Investigator-Reported Efficacy of Azelaic Acid Foam 15% in Patients With Papulopustular Rosacea: Secondary Efficacy Outcomes From a Randomized, Controlled, Double-blind, Phase 3 Trial

James A. Solomon, MD, PhD; Stephen Tyring, MD, PhD; Gerald Staedtler, MSc; Meike Sand, MSc; Richard Nkulikiyinka, MD; Kaweh Shakery, MD

PRACTICE **POINTS**

- Papulopustular rosacea (PPR) is a common chronic inflammatory dermatosis.
- A novel hydrophilic foam formulation of azelaic acid (AzA) was approved for the treatment of PPR.
- In addition to effectively treating papules and pustules, AzA foam also may reduce rosacea-associated erythema.
- The unique AzA foam vehicle may improve epidermal barrier integrity and function, thereby offering patients a distinct topical approach to rosacea management.

Papulopustular rosacea (PPR) is characterized by centrofacial papules and pustules commonly associated with erythema. To compare investigator-reported efficacy outcomes for azelaic acid (AzA) foam 15% versus vehicle foam in PPR, a randomized, vehicle-controlled, double-blind phase 3 clinical trial was conducted at 48 US sites. Participants received AzA foam or vehicle foam for 12 weeks. Secondary efficacy outcomes included change in inflammatory lesion count (ILC), therapeutic response rate according to investigator global assessment (IGA), and change in erythema rating. This study was comprised of 961 participants with PPR. The results support the therapeutic superiority of AzA foam over vehicle foam.
Cutis. 2016;98:187-194.

Dr. Solomon is from Ameriderm Research, Ormond Beach, Florida. Dr. Tyring is from the Department of Dermatology, University of Texas Health Science Center, Houston. Mr. Staedtler, Mr. Sand, and Drs. Nkulikiyinka and Shakery are from Bayer Pharmaceuticals, Berlin, Germany.
Funding for this study was provided by Bayer Pharmaceuticals.
Dr. Solomon is an employee of Ameriderm Research and his employer has received grants from Allergan, Inc; Anacor Pharmaceuticals, Inc; AstraZeneca; Bayer Pharmaceuticals; Eli Lilly and Company; Galderma Laboratories, LP; Genentech USA, Inc; LEO Pharma; Merck & Co, Inc; Novartis; Pfizer Inc; Polynoma LLC; Regeneron Pharmaceuticals, Inc; Roche; SciQuus; and Stiefel, a GSK company. Dr. Tyring has received grants from Bayer Pharmaceuticals. Mr. Staedtler, Mr. Sand, and Drs. Nkulikiyinka and Shakery are employees of Bayer Pharmaceuticals. Mr. Staedtler and Dr. Shakery also are stockholders of Bayer AG.
This study was registered on March 13, 2012, at www.clinicaltrials.gov with the identifier NCT01555463.
Correspondence: James A. Solomon, MD, PhD, 725 W Granada Blvd, Ste 44, Ormond Beach, FL 32174 (drjsolomon@ameridermresearch.com).

Papulopustular rosacea (PPR) is characterized by centrofacial papules, pustules, erythema, and occasionally telangiectasia.[1,2] A myriad of factors, including genetic predisposition[3] and environmental triggers,[4] have been associated with dysregulated inflammatory responses,[5] contributing to the disease pathogenesis and symptoms. Inflammation associated with PPR may decrease skin

barrier function, increase transepidermal water loss, and reduce stratum corneum hydration,[6,7] resulting in heightened skin sensitivity, pain, burning, and/or stinging.[5,8]

Azelaic acid (AzA), which historically has only been available in gel or cream formulations, is well established for the treatment of rosacea[9]; however, these formulations have been associated with application-site adverse events (AEs)(eg, burning, erythema, irritation), limited cosmetic acceptability, and reduced compliance or efficacy.[10]

For select skin conditions, active agents delivered in foam vehicles may offer superior tolerability with improved outcomes.[11] An AzA foam 15% formulation was approved for the treatment of mild to moderate PPR. Primary outcomes from a phase 3 trial demonstrated the efficacy and safety of AzA foam in improving inflammatory lesion counts (ILCs) and disease severity in participants with PPR. The trial also evaluated additional secondary end points, including the effect of AzA foam on erythema, inflammatory lesions, treatment response, and other manifestations of PPR.[12] The current study evaluated investigator-reported efficacy outcomes for these secondary end points for AzA foam 15% versus vehicle foam.

Methods

Study Design—This phase 3 multicenter, randomized, double-blind, vehicle-controlled, parallel-group clinical trial was conducted from September 2012 to January 2014 at 48 US study centers comparing the efficacy of AzA foam versus vehicle foam in patients with PPR. Eligible participants were 18 years and older with PPR rated as moderate or severe according to investigator global assessment (IGA), plus 12 to 50 inflammatory lesions and persistent erythema with or without telangiectasia. Exclusion criteria included known nonresponse to AzA, current or prior use (within 6 weeks of randomization) of noninvestigational products to treat rosacea, and presence of other dermatoses that could interfere with rosacea evaluation.

Participants were randomized into the AzA foam or vehicle group (1:1 ratio). The study medication was applied in 0.5-g doses twice daily until the end of treatment (EoT) at 12 weeks. Efficacy and safety parameters were evaluated at baseline and at 4, 8, and 12 weeks of treatment, and at a follow-up visit 4 weeks after EoT (week 16).

Results for the coprimary efficacy end points—therapeutic success rate according to IGA and nominal change in ILC—were previously reported.[12]

Investigator-Reported Secondary Efficacy Outcomes—The secondary efficacy end points were grouped change in erythema rating, grouped change in telangiectasia rating, grouped change in IGA score, therapeutic response rate according to IGA, percentage change in ILC from baseline, and facial skin color rating at EoT.

Grouped change for all secondary end points was measured as improved, no change, or worsened relative to baseline. For grouped change in erythema and telangiectasia ratings, a participant was considered improved if the rating at the postbaseline visit was lower than the baseline rating, no change if the postbaseline and baseline ratings were identical, and worsened if the postbaseline rating was higher than at baseline. For grouped change in IGA score, a participant was considered improved if a responder showed at least a 1-step improvement postbaseline compared to baseline, no change if postbaseline and baseline ratings were identical, and worsened if the postbaseline rating was higher than at baseline.

For the therapeutic response rate, a participant was considered a treatment responder if the IGA score improved from baseline and resulted in clear, minimal, or mild disease severity at EoT.

Safety—Adverse events also were assessed.

Statistical Analyses—Secondary efficacy and safety end points were assessed for all randomized participants who were dispensed the study medication. Missing data were imputed using last observation carried forward.

For the percentage change in ILC from baseline, therapeutic response rate, and grouped change in erythema rating, confirmatory analyses were conducted in a hierarchical manner (in the order listed), with testing stopped as soon as a null hypothesis of superior treatment effect could not be rejected. Analyses without significance level were exploratory. The Cochran-Mantel-Haenszel van Elteren test stratified by study center was used for grouped change in erythema rating (1-tailed, 2.5%) and IGA score (2-tailed, 5%); Wilcoxon rank sum tests also were performed. Percentage change in ILC from baseline was evaluated using the Student *t* test and *F* test of analysis of covariance (1-tailed, 2.5%). Therapeutic response rate was evaluated using the Cochran-Mantel-Haenszel van Elteren test stratified by study center and the Pearson χ^2 test. Facial skin color and grouped change in telangiectasia rating were evaluated using the Wilcoxon rank sum test.

Adverse events beginning or worsening after the first dose of the study drug were considered treatment emergent and were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1. Statistical analyses were performed using SAS software version 9.2.

Results

Study Participants—The study included 961 total participants; 483 were randomized to the AzA foam group and 478 to the vehicle group (Figure 1). Overall, 803 participants completed follow-up; however, week 16 results for the efficacy outcomes include data for 4 additional patients (2 per study arm) who did not formally meet all requirements for follow-up completion. The mean age was 51.5 years, and the majority of the participants were white and female (Table 1). Most participants (86.8%) had moderate PPR at baseline, with the remaining rated as having severe disease (13.2%). The majority (76.4%) had more than 14 inflammatory lesions with moderate (76.4%) or severe (15.1%) erythema at baseline.

Efficacy—Significantly more participants in the AzA group than in the vehicle group showed an improved erythema rating at EoT (61.5% vs 51.3%; $P<.001$)(Figure 2), with more participants in the AzA group showing improvement at weeks 4 ($P=.022$) and 8 ($P=.002$).

A significantly greater mean percentage reduction in ILC from baseline to EoT was observed in the AzA group versus the vehicle group (61.6% vs 50.8%; $P<.001$)(Figure 3), and between-group differences were observed at week 4 ($P<.001$), week 8 ($P=.003$), and week 16 (end of study/follow-up)($P=.002$).

A significantly higher proportion of participants treated with AzA foam versus vehicle were considered responders at week 12/EoT (66.3% vs 54.4%; $P<.001$) (Figure 4). Differences in responder rate also were observed at week 4 ($P=.026$) and week 8 ($P=.026$).

Differences in grouped change in IGA score were observed between groups at every evaluation during the treatment phase (Figure 5). Specifically, IGA score was improved at week 12/EoT relative to baseline in 71.2% of participants in the AzA group versus 58.8% in the vehicle group ($P<.001$).

For grouped change in telangiectasia rating at EoT, the majority of participants in both treatment groups showed no change (Table 2). Regarding facial skin color, the majority of participants in both the AzA and vehicle treatment groups (80.1% and 78.7%, respectively) showed normal skin color compared to nontreated skin EoT; no between-group differences were detected for facial skin color rating ($P=.315$, Wilcoxon rank sum test).

Safety—The incidence of drug-related AEs was greater in the AzA group than the vehicle group (7.7% vs 4.8%)(Table 3). Drug-related AEs occurring in at least 1% of the AzA group were pain at application site (eg, tenderness, stinging, burning)(AzA group, 3.5%; vehicle group, 1.3%), application-site pruritus (1.4% vs 0.4%), and

Table 1.

Baseline Characteristics of Study Participants[a]

Characteristic	AzA Foam (n=483)	Vehicle Foam (n=478)
Mean age (range), y	51.2 (19–92)	51.9 (19–83)
Gender, n (%)		
Male	129 (26.7)	130 (27.2)
Female	354 (73.3)	348 (72.8)
Race, n (%)		
White	463 (95.9)	455 (95.2)
Nonwhite[b]	12 (2.5)	14 (2.9)
Not reported	8 (1.7)	9 (1.9)
IGA, n (%)		
Clear	0 (0)	0 (0)
Minimal	0 (0)	0 (0)
Mild	0 (0)	0 (0)
Moderate	418 (86.5)	416 (87.0)
Severe	65 (13.5)	62 (13.0)
Mean ILC (range)	21.7 (12–50)	21.2 (12–50)
Erythema rating, n (%)		
Clear or almost clear	0 (0)	0 (0)
Mild	43 (8.9)	39 (8.2)
Moderate	364 (75.4)	370 (77.4)
Severe	76 (15.7)	69 (14.4)
Telangiectasia rating, n (%)		
None	61 (12.6)	65 (13.6)
Mild	181 (37.5)	186 (38.9)
Moderate	202 (41.8)	181 (37.9)
Severe	39 (8.1)	46 (9.6)
Facial skin color rating, n (%)		
Normal	382 (79.1)	375 (78.5)
Barely visible skin lightening	21 (4.3)	25 (5.2)
Mild skin lightening	45 (9.3)	39 (8.2)
Moderate skin lightening	30 (6.2)	34 (7.1)
Severe skin lightening	5 (1.0)	5 (1.0)

Abbreviations: AzA, azelaic acid; IGA, investigator global assessment; ILC, inflammatory lesion count.

[a]No significant differences were present between the treatment groups for any baseline characteristics listed.

[b]Nonwhite categories included black, Asian, American Indian or Alaskan native, Native Hawaiian or Other Pacific Islander, or multiple.

Table 2.

Grouped Change From Baseline in Telangiectasia Rating at EoT

Telangiectasia Rating[a]	AzA Foam, n (%) (n=483)	Vehicle, n (%) (n=478)
Improved	132 (27.3)	108 (22.6)
No change	318 (65.8)	333 (69.7)
Worsened	33 (6.8)	37 (7.7)

Abbreviations: EoT, end of treatment; AzA, azelaic acid.
[a]*P*=.049, Wilcoxon rank sum test (1-tailed).

application-site dryness (1.0% vs 0.6%). A single drug-related AE of severe intensity (ie, application-site dermatitis) was observed in the vehicle group; all other drug-related AEs were mild or moderate. The incidence of withdrawals due to AEs was lower in the AzA group than the vehicle group (1.2% vs 2.5%). This AE profile correlated with a treatment compliance (the percentage of expected doses that were actually administered) of 97.0% in the AzA group and 95.9% in the vehicle group. One participant in the vehicle group died due to head trauma unrelated to administration of the study drug.

Comment

The results of this study further support the efficacy of AzA foam for the treatment of PPR. The

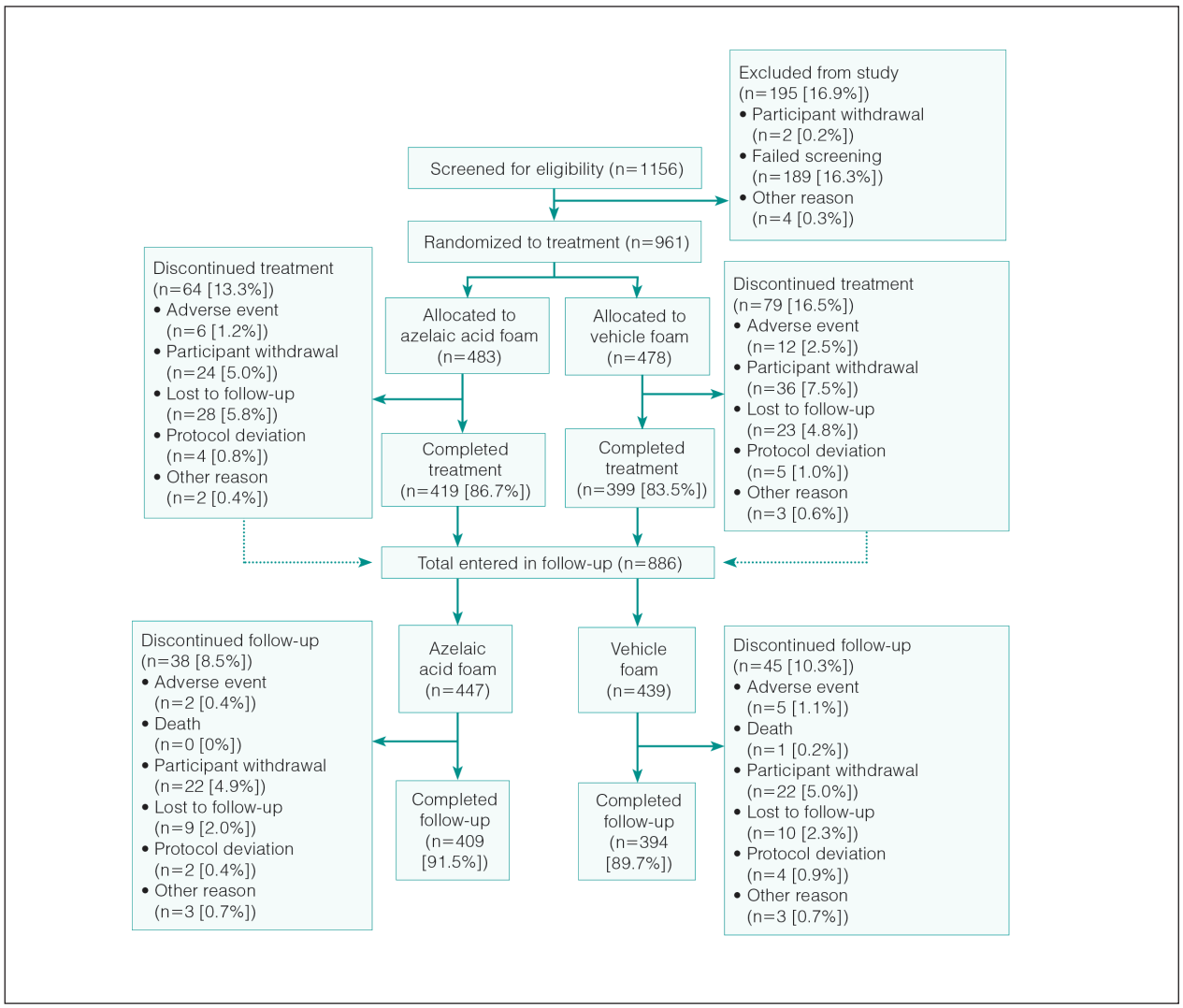

Figure 1. Participant disposition. Participants who completed treatment did not necessarily enter follow-up. After completion of treatment, participants (including those who prematurely discontinued treatment) were invited to enter the follow-up.

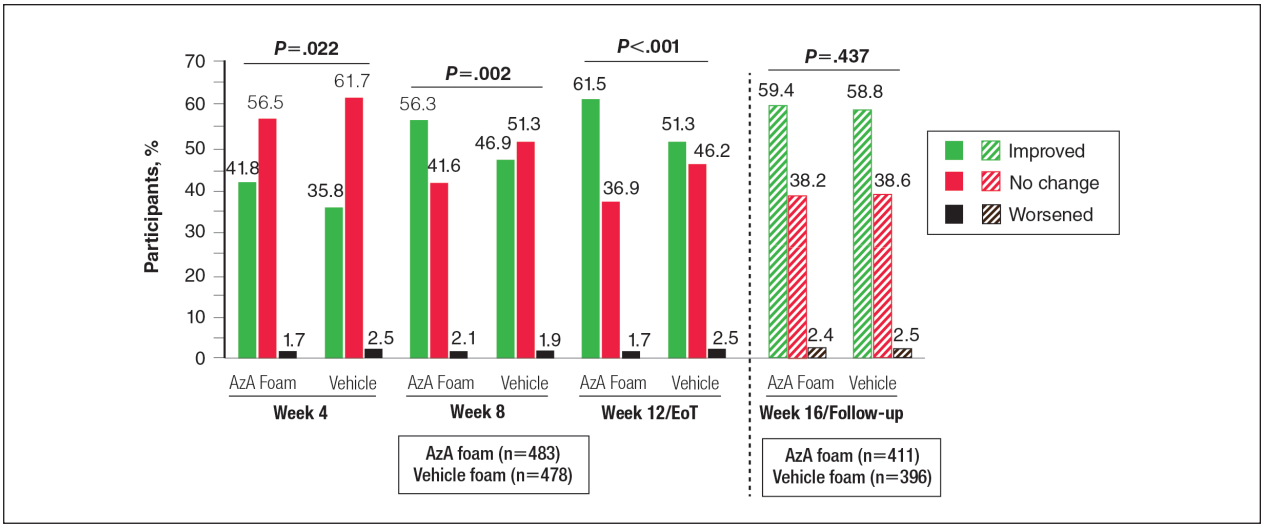

Figure 2. Grouped change from baseline in erythema rating by study period. All *P* values (1-tailed) derived from Wilcoxon rank sum test; week 12/end of treatment (EoT) *P* value (1-tailed) derived from Cochran-Mantel-Haenszel van Elteren test stratified by study center. No study drug was administered between week 12/EoT and week 16/follow-up; last observation carried forward was not applied to week 16/follow-up analysis. AzA indicates azelaic acid.

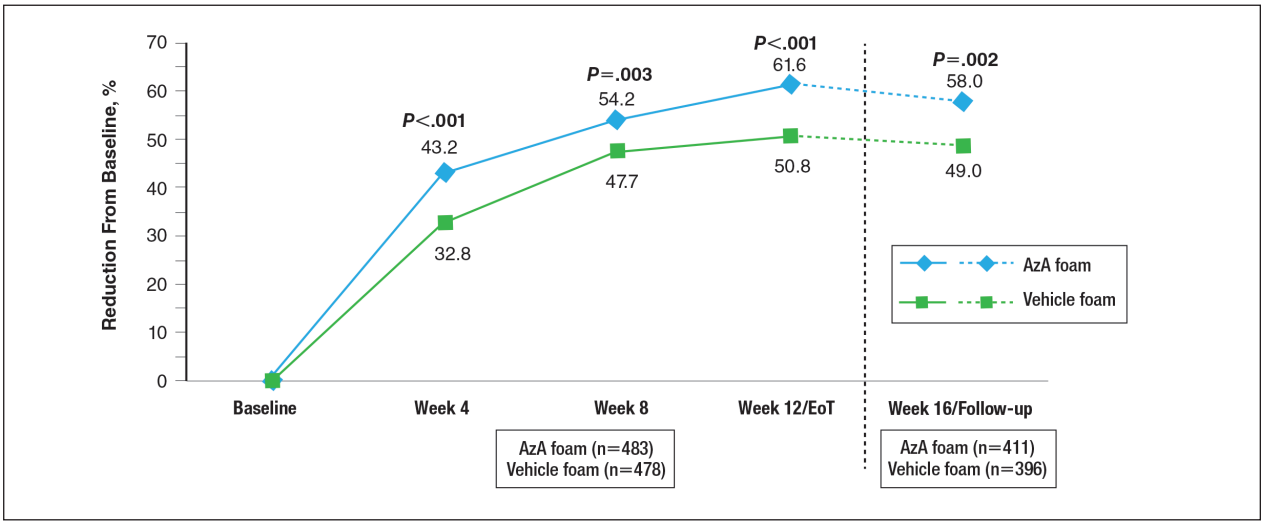

Figure 3. Mean percentage change from baseline in inflammatory lesion count (ILC) by study period. Percentage change in ILC is nominal change from baseline to postbaseline in ILC divided by number of baseline lesions. All *P* values (1-tailed) derived from Student *t* test. Week 12/end of treatment (EoT) adjusted mean percentage reduction in ILC was 60.7% in the azelaic acid (AzA) group versus 49.5% in the vehicle group (*P*<.001, *F* test of analysis of covariance). No study drug was administered between week 12/EoT and week 16/follow-up; last observation carried forward was not applied to week 16/follow-up analysis.

percentage reduction in ILC was consistent with nominal decreases in ILC, a coprimary efficacy end point of this study.[12] Almost two-thirds of participants treated with AzA foam achieved a therapeutic response, indicating that many participants who did not strictly achieve the primary outcome of therapeutic success nevertheless attained notable reductions in disease severity. The number of participants who showed any improvement on the IGA scale increased throughout the course of treatment (63.8% AzA foam vs 55.0% vehicle at week 8) up to EoT (71.2% vs 58.8%)(Figure 5). In addition, the number of participants showing any improvement at week 8 (63.8% AzA foam vs 55.0% vehicle)(Figure 5) was comparable to the number of participants achieving therapeutic response at week 12/EoT (66.3% vs 54.4%)(Figure 4). These data suggest that increasing time of treatment increases the likelihood of achieving better results.

Table 3.

AEs That Started or Worsened After First Dose of Study Drug

Characteristic	AzA Foam (n=483)		Vehicle (n=478)	
	All	Drug Related	All	Drug Related
≥1 AE, %	30.8	7.7	24.9	4.8
Highest severity level of reported AEs,[a] %				
Mild	16.4	5.2	15.1	2.9
Moderate	13.3	2.5	8.4	1.7
Severe	1.2	0	1.5	0.2
≥1 local cutaneous AE, %	8.9	7.0	6.1	4.6
≥1 SAE,[b] %	0.6	0.0	0.8	0.0
≥1 AE that resolved with sequelae, %	3.3	0.6	2.1	0.6
≥1 AE that did not resolve, %	0.6	0.2	0.2	0.0
≥1 AE leading to study drug withdrawal, %	1.2	0.6	2.5	1.3
Death due to AE, %	0.0	0.0	0.2	0.0
Frequency of AE by time interval, n				
Baseline–week 4	119	50	61	20
Week 5–week 8	105	20	80	23
Week 9–week 12 (EoT)	93	17	60	17
Week 13–week 16 (follow-up)	66	13	40	8

Abbreviations: AE, adverse event; AzA, azelaic acid; SAE, serious adverse event; EoT, end of treatment.
[a]Participants who reported multiple AEs were only counted once in the highest severity category.
[b]Serious AEs were defined as any occurrence that resulted in death, was life-threatening, required or prolonged hospitalization, resulted in disability/incapacity, was a congenital anomaly/birth defect, or was a medically important serious event.

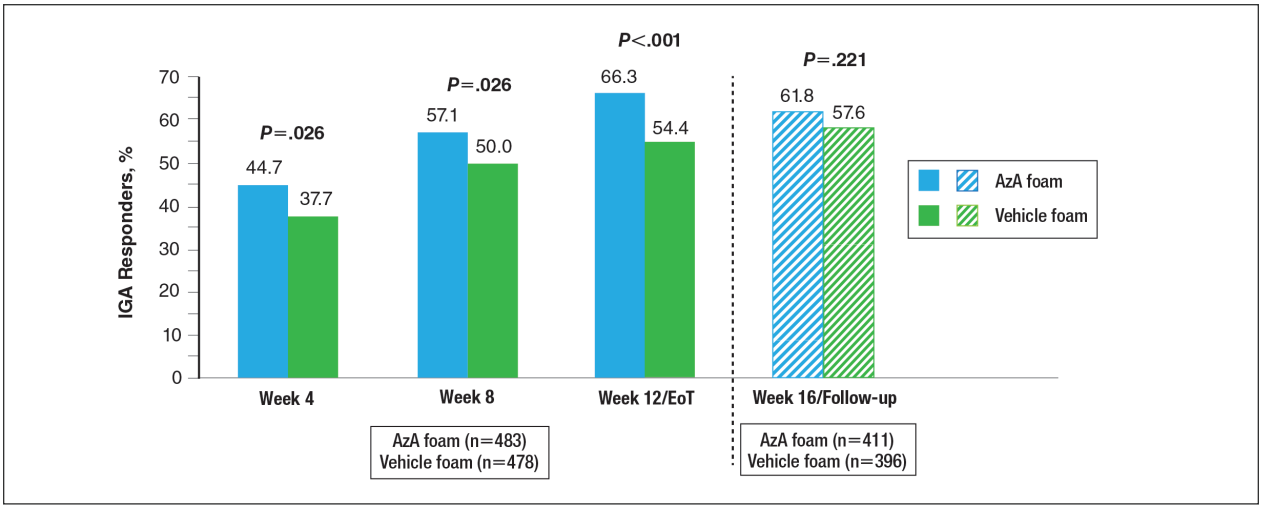

Figure 4. Therapeutic response rate by study period. All *P* values (2-tailed) derived from Pearson χ^2 test; week 12/end of treatment (EoT) *P* value (2-tailed) derived from Cochran-Mantel-Haenszel van Elteren test stratified by study center. No study drug was administered between week 12/EoT and week 16/follow-up; last observation carried forward was not applied to week 16/follow-up analysis. AzA indicates azelaic acid; IGA, investigator global assessment.

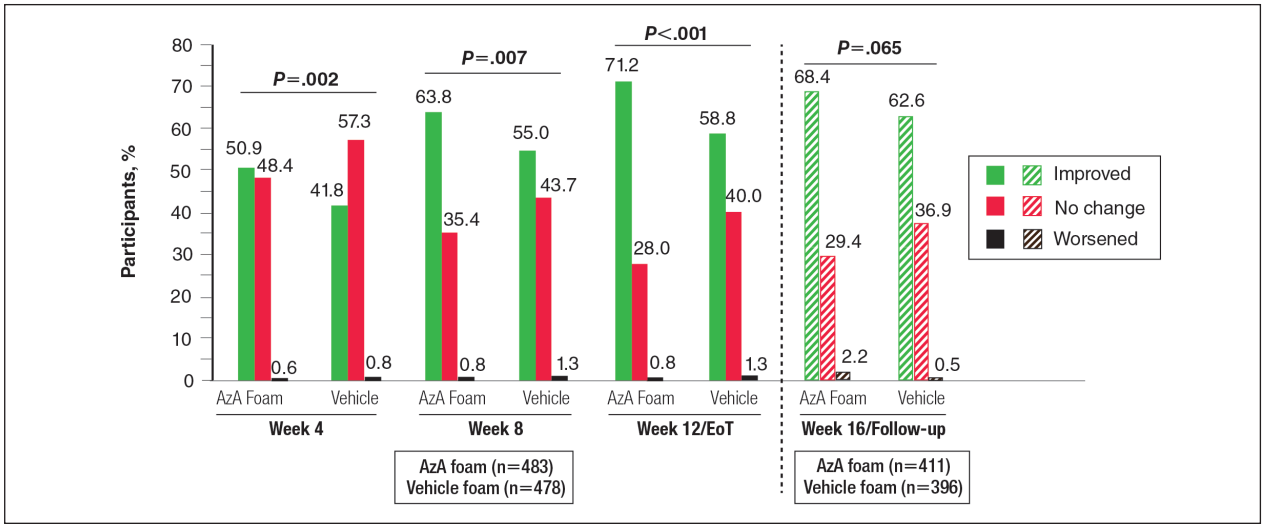

Figure 5. Grouped change from baseline in investigator global assessment score by study period. All *P* values (1-tailed) derived from Wilcoxon rank sum test; week 12/end of treatment (EoT) *P* value (1-tailed) derived from Cochran-Mantel-Haenszel van Elteren test stratified by study center. No study drug was administered between week 12/EoT and week 16/follow-up; last observation carried forward was not applied to week 16/follow-up analysis. AzA indicates azelaic acid.

Erythema also appeared to respond to AzA foam, with 10.2% more participants in the AzA group demonstrating improvement at week 12/EoT compared to vehicle. The difference in grouped change in erythema rating also was statistically significant and favored AzA foam, sustained up to 4 weeks after EoT.

The outcomes for percentage change in ILC, therapeutic response rate, and grouped change in erythema rating consequently led to the rejection of all 3 null hypotheses in hierarchical confirmatory analyses, underscoring the benefits of AzA foam treatment.

The therapeutic effects of AzA foam were apparent at the first postbaseline evaluation and persisted throughout treatment. Differences favoring AzA foam were observed at every on-treatment evaluation for grouped change in erythema rating, percentage change in ILC, therapeutic response rate, and grouped change in IGA score. Symptoms showed minimal resurgence after treatment cessation, and there were no signs of disease flare-up within the 4 weeks of observational follow-up. In addition, the percentage reduction in ILC remained higher in the AzA foam group during follow-up.

These results also show that AzA foam was well tolerated with a low incidence of discontinuation because of drug-related AEs. No serious drug-related AEs were reported for this study or in the preceding phase 2 trial.[12,13] Although not directly evaluated, the low incidence of cutaneous AEs suggests that AzA foam may be better tolerated than prior formulations of AzA[14,15] and correlates with high compliance observed during the study.[12] Azelaic acid foam appeared to have minimal to no effect on skin color, with more than 88% of participants reporting barely visible or no skin lightening.

Interestingly, the vehicle foam showed appreciable efficacy independent of AzA. Improvements in erythema were recorded in approximately half of the vehicle group at week 12/EoT. A similar proportion attained a therapeutic response, and ILC was reduced by 50.8% at week 12/EoT. Comparable results also were evident in the vehicle group for the primary end points of this study.[12] Vehicles in dermatologic trials frequently exert effects on diseased skin[16,17] via a skin care regimen effect (eg, moisturization and other vehicle-related effects that may improve skin barrier integrity and function) and thus should not be regarded as placebo controls. The mechanism underlying this efficacy may be due to the impact of vehicle composition on skin barrier integrity and transepidermal water loss.[18] The hydrophilic emulsion or other constituents of AzA foam (eg, fatty alcohols) may play a role.

A notable strength of our study is detailed clinical characterization using carefully chosen parameters and preplanned analyses that complement the primary end points. As the latter are often driven by regulatory requirements, opportunities to characterize other outcomes of interest to clinicians may be missed. The additional analyses reported here hopefully will aid dermatologists in both assessing the

role of AzA foam in the treatment armamentarium for PPR and counseling patients.

Because participants with lighter skin pigmentation dominated our study population, the impact of AzA foam among patients with darker skin complexions is unknown. Although AzA is unlikely to cause hypopigmentation in normal undiseased skin, patients should be monitored for early signs of hypopigmentation.[19,20] Our data also do not allow assessment of the differential effect, if any, of AzA foam on erythema of different etiologies in PPR, as corresponding information was not collected in the trial.

Conclusion

Azelaic acid foam 15% combines a well-established treatment of PPR with new vehicle technology to deliver effective therapy across multiple disease dimensions. In addition, the vehicle foam appears to demonstrate inherent therapeutic properties independent of AzA. The availability of this novel, efficacious, and well-tolerated option for PPR has the potential to improve patient care, reduce disease burden, and minimize unnecessary costs through increased tolerability and compliance.[21]

Acknowledgment—Editorial support through inVentiv Medical Communications (New York, New York) was provided by Bayer Pharmaceuticals.

References

1. Tan J, Berg M. Rosacea: current state of epidemiology. *J Am Acad Dermatol*. 2013;69(6, suppl 1):S27-S35.
2. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2002;46:584-587.
3. Chang AL, Raber I, Xu J, et al. Assessment of the genetic basis of rosacea by genome-wide association study. *J Invest Dermatol*. 2015;135:1548-1555.
4. Abram K, Silm H, Maaroos HI, et al. Risk factors associated with rosacea. *J Eur Acad Dermatol Venereol*. 2010;24:565-571.
5. Yamasaki K, Di Nardo A, Bardan A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med*. 2007;13:975-980.
6. Yamasaki K, Kanada K, Macleod DT, et al. TLR2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes. *J Invest Dermatol*. 2011;131:688-697.
7. Darlenski R, Kazandjieva J, Tsankov N, et al. Acute irritant threshold correlates with barrier function, skin hydration and contact hypersensitivity in atopic dermatitis and rosacea. *Exp Dermatol*. 2013;22:752-753.
8. Del Rosso JQ, Levin J. The clinical relevance of maintaining the functional integrity of the stratum corneum in both healthy and disease-affected skin. *J Clin Aesthet Dermatol*. 2011;4:22-42.
9. van Zuuren EJ, Kramer SF, Carter BR, et al. Effective and evidence-based management strategies for rosacea: summary of a Cochrane systematic review. *Br J Dermatol*. 2011;165:760-781.
10. Tan X, Feldman SR, Chang J, et al. Topical drug delivery systems in dermatology: a review of patient adherence issues. *Expert Opin Drug Deliv*. 2012;9:1263-1271.
11. Stein L. Clinical studies of a new vehicle formulation for topical corticosteroids in the treatment of psoriasis. *J Am Acad Dermatol*. 2005;53(1, suppl 1):S39-S49.
12. Draelos ZD, Elewski BE, Harper JC, et al. A phase 3 randomized, double-blind, vehicle-controlled trial of azelaic acid foam 15% in the treatment of papulopustular rosacea. *Cutis*. 2015;96:54-61.
13. Draelos ZD, Elewski B, Staedtler G, et al. Azelaic acid foam 15% in the treatment of papulopustular rosacea: a randomized, double-blind, vehicle-controlled study. *Cutis*. 2013;92:306-317.
14. Finacea gel [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2016.
15. Elewski BE, Fleischer AB Jr, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. *Arch Dermatol*. 2003;139:1444-1450.
16. Daniels R, Knie U. Galenics of dermal products—vehicles, properties and drug release. *J Dtsch Dermatol Ges*. 2007;5:367-383.
17. Shamsudin N, Fleischer AB Jr. Vehicle or placebo? Investigators use incorrect terminology in randomized controlled trials half of the time: a systematic review of randomized controlled trials published in three major dermatology journals. *J Drugs Dermatol*. 2010;9:1221-1226.
18. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 2: a status report on topical agents. *Cutis*. 2013;92:277-284.
19. Finacea foam [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2015.
20. Solano F, Briganti S, Picardo M, et al. Hypopigmenting agents: an updated review on biological, chemical and clinical aspects. *Pigment Cell Res*. 2006;19:550-571.
21. Hammarstrom B, Wessling A, Nilsson JL. Pharmaceutical care for patients with skin diseases: a campaign year at Swedish pharmacies. *J Clin Pharm Ther*. 1995;20:327-334.