6-1-2019

Randomized phase 3 evaluation of trifarotene 50 μg/g cream treatment of moderate facial and truncal acne.

Jerry Tan

Diane Thiboutot

Georg Popp

Melinda Gooderham

Charles Lynde

See next page for additional authors

Authors
Jerry Tan, Diane Thiboutot, Georg Popp, Melinda Gooderham, Charles Lynde, James Del Rosso, Jonathan Weiss, Ulrike Blume-Peytavi, Jolanta Weglovska, Sandra Johnson, Lawrence Parish, Dagmara Witkowska, Nestor Sanchez Colon, Alessandra Alió Saenz, Faiz Ahmad, Michael Graeber, and Linda Stein Gold

Randomized phase 3 evaluation of trifarotene 50 μg/g cream treatment of moderate facial and truncal acne

Jerry Tan, MD,[a] Diane Thiboutot, MD,[b] Georg Popp, MD,[c] Melinda Gooderham, MD,[d] Charles Lynde, MD,[e] James Del Rosso, DO,[f] Jonathan Weiss, MD,[g] Ulrike Blume-Peytavi, MD,[h] Jolanta Weglovska, MD,[i] Sandra Johnson, MD,[j] Lawrence Parish, MD,[k] Dagmara Witkowska, MD,[l] Nestor Sanchez Colon, MD,[m] Alessandra Alió Saenz, MD,[n] Faiz Ahmad, MS,[n] Michael Graeber, MD,[n] and Linda Stein Gold, MD[o]

Windsor, Peterborough, and Markham, Ontario, Canada; Hershey and Philadelphia, Pennsylvania; Augsburg and Berlin, Germany; Las Vegas, Nevada; Snellville Georgia; Wrocław, Poland; Fort Smith, Arkansas; San Juan, Puerto Rico; Fort Worth Texas; and Detroit, Michigan

Background: Acne vulgaris often affects the face, shoulders, chest, and back, but treatment of nonfacial acne has not been rigorously studied.

Objectives: Assess the safety and efficacy of trifarotene 50 μg/g cream, a novel topical retinoid, in moderate facial and truncal acne.

Methods: Two phase III double-blind, randomized, vehicle-controlled, 12-week studies of once-daily trifarotene cream versus vehicle in subjects aged 9 years or older. The primary end points were rate of success on the face, as determined by the Investigator's Global Assessment (clear or almost clear and ≥2-grade improvement), and absolute change from baseline in inflammatory and noninflammatory counts from baseline to week 12. The secondary end points were rate of success on the trunk (clear or almost clear and ≥2-grade improvement) and absolute change in truncal inflammatory and noninflammatory counts from baseline to week 12. Safety was assessed through adverse events, local tolerability, vital signs, and routine laboratory testing results.

From Department of Medicine,[a] University of Western Ontario, Windsor; Penn State Hershey Medical Center and Penn State College of Medicine[b]; Licca Clinical Research Institute,[c] Augsburg; SKIN Centre for Dermatology and SKIN Laser Clinic,[d] Peterborough; Lynde Institute for Dermatology,[e] Markham; JDR Dermatology Research/Thomas Dermatology,[f] Las Vegas; Gwinnett Dermatology, PC, and Gwinnett Clinical Research Center, INC,[g] Snellville; Department of Dermatology and Allergy,[h] Charité Universitätsmedizin, Berlin; Niepubliczny Zakład Opieki Zdrowotnej multiMedica,[i] Wrocław; Johnson Dermatology,[j] Fort Smith; Department of Dermatology and Cutaneous Biology and the Jefferson Center for International Dermatology,[k] Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia; DermMedica Sp,[l] Wrocław; University of Puerto Rico, School of Medicine,[m] San Juan; Galderma R&D LLC,[n] Fort Worth; Henry Ford Medical Center, Department of Dermatology,[o] Detroit.

Funding sources: Supported by Nestle Skin Health Care- Galderma R&D, LLC, Fort Worth, Texas, USA.

Disclosure: Dr Tan has served as a consultant, speaker, and investigator for Galderma. Dr Thiboutot has served as an investigator and consultant for Galderma, Dermik, Novan, Cassiopea, Novartis, and Botanix. Dr Popp, Dr Gooderham, Dr Weiss, Dr Sanchez Colon, Dr Witkowska, and Dr Parish have served as investigators for Galderma. Dr Del Rosso and Dr Johnson have served as investigators, consultants, and speakers for Galderma. Dr Lynde has served as consultant, speaker, and investigator and has participated in advisory boards for Valeant Pharma and Galderma; in addition, he has served as an investigator for Xenon and Demira. Dr Blume-Peytavi has received honoraria for lectures from Nestlé Skin Health—Galderma and has received fees for the conduct of clinical studies. Dr Weglovska has served as an advisory board member and investigator for Galderma and has served as a consultant and investigator for Dermira, Regeneron, UCB, Leo Pharma, Mercu, and Amgen. Dr Stein Gold has served as an investigator, advisor, and speaker for Galderma, Valeant, Novartis, and Allergan and as an investigator and advisor for Derma; in addition, she has also served as an investigator for Novan and Cassiopea. Dr Graeber, Mr Ahmad, and Dr Alió Saenz are employees of Galderma Research and Development LLC.

Accepted for publication February 19, 2019.

Correspondence to: Alessandra Alió Saenz, MD, Galderma Laboratories, LLP, 14501 N Freeway Service Road E, Fort Worth, TX 76177. E-mail: alessandra.alio@galderma.com.

Published online February 22, 2019.

0190-9622

https://doi.org/10.1016/j.jaad.2019.02.044

Results: In both studies, at week 12 the facial success rates according to the Investigator's Global Assessment and truncal Physician's Global Assessment and change in inflammatory and noninflammatory lesion counts (both absolute and percentage) were all highly significant ($P < .001$) in favor of trifarotene when compared with the vehicle.

Limitations: Adjunctive topical or systemic treatments were not studied.

Conclusion: These studies demonstrate that trifarotene appears to be safe, effective, and well tolerated in treatment of both facial and truncal acne. (J Am Acad Dermatol 2019;80:1691-9.)

Key words: acne vulgaris; phase 3 trial; pivotal trials; trifarotene; truncal acne.

CAPSULE SUMMARY

- Trifarotene is a new retinoic acid receptor gamma-γ—selective topical retinoid cream formulation that is suitable for use on the face and trunk.
- Trifarotene appears to be safe and efficacious as treatment of moderate acne on the face and trunk. Local tolerability was acceptable and manageable on the face and trunk.

Acne vulgaris (AV) is one of the most common skin diseases, and it has a multifactorial pathogenesis that centers on pilosebaceous units.[1,2] Because the pathophysiology and clinical presentations of facial and truncal acne are considered to be similar, clinicians often apply the same therapeutic approach for facial and nonfacial lesions despite a lack of evidence in truncal AV.[3-5] A variety of treatment options are currently available for AV, but they have not been rigorously studied in truncal disease.

Trifarotene 50 μg/g cream is a new selective retinoic acid receptor (RAR)-γ (RARγ) topical retinoid and is unique in that its clinical development program included evaluation of performance in both moderate facial and truncal acne. The selectivity of trifarotene for RARγ distinguishes it from the existing first- and third-generation topical retinoids, which target both RARβ and RARγ.[6] Trifarotene is pharmacokinetically stable in keratinocytes but is rapidly metabolized in hepatic microsomes, predicting a favorable safety profile; in addition, it has comedolytic, anti-inflammatory, and antipigmenting properties. The primary efficacy results from 2 large-scale phase III studies (PERFECT 1 and PERFECT 2 ClinicalTrials.gov registration number NCT02566369 and NCT02556788, respectively, and European Clinical Trials Database numbers 2016-002860-15 and 2016-002540-13, respectively]) are reported here.

METHODS

Study design

PERFECT 1 and PERFECT 2 were identical in design and conducted in the United States, Canada, Europe, and Russia from 2015 to 2017. Both studies were 12-week, double-blinded, multicenter, and vehicle controlled, with a 1:1 randomization pattern (once-daily trifarotene 50 μg/g or vehicle cream). Randomization was stratified by study center with use of an interactive response technology system. The clinical study was conducted according to standard recognized practices, as detailed in the Supplemental Information (additional details about the methods and a complete disposition chart are available at http://dx.doi.org/10.17632/cfjst82z93.1).

Instruction was provided to all patients or caregivers about how to apply a thin layer of the study drug daily at bedtime on the face and self-reachable trunk, including areas with no clinically evident acne. Patients were also instructed to cleanse the skin and not apply moisturizer 1 hour before or 1 hour after application of the study drug. Use of moisturizer was encouraged from the initiation of treatment. Investigators could reduce the frequency of application to alternate days for a maximum of 2 weeks in the first 4 weeks following the baseline visit, when needed to manage irritation.

Study participants

The eligibility criteria were patient age 9 years and older, moderate facial acne (defined as an Investigator's Global Assessment [IGA] score of 3 on the face [≥20 inflammatory lesions and ≥25 noninflammatory lesions]), and moderate truncal acne (defined as a Physician's Global Assessment [PGA] score of 3 at screening and baseline [≥20 inflammatory lesions and 20 to <100 noninflammatory lesions on the areas of the trunk reachable for self-application]). Accessible treated areas of the trunk were defined for the study. The trunk anatomic

Abbreviations used:

AE: adverse event
AV: acne vulgaris
IGA: Investigator's Global Assessment (facial acne)
PGA: Physician's Global Assessment (truncal acne)
RAR: retinoic acid receptor
RARγ: retinoic acid receptor-γ
TEAE: treatment-emergent adverse event

region assessment was predefined by a size-fitted T-shirt (patent No. US00D758048S [approved June 7, 2016]). This ensured consistency for study assessment areas throughout the study duration. For subjects aged 9 to 11 years, the inclusion criteria regarding truncal acne were optional owing to the relative rarity of truncal involvement (compared with facial involvement) in this age group.

The exclusion criteria were severe forms of acne; more than 1 nodule on the face; more than 1 nodule on the trunk; presence of acne cysts, beard, or facial hair that could interfere with study assessments; presence of tattoos that could interfere with study assessments; uncontrolled or serious disease or medical condition; clinically significant abnormal laboratory values; known or suspected allergies or sensitivities to the planned study drugs; and lactation or intent to conceive during the study in women. In addition, prohibited medication use and washout periods of 1 to 4 weeks were specified for use of antiacne treatments (prescription and over-the-counter), nonsteroidal anti-inflammatory drugs, corticosteroids, and antibiotics (but 6 months for use of oral retinoids and immunomodulators).

Efficacy and safety assessments

The 3 coprimary efficacy end points were rate of success, as determined according to the IGA (defined as the percentage of subjects who achieved an IGA face rating of clear [0] or almost clear [1]) and at least a 2-grade change from baseline) at week 12; the absolute change in facial inflammatory lesion count; and the absolute change in noninflammatory lesion count from baseline to week 12. There were also 3 secondary efficacy end points: rate of success, as determined according to the PGA (defined as percentage of subjects achieving a rating of clear or almost clear on and at least a 2-grade change from baseline) at week 12; absolute change in truncal inflammatory lesion count from baseline to week 12; and absolute change in truncal noninflammatory lesion count from baseline to week 12. The definitions of severity for the IGA and PGA scales (5-point scales ranging from 0 [clear] to 4 [severe]) were the same.

Lesion counts were performed, and IGA and PGA scores were assessed at screening; at baseline; and at the week 1, 2, 4, 8, and 12/early termination visits.

The safety assessments included treatment-emergent adverse events (TEAEs); standard laboratory safety test results at screening; and results at the last study visit, including the following: hematology, blood chemistry, and urinalysis results (BARC Central Laboratory, Lake Success, NY, and Gent, Belgium); physical examination findings; and monitoring of vital signs. Local tolerability signs and symptoms expected with a topical retinoid were collected separately from adverse events (AEs) to better characterize the tolerability profile of trifarotene cream. These included erythema, scaling, dryness, and stinging/burning, which were scored on a 4-point scale (according to which a score of 0 indicated none, 1 indicated mild, 2 indicated moderate, and 3 indicated severe). Subjects were specifically queried at each study visit, including at baseline, for the presence of local signs or symptoms. Signs and/or symptoms of local cutaneous irritation assessed with the tolerability scale were considered to be AEs if they were severe enough to lead to permanent discontinuation of treatment with the study product or if they required use of concomitant treatment (including over-the-counter products other than moisturizers).

Statistical analysis

All efficacy end points, local tolerability, laboratory test results, and vital signs were summarized by analysis visit. Categoric data were summarized by frequency and percentage for each response category, and the continuous data were summarized by using means, medians, minimums, maximums, and standard deviations. For composite end points, success rates were analyzed via the Cochran-Mantel-Haenszel methodology stratified by analysis center. Changes in lesion counts were evaluated through analysis of covariance using baseline counts, analysis center, and treatment as factors. The same statistical methods were used for the composite secondary end points. Multiple imputation methodology was used for missing values.

TEAEs, regardless of relationship to study medication, were tabulated and summarized by incidence as application site or non—application site events. Relationship to treatment was determined by the investigator. Common AEs were defined as those experienced by at least 1% of all patients. Laboratory evaluations were summarized with the use of descriptive statistics.

Table I. Patient characteristics (intent-to-treat population)

Characteristic	PERFECT 1			PERFECT 2		
	Trifarotene 50 μg/g (n = 612)	Vehicle (n = 596)	Overall (N = 1208)	Trifarotene 50 μg/g (n = 602)	Vehicle (n = 610)	Overall (N = 1212)
Age, y						
n	612	596	1208	602	610	1212
Mean (SD)	19.6 ± 6.88	19.3 ± 5.89	19.4 ± 6.41	19.6 ± 6.2	19.9 ± 6.4	19.7 ± 6.3
Median	17	18	18	18	18	18
(Min, max)	(9, 58)	(10, 50)	(9, 58)	(11.0, 49.0)	(11.0, 46.0)	(11.0, 49.0)
Age categories, n (%)						
<18 y	314 (51.3)	278 (46.6)	592 (49.0)	276 (45.8)	294 (48.2)	570 (47.0)
≥18 y	298 (48.7)	318 (53.4)	616 (51.0)	326 (54.2)	316 (51.8)	642 (53.0)
Sex, n (%)						
Male	307 (50.2)	272 (45.6)	579 (47.9)	245 (40.7)	272 (44.6)	517 (42.7)
Female	305 (49.8)	324 (54.4)	629 (52.1)	357 (59.3)	338 (55.4)	695 (57.3)
Race, n (%)						
White	508 (83.0)	484 (81.2)	992 (82.1)	565 (93.9)	554 (90.8)	1119 (92.3)
Black or African American	47 (7.7)	49 (8.2)	96 (7.9)	27 (4.5)	42 (6.9)	69 (5.7)
Asian	23 (3.8)	32 (5.4)	55 (4.6)	2 (0.3)	6 (1.0)	8 (0.7)
American Indian or Alaska Native	11 (1.8)	5 (0.8)	16 (1.3)	1 (0.2)	2 (0.3)	3 (0.2)
Native Hawaiian or other Pacific Islander	1 (0.2)	1 (0.2)	2 (0.2)	0 (0.0)	1 (0.2)	1 (0.1)
Multiple	8 (1.3)	10 (1.7)	18 (1.5)	2 (0.3)	2 (0.3)	4 (0.3)
Other	14 (2.3)	15 (2.5)	29 (2.4)	5 (0.8)	3 (0.5)	8 (0.7)
Ethnicity, n (%)						
Hispanic or Latino	135 (22.1)	148 (24.8)	283 (23.4)	60 (10.0)	62 (10.2)	122 (10.1)
Not Hispanic or Latino	477 (77.9)	448 (75.2)	925 (76.6)	542 (90.0)	548 (89.8)	1090 (89.9)
Skin phototype, n (%)						
Type I	31 (5.1)	34 (5.7)	65 (5.4)	36 (6.0)	37 (6.1)	73 (6.0)
Type II	197 (32.2)	182 (30.5)	379 (31.4)	274 (45.5)	249 (40.8)	523 (43.2)
Type III	233 (38.1)	227 (38.1)	460 (38.1)	233 (38.7)	248 (40.7)	481 (39.7)
Type IV	97 (15.8)	91 (15.3)	188 (15.6)	33 (5.5)	38 (6.2)	71 (5.9)
Type V	43 (7.0)	48 (8.1)	91 (7.5)	14 (2.3)	19 (3.1)	33 (2.7)
Type VI	11 (1.8)	14 (2.3)	25 (2.1)	12 (2.0)	19 (3.1)	31 (2.6)
Baseline disease characteristics, mean ± SD						
Facial inflammatory lesions	34.7 ± 13.02	34.8 ± 13.612	34.8 ± 13.31	36.1 ± 12.47	37.1 ± 15.06	36.6 ± 13.84
Facial noninflammatory lesions	54.0 ± 28.55	52.8 ± 26.08	53.4 ± 27.35	50.6 ± 25.93	51.2 ± 25.75	50.9 ± 25.83
Trunk inflammatory lesions	36.9 ± 17.89	35.6 ± 16.70	35.3 ± 17.32	39.0 ± 16.16	39.1 ± 17.41	39.1 ± 16.80
Trunk noninflammatory lesions	46.4 ± 21.57	47.5 ± 21.94	46.9 ± 21.75	46.1 ± 20.17	45.7 ± 19.58	45.9 ± 19.87

SD, Standard deviation.

RESULTS

Subject disposition, demographics, and baseline characteristics

In PERFECT 1, a total of 1524 subjects were screened and 1208 were randomized; of the randomized subjects, 612 received trifarotene cream and 596 received vehicle. There were 72 discontinuations in the trifarotene arm and 61 in the vehicle arm, and in both cases the discontinuations were primarily due to withdrawal by the subject and loss to follow-up. In PERFECT 2, a total of 1293 subjects were screened and 1212 were randomized; of the randomized subjects, 602 received trifarotene cream and 610 received vehicle. There were 44 discontinuations in the trifarotene arm and 37 in the vehicle arm, and in both cases they were primarily due to withdrawal by the subject and loss to follow-up. Demographic and baseline data are presented in Table I. The treatment groups were similar, with an even distribution of pediatric and adult subjects, no significant sex differences, and primarily white subjects with skin phototypes I to III.

Table II. Summary efficacy results

	PERFECT 1		PERFECT 2	
Face: Coprimary end points	**Trifarotene cream (n = 612)**	**Vehicle cream (n = 596)**	**Trifarotene cream (n = 602)**	**Vehicle cream (n = 610)**
IGA success	29.4%*	19.5%	42.3%*	25.7%
Inflammatory lesions				
Mean absolute change from baseline	−19.0*	−15.4	−24.2*	−18.7
Mean % change from baseline	−54.4%*	−44.8%	−66.2%*	−51.2%
Noninflammatory lesions				
Mean absolute change from baseline	−25.0*	−17.9	−30.1*	−21.6
Mean % change from baseline	−49.7%*	−35.7%	−57.7%*	−43.9%
	PERFECT 1		**PERFECT 2**	
Trunk: secondary end points	**Trifarotene cream (n = 600)**	**Vehicle cream (n = 585)**	**Trifarotene cream (n = 598)**	**Vehicle cream (n = 609)**
PGA success	35.7%*	25.0%	42.6%*	29.9%
Inflammatory lesions				
Mean absolute change from baseline	−21.4*	−18.8	−25.5*	−19.8
Mean % change from baseline	−57.4%*	−50.0%	−65.4%*	−51.1%
Noninflammatory lesions				
Mean absolute change from baseline	−21.9*	−17.8	−25.9*	−20.8
Mean % change from baseline	−49.1%*	−40.3%	−55.2%*	−45.1%

Intent-to-treat, multiple imputation; success defined as at least a 2-grade improvement and IGA/PGA rating of clear (0) or almost clear (1).
IGA, Investigator's Global Assessment; PGA, Physician's Global Assessment.
*P less than .001 versus vehicle cream.

Efficacy

The results of all coprimary and cosecondary efficacy assessments in both studies at week 12 were statistically significant ($P < .001$) in favor of trifarotene versus vehicle (Table II).

For the 1214 patients treated with trifarotene and 1206 treated with vehicle, the week 12 facial success rates according to the IGA were 29.4% in PERFECT 1 and 42.3% in PERFECT 2 (vs 19.5% and 25.7% for vehicle [$P < .001$]); trifarotene had statistically significant superior success rates at week 4 (PERFECT 1) and week 8 (PERFECT 2). Trifarotene treatment achieved significantly superior reductions in facial lesion counts as well, with statistical differences apparent as early as weeks 2 and 1: with trifarotene treatment, the mean absolute inflammatory lesion counts were reduced by19.0 and 24.2 (vs by 15.4 and 18.7 with vehicle [$P < .001$]) and the mean absolute noninflammatory lesion counts were reduced by 25.0 and 30.1 (vs by 17.9 and 21.6 with vehicle [$P < .001$]). The 3 coprimary end points from baseline to week 12 are shown in Figure 1.

The secondary end points showing the treatment effect on truncal acne from baseline to week 12 are presented in Figure 2. At week 12, the rates of success with trifarotene according to the truncal PGA were 35.7% in PERFECT 1 and 42.6% in PERFECT 2 (vs 25.0% and 29.9%, respectively for vehicle [each $P < .001$]). In both PERFECT 1 and 2, trifarotene was statistically significantly superior in achieving reductions in inflammatory and noninflammatory lesions on the trunk starting by week 4 in PERFECT 1 and by week 2 in PERFECT 2. Rates of success on the trunk were statistically significant for trifarotene versus for vehicle starting at week 8 in both studies.

Safety

Local tolerability. Local irritation related to trifarotene cream was transient and consistent with the known pattern of topical retinoid dermatitis (Fig 3); tolerability was better on the trunk than on the face. Local tolerability signs and symptoms related to trifarotene cream included erythema, scaling, dryness, and stinging/burning. These were mostly mild to moderate by investigator assessment, with few being severe. For facial acne, a worst postbaseline score of moderate local tolerability signs and symptoms compared with baseline was reported for up to 33.2% of patients (in PERFECT 1: erythema, 23.7%; scaling, 21.4%; dryness, 23.0%; and stinging/burning, 16.3%; in PERFECT 2: erythema, 33.2%; scaling, 32.9%; dryness, 36.4%; and stinging/burning, 24.9%) and severe for up to 10.0% of patients (in PERFECT 1: erythema, 2.5%; scaling, 2.9%; dryness, 2.5%; and stinging/burning, 4.2%; in

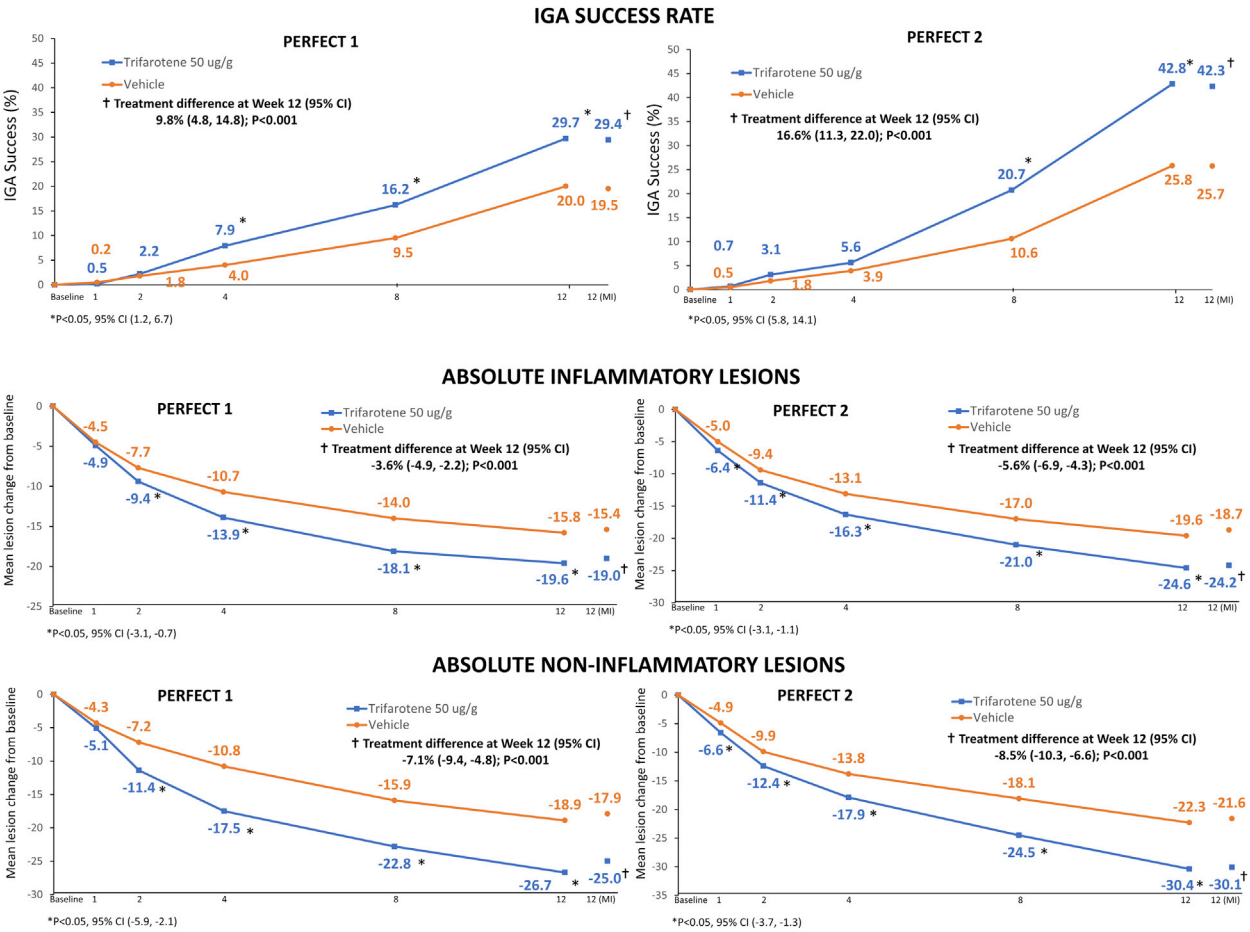

Fig 1. Facial acne vulgaris: coprimary end point from baseline to week 12. Success according to the facial Investigator's Global Assessment (IGA) is defined as clear or almost clear and at least a 2-grade improvement (intent-to-treat population; multiple imputation [MI]).

PERFECT 2: erythema, 10.0%; scaling, 6.8%; dryness, 7.1%; and stinging/burning, 7.6%). On the trunk, the corresponding percentages of worst postbaseline local tolerability signs and symptoms were moderate for up to 23.2% of patients (in PERFECT 1: erythema, 14.6%; scaling, 10.8%; dryness, 11.3%; and stinging/burning, 9.0%; in PERFECT 2: erythema, 23.2%; scaling, 16.7%; dryness, 20.9%; and stinging/burning, 12.9%) and severe for up to 7.2% of patients (in PERFECT 1: erythema, 3.3%; scaling, 0.3%; dryness, 1.2%; and stinging/burning, 3.0%; in PERFECT 2: erythema, 7.2%; scaling, 3.0%; dryness, 2.5%; and stinging/burning, 5.7%). The scores reached maximum severity at week 1 for the face and at weeks 2 to 4 on the trunk; after these time points, scores diminished.

AEs. Most TEAEs related to trifarotene were cutaneous and occurred at the application site. Severe AEs considered related to trifarotene therapy were reported in 6 subjects (in PERFECT 1: 4 with skin irritation, 1 with sunburn, and 1 with allergic dermatitis) and 3 subjects (in PERFECT 2: 1 with application site pain, 1 with application site erosion, and 1 with application site irritation) versus none in the vehicle group, but no AE was serious. AEs led to discontinuation in 1.9% (PERFECT 1) and 1.2% (PERFECT 2) of the those in the trifarotene cream and in no patients in the vehicle group; these AEs were most commonly application site irritation, allergic dermatitis, and skin irritation. There were no significant clinically relevant changes in vital signs, physical examination findings, or laboratory parameters. There were 4 pregnancies (0.2%) among the 2420 patients (1 pregnant patient was exposed to trifarotene cream and 3 were exposed to vehicle cream). The subject exposed to trifarotene was lost to follow-up.

DISCUSSION

The 2 large-scale phase III studies generated independent and substantial evidence of the efficacy and safety of trifarotene cream in moderate

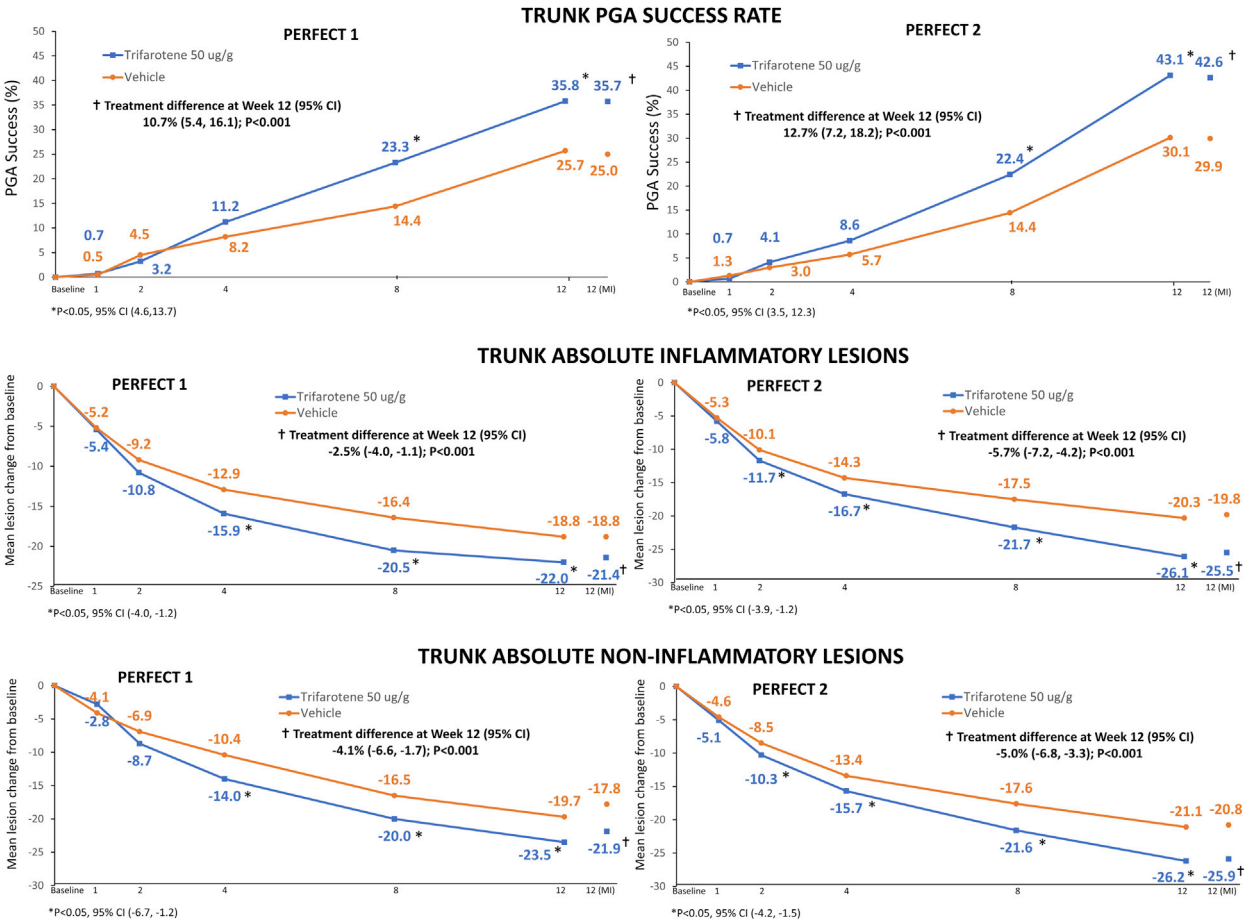

Fig 2. Truncal acne vulgaris: secondary end points from baseline to week 12. Success rate according to the Physician's Global Assessment (PGA) of truncal acne is defined as a PGA score of 0 or 1 and at least a 2-grade improvement. (intent-to-treat trunk population; multiple imputation [MI]).

facial and truncal acne. In both anatomic regions (face and trunk), trifarotene cream was significantly superior to vehicle in success rates and in reduction of inflammatory and noninflammatory lesion counts.

There is sparse literature for the prevalence and treatment of chest and back acne despite it being a very common condition. Truncal acne often accompanies facial acne in adolescence, or it may first occur in and, indeed, persist well into adulthood.[4] Truncal acne has been estimated to occur in 56% of patients with acne, with only a slightly higher predominance in males (55% vs 46%).[7] Back acne, once thought to be a predominantly male disease, has been shown to be prevalent in females.[6]

The pathophysiologic mechanism of acne on the chest and back is similar to that of facial acne and centers on the physiology and properties of the pilosebaceous unit.[3,4,8] Both anatomic areas are considered sebum-rich locations, although the sebaceous follicles on the back have a histologic appearance different from those on the face.[8] Few studies have evaluated drugs in the treatment of truncal acne and there are no well-designed comparative studies. Most studies have been small in scale and not rigorously controlled.[3,4] A review of the sparse evidence of the treatment outcomes of acne located in different anatomic regions has shown varying responses to systemic therapy when the face and trunk are involved.[8] The onset of effect of trifarotene 50 μg/g cream versus that of its vehicle was rapid, with significant reductions in both inflammatory and noninflammatory lesion counts seen as early as 1 week after treatment on the face and as early as 2 weeks after treatment on the trunk. This observation is consistent with the findings of a 12-month, long-term safety study of trifarotene 50 μg/g cream, in which the success rate for the face and trunk demonstrated a consistent continuous clinical improvement over time and within the same subject (separate analysis).[9]

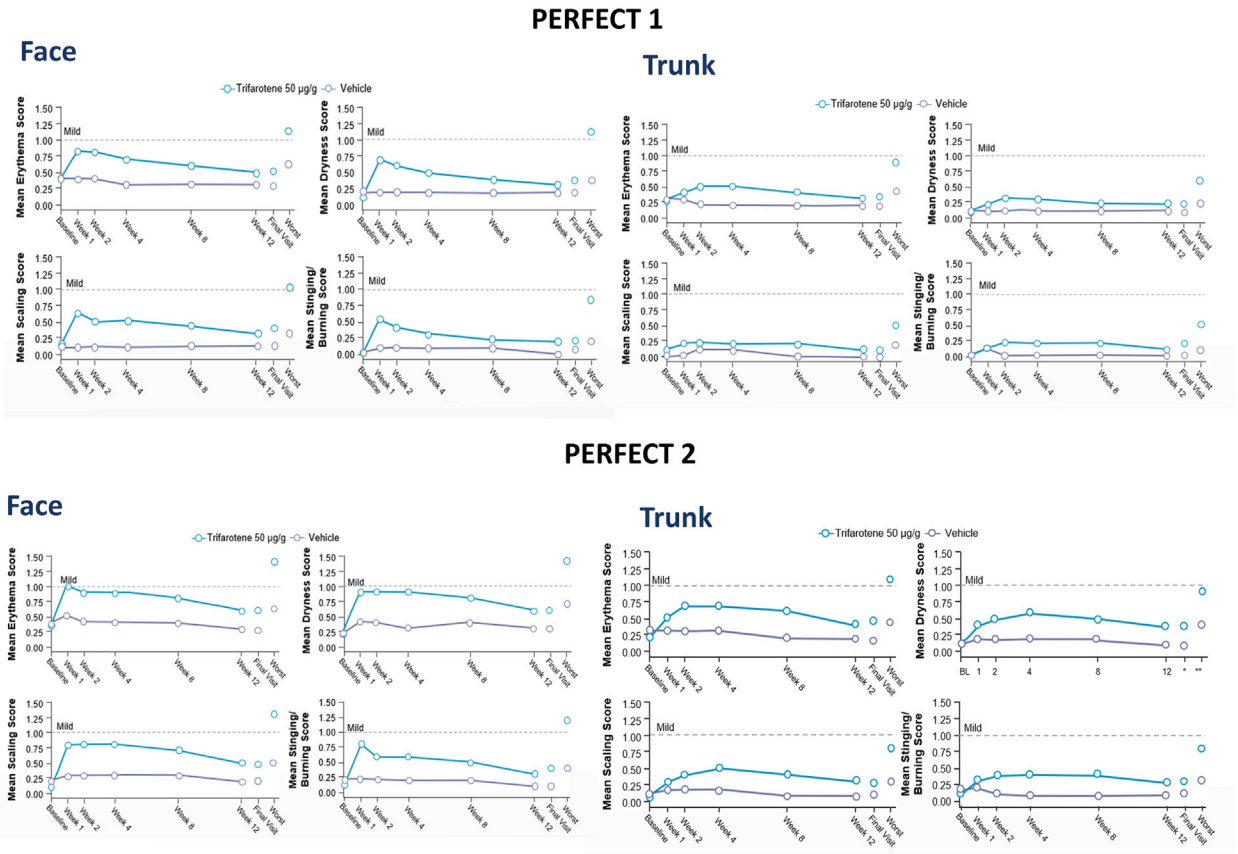

Fig 3. Tolerability profile of trifarotene and vehicle from baseline to week 12 in facial and truncal acne. Severity scale score indicates: 0 (none), 1 (mild), 2 (moderate) and 3 (severe).

Trifarotene had a manageable safety and tolerability profile, with the majority of AEs being local cutaneous irritation that began mainly during the first weeks of treatment and improved thereafter. Local tolerability was better on the trunk than on the face. Similar results were reported in a long-term safety study of trifarotene.[9] In the combined pool from both studies, the local signs and symptoms for the face and trunk that worsened after baseline (skin dryness, erythema, scaling, stinging, and burning) were mild to moderate in severity, with few subjects who experienced severe tolerability problems. The implementation of routine standard skin care, such as use of noncomedogenic moisturizers and gentle cleanser, and dosing regimen adjustments were sufficient to ensure treatment management and compliance in the majority of patients. There were no relevant changes in laboratory safety test results when trifarotene 50 μg/g cream was applied to large surface areas. Study limitations include absence of well-established optimal regimens and dosing strategies for truncal acne. These two phase 3 studies showed that once-daily trifarotene cream appears effective and safe, with manageable local tolerability, for the treatment for facial and truncal acne. The studies provide substantial evidence to support use of this new topical retinoid in facial and truncal acne.

CONCLUSIONS

Trifarotene 50 μg/g cream appears to be effective and safe in the treatment of moderate acne on the face and trunk, meeting all primary and secondary efficacy end points of 2 independent, randomized, well-controlled studies. Trifarotene exhibited the expected local tolerability profile of a topical retinoid. In both studies, the local tolerability profile of trifarotene was mostly mild or moderate and manageable when it was applied to the face as well as to the larger body surface areas of the trunk.

We thank our colleagues in Galderma International, Galderma R&D in Sophia Antipolis, and Galderma Laboratories and the Trifarotene study Group, as well as all investigators in United States, Canada, Europe, and Russia who participated in these clinical trials, including the following: in the United States, W. Abramovits (TX), K. Abson (WA), V. Afsahi, R. Agha (IL), J. Alonso-Llamazares, M. Appell (AL), F. Armstrong (FL), R. Asarch (CO), F. Badar (CA), R. Basler (NE), E. Becker (TX), K. Beer (FL), J. Berlin

(CA), K. Belasco (CA), S. Bruce (TX), N. Brystol (AZ), M. Bukhalo (IL), V. Callender (MD), D. Carrasco (TX), J. Cather (TX), J. Crane (NC), S. Checketts (UT), K. Coleman (LA), G. Cortes-Maisonet (PR), A. Cruz (PR), R. Dakour (TX), M. Blahey (TX), S. Davis (TX), J. De Maria (OH), S. Dhawan (CA), V. Dimitropoulos (IL), J. Dubois (TX), J. Earl (NC), C. Effron (CA), D. Fivenson (MI), R. Fixler (OH), F. Flores (FL), R. Forconi (FL), R. Fried (PA), S. Glick (NY), D. Goldberg (NJ), D. Greenstein (MA), S. Grekin (MI), L. Gremillion (LA), P. Grimes (CA), S. Guenthner (IN), R. Haber (OH), F. Hamzavi (MI), E. Heilman (NY), A. Herbert (TX), D. Hensley (TX), C. Hull (AR), J. Humeniuk (SC), J. Campbell (NH), A. Jarell (NH), S. Jazayeri (AZ), S. Johnson (AR), T. Kaufmann (NY), L. Kircik (KY), M. Knuckles (KY), V. Kuohung (MA), B. Kuttner (FL), E. Lain (TX), J. Lee (TN), M. Lee (TX), P. Lee (TX), M. Limova (CA), B. Lockshin (MD), K. Loven (TN), A. Martin (MO), M. Mc Cune (KS), W. Mc Falda (MI), M. Mc Guiness (TX), S. Miller (TX), M. Nestor (FL), L. Parish (PA), J. Pehoushek (AZ), M. Peredo (NY), C. Pointon (NC), A. Pollack (PA), E. Primka (TN), A. Racette (AZ), E. Rafal (NY), N. Sadick (NY), J. Samady (CA), F. Samarin (CO), N. Sanchez Colon (PR), S. Sanchez Rivera (PR), T. Schlesinger (SC), B. Schlosser (IL), G. Schmieder (FL), E. Schweiger (NY), L. Sewell (ID), K. Shrock (FL), D. Sire (CA), E. Smith (WA), S. Smith (CA), J. Solomon (FL), J. Soung (CA), D. Steward (MI), D. Stoll (CA), M. Stone (MD), D. Stough (AR), T. Sullivan (FL), L. Swinyer (UT), J. Thiele (CA), A. Trovato (AL), A. Truett (KY), S. Tyring (TX), J. Weiss (GA), H. Wiltz (FL), P. Yamauchi (CA), M. Zaiac (FL), and M. Zook (FL); in Canada, L. Albrecht, A. Devani, M. Gooderham, A. Gupta, J. Keddy-Grant, K. Papp, M. Raman, L. Rosoph, S. Sapra, M. Shayesteh-Alam, R. Vender; in the Czech Republic, A. Cerna, K. Ettler, B. Havlickova, R. Kucerova, R. Neumonnova, L. Petru, I. Stejskalova, and D. Stuchlik; in Germany, M. Podda, B. Gerlach, N. Magnolo, A. Tsianakas, R. Aschoff, C. Zouboulis, B. Schwarz, O. Weirich, and K. Reich; in Hungary, E. Apostol, K. Bajor, N. Bakos, R. Gyulai, B. Irinyi, R. Kriston, G. Nagy, Z. Nagy, R. Nemeth, E. Peterfai, E. Remenyik, Z. Szalai, M. Thoma, A. Vago, and I. Vincz; in Poland, M. Ambroziak, D. Bystrzanowska, M. Czubek, B. Imko-Walczuk, E. Krolikowska, M. Mackowiak, E. Meszynska, R. Nowicki, J. Sicinska, M. Szedel, J. Weglowska, D. Witkowska, A. Wronski, and M. Zakrzewski; in Romania, G. Fekete, I. Florea, S. Ianosi, D. Mihalache, and A. Purcaru; in Russia, A. Khotko, A. Kubanov, Y. Perlamutrov, A. Sukharev, L. Sukhova, D. Zaslavskiy, and O. Zhukova; in Spain, M. Campos, E. Roe, M. Vicente, and V. Zaragoza; and in Ukraine, Y. Andrashko, A. Dyudyun, L. Kaliuzhna, Y. Kutasevych, O. Nadashkevich, V. Stepanenko, T. Sviatenko, and I. Tsidylo. We also acknowledge the writing support of Valerie Sanders of Sanders Medical Writing in the United States.

REFERENCES

1. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2003;49:S1-S37.
2. Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. *J Am Acad Dermatol*. 2009; 60:S1-S50.
3. Bikowski J. Back in the spotlight: effective options for truncal acne Available at: http://practicaldermatology.com/2010/02/back-in-the-spotlight-effective-options-for-truncal-acne. Accessed July 17, 2018.
4. Del Rosso JQ. Management of truncal acne vulgaris: current perspectives on treatment. *Cutis*. 2006;77:285-289.
5. Liu C-W, Tan J. Understanding truncal acne: a practical guide to diagnosis and management Available at: http://www.skintherapyletter.com/conditions/acne/truncal-diagnosis-management/. Accessed July 16, 2018.
6. Aubert J, Piwnica D, Bertino B, et al. Non-clinical and human pharmacology of the potent and selective topical RAR-g agonist trifarotene. *Br J Dermatol*. 2018;179:442-456.
7. Del Rosso JQ. Truncal acne vulgaris: the relative roles of topical and systemic antibiotic therapy. *J Drugs Dermatol*. 2007;6:148-151.
8. Tsatsou F, Zouboulis CC. Anatomy of the sebacous gland. In: Zouboulis C, Katsambas A, Kligman AM, eds. *Pathogenesis and Treatment of Acne and Rosacea*. London: Springer; 2014:27-31.
9. Blume-Peytavi UF, Lajos K, Draelos Z, et al. Long-term safety and efficacy of trifarotene 50 g/g cream, a first-in-class RAR gamma selective topical retinoid, in subjects with moderate facial and truncal acne. *J Eur Acad Dermatol Venereol*. In press.