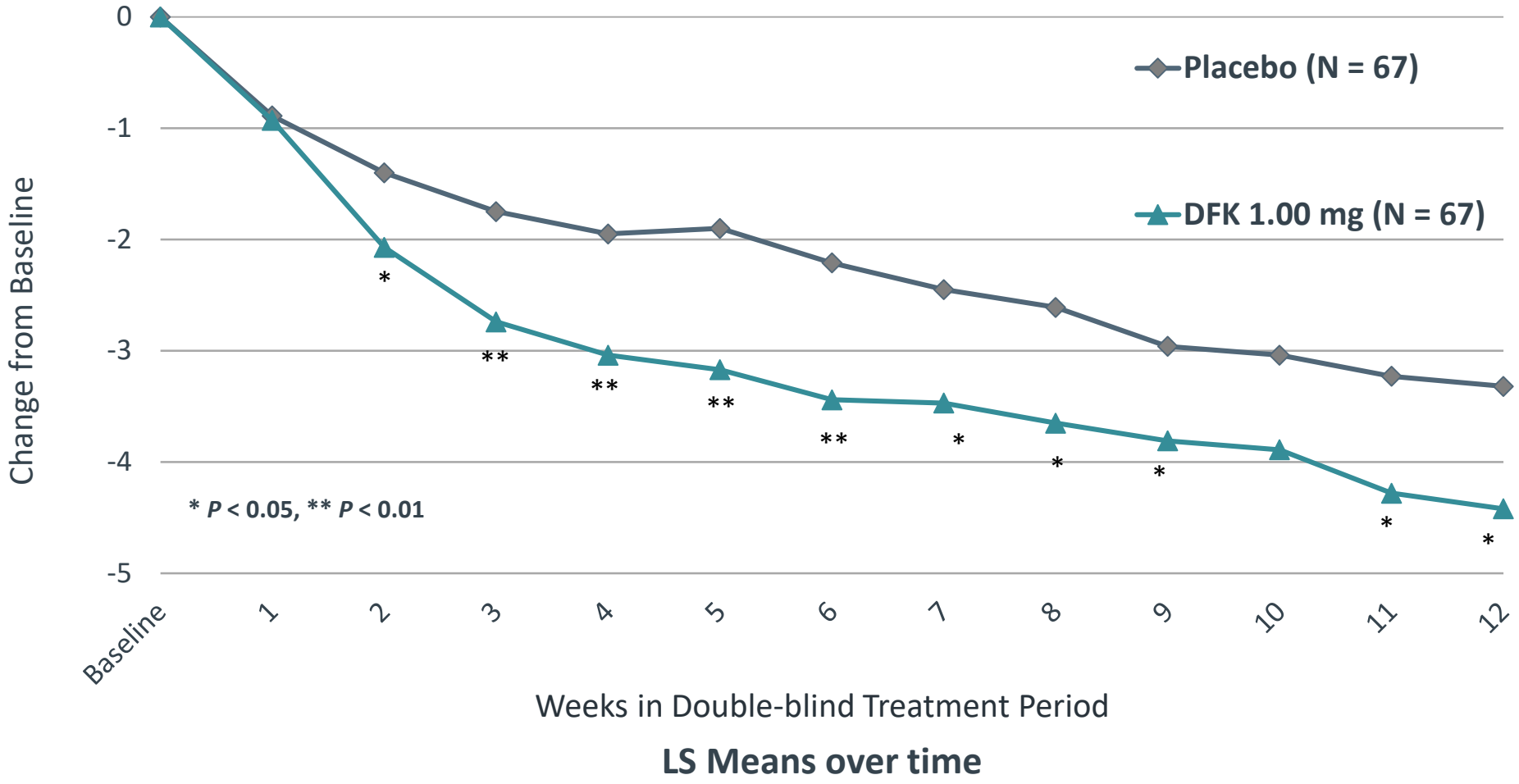
Significant difference in WI-NRS in patients treated with 1 mg oral KORSUVA™ compared to placebo



LS Mean from MMRM with terms for treatment group, week, week by treatment interaction as fixed effects; baseline score and strata as covariates; patient as a repeated measures
Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption

Change in Worst Itching Intensity NRS Over Time

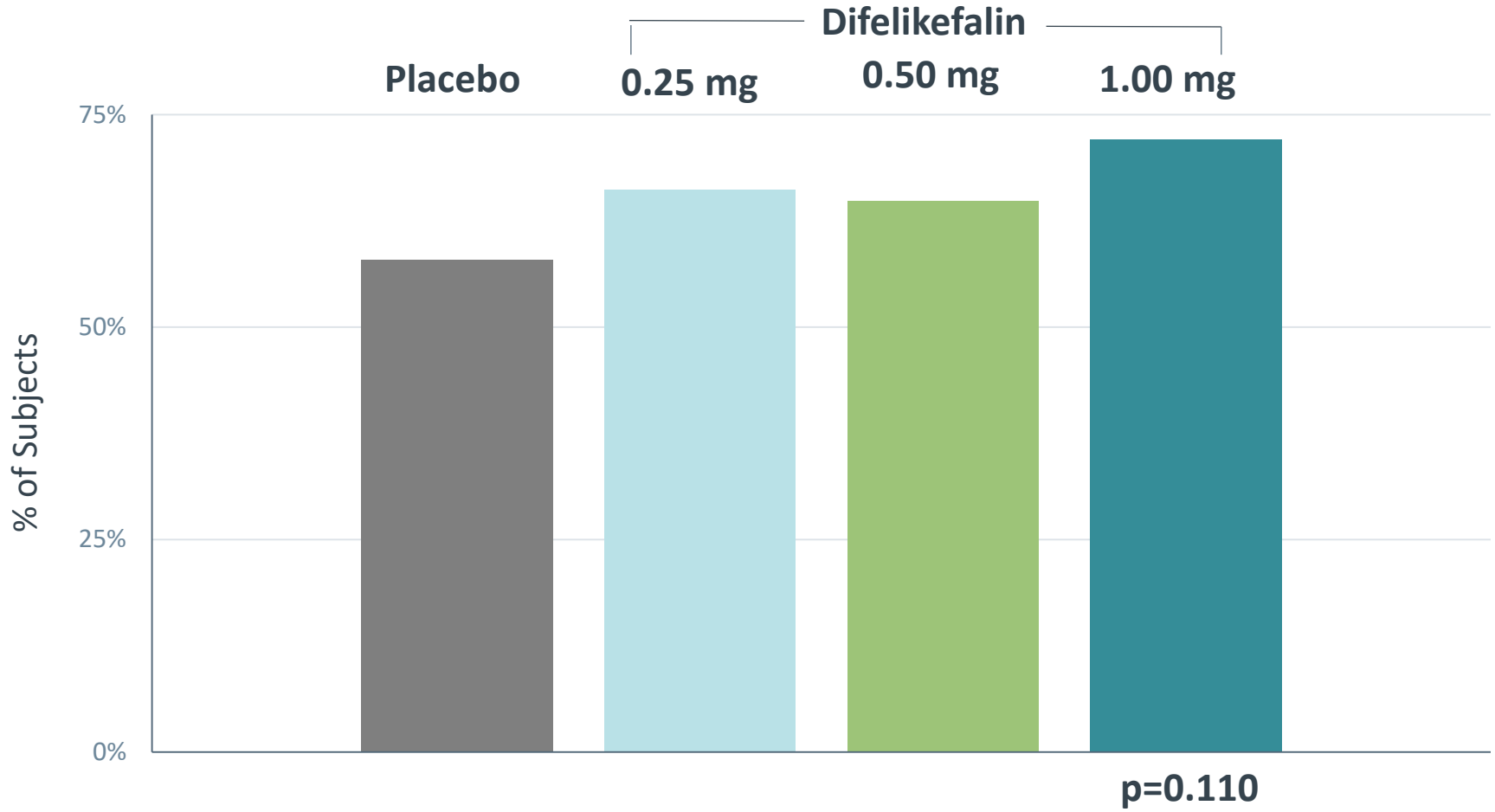
Significant differences between 1mg oral KORSUVA and placebo observed in WI-NRS starting at week 2



LS Mean from MMRM with terms for treatment group, week, week by treatment interaction as fixed effects; baseline score and strata as covariates; patient as a repeated measures
Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption

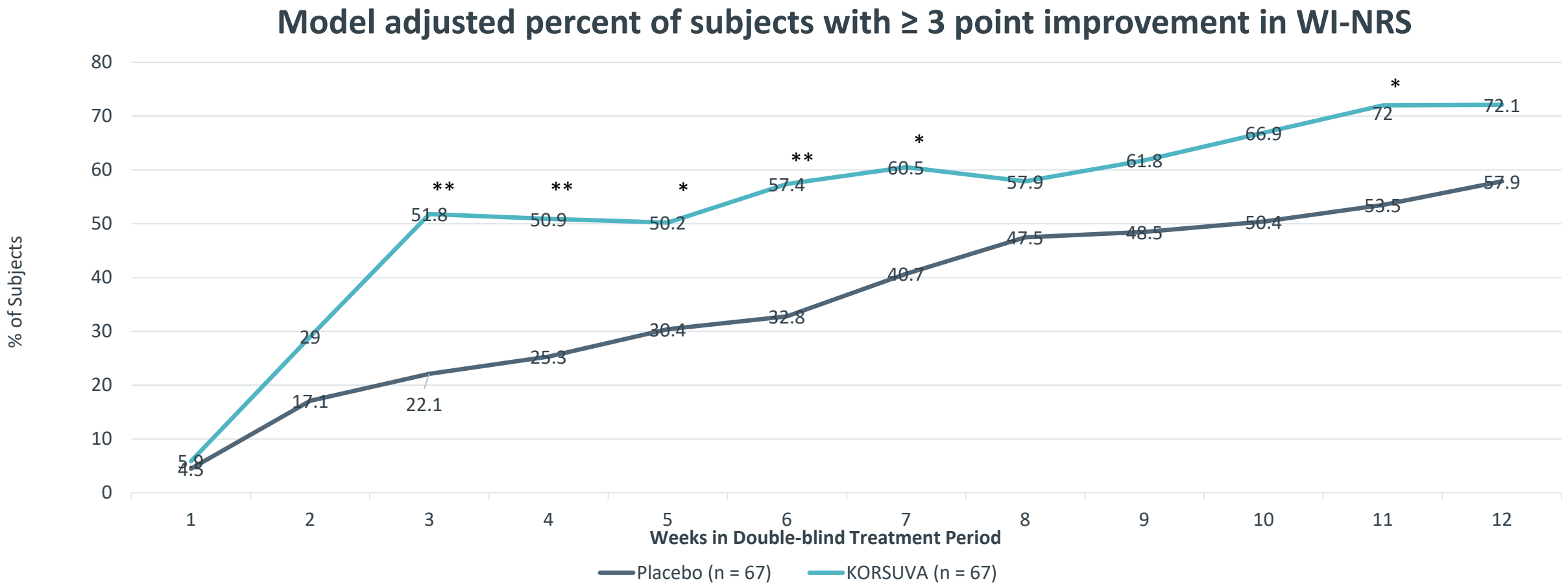
Secondary Endpoint: ≥ 3 point improvement in WI-NRS at week 12

72% of Oral KORSUVA 1.0 mg subjects experienced ≥ 3 point improvement from baseline



Estimated percentage; P-values; and Odds ratios are based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and renal disease status
Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption

Proportion of subjects with ≥ 3 point improvement in WI-NRS over time



* $P < .05$, ** $P < .01$

Estimated percentage & P-value based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and renal disease status

Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption

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Secondary Endpoints - Change from Baseline to Week 12 for QoL (Skindex-10 and 5-D Itch Scales)

- Subjects on Oral KORSUVA showed dose-related improvements vs. placebo in both Skindex-10 and 5D- Itch.
- An approximate 20% improvement over placebo was observed in both Skindex-10 and 5D-Itch in the 1mg group but did not achieve statistical significance.

Oral KORSUVA™ for CKD-aP: Summary of Adverse Events

N (%)	Placebo	Difelikefalin		
	N = 67	0.25 mg N = 69	0.5 mg N = 66	1.0 mg N = 67
Subjects with at least one TEAE	34 (51)	35 (51)	34 (52)	39 (58)
Subjects with at least one serious TEAE	5 (7.5)	9 (13.0)	9 (13.6)	9 (13.4)
Deaths	3	0	0	1
Non-fatal SAEs	2	9	9	8
Subjects with TEAE resulting in treatment discontinuation	5 (7.5)	2 (2.9)	5 (7.6)	9 (13.4)

Reasons for death include acute respiratory failure (Placebo = 2), coronary arterial disease (DFK 1mg = 1) and cardiac arrest (Placebo = 1).

Oral KORSUVA™ for CKD-aP: Most Commonly Reported TEAEs

N (%)	Placebo	Difelikefalin		
	N = 67	0.25 mg N = 69	0.5 mg N = 66	1.0 mg N = 67
Dizziness	0	0	2 (3.0)	5 (7.5)
Fall	0	0	3 (4.5)	4 (6.0)
Constipation	2 (3.0)	2 (2.9)	2 (3.0)	4 (6.0)
Diarrhea	1 (1.5)	2 (2.9)	3 (4.5)	4 (6.0)
Fatigue	1 (1.5)	4 (5.8)	1 (1.5)	3 (4.5)
Urinary tract infection	0	4 (5.8)	2 (3.0)	3 (4.5)
Hypertension	1 (1.5)	4 (5.8)	0	1 (1.5)
Gastro-esophageal reflux disease	0	0	4 (6.1)	0

Most common TEAE = incidence ≥ 5% in at least one treatment group and strictly greater than placebo

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Conclusions

- CR845 210301 Phase 2 study of Oral KORSUVA™ met the primary endpoint
- Oral KORSUVA™ was generally well tolerated with a safety profile consistent with prior studies
- Oral KORSUVA™ 1mg was identified as the appropriate dose to be advanced into Phase 3
- Aim to initiate Phase 3 development program in 2020

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Acknowledgement

We thank all the investigators and patients who participated in this study.