

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

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PRACTICE POINTS

- Patient perceptions of treatment are an important consideration in developing topical therapeutic strategies for papulopustular rosacea.
- A novel hydrophilic foam formulation of azelaic acid (AzA) provided substantial benefits in patient-reported measures of treatment response and quality of life.
- Patients reported high levels of satisfaction with the usability, tolerability, and practicability of AzA foam.
- The positive treatment experience described by patients parallels investigator-reported measures of clinical efficacy reported elsewhere.

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Patient-reported treatment outcomes are important for evaluating the impact of drug therapies on patient experience. A randomized, double-blind, vehicle-controlled, parallel-group, multicenter, phase 3 study was conducted in 961 participants to assess patient perception of efficacy, utility, and effect on quality of life (QOL) of an azelaic acid (AzA) 15% foam formulation for the treatment of papulopustular rosacea (PPR). Secondary end points included patient-reported global assessment of treatment response, global assessment of tolerability, and opinion on cosmetic acceptability and practicability of product use. Quality of life assessments included the Dermatology Quality of Life Index (DLQI) and Rosacea Quality of Life Index (RosaQOL). Self-reported global assessment of treatment response favored AzA foam over vehicle foam ($P < .001$), with 57.2% of the AzA foam group reporting excellent or good improvement

versus 44.7% in the vehicle foam group. Tolerability was rated excellent or good in 67.8% of the AzA foam group versus 78.2% of the vehicle foam group. Mean overall DLQI scores at end of treatment (EoT) were improved ($P=.018$) in favor of the AzA foam group compared with the vehicle foam group. Both treatment groups showed improvements in RosaQOL. Treatment with AzA foam was associated with improved QOL and meaningful reductions in the patient-perceived burden of PPR, which correlates with earlier reported primary end points of this study and supports the inclusion of patient perspectives in studies evaluating the effects of topical dermatologic treatments.

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Rosacea is a chronic inflammatory disorder that may negatively impact patients' quality of life (QOL).^{1,2} Papulopustular rosacea (PPR) is characterized by centrop facial inflammatory lesions and erythema as well as burning and stinging secondary to skin barrier dysfunction.³⁻⁵ Increasing rosacea severity is associated with greater rates of anxiety and depression and lower QOL⁶ as well as low self-esteem and feelings of embarrassment.^{7,8} Accordingly, assessing patient perceptions of rosacea treatments is necessary for understanding its impact on patient health.^{6,9}

The Rosacea International Expert Group has emphasized the need to incorporate patient assessments of disease severity and QOL when developing therapeutic strategies for rosacea.⁷ Ease of use, sensory experience, and patient preference also are important dimensions in the evaluation of topical medications, as attributes of specific formulations may affect usability, adherence, and efficacy.^{10,11}

An azelaic acid (AzA) 15% foam formulation, which was approved by the US Food and Drug Administration in 2015, was developed to deliver AzA in a vehicle designed to improve treatment experience in patients with mild to moderate PPR.¹² Results from a clinical trial demonstrated superiority of AzA foam to vehicle foam for primary end points that included therapeutic success rate and change in inflammatory lesion count.^{13,14} Secondary end points assessed in the current analysis included patient perception of product usability, efficacy, and effect on QOL. These patient-reported outcome (PRO) results are reported here.

Methods

Study Design—The design of this phase 3 multicenter, randomized, double-blind, vehicle-controlled, parallel-group clinical trial was described in more

detail in an earlier report.¹³ This study was approved by all appropriate institutional review boards. Eligible participants were 18 years and older with moderate or severe PPR, 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 (0.5 g) or vehicle foam was applied twice daily to the entire face 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 investigator global assessment and nominal change in inflammatory lesion count—were previously reported,¹³ as well as secondary efficacy outcomes including change in inflammatory lesion count, therapeutic response rate, and change in erythema rating.¹⁴

Patient-Reported Secondary Efficacy Outcomes—The secondary PRO end points were patient-reported global assessment of treatment response (rated as excellent, good, fair, none, or worse), global assessment of tolerability (rated as excellent, good, acceptable despite minor irritation, less acceptable due to continuous irritation, not acceptable, or no opinion), and opinion on cosmetic acceptability and practicability of product use in areas adjacent to the hairline (rated as very good, good, satisfactory, poor, or no opinion).

Additionally, QOL was measured by 3 validated standardized PRO tools, including the Rosacea Quality of Life Index (RosaQOL),¹⁵ the EuroQOL 5-dimension 5-level questionnaire (EQ-5D-5L),¹⁶ and the Dermatology Life Quality Index (DLQI). The RosaQOL is a rosacea-specific instrument assessing 3 constructs: (1) symptom, (2) emotion, and (3) function. The EQ-5D-5L questionnaire measures overall health status and comprises 5 constructs: (1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort, and (5) anxiety/depression. The DLQI is a general, dermatology-oriented instrument categorized into 6 constructs: (1) symptoms and feelings, (2) daily activities, (3) leisure, (4) work and school, (5) personal relationships, and (6) treatment.

Statistical Analyses—Patient-reported outcomes were analyzed in an exploratory manner and evaluated at EoT relative to baseline. Self-reported global assessment of treatment response and change in

RosaQOL, EQ-5D-5L, and DLQI scores between AzA foam and vehicle foam groups were evaluated using the Wilcoxon rank sum test. Categorical change in the number of participants achieving an increase of 5 or more points in overall DLQI score was evaluated using a χ^2 test.

Safety—Safety was analyzed for all randomized patients who were dispensed any study medication. All analyses were performed using SAS version 9.2.

Results

Of the 961 participants included in the study, 483 were randomized to receive AzA foam and 478 were randomized to receive vehicle foam. The mean age was 51.5 years, and the majority of participants were female (73.0%) and white (95.5%) (Table). At baseline, 834 (86.8%) participants had moderate PPR and 127 (13.2%) had severe PPR. The mean inflammatory lesion count (SD) was 21.4 (8.9). No significant differences in

baseline characteristics were observed between treatment groups.

Patient-reported global assessment of treatment response differed between treatment groups at EoT ($P < .001$) (Figure 1). Higher ratings of treatment response were reported among the AzA foam group (excellent, 17.2%; good, 40.0%) versus vehicle foam (excellent, 9.7%; good, 35.0%). The number of participants reporting no treatment response was 13.1% in the AzA foam group, with 1.8% reporting worsening of their condition, while 19.4% of participants in the vehicle foam group reported no response, with 6.3% reporting worsening of their condition (Figure 1).

Tolerability was rated excellent or good in 67.8% of the AzA foam group versus 78.2% of the vehicle foam group (Figure 2A). Approximately 38.4% of the AzA foam group versus 38.2% of the vehicle foam group rated treatment tolerability as excellent, while 93.5% of the AzA foam group rated tolerability as

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 (SD)	21.7 (9.1)	21.2 (8.7)
Mean EQ-VAS score (SD)	85.1 (11.7)	84.6 (13.0)

Abbreviations: AzA, azelaic acid; IGA, investigator global assessment; ILC, inflammatory lesion count; EQ-VAS, EuroQOL visual analog scale; QOL, quality of life.

^aNo significant differences were present between the treatment groups for any baseline characteristics listed.

^bNonwhite categories included black, Asian, American Indian or Alaskan native, Native Hawaiian or Other Pacific Islander, or multiple.

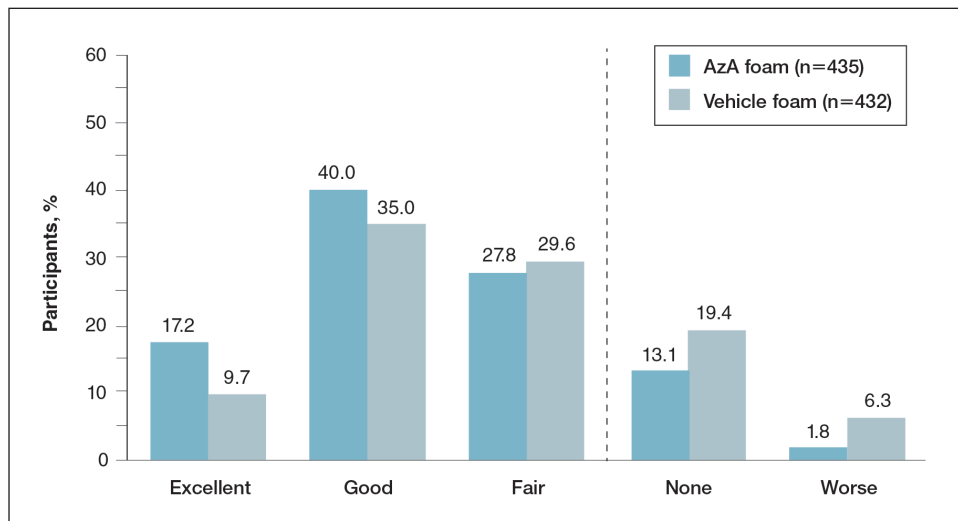


Figure 1. Patient-reported global assessment of treatment response at end of treatment. AzA indicates azelaic acid. *P* value derived from Wilcoxon rank sum test comparing distribution of ratings between AzA foam versus vehicle foam groups ($P < .001$). The sum of excellent, good, and fair responses was 85.1% (AzA foam) and 74.3% (vehicle foam). Note that the total sample does not equal 961 because of missing data for these outcomes.

acceptable, good, or excellent compared with 89.5% of the vehicle foam group. Only 1.4% of participants in the AzA foam group indicated that treatment was not acceptable due to irritation. In addition, a greater proportion of the AzA foam group reported cosmetic acceptability as very good versus the vehicle foam group (40.5% vs 28.7%) (Figure 2B), with two-thirds reporting cosmetic acceptability as very good or good. Practicability of product use in areas adjacent to the hairline was rated very good by substantial proportions of both the AzA foam and vehicle foam groups (42.8% vs 35.9%) (Figure 2C).

At baseline, average disease burden was moderate according to mean overall DLQI scores (SD) for the AzA foam (5.4 [4.8]) and vehicle foam (5.4 [4.9]) groups. Mean overall DLQI scores improved at EoT, with greater improvement occurring in the AzA foam group (2.6 vs 2.1; $P = .018$) (Figure 3). A larger proportion of participants in the AzA foam group versus the vehicle foam group also achieved a 5-point or more improvement in overall DLQI score (24.6% vs 19.0%; $P = .047$). Changes in specific DLQI subscore components were either balanced or in favor of the AzA foam group, including daily activities (0.5 vs 0.4; $P = .019$), symptoms and feelings (1.2 vs 1.0; $P = .069$), and leisure (0.5 vs 0.4; $P = .012$). Specific DLQI items with differences in scores between treatment groups from baseline included the following questions: Over the last week, how embarrassed or self-conscious have you been because of your skin? ($P < .001$); Over the last week, how much has your skin interfered with you going shopping or

looking after your home or garden? ($P = .005$); Over the last week, how much has your skin affected any social or leisure activities? ($P = .040$); Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives? ($P = .001$). Differences between treatment groups favored the AzA foam group for each of these items.

Participants in the AzA foam and vehicle foam groups also showed improvement in RosaQOL scores at EoT (6.8 vs 6.4; $P = .67$), while EQ-5D-5L scores changed minimally from baseline (0.006 vs 0.007; $P = .50$).

Safety—The incidence of drug-related adverse events (AEs) was greater in the AzA foam group versus the vehicle foam group (7.7% vs 4.8%). Drug-related AEs occurring in 1% of the AzA foam group were application-site pain including tenderness, stinging, and burning (3.5% for AzA foam vs 1.3% for vehicle foam); application-site pruritus (1.4% vs 0.4%); and application-site dryness (1.0% vs 0.6%). One drug-related AE of severe intensity—application-site dermatitis—occurred in the vehicle foam group; all other drug-related AEs were mild or moderate.¹⁴ More detailed safety results are described in a previous report.¹³

Comment

The PRO outcome data reported here are consistent with previously reported statistically significant improvements in investigator-assessed primary end points for the treatment of PPR with AzA foam.^{13,14}

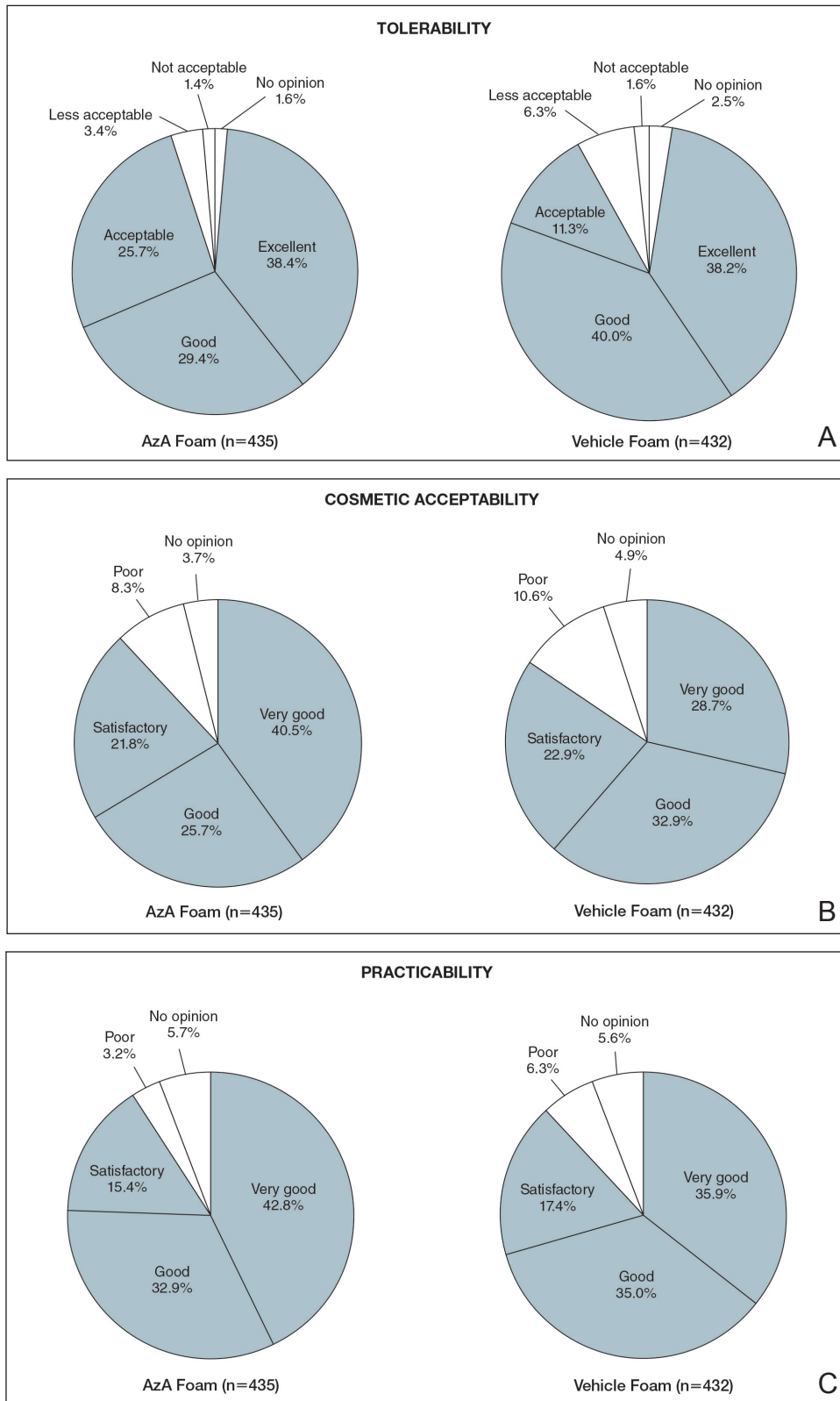


Figure 2. Global assessment of tolerability at end of treatment (EoT)(A). Opinion on cosmetic acceptability at EoT (B). Opinion on practicability of product use in areas adjacent to hairline at EoT (C). AzA indicates azelaic acid. For global assessment of tolerability, acceptable indicates acceptable despite minor irritation; less acceptable, less acceptable due to continuous irritation. Note that the total sample does not equal 961 because of missing data for these outcomes.

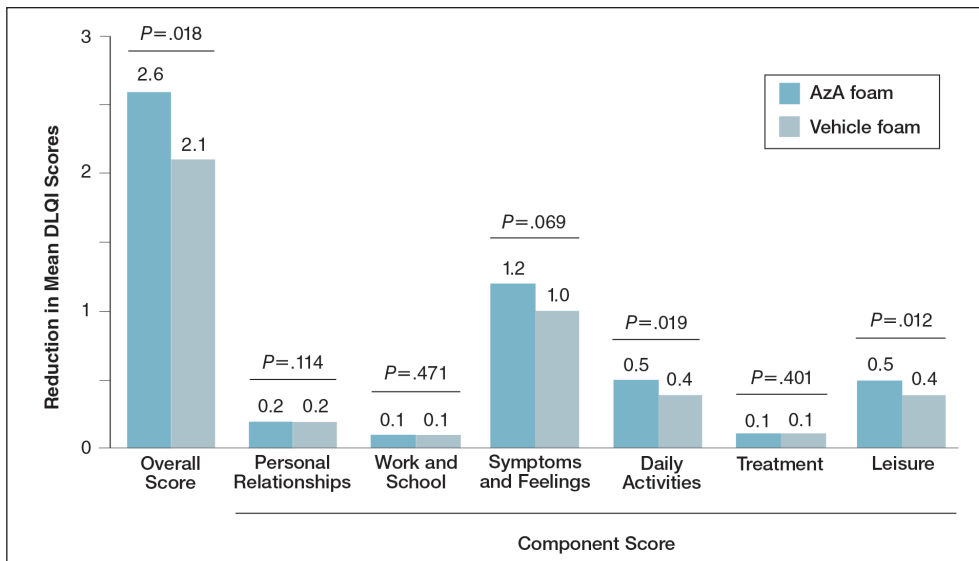


Figure 3. Reduction in mean Dermatology Life Quality Index (DLQI) scores from baseline to end of treatment. AzA indicates azelaic acid. *P* values derived from Wilcoxon rank sum test. For personal relationships and work/school, AzA foam (n=435); vehicle foam (n=431). For symptoms/feelings and daily activities, AzA foam (n=435); vehicle foam (n=430). For leisure, AzA foam (n=435); vehicle foam (n=429). Component score responses do not include missing data.

The data demonstrate that AzA foam benefits both clinical and patient-oriented dimensions of rosacea disease burden and suggest an association between positive treatment response and improved QOL.

Specifically, patient evaluation of treatment response to AzA foam was highly favorable, with 57.2% reporting excellent or good response and 85.1% reporting positive response overall. Recognizing the relapsing-remitting course of PPR, only 1.8% of the AzA foam group experienced worsening of disease at EoT.

The DLQI and RosaQOL instruments revealed notable improvements in QOL from baseline for both treatment groups. Although no significant differences in RosaQOL scores were observed between groups at EoT, significant differences in DLQI scores were detected. Almost one-quarter of participants in the AzA foam group achieved at least a 5-point improvement in DLQI score, exceeding the 4-point threshold for clinically meaningful change.¹⁷ Although little change in EQ-5D-5L scores was observed at EoT for both groups with no between-group differences, this finding is not unexpected, as this instrument assesses QOL dimensions such as loss of function, mobility, and ability to wash or dress, which are unlikely to be compromised in most rosacea patients.

Our results also underscore the importance of vehicle in the treatment of compromised skin. Studies of topical treatments for other dermatoses suggest that vehicle properties may reduce disease severity and improve QOL independent of active ingredients.^{10,18} For example, ease of application, minimal residue,

and less time spent in application may explain the superiority of foam to other vehicles in the treatment of psoriasis.¹⁸ Our data demonstrating high cosmetic favorability of AzA foam are consistent with these prior observations. Increased tolerability of foam formulations also may affect response to treatment, in part by supporting adherence.¹⁸ Most participants receiving AzA foam described tolerability as excellent or good, and the discontinuation rate was low (1.2% of participants in the AzA foam group left the study due to AEs) in the setting of near-complete dosage administration (97% of expected doses applied).¹³

Conclusion

These results indicate that use of AzA foam as well as its novel vehicle results in high patient satisfaction and improved QOL. Although additional research is necessary to further delineate the relationship between PROs and other measures of clinical efficacy, our data demonstrate a positive treatment experience as perceived by patients that parallels the clinical efficacy of AzA foam for the treatment of PPR.^{13,14}

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REFERENCES

- Cardwell LA, Farhangian ME, Alinia H, et al. Psychological disorders associated with rosacea: analysis of unscripted comments. *J Dermatol Surg.* 2015;19:99-103.

2. Moustafa F, Lewallen RS, Feldman SR. The psychological impact of rosacea and the influence of current management options. *J Am Acad Dermatol*. 2014;71:973-980.
3. 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.
4. Yamasaki K, Gallo RL. The molecular pathology of rosacea. *J Dermatol Sci*. 2009;55:77-81.
5. Del Rosso JQ. Advances in understanding and managing rosacea: part 1: connecting the dots between pathophysiological mechanisms and common clinical features of rosacea with emphasis on vascular changes and facial erythema. *J Clin Aesthet Dermatol*. 2012;5:16-25.
6. Bohm D, Schwanitz P, Stock Gissendanner S, et al. Symptom severity and psychological sequelae in rosacea: results of a survey. *Psychol Health Med*. 2014;19:586-591.
7. Elewski BE, Draelos Z, Dreno B, et al. Rosacea—global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group. *J Eur Acad Dermatol Venereol*. 2011;25:188-200.
8. Dirschka T, Micali G, Papadopoulos L, et al. Perceptions on the psychological impact of facial erythema associated with rosacea: results of international survey [published online May 29, 2015]. *Dermatol Ther (Heidelb)*. 2015;5:117-127.
9. Abram K, Silm H, Maaros HI, et al. Subjective disease perception and symptoms of depression in relation to healthcare-seeking behaviour in patients with rosacea. *Acta Derm Venereol*. 2009;89:488-491.
10. 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.
11. Yentzer BA, Camacho FT, Young T, et al. Good adherence and early efficacy using desonide hydrogel for atopic dermatitis: results from a program addressing patient compliance. *J Drugs Dermatol*. 2010;9:324-329.
12. Finacea (azelaic acid) foam 15% [package insert]. Whippany, NJ: Bayer Pharmaceuticals; 2015.
13. 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.
14. Solomon JA, Tyring S, Staedtler G, et al. 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. *Cutis*. 2016;98:187-194.
15. Nicholson K, Abramova L, Chren MM, et al. A pilot quality-of-life instrument for acne rosacea. *J Am Acad Dermatol*. 2007;57:213-221.
16. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20:1727-1736.
17. Basra MK, Salek MS, Camilleri L, et al. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology*. 2015;230:27-33.
18. Bergstrom KG, Arambula K, Kimball AB. Medication formulation affects quality of life: a randomized single-blind study of clobetasol propionate foam 0.05% compared with a combined program of clobetasol cream 0.05% and solution 0.05% for the treatment of psoriasis. *Cutis*. 2003;72:407-411.