Trial Title	Phase 1b, open label study to evaluate the safety, tolerability, and efficacy of a 1% topical formulation of KM-001 for the treatment of type I Punctate Palmoplantar Keratoderma or Pachyonychia Congenita
Internal Ref. No. (Sponsors No.)	KM001-B1B
Clinical Phase	1b
Trial Design	In this phase 1b, open label trial, 2 cohorts of patients diagnosed with confirmed type I Punctate Palmoplantar Keratoderma (PPPK1) or Pachyonychia congenita (PC) were to be recruited: 1. Cohort 1: up to 11 eligible patients to be treated twice daily, for 12 weeks, with 1% topical KM-001, on the plantar surfaces (2 feet) 2. Cohort 2: up to 7 eligible patients, to be treated twice daily, for 16 weeks, with 1% topical KM-001, on the plantar surfaces (2 feet) During the study, safety, tolerability, efficacy, and PK were assessed. Four (4) weeks after the end of active treatment, patients returned to the clinic for additional safety, efficacy, and PK assessments. Safety, tolerability, and efficacy parameters were assessed during in-clinic visits (Cohort 1: during Screening, Enrolment, and on Days 7, 28, 42, 63, 84 [end of treatment, EoT], 112 [End of Study, EoS] post first investigational medicinal product (IMP) administration; Cohort 2: during Screening, Enrolment, and on Days 7, 28, 42, 63, 84, 112 [EoT], 140 [EoS] post first IMP administration. Safety and treatment compliance assessment were also done by phone calls on - Cohort 1: Days 14, 49, 70, and 98 (follow-up); Cohort 2: Days 14, 49, 70, 98, and 126 (follow-up). Blood samples for pharmacokinetic (PK) assessment were be collected on: – Screening (Day -14 to -0): any time during the visit. (or on Day 1 up to 30 minutes pre-dose if missed during Screening) – Day 7 and at EoT (Cohort 1: Day 84; Cohort 2: Day 112) up to 30 minutes pre-dose, and at 1 h, 2 h, 3 h, 6 h (+15 min) post-dose. – Days 28, 42 for both Cohorts, and Day 84 for Cohort 2: 1 sample after the first dose, before the second dose, as late as possible in the visit. – End of Study (EoS, Day 112 (Cohort 1) or Day 140 (cohort 2)), or at Early Termination (ET): at any time during the visit. The patient filled a patient-reported diary, consisting of treatment compliance, self-assessments for efficacy and safety.

Trial patients	Male and female, aged 18 to 75 (cohort 1), and 16 to 75 (cohort 2) years (inclusive) at the time of screening with a clinical diagnosis of: PPPK1 disease with confirmed heterozygous mutation in alpha and gamma adaptin binding protein (AAGAB) gene OR PC with confirmed heterozygous mutation in either keratin (KRT) 16, KRT17, KRT6A, KRT6B or KRT6C mutations and a target treatment region of 0.5% to 4% body surface area (BSA) which includes target lesion(s).	
Planned Sample Size	Cohort 1: up to 13 patients will be screened in order to enrol 11 patients and achieve 10 evaluable completers. Cohort 2: up to 8 patients will be screened in order to enrol 7 patients and achieve 5 completers	
Treatment Duration per Patient	Cohort 1: 12 weeks Cohort 2: 16 weeks	
Follow-up Duration per Patient	4 weeks	
Planned Trial Period	December 2022 to June 2024	
	Objectives	**Outcome Measures**
Primary	*Primary Objective (Safety)*	*Primary Outcome Measures*
	To assess the safety and tolerability of KM-001 1% topical formulation for the treatment of patients with PPPK1 and PC	Recording of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) grouped by body system
		Assessment of clinical laboratory parameters.
		Assessment of vital signs (body temperature, pulse, blood pressure)
		Assessment of electrocardiogram (ECG) parameters
Secondary	*Secondary Objective (Efficacy)*	*Secondary Outcome Measures*
	To assess the efficacy of KM-001 1% topical formulation	Clinical global impression of severity (CGI-S) of disease scale (0= “none” to 4= “very severe”)

	in clearing lesions resulted from PPPK1 and PC	Assessment using patient global impression of severity (PGI-S) scale
		Assessment using patient global impression of change (PGI-C) scale
Exploratory	*Exploratory Objectives:*	*Exploratory Outcome Measures*
	To characterise the PK profile of KM-001	Concentration of KM-001 in plasma samples from patients
	To assess the efficacy of KM-001 1% in pain and itch reduction resulted from PPPK1 and PC	Pain assessment by visual analogue scale (VAS) (0= "no pain" to 100= "severe intolerable pain")
		Itch assessment using the peak pruritus-numerical rating scale (PP-NRS) (0= "no itch" to 10= "worst imaginable itch").
	To assess the changes in the surface of the callus	Examination of the surface of the callus (fissuring, neurovascular structures, and erythema around the calluses) including lesion photography
IMP	KM-001 cream 1%	
Formulation, Dose, Route of Administration	Topical application to the affected plantar area on both feet. Approximately (approx.) 2 g of cream will be applied per defined treatment area (up to 4% BSA including target lesion(s) [minimum 0.5% to maximum 4% BSA]), twice daily, during a 12-week treatment period (Cohort 1: from enrolment to Day 83 and 1 additional application in the morning of Day 84, i.e., 169 treatments), or a 16-week treatment period (Cohort 2: from enrolment to Day 111 and 1 additional application in the morning of Day 112, i.e., 225 treatments). • Daily cream dosage: ○ Cohort 1: approx. 4 g (2 g BID [twice daily]) on Days 1 to 83, 2 g on Day 84 (EoT); Total cream dose: approx. 338 g ○ Cohort 2: approx. 4 g (2 g BID [twice daily]) on Days 1 to 111, 2 g on Day 112 (EoT); Total cream dose: approx. 450 g • Daily active pharmaceutical ingredient (API) dosage: ○ Cohort 1: approx. 40 mg (20 mg BID) on Days 1 to 83, 20 mg on Day 84 (EoT);	

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Total API dose: approx. 3380 mg

Cohort 2: approx. 40 mg (20 mg BID) on Days 1 to 111, 20 mg on Day 112 (EoT);

Total API dose: approx. 4500 mg

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<tr><td colspan="2">Results</td></tr>
<tr><td>Patients disposition</td><td>

Cohort 1: A total of 12 patients were screened for this study on one site. Nine (9) patients enrolled and 8 completed the 84 days treatment: 7 PC patients and one PPPK1 patient. One PC patient terminated early due to withdrawal consent.
Cohort 2: A total of 10 patients were screened, eight (8) PC patients enrolled for the 112 days treatment, all completed the study.
In summary, 16 patients completed the study.

<table>
<tr><th>Analysis Sets</th><th>N
Cohort 1</th><th>N
Cohort 2</th></tr>
<tr><td>Screened</td><td>12</td><td>10</td></tr>
<tr><td>Safety Set (Treated)</td><td>9</td><td>8</td></tr>
<tr><td>Efficacy Set</td><td>9</td><td>8</td></tr>
<tr><td>Subject Status</td><td></td><td></td></tr>
<tr><td>Consent withdrawal</td><td>1 (11.1%)</td><td>0</td></tr>
<tr><td>Study completed per protocol</td><td>8 (88.9%)</td><td>8 (100%)</td></tr>
<tr><td>Early termination reason</td><td></td><td></td></tr>
<tr><td>Consent withdrawal</td><td>1 (100%)</td><td>0</td></tr>
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<tr><td>Demographics</td><td>In cohort 1, 1 patient was diagnosed with PPPK1 with a mutation in the AAGAB gene, while 7 were diagnosed with PC: one of each: KRT6C mutation, KRT6B mutation, KRT6A mutation and 4 with KRT16 Mutation. The mean time from diagnosis was 16.9 (±15.2) years.
In cohort 2 All 8 patients were diagnosed with PC: one with a KRT6C mutation, one with a KRT6B mutation, one with a KRT6A mutation, and five with a KRT16 mutation. The mean time from diagnosis was 40.71 (±23.54) years.
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<tr><td></td><td>KM-001 1% (N = 9) Cohort 1</td><td>KM-001 1% (N = 8) Cohort 2</td></tr>
<tr><td colspan="3">Age</td></tr>
<tr><td>n</td><td>9</td><td>8</td></tr>
<tr><td>mean</td><td>44</td><td>50.3</td></tr>
<tr><td>SD</td><td>13.5</td><td>14.9</td></tr>
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	med	43	52
	Min	18	24
	Max	65	72
	Sex		
	n	9	8
	Female	3 (33.3%)	2 (25%)
	Male	6 (66.7%)	6 (75%)
	Race		
	n	9	8
	Caucasian	9 (100%)	8 (100%)
Patients Baseline characteristics		KM-001 1% Cohort 1 (N =9)	KM-001 1% Cohort 2 (N =8)
	BMI		
	n	9	8
	Mean	30.1	29.13
	SD	6.6	8.06
	Med	28.8	28.71
	Min	22	19.68
	Max	43.5	44.75
	Clinical diagnostics		
	n	9	8
	PC	8 (88.9%)	8 (100%)
	PPK	1 (11.1%)	0
	Time since diagnostics		
	n	9	7
	Mean	16.9	40.71
	SD	15.2	23.54
	Med	11.9	45
	Min	1.2	3

	Max	49.2	72
Safety Outcomes	• Over the course of the clinical study, a total of 43 TEAEs were reported in 14 of the 17 enrolled patients (82.3%). All of them were non-serious TEAEs and none of them was classified as an SAE. None of the TEAEs led to withdrawal from the clinical trial. • Four TEAEs (9.3%), reported in 3 patients, were defined as 'Possibly related' to the study drug. All were local to the treated area and of mild intensity, three (3) of them resolved spontaneously without sequalae ('Burning in feet', 'Tingling in feet' and 'Stabbing Pain in sole of foot'), and one was ongoing at the end of the follow up period ('Mild Erythema'). • All other TEAEs were unrelated or 'unlikely' related to KM-001.		
PK outcomes	• The sampling schedule and high proportion of BLQ PK samples may have biased the results and conclusion, further investigation may be required. • Following topical application of KM001 1% cream formulations twice daily for 84 days, KM-001 could not be detected in plasma of most of the treated patients (80%). In the measured samples, KM-001 plasma concentrations were low and close to the lower limit of quantification (0.3ng/ml). • In the detectable samples, some elevation of KM-001 concentration was observed from Day 7 to Day 84. • Exposure, as based on AUC, was low, with mean AUC0-t of 3.42 ng*h/mL (coefficient of variation [CV%]: 51.6%) for cohort 1 (N=2 patients only) on Day 84 and and 4.3 ng*h/mL [CV%]: 102.3%) for cohort 2 (N=2 patients only)		
Efficacy outcomes	• The main efficacy endpoint was defined as percent of responders at the end of treatment (Day 84, cohort 1 or D112, cohort 2) compared to baseline (Day 1, Visit 2). A responder was defined to have an improvement in at least 1 parameter of the efficacy assessment scales; PGI-S, CGI-S, PGI-C, VAS pain score and PP-NRS. The efficacy endpoint analysis demonstrated a robust and sustained response to KM-001 1% cream treatment across both Cohort 1 and Cohort 2. • In Cohort 1, the proportion of responders increased steadily from 44.4% on Day 7 (95% CI: 18.9%–73.3%) to 87.5% by Day 84 (95% CI: 52.9%–97.8%). Similarly, in Cohort 2, the response rate rose from 25% on Day 7 (95% CI: 7%–59%) to 88% by Day 42 (95% CI: 53%–98%), and this high level of response was maintained through Days 63, 84, and 112. • Exploratory efficacy endpoint included the change from baseline in PGI-S, CGI-S, PGI-C, VAS pain score and PP-NRS. Despite no significant absolute change over time in these		

	metrics in both cohorts, patients and physicians reported improvement in disease severity towards the treatment completion, including meaningful pain reductions which were reported by 50% of PC patients in Cohort 1 (Day 84) and 44% in Cohort 2 (Day 112). • These findings highlight that KM-001 1% cream elicited a significant and consistent improvement in at least one efficacy parameter (PGI-S, CGI-S, PGI-C, VAS pain score, or PP-NRS) in the majority of patients in both cohorts, with responses starting as early as Day 28 and remaining stable through the end of treatment.
Discussion and conclusions	The purpose of this Phase Ib, open label study was to evaluate safety (primary) and efficacy (secondary) of KM-001 1% topical cream for the treatment of Pachyonychia congenita (PC) and Punctate palmoplantar keratoderma type 1 (PPPK1). The primary endpoint focused on safety, indicating that the use of topically applied KM-001 1% was generally well-tolerated and deemed safe. The most frequent adverse events that could potentially be related to KM-001 treatment were mild and localized, such as burning sensation and erythema, and mostly resolved on their own. The results indicate that the efficacy endpoint of proportion of responders at Day 84 for Cohort 1 or day 112 for cohort 2 (EoT) was met, as 87%- 88% of the patients had an improvement in at least one of the scales assessed (CGI-S, PGI-S, PGI-C, Vas pain and PP-NRS). It is notable that the majority of patients recruited to this study had a baseline CGI-S score which was “Very severe” or “Severe” (62.5%), yet an improvement was observed following treatment of just 3 months. Treatment prolongation may result in further improvement in the severity scores. A unique assessment in this study was the PP-NRS, a validated scale for itch. Most of the patients didn’t score itch as a symptom which disturbs them, however, one patient who had a score of PP-NRS=6 (moderate itch) at baseline, had a clinically significant reduction of 4 points in his itch score at day 84, EoT (PP-NRS=1). In summary, KM-001% successfully met the efficacy endpoint for treating PC and PPPK1 patients and displayed a favorable safety profile. Consequently, it emerges as a promising candidate for further progression in clinical development.