



# Topical Isotretinoin (TMB-001) Treatment for 12 Weeks Did Not Result in Clinically Relevant Laboratory Abnormalities in Participants with Congenital Ichthyosis in the Phase 2b CONTROL Study

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## ABSTRACT

**Introduction:** Treatment with oral retinoids can be effective in patients with congenital ichthyosis (CI) but may be associated with clinically significant laboratory changes. In this Phase 2b CONTROL study analysis, we characterize the effects of TMB-001, a novel topical isotretinoin formulation, on laboratory values in participants with X-linked recessive (XLRI)

and autosomal recessive lamellar (ARCI-LI) ichthyosis at 12 weeks.

**Methods:** A randomized, double-blind, vehicle-controlled, Phase 2b study was conducted with participants  $\geq 9$  years of age with confirmed XLRI and ARCI-LI. Participants were randomized 1:1:1 and stratified by CI subtype to receive TMB-001 0.05%:TMB-001 0.1%:vehicle twice daily for 12 weeks. Laboratory analyses were performed at screening and Week 12.

**Results:** Among 33 enrolled participants (TMB-001 0.05%  $n = 11$ , TMB-001 0.1%  $n = 10$ , and

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vehicle  $n = 12$ ), 52% had ARCI-LI and 48% had XLRI. At 12 weeks, there were single reports of anemia, neutropenia, leukopenia, lymphocytosis, and leukocytosis after vehicle treatment; neutropenia was reported in one participant receiving TMB-001 0.1%. There were single reports of abnormal biochemistry values—liver enzymes, creatinine, urea nitrogen, hyperkalemia, and hyperproteinemia—across treatment cohorts. Non-fasting hyperglycemia was observed in three participants receiving TMB-001 0.1% and one participant receiving vehicle. Urinalysis abnormalities reported in > 1 participant included urobilinogen (TMB-001 0.1%  $n = 2$ , vehicle  $n = 2$ ), protein (TMB-001 0.1%  $n = 3$ , vehicle  $n = 2$ ), and leukocyte esterase (TMB-001 0.1%  $n = 2$ ). Laboratory parameter changes were asymptomatic and did not require study discontinuation or drug withdrawal.

**Conclusion:** There were no clinically significant laboratory changes in participants receiving TMB-001 isotretinoin ointment through 12 weeks of treatment, which differs from reported results for systemic isotretinoin. Trial Registration: NCT04154293.

**Keywords:** Autosomal recessive lamellar; Congenital ichthyosis; Isotretinoin; TMB-001; X-linked recessive ichthyosis

### Key Summary Points

In participants with severe forms of congenital ichthyosis, treatment with systemic retinoids has been effective for managing ichthyosis symptoms, though chronic use of systemic retinoids is associated with dose-limiting adverse effects and systemic toxicities, including neutropenia, leukocyte changes, increased or decreased platelet counts, and lipid and transaminase abnormalities.

TMB-001 is a proprietary, novel, topical isotretinoin ointment formulation to treat patients with congenital ichthyosis; it demonstrated a favorable safety profile with no evidence of significant systemic exposure to isotretinoin and positive efficacy results through 12 weeks of treatment in Phase 2a and Phase 2b studies.

There were no clinically significant laboratory changes observed in participants  $\geq 9$  years of age receiving TMB-001 ointment through 12 weeks of treatment, supporting the potential use of TMB-001 as an alternative to systemic retinoids to treat congenital ichthyosis, with a reduced risk of hematological and blood chemistry laboratory abnormalities.

## INTRODUCTION

Congenital ichthyosis (CI) includes a wide range of keratinizing disorders, generally resulting from gene mutations that produce defects in the biosynthesis of proteins and lipids important for normal skin barrier formation and leading to severe impairments in barrier function [1–3]. Hyperkeratosis and widespread skin scaling are clinical hallmarks of the more common X-linked recessive (XLRI) and less common autosomal recessive lamellar (ARCI-LI) ichthyosis subtypes [4], which have an estimated prevalence of 1:2000 to 1:6000 and 1:100,000, respectively [3, 4]. Treatments for ichthyoses typically focus on ameliorating symptoms by improving skin barrier function with the use of emollients and other topical treatments [2]. In participants with more severe forms of CI (e.g., ARCI-LI and XLRI subtypes), treatment with systemic retinoids has been effective for managing CI symptoms [1, 5]. However, chronic use of systemic retinoids is associated with dose-limiting adverse effects and systemic toxicities [1]. Oral isotretinoin treatment of  $\geq 4$  weeks has been shown to

produce statistically significant changes from baseline in laboratory values for hepatic enzymes, total cholesterol, triglycerides, and white blood cell counts [6], which can result in clinically significant effects on renal, inflammatory, and immune functions [7], underscoring a critical need for effective and safe topical treatments that can be used for long-term therapy in participants with CI.

TMB-001 is a proprietary, novel, topical isotretinoin ointment formulation that uses a patented polyethylene glycol (IPEG<sup>TM</sup>) technology isotretinoin delivery system developed to improve skin hydration and reduce scaling in participants with CI. It demonstrated a favorable safety profile with no evidence of significant systemic exposure to isotretinoin through 12 weeks of treatment in the Phase 2a study [8]. In the Phase 2b study, the primary and key secondary efficacy endpoints—a 50% improvement in Visual Index for Ichthyosis Severity scaling scores (VIIS-50) and  $\geq 2$ -grade improvement in Investigator's Global Assessment (IGA) scores from baseline, respectively—were achieved by 64%, 40%, and 33% (VIIS-50) and 55%, 40%, and 8% (IGA success) of participants receiving TMB-001 0.05%, TMB-001 0.1%, and vehicle, respectively (intent-to-treat [ITT] population) [9]. Here, we report safety results from the Phase 2b CONTROL study, detailing changes in clinical laboratory assessments following treatment with two concentrations of TMB-001 or vehicle in participants with XLRI and ARCI-LI, and use these changes as surrogates for systemic absorption of TMB-001.

## METHODS

### Study Design and Participants

This was a randomized, parallel, double-blind, vehicle-controlled, Phase 2b study (NCT04154293) designed to evaluate safety and efficacy of TMB-001 for treatment of CI in participants with ARCI-LI or XLRI subtypes in 11 study centers in the USA and Australia. The study was approved by institutional review boards/independent ethics committees at each

center and was conducted according to the International Council for Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki principles. All participants provided written informed consent. Legal guardians or parents provided written informed assent for participants < 18 years of age.

Eligible participants were  $\geq 9$  years of age with moderate-to-severe CI genetically confirmed to be ARCI-LI or XLRI, involving 10–90% of total body surface area and at least two of the four VIIS [10] assessment areas with a scaling score  $\geq 3$ . Women of child-bearing potential had to be surgically sterile or have a negative urine pregnancy test at baseline and continued use of contraception during the study. Exclusion criteria included inflammatory skin diseases unrelated to ichthyosis (e.g., atopic dermatitis), ichthyosis refractory to previous oral and/or topical retinoid treatment, ultraviolet treatment within  $\leq 4$  weeks of baseline, other topical treatments (including emollients) at baseline prior to randomization, and systemic retinoid use  $\leq 12$  weeks before baseline. Participants meeting all inclusion criteria were randomized 1:1:1 to receive TMB-001 0.05%:TMB-001 0.1%:vehicle twice daily to the investigator-determined treatment areas for 12 weeks. Participants were allowed to apply the study drug to the entire body affected with CI, excluding the hands, face, neck, scalp, and genitalia. However, assessments were performed on designated VIIS assessment areas within the overall treatment area, including the upper back (encompassing T1 to T10 vertebrae), the left or right upper arm (excluding the elbow), the left or right shin/lower leg, and the left or right dorsal foot. The vehicle was designed to have emollient properties to ensure participants were receiving standard of care. Compliance was measured as application between 80% and 120% of the expected number of doses.

### Assessments

The primary efficacy endpoint was the proportion of participants achieving VIIS-50 treatment success at the end of the study—defined as a  $\geq 50\%$  improvement from baseline for the sum

of VIIS scaling scores at target sites with a baseline score  $\geq 3$  [10]. The key secondary efficacy endpoint was the proportion of participants achieving IGA treatment success, defined as at least a 2-grade reduction in IGA severity score compared with baseline at the end of the study. Safety assessments included the monitoring of adverse events (AEs) and local skin reactions (LSRs), including burning/stinging, erythema, erosions, and edema. Evaluation of vital signs and clinical laboratory analyses, including hematology, biochemistry, and urinalysis, were performed at screening and at Week 12.

### Statistical Analysis

As this was the first study of TMB-001 using the VIIS index, no formal power calculations were performed to establish sample size. The ITT population included all randomized participants who took at least one dose of study medication. All participants enrolled in the study who took at least one dose of study treatment were included in the safety population. All laboratory test results were summarized for each treatment group using descriptive statistics for raw numbers and change from baseline. The incidence of treatment-emergent abnormal laboratory values was also summarized using descriptive statistics. All analyses were performed using SAS version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

## RESULTS

### Participant Disposition, Demographics, and Clinical Characteristics

Overall, 33 participants were randomized to TMB-001 0.05% ( $n = 11$ ), TMB-001 0.1% ( $n = 10$ ), and vehicle ( $n = 12$ ; Fig. 1). The ITT population included 17 (52%) participants with ARCI-LI and 16 (48%) with XLRI (Table 1). The mean  $\pm$  standard deviation age (in years) was  $34.5 \pm 20.7$ , with similar mean ages observed across treatment cohorts (Table 1). Of the total enrolled participants, most were male (64%)

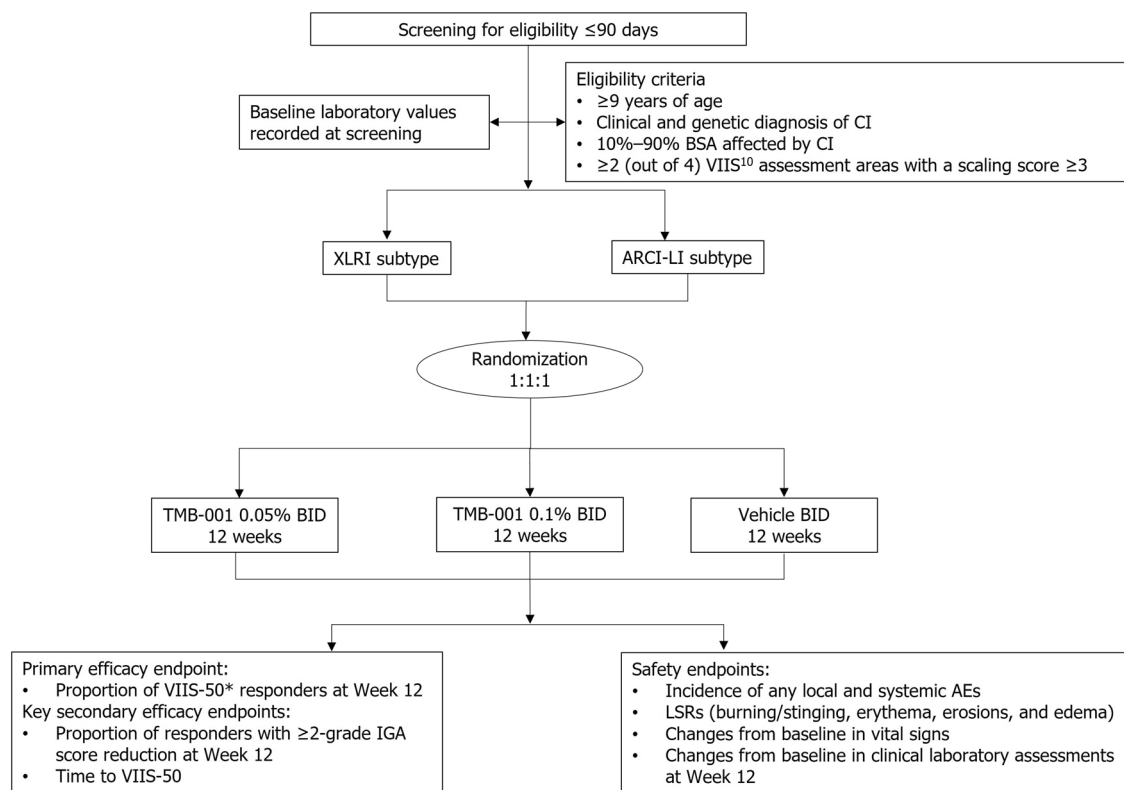
and white (79%), with six participants (18%) identifying as Hispanic, three participants identifying as Asian, and one participant identifying as black. Mean body surface area affected with ichthyosis at baseline was 74%, and the estimated range of TMB-001 isotretinoin administered to the skin was 9.0–22.5 mg per dose. Three (9%) participants had treatment-emergent AEs leading to study withdrawal, including one participant from each treatment arm. There were no reported participant serious AEs or deaths during the study.

### Hematology Results

In the majority of participants, hematology values remained within clinically normal limits at the end of the study (Table 2). In the vehicle cohort, there were single reports of participants with anemia, neutropenia, leukopenia, lymphocytosis, and leukocytosis. There was one participant receiving TMB-001 0.1% who had a low neutrophil count. There were no hematological abnormalities reported in participants receiving TMB-001 0.05%, and there were no hematological abnormalities reported in levels of platelets, reticulocytes/erythrocytes, eosinophils, or basophils at 12 weeks in any treatment cohort.

### Biochemistry Results

At 12 weeks, there were multiple single reports of elevated levels of creatinine, urea nitrogen, alkaline phosphatase, hyperkalemia, hyperglycemia, hyponatremia, and hyperproteinemia across treatment cohorts (Fig. 2). In each treatment cohort, there was one participant exhibiting elevated levels of alanine aminotransferase and aspartate aminotransferase. Biochemistry abnormalities that occurred with higher frequency (at least one participant) included elevated alkaline phosphatase levels in three participants receiving TMB-001 0.1% and two participants receiving vehicle, and non-fasting hyperglycemia in three participants receiving TMB-001 0.1%. There were no biochemistry abnormalities occurring in one or more participants in the TMB-001 0.05%



**Fig. 1** Study design. \*VIIS-50 was defined as  $\geq 50\%$  improvement relative to baseline in the sum of scores for VIIS scaling target sites that had baseline scores  $\geq 3$ . *AE* adverse event, *ARCI-LI* autosomal recessive lamellar ichthyosis, *BID* twice daily, *BSA* body surface area, *CI*

congenital ichthyosis, *IGA* Investigator’s Global Assessment, *LSR* local skin reaction, *VIIS* Visual Index for Ichthyosis Severity, *VIIS-50*  $\geq 50\%$  reduction in VIIS, *XLRI* X-linked recessive ichthyosis

cohort, and there were no clinically significant changes in direct bilirubin, bilirubin, or calcium levels reported at 12 weeks in any treatment arm.

### Urinalysis Results

At 12 weeks, multiple participants exhibited a single abnormal urinalysis result, including bilirubin, ketones, epithelial cells, occult blood, and specific gravity (Fig. 3). Urinalysis abnormalities that occurred with higher frequency (at least one participant) included abnormal urobilinogen levels in two participants receiving TMB-001 0.1% and two participants receiving vehicle; abnormal protein levels in one, three, and two participant(s) receiving TMB-001 0.05%, TMB-001 0.1%, and vehicle,

respectively; and abnormal leukocyte esterase levels in two and one participant(s) receiving TMB-001 0.1% and vehicle, respectively. The majority of urinalysis abnormalities occurring in at least one participant were reported in the TMB-001 0.1% and vehicle groups. There were no clinically significant changes in glucose, nitrite, or pH values, nor correlation with reduced kidney function reported from biochemistry evaluation at 12 weeks in any treatment cohort.

### DISCUSSION

In this Phase 2b randomized CONTROL study, clinical efficacy appears to have been accompanied by no clinically significant laboratory changes observed in participants  $\geq 9$  years of

**Table 1** Participant demographics and baseline clinical characteristics

Parameter	TMB-001 0.05% <i>n</i> = 11	TMB-001 0.1% <i>n</i> = 10	Vehicle <i>n</i> = 12
Age, mean (SD), years	31.9 (18.6)	34.5 (19.7)	36.8 (24.6)
Sex, male	8 (73)	5 (50)	8 (67)
Race			
American Indian or Alaskan Native	1 (9)	0	0
Asian	1 (9)	1 (10)	1 (8)
Black or African American	0	1 (10)	0
White	8 (73)	8 (80)	10 (83)
Other	1 (9)	0	1 (8)
Ethnicity			
Hispanic or Latino	2 (18)	1 (10)	3 (25)
Not Hispanic or Latino	9 (82)	9 (90)	9 (75)
Congenital ichthyosis subtype			
ARCI-LI	4 (36)	6 (60)	7 (58)
XLRI	7 (64)	4 (40)	5 (42)
BMI, mean (SD), kg/m <sup>2</sup>	28.25 (7.59)	28.03 (6.75)	25.95 (5.74)
VIIS scaling, mean	2.9	3.1	2.8
IGA score, mean	3.2	3.6	3.3
DLQI score, mean	7.8	5.1	8.3
cDLQI, mean	1.3	3.0	1.3
I-NRS, mean	4.5	2.0	3.1

All data presented as *n* (%) unless otherwise noted

*ARCI-LI* autosomal recessive lamellar ichthyosis, *BMI* body mass index, *cDLQI* Children's Dermatology Life Quality Index, *DLQI* Dermatology Life Quality Index, *IGA* Investigator's Global Assessment, *I-NRS* Itch-Numeric Rating Scale, *SD* standard deviation, *VIIS* Visual Index for Ichthyosis Severity, *XLRI* X-linked recessive ichthyosis

age receiving TMB-001 ointment through 12 weeks of treatment. There were single reports of abnormal laboratory values that were not clinically significant in participants across treatment arms; however, laboratory values remained within clinically normal limits for most participants. Clinical abnormalities occurred at similar frequencies in participants receiving TMB-001 ointment and those receiving vehicle, and the most frequent clinical

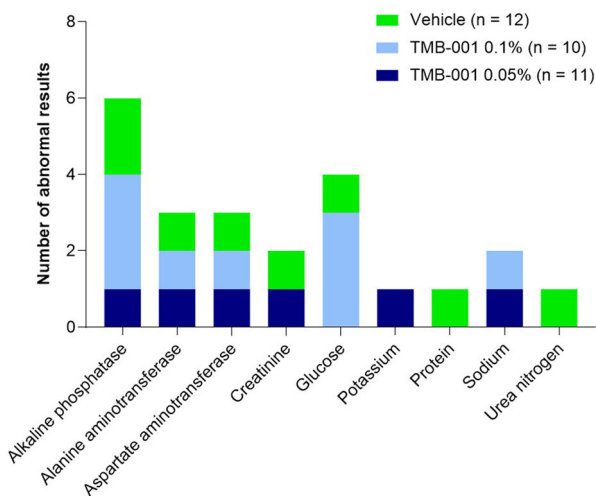
abnormalities included non-fasting hyperglycemia and elevated levels of alkaline phosphatase, urobilinogen, protein, and leukocyte esterase. None of these events led to study discontinuation or temporary drug stoppage, and these results are consistent with previous studies evaluating the safety of TMB-001 in participants with CI. A smaller, previous Phase 2a study evaluating the efficacy, safety, and tolerability of TMB-001 in participants



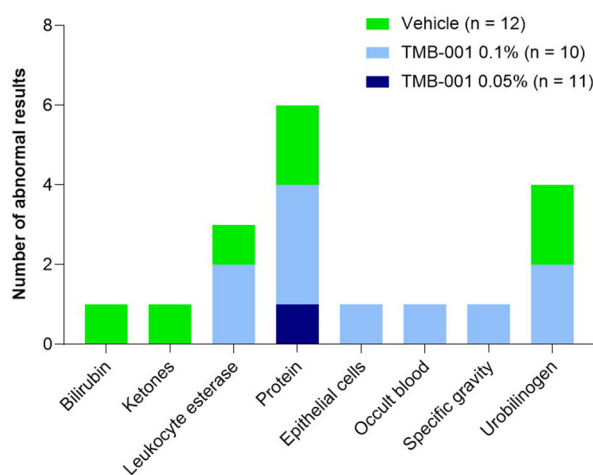
**Table 2** Hematology results at Week 12

	TMB-001 0.05% (n = 11)		TMB-001 0.1% (n = 10)		Vehicle (n = 12)	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Platelets	7 (64)	0	8 (80)	0	7 (58)	0
Erythrocytes	7 (64)	0	8 (80)	0	6 (50)	1 (8)
Hemoglobin	7 (64)	0	8 (80)	0	6 (50)	1 (8)
Hematocrit	7 (64)	0	8 (80)	0	6 (50)	1 (8)
Reticulocytes/erythrocytes	7 (64)	0	8 (80)	0	7 (58)	0
Erythrocyte mean corpuscular volume	7 (64)	0	8 (80)	0	6 (50)	1 (8)
Erythrocyte mean corpuscular hemoglobin	7 (64)	0	8 (80)	0	6 (50)	1 (8)
Neutrophils	7 (64)	0	7 (70)	1 (10)	6 (50)	1 (8)
Lymphocytes	7 (64)	0	8 (80)	0	6 (50)	1 (8)
Monocytes	7 (64)	0	8 (80)	0	6 (50)	1 (8)
Eosinophils	7 (64)	0	8 (80)	0	7 (58)	0
Basophils	7 (64)	0	8 (80)	0	7 (58)	0
Leukocytes	7 (64)	0	8 (80)	0	6 (50)	1 (8)

Data shown as *n* (%), where the percentage is calculated as the number of observations per number of expected observations



**Fig. 2** Abnormal biochemistry results in participants receiving TMB-001 0.05%, TMB-001 0.1%, and vehicle at 12 weeks by treatment. Bars represent the number of abnormal values reported at 12 weeks in participants receiving TMB-001 0.05%, TMB-001 0.1%, and vehicle



**Fig. 3** Abnormal urinalysis results in participants receiving TMB-001 0.05%, TMB-001 0.1%, and vehicle at 12 weeks by treatment. Bars represent the number of abnormal values reported at 12 weeks in participants receiving TMB-001 0.05%, TMB-001 0.1%, and vehicle

aged  $\geq 12$  years with XLRI or ARCI-LI also reported no significant changes in laboratory values through 12 weeks of treatment [8].

Most persons with CI require lifelong treatment, typically with daily applications of emollients and other topical agents aimed at improving the barrier function of the skin. Another key component in the management of CI has been the use of oral or topical retinoids, which exert keratolytic effects that facilitate the reduction of scaling and prevent hyperkeratosis [3, 5]. Importantly, laboratory monitoring is essential for participants receiving long-term treatment with systemic retinoids due to significant risks for AEs and systemic toxicities, including cheilitis, hyperlipidemia, elevated liver enzymes, bone toxicities, and teratogenicity [1]. Oral isotretinoin treatment has been associated with significant changes in laboratory values for hepatic enzymes, total cholesterol, triglycerides, white blood cell and platelet counts, and increases in hemoglobin and blood urea nitrogen [6, 7]. The results from this analysis indicate that TMB-001 did not result in any clinically significant changes to hematology, biochemistry, or urinalysis values during 12 weeks of treatment, similar to vehicle, underscoring its safety and lack of significant systemic absorption, which is consistent with results observed in a Phase 2a study with TMB-001 [8]. Ultimately, this topical retinoid formulation may provide an alternative to systemic retinoids, with a reduced risk of laboratory abnormalities during long-term treatment of CI.

The limitations of this study include a small sample size, a limited study timeframe of 12 weeks, a lack of power for statistical analyses, few participants with skin of color, and the lack of lipid profile analysis.

## CONCLUSIONS

The results from this Phase 2b study indicating no clinically significant laboratory abnormalities between the two active TMB-001 topical isotretinoin treatments and vehicle, as well as no substantial systemic AEs commonly associated with oral retinoids, such as headaches,

vision changes, epistaxis, cheilitis, pancreatitis, or nail abnormalities [9], provide support for future safety and efficacy investigations of TMB-001 as a promising and safe therapeutic alternative to systemic retinoids. A Phase 3 study currently recruiting participants (NCT05295732) has begun to expand on these results and further establish the long-term safety and efficacy of TMB-001 0.05% in participants with CI, including a broader study of incidence of hyperlipidemia with TMB-001 treatment.

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**Author Contributions.** All authors contributed to the study design, data collection and analysis, and drafting and critical review of the manuscript. All authors approve of the final manuscript and accept accountability for the accuracy and integrity of the final manuscript.

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Atacama, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Cara, Cassiopeia, Celgene, Concert Pharmaceuticals, Crown Therapeutics, Cutanea, Dermavant, Dermira, Edesa, Eli Lilly, Foamix, Forte, Gage, Galderma, Glenmark, Incyte, Janssen, LEO Pharma, Novan, Novartis, Novum, Pfizer, Rapt, Regeneron, Sanofi Genzyme, Sun Pharma, Timber Pharmaceuticals, Vanda, Verrica, Vidac, and UCB Pharma. Christopher G. Bunick served as an investigator for Almirall; a consultant for Almirall, Arcutis, Biofrontera, EPI Health, LEO Pharma, Sanofi-Regeneron, and UCB; and as a speaker for and a recipient of honoraria from Allergan, Almirall, LEO Pharma, and UCB. Steven Kempers served as a consultant for Arcutis Biotherapeutics and a clinical trial investigator for AbbVie, Amgen, Arcutis Biotherapeutics, Brickell Biotech, Bristol Myers Squibb, Candesant Biomedical, Concert Pharmaceuticals, Dermira, Edesa Biotech, Eli Lilly, Forte Biosciences, Galderma, Incyte Corporation, NFlection Therapeutics, Novan, Novartis, Palvella Therapeutics, and Timber Pharmaceuticals. Leslie Castelo-Soccio received honoraria from and served on an advisory panel for Pfizer. Alan M. Mendelsohn and Jessica Raiz are employees of Timber Pharmaceuticals. Dédée F. Murrell served as an investigator and advisor for AbbVie, Amgen, ArgenX, Dermira, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Principia Biopharma, Roche, Sanofi, Sun Pharma, and Timber Pharmaceuticals, and served on an advisory board for Eli Lilly, Immune Pharmaceuticals, and Principia Biopharma.

**Compliance With Ethics Guidelines.** The study was approved by institutional review boards/independent ethics committees at each center and was conducted according to the International Council for Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki principles. All participants provided written informed consent. Legal guardians or parents provided written informed assent for participants < 18 years of age.

**Data Availability.** The datasets generated during and/or analyzed during the current

study are available from the corresponding author on reasonable request.

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