SYNOPSIS

Name of Sponsor: Mayne Pharma	Individual Study Table Referring to Part of the Dossier	**(For National Authority Use only)**
Name of Finished Product: trifarotene cream HE1	Volume:	
Name of Active Ingredient: CD5789	Page:	

Title of Study:	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 90-Day, Safety, Efficacy, and Systemic Exposure Study followed by a 90-Day Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale
Investigator(s):	This was a multicenter study
Publication (Reference):	None
Study Period:	Date of First Consent: 17-Jun-2019 Date of Last Follow-up Visit: 02-Sep-2021 Date of Early Termination 30-Jul-2021
Phase of Development:	Phase 2
Objectives:	
Primary:	To compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle, in adults and adolescents with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 90 days of treatment.
Secondary:	• To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% body surface area (BSA) twice weekly. • To assess safety for up to 180 days of dosing with open-label trifarotene cream HE1 200 µg/g.
Methodology:	This was a 2-cohort, multicenter study in subjects with moderate to severe LI (i.e., 3-4 on a 5-point Investigator's Global Assessment [IGA] where 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe). The first cohort of subjects (Cohort A) randomized adults (≥18 years old) in a 1:1:1 ratio to trifarotene (CD5789) cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle. After the initial 15 subjects completed at least 28 days of treatment, an independent data safety monitoring board (DSMB) reviewed aggregate safety and tolerability data (including pharmacokinetic [PK] and electrocardiogram [ECG] data). Adult subjects continued to be enrolled in the study, until DSMB evaluation, at which time, 22 adult subjects had been enrolled and 7 had participated in the PK substudy. No safety issues were identified clinically; although several subjects had detectable serum levels of the study drug and metabolites, these were evaluated as not clinically significant; therefore, adolescents (ages 12 to 17 years, inclusive) were allowed to enroll together with adults in Cohort B. Subjects in Cohort B were randomized and treated in the same manner as subjects in Cohort A.

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	All subjects (Cohort A and Cohort B) who completed the 90-day Double-blind Treatment Period were eligible to enroll in the 90-day Open-label Extension (OLE). Subjects in the OLE received open-label trifarotene cream HE1 200 µg/g twice weekly for 90 days. Since this study was terminated by the sponsor on 30-Jul-2021, the findings of the study are presented in an abbreviated CSR.
Number of Subjects (Planned and Analyzed):	Planned: 120 Screened: 99 Enrolled: 65 Randomized: 65 Early Termination: 13 Completed Double-blind: 52 Entered OLE: 49 Analyzed (Safety): 65
Diagnosis and Main Criteria for Inclusion:	For the purposes of this study, diagnosis of LI was a clinical diagnosis. For Cohort A subjects must have been ≥18 years old; for Cohort B subjects must have been ≥12 years old. Subjects of childbearing potential were not to be pregnant or lactating. Females of reproductive potential, males and their partners capable of reproduction had to be using 2 effective forms of contraception during the study and for at least 1 month after study drug application. Males could not donate sperm for at least 1 month after study drug application.
Test Products, Dose and Mode of Administration, Lot Numbers:	Trifarotene (CD5789) cream HE1 • Double-blind Period dose, route, frequency: Up to 36 g per dose of 100 µg/g, 200 µg/g applied topically twice weekly on up to 90% body surface area (BSA) • Open-label Extension dose, route, frequency: Up to 36 g per dose of 200 µg/g applied topically twice weekly on up to 90% BSA **Lot Numbers:**

Drug Information	Catalent Lot	Supplier Lot
Trifarotene placebo cream 50g tube	4353267	312376
Trifarotene 200mcg/g cream 50g tube	4353265	328132
Trifarotene 100mcg/g cream 50g tube	4353263	312377
Trifarotene 200mcg/g cream 50g tube	4262038	328132
Trifarotene 200mcg/g cream 50g tube	3924529	312378
Trifarotene 200mcg/g cream 50g tube	3924527	312378
Trifarotene 100mcg/g cream 50g tube	3924526	312377
Trifarotene placebo cream 50g tube	3924524	312376

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Reference Therapy, Dose and Mode of Administration, Batch Number:	Vehicle cream • Double-blind Period dose, route, frequency: Up to 36 g per dose applied topically twice weekly on up to 90% BSA	
Duration of Study Participation:	The sequence and maximum duration of the study periods for each subject were as follows: 1. Screening: Up to 97 days. Before asking a subject to enter washout, investigators were to confirm the subject met study eligibility criteria, except for LI severity (Inclusion Criterion #3), which would be assessed after washout. Washout could be up to 90 days. After completing any necessary Washout Period, subjects returned to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and final study eligibility requirements determined. 2. Double-blind study drug application: Twice weekly for 90 days. 3. Optional Open-label Extension: Twice weekly for 90 days. 4. Follow-up: 14 days after last study drug application. The maximum treatment duration for each subject was approximately 90 days for subjects who chose not to continue into the OLE, and 180 days for those who chose to continue. The maximum study duration for each subject was approximately 291 days.	
Criteria for Evaluation:		
Efficacy:	The proportion of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear on treated areas and at least a 2-grade change from Baseline at Day 90/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA full body scale. Secondary endpoints: • The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through Day 90 • 5-point Visual Index for Ichthyosis Severity (VIIS) for scaling (overall 16 points for scaling, i.e. 0–4 points for 4 body areas: chest/abdomen, back, arms and legs) • Individual score for roughness overall (Scale: 0–4) • Palm/sole Assessment (Scale: 0–4) • Quality of life per Dermatology Life Quality Index (DLQI) and children's DLQI (cDLQI)	

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Safety:	• The difference in proportion of subjects with presence of fissures on palms/soles (presence/absence, number of fissures, and pain associated with fissures on a 0-3 scale) at Day 90 between the active trifarotene cream HE1 and vehicle groups • Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs • Local tolerability (stinging/burning, pruritus, or erythema on 0–3 scales [none, mild, moderate, severe], determined by the investigator) for each body area (chest/abdomen, back, legs, arms, and face/neck)
Pharmacokinetic:	• Plasma concentrations of CD5789 and its major metabolites were to be measured
Exploratory:	• The difference in mean ectropion scores (ESS of 0–8) between the active trifarotene cream HE1 and vehicle groups from Baseline through Day 90 • The difference in quality of life per EQ-5D-5L and EQ-5D-Y scores between the active trifarotene cream HE1 and vehicle groups from Baseline through Day 90
Statistical Methods:	The study sponsor terminated this study for futility on 30-Jul-2021 after inclusion of 65 randomized subjects. Study flow, subject disposition, and descriptive data are presented in this abbreviated report. No formal statistical analyses were conducted. This study did not satisfy the enrollment requirements of its protocol, hence, it failed to meet the expectations required for meaningful statistical analysis. Nevertheless, all analyses were conducted in accordance with the statistical analysis plan (although all reported P-values should be considered only as informative).
SAFETY RESULTS	This study failed to satisfy the enrollment requirements of its protocol; hence, it failed to meet the expectations required for meaningful analysis.
CONCLUSION:	The evaluation of AEs, routine laboratory examinations, physical examinations, ECG recordings, and measurements of vital signs (blood pressure and pulse rate) revealed no safety concerns. No deaths, SAEs, or other significant AEs occurred within this study. No subject was withdrawn from the study due to an AE. All TEAEs were of mild or moderate severity; there were no severe TEAEs during the study. The majority of TEAEs were considered not related to study treatment. As expected, the most common TEAEs during the Double-blind Period were in the Skin and subcutaneous tissue disorders SOC, but only pruritus was experienced by ≥5% of subjects in any treatment group (2 subjects, 8.7% in the trifarotene cream HE1 200 µg/g group).

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	Other common TEAEs (≥5% overall) in the overall safety population during the Double-blind Period included back pain, headache, and dysmenorrhea, none of which was considered related to study treatment. During the OLE Period, headache and back pain were the most common TEAEs, and none was considered related to study treatment. No related TEAE was experienced by more than 1 subject overall in either period of the study. Local tolerability assessments were generally good; the majority of subjects in each treatment group reporting no erythema, stinging/burning, or pruritus for any of the locations (face/neck, chest/abdomen, back, legs, or arms) in both study periods.	
Date of the Report:	18-Jan-2022	