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Responsiveness of the Acne-Specific Quality of Life Questionnaire (Acne-QoL) to treatment for acne vulgaris in placebo-controlled clinical trials

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Abstract

The Acne-Specific Quality of Life Questionnaire (Acne-QoL) was developed to measure the impact of facial acne across four dimensions of patient quality of life. The main objective of the current study was to evaluate the responsiveness of this instrument. Secondarily, this study provided an opportunity to extend the developer's psychometric validation. The Acne-QoL was utilized in two randomized, double-blind, placebo-controlled studies of the efficacy of Estrostep® (norethindrone acetate/ethinyl estradiol) in the treatment of facial acne; a total of 296 Estrostep® and 295 placebo patients were evaluated. The Acne-QoL was completed at the beginning, middle (cycle 3), and end (cycle 6) of the 6-month treatment period. The responsiveness of the Acne-QoL was demonstrated through its ability to detect both small (baseline to mid-study) and moderate (baseline to study end) treatment advantages for Estrostep® patients. Confirmatory factor analysis supported the subscale structure, and internal consistency estimates were excellent. Convergent and discriminant validity were supported by correlations between Acne-QoL scores and clinical measures that were both in the direction and relative magnitude hypothesized. Finally, item response theory analyses confirmed that each item is highly related to its subscale's latent construct and that each subscale is sensitive across a broad range of the underlying continuum. The results of this evaluation confirm that the Acne-QoL is responsive, internally consistent, and valid.

Key words: Acne vulgaris, Facial dermatoses, Psychometrics, Quality of life, Skin diseases

Abbreviations: Acne-QoL – Acne-Specific Quality of Life Questionnaire; AGFI – Adjusted-Goodness-of-Fit Index; CFI – Comparative Fit Index; FAGA – Facial Acne Global Assessment; GFI – Goodness-of-Fit Index; IRT – item response theory; mg – milligrams; μg – micrograms; QoL – quality of life; RMSEA – Root Mean Square Error of Approximation

Introduction

Acne vulgaris is a common skin condition that affects approximately 17 million Americans, causing both distress and disfigurement [1]. While acne is most common in adolescence, it is also prevalent among adults and can lead to lifelong scarring. In addition to its substantial physical effects, facial acne has been associated with a range of psychosocial effects that impact health-related quality of life, including anxiety, depression, self-consciousness, embarrassment, low self-esteem, and social withdrawal [2–4].

In the past, much of the literature on acne has been devoted to the clinical assessment of acne in terms of lesion counts or severity classifications,

and treatment outcomes have been assessed through global improvement ratings (provided by either the dermatologist or patient). Neither severity nor global measures, however, are designed to detect changes in a patient's health-related quality of life. Although generic quality of life instruments are preferable in some situations, disease-specific measures have greater power to detect change by focusing on aspects of functioning that are most affected by the disease and tend to be of greatest importance to patients [5]. To measure health-related quality of life among patients with facial acne, therefore, a new questionnaire, the Acne-Specific Quality of Life Questionnaire (Acne-QoL), was developed and validated for use in clinical trials [6–8].

This report describes the first assessment of the responsiveness of the Acne-QoL in placebo-controlled clinical trials and provides further psychometric validation.

Methods

The development and validation of the Acne-QoL has been described in detail elsewhere [6–8]. Briefly, the Acne-QoL is a patient-completed questionnaire with a 1-week recall period composed of 19 items in four subscales: Self-Perception, Role-Emotional, Role-Social, and Acne Symptoms. Table 1 provides a summary of the instrument's content, and the full questionnaire is provided by Martin et al. [8] Instrument scoring is accomplished by summing the responses within the subscales to yield four overall domain scores, where higher scores indicate more favorable quality of life.

The Acne-QoL was included in two similarly designed, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies of the efficacy and safety of Estrostep® (norethindrone acetate/ethinyl estradiol) on moderate acne vulgaris [9]. Estrostep® is an oral contraceptive pill combining low-dose phasic ethinyl estradiol (20, 30, and 35 μg for 5, 7, and 9 days, respectively) with a constant 1 mg dose of norethindrone acetate. The protocols of the trials were identical, except that in one trial, blood samples were collected at selected sites to analyze androgen levels and pharmacokinetics of ethinyl estradiol and norethindrone acetate, and in the other trial, photographs of subjects' facial acne were taken at selected sites. By combining the data from the two trials, a total of 296 patients receiving Estrostep® and 295 placebo patients were evaluated.

Female subjects aged from 14 to 49 years, at least 1 year postmenarche, with a baseline menstrual cycle less than 42 days in duration, were eligible for randomization if they had (1) moderate facial acne (20–100 comedones and 20–65 inflam-

Table 1. Domain structure of the Acne-QoL

Self-Perception	Role-Emotional	Role-Social	Symptoms
Feeling unattractive	Upset about having facial acne	Concern about meeting new people	Bumps on your face[a]
Feeling embarrassed	Annoyed about time spent cleaning and treating face	Concern about going out in public	Bumps full of pus on face[a]
Feeling self-conscious	Concern about not looking your best	Socializing a problem	Scabbing from facial acne[a]
Dissatisfied with appearance	Concern about acne medication not working fast enough	Interacting with the opposite sex a problem	Concern about scarring from facial acne
Self-confidence (negatively affected)	Bothered by need to have medication and cover-up available		Oily facial skin

All questions are framed to be disease specific ('... because of your facial acne').
The response options for all but three questions include: extremely, very much, quite a bit, a good bit, somewhat, a little bit, and not at all.
[a] The response options for these questions include: extensive, a whole lot, a lot, a moderate amount, some, very few, and none.

matory lesions, and no more than 5 nodules) and had not adequately responded to topical anti-acne therapy; and (2) agreed to avoid using any topical or systemic acne treatment. Major exclusion criteria consisted of other significant facial skin disease for which topical treatment would be required during the study, significant endocrinopathy such as marked hirsutism, evidence of severe androgen excess (i.e., testosterone levels >150 ng/dL), or if the patient was pregnant or nursing.

The efficacy of Estrostep® was assessed through changes in the number of acne lesions and a physician-completed Facial Acne Global Assessment (FAGA) at each follow-up visit. The FAGA provides a global assessment of acne severity and was completed by physicians before they performed the lesion counts.[1] Two supplemental measures were completed by patients at study exit to examine patients' perceptions of treatment-related changes, however neither of these measures were used in the current psychometric evaluation In addition, the Acne-QoL was completed by patients at the beginning, middle (cycle 3), and end (cycle 6) of the 6-month treatment period. The methodology and results of these clinical trials are fully described in Maloney et al. [9] and formed the basis for the FDA's approval of an acne indication for Estrostep®. These data were pooled for this submission because there were no differences in study design, no meaningful population differences, and the efficacy results were statistically indistinguishable [9].

For the current study the same (pooled) data from these trials were utilized to assess the responsiveness of the Acne-QoL within placebo-controlled trials and secondarily to confirm previous psychometric validation of the Acne-QoL. Missing item-level data were handled according to developer recommendations [7]. Specifically, each subscale score was computed only for patients who answered three or more items within the domain. If patients failed to answer one or two items within a domain, responses for these items were imputed through mean substitution prior to the computation of the subscale score. In addition, data obtained at study exit for patients discontinuing between visits were carried forward and included in analyses involving the next visit. Using this method, 231 Estrostep® and 219 placebo patients provided Acne-QoL data throughout the study. As reported in Maloney et al. [9], the dropout rates for this study were comparable to other placebo-controlled acne studies and did not influence the conclusions regarding QoL.

Responsiveness of the instrument was assessed by evaluating treatment differences (as measured by change in Acne-QoL scores from baseline) at the middle and end of the study. Following a series of repeated measures ANOVAs, effect size statistics were computed to more fully elucidate this issue. Specifically, Guyatt's responsiveness statistic, which is defined as the difference in average change scores between the two treatment groups divided by the standard deviation of change scores in the placebo group, was calculated for each subscale [10].

In addition to evaluating the responsiveness of the Acne-QoL, the opportunity was taken to further the developer's validation of this instrument [6–8]. First, the subscale structure of the instrument was confirmed. Specifically, after utilizing PRELIS Version 2.0 to obtain the polychoric correlation and corresponding asymptotic covariance matrices, confirmatory factor analysis of the baseline Acne-QoL data was conducted in LISREL Version 8.30 using weighted least squares estimation [11]. Model fit was evaluated using the Goodness-of-Fit Index (GFI), the Adjusted-Goodness-of-Fit Index (AGFI), and the Comparative Fit Index (CFI). Schumacker and Lomax (1996) suggest that, for each of these goodness-of-fit indices, values greater than 0.90 are desirable [12]. Cronbach's alphas were computed to assess the internal consistency reliability of each Acne-QoL subscale.

Additional evidence for the convergent and discriminant validity of the instrument was then gathered by correlating each of the four domain scores with a range of clinical measures: some of these clinical measures were theoretically related to acne-specific QoL (e.g., lesion counts and FAGAs), while others were not (e.g., blood pressure and heart rate). Implicit in the examination of the relations between the Acne-QoL subscale scores and the two clinical measures of acne severity, lesion counts and FAGAs, is the assumption that

[1]To complete the FAGA, physicians categorize patients' facial acne as one of the following: 'absent, minimal, mild, mild to moderate, moderate, marked or severe'. Each category is defined in detail on the assessment form.

acne-specific quality of life (QoL) and acne severity are related. Gathering support for convergent validity then involves showing that the Acne-QoL measures acne-specific QoL precisely enough to demonstrate this relation. Because values of the Acne-QoL increase with better QoL and the two clinical measures increase with greater severity, it was expected that the correlations between these measures would be negative in sign. Moreover, it was expected that these correlations would be moderate rather than large in magnitude both because the respondents differ between the two types of measures (i.e., patient vs. clinician) and because the constructs addressed by each measure, while related, are not redundant.

Item response theory (IRT) fits statistical models to item responses in order to examine the properties of items and estimate latent traits for individuals. Because the Acne-QoL utilizes ordinal response categories, Samejima's [13] graded response model was applied to assess both the sensitivity and discriminating ability of each item. IRT item parameter estimates were obtained using marginal maximum *a posteriori* estimation as implemented in Multilog Version 6.0 [14], and each of the four subscales was calibrated separately to satisfy the assumption of unidimensionality.

Results

Descriptive analyses

The treatment groups in both trials were similar with respect to demographic and clinical characteristics at randomization (Table 2), with an overall mean age of 24.1 years (range: 13–48 years). The majority of the patients in both groups were Caucasian (68%) and their mean (±SD) baseline lesion counts were similar (Estrostep®, 73.7 ± 25.9; placebo, 72.3 ± 27.7).

Table 2. Baseline demographic and clinical characteristics: intent-to-treat population

Characteristics	Estrostep® N = 296	Placebo N = 295
Age, year		
Mean (SD)	24.28 (7.56)	23.92 (7.42)
Race, N (%)		
White/Caucasian	202 (68%)	202 (68%)
Black	38 (13%)	46 (16%)
Asian	18 (6%)	7 (2%)
Hispanic	30 (10%)	34 (12%)
Other	8 (3%)	6 (2%)
Total lesion count		
Mean (SD)	73.68 (25.91)	72.26 (27.66)

Descriptive statistics for all four Acne-QoL subscales at each visit are reported in Table 3. Overall, the pattern of these descriptive statistics suggests an advantage for the patients who received Estrostep® (i.e., average scores for all four subscales are higher for the Estrostep® patients at both the mid-study and final visits). Treatment analysis results showed that Estrostep®-treated subjects experienced greater (statistically significant) improvements in all four domains of the Acne-QoL when compared with placebo-treated subjects at cycle 3 and that these treatment advantages continued to increase throughout the remainder of the study [9]. Additional work has

Table 3. Descriptive subscale-level statistics for the Acne-QoL

	Baseline visit			Mid-study visit			Last visit		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Estrostep®									
Self-Perception	292	15.15	7.9	263	20.08	7.7	232	23.05	6.7
Role-Emotional	292	13.79	7.8	263	18.60	7.9	232	21.61	7.5
Role-Social	292	15.50	6.8	262	18.76	6.1	231	20.62	5.1
Acne Symptoms	292	13.75	5.3	263	18.32	5.8	230	20.97	5.4
Placebo									
Self-Perception	290	14.97	7.5	247	18.71	8.5	219	19.58	7.8
Role-Emotional	290	14.19	7.5	247	17.19	8.6	219	18.24	8.3
Role-Social	288	15.73	6.7	247	17.53	6.8	219	18.33	6.0
Acne Symptoms	287	14.10	5.3	247	16.84	5.9	219	18.37	5.8

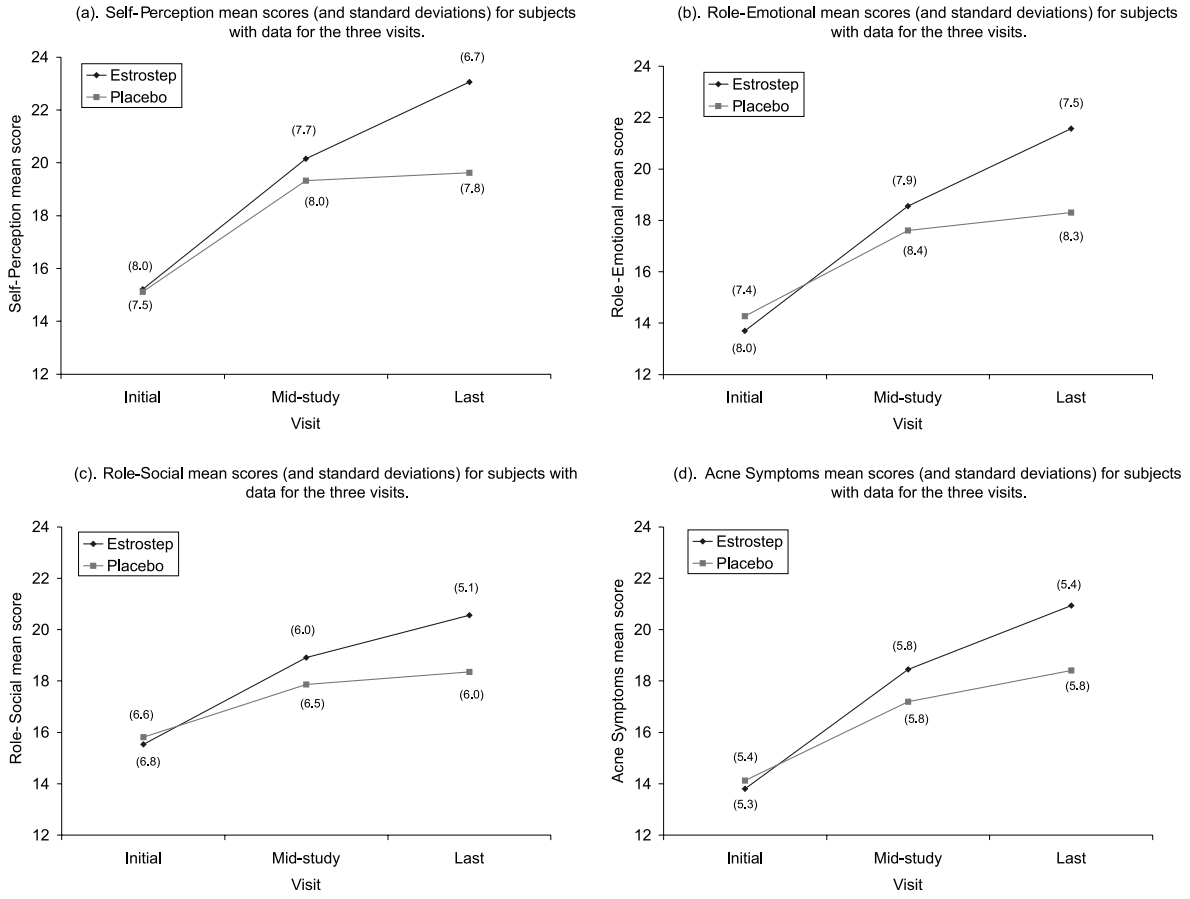

Figure 1. (a–d). Subscale mean scores at baseline, midpoint, and final visit. Higher scores on the Acne-QoL subscales indicate a higher level of QoL. The group differences are significant for all subscales between the midpoint and the final visit ($p < 0.0001$). The standard deviations are provided in parentheses.

recently been completed which shows that these statistically significant findings are also clinically meaningful (manuscript in progress).

Responsiveness

In a series of repeated measures ANOVAs, statistically significant interactions between visit (baseline, mid-study, and last) and treatment group (Estrostep® vs. placebo) were observed for all subscales ($p < 0.0001$), with larger improvements in average Acne-QoL subscale scores for Estrostep® patients when compared to the placebo patients (see Figure 1). All contrasts also showed statistically significant differences, except for the comparison between scores at the baseline and mid-study visit for the Self-Perception subscale. These results imply that, while Acne-QoL subscale scores improved for both sets of patients across the course of the study, the Acne-QoL was sufficiently sensitive to demonstrate that the Estrostep® patients experienced significantly greater improvements in all four acne-specific QoL domains than patients in the placebo group.

As shown in Tables 4 and 5, values of Guyatt's responsiveness statistic ranged from 0.14 to 0.28 and 0.41 to 0.49 at the mid-study and final visits, respectively. Using Cohen's (1977) guideline for effect-size interpretation,[2] these values indicate that the Acne-QoL is sufficiently responsive to

[2]Cohen (1977) suggested that effect sizes near 0.20 represent small effects, those near 0.50 represent moderate effects, and those near 0.80 represent large effects [15].

Table 4. Mean change in Acne-QoL subscale scores and effect sizes between the baseline and mid-study visits

Subscale	Estrostep®			Placebo			Effect size
	N	Mean	SD	N	Mean	SD	
Self-Perception	262	4.75	7.45	247	3.66	7.91	0.14
Role-Emotional	262	4.64	7.71	247	2.94	7.52	0.23
Role-Social	261	3.11	5.80	246	1.71	5.55	0.25
Acne Symptoms	262	4.47	5.59	245	2.84	5.86	0.28

Table 5. Mean change in Acne-QoL subscale scores and effect sizes between the baseline and final visits

Subscale	Estrostep®			Placebo			Effect size
	N	Mean	SD	N	Mean	SD	
Self-Perception	231	7.95	8.77	219	4.50	8.38	0.41
Role-Emotional	231	8.04	9.33	219	4.01	8.14	0.49
Role-Social	230	5.09	6.66	218	2.51	5.85	0.44
Acne Symptoms	229	7.21	5.81	217	4.25	6.00	0.49

pick up small treatment advantages (for Estrostep® as compared to placebo) such as those found between the baseline and mid-study visits, as well as moderate treatment advantages, such as those found between the baseline and final visits [15]. Taken together, these two sets of results provide strong evidence for responsiveness within the context of placebo-controlled trials.

Confirmatory psychometric analyses

Confirmatory factor analysis supported the subscale structure previously identified by the developers. However, all four Acne-QoL subscales were found to be highly correlated, particularly the Self-Perception, Role-Emotional, and Role-Social subscales (inter-factor correlations ranged from 0.91 to 0.97), and inter-factor correlations between those three subscales and the Acne Symptoms subscale were between 0.82 and 0.85. The majority of the items produced high factor loadings (i.e., values close to 1), suggesting that they fit quite well within their assigned subscales, and the values for the goodness-of-fit indices provide further evidence of appropriate model fit: 0.98 (GFI), 0.97 (AGFI), and 0.99 (CFI). The Root Mean Square Error of Approximation (RMSEA) was 0.07, slightly higher than the typically accepted 0.05 [11]. However, in light of the excellent goodness-of-fit indices and high factor loadings, as well as the results of prior testing, the domain structure was supported.

Internal consistency (as measured by Cronbach's α) ranged from 0.87 to 0.96 across the three time-points for the Self-Perception, Role-Emotional, and Role-Social subscales. As is common for symptom-related subscales, the estimates were slightly lower for the Acne Symptoms subscale (range: 0.77–0.86). Using Streiner and Norman's (1995) guideline that Cronbach's α for health-related scales should not be lower than 0.70, each of the Acne-QoL subscales was shown to be internally consistent [16].

The modest negative correlations shown in the first two columns of Table 6 support the convergent validity of the Acne-QoL by demonstrating that acne severity as reported by clinicians is associated with acne-specific QoL as reported by patients. Likewise, discriminant validity was supported by the very low correlations obtained between the Acne-QoL subscale scores and clinical measures assumed to be unrelated to acne-specific QoL, such as blood pressure, heart rate, and height (Table 6).

Item response theory analyses

The IRT models generally fit the data well: the solutions converged easily, the parameter estimates were plausible, and the standard errors were generally very small.

Table 6. Correlations between the four Acne-QoL subscale scores and five clinical measures (both related and unrelated to QoL)

Subscale	Total lesion count	FAGA	Systolic blood pressure	Heart rate	Height
Mid-study visit					
Self-Perception	−0.27*	−0.30*	−0.01	−0.02	0.05
Role-Emotional	−0.28*	−0.30*	−0.00	−0.04	0.09**
Role-Social	−0.21*	−0.24*	0.02	−0.06	0.09**
Acne Symptoms	−0.28*	−0.37*	0.02	0.00	0.03
Last visit					
Self-Perception	−0.30*	−0.36*	0.03	−0.07	0.10**
Role-Emotional	−0.29*	−0.37*	0.06	−0.07	0.14***
Role-Social	−0.25*	−0.32*	0.06	−0.03	0.12***
Acne Symptoms	−0.35*	−0.44*	0.09	−0.01	0.07

FAGA – Facial Acne Global Assessment.
* $p < 0.0001$; ** $p < 0.05$; *** $p < 0.01$.

A large slope (large a value) indicates that an item is highly related to the construct underlying the subscale and can be used to differentiate among individuals. The item discriminations or a parameters for each of the four Acne-QoL subscales were generally quite high (only two were less than 1.5), suggesting that every item was strongly related to the latent constructs measured by the subscales.

The threshold or b parameters serve to locate the scale value of the item response on the underlying z-score scale of the latent construct. The threshold estimates or b parameters for each of the four subscales generally cover a wide range of the underlying continuum. For example, the threshold estimates for the Self-Perception subscale range from −2.40 to 2.36. Because the items within each Acne-QoL subscale produce a wide range of threshold estimates, they are appropriate for distinguishing among individuals across all plausible levels of the underlying continuum.

Discussion

The results of this study confirm that the subscale configuration of the Acne-QoL is appropriate and that the instrument is both valid and internally consistent, as well as sensitive to change and capable of detecting treatment differences in clinical trials. A prior study also showed good test–retest reliability for the Acne-QoL [8].

While high correlations among the Self-Perception, Role-Emotional, and Role-Social subscales suggest that it might be possible to combine these subscales into one, yielding a more parsimonious two-subscale configuration, in practice, patients' subscale scores are not likely to be as highly related as the inter-factor correlations suggest. In particular, the inter-factor correlations were obtained through weighted least squares estimation using the polychoric correlation and asymptotic covariance matrices, which are based on the theoretical relations among the continuous latent variables hypothesized to underlie each item. Although this computational method is the gold standard for confirmatory factor analyses involving ordinal items [11], it is likely to overestimate the degree of inter-relatedness among the subscales. Furthermore any change in the subscale structure of the Acne-QoL should only be made if it both improves the utility of the questionnaire and is consistent with clinical considerations.

In a previous study, the Acne-QoL was found to be responsive to changes in the severity of patients' facial acne following usual care therapy [8]. Because the aforementioned study did not include a control group, the current research was necessary to confirm the responsiveness of the Acne-QoL in the context of placebo-controlled randomized clinical trials. Within these trials, the Acne-QoL was sufficiently responsive to pick up both small and moderate treatment advantages for the patients who received Estrostep® as compared to placebo. These findings confirm the utility of the Acne-QoL for demonstrating the efficacy of new acne medications in placebo-controlled clinical trials. Just as the accumulation of additional

validation information in various populations and settings is always beneficial, however, further evaluation of this instrument's responsiveness would also be valuable.

The results of the IRT analyses indicated that nearly every item is strongly related to the construct underlying the subscale to which it belongs. At the same time, because all the slope estimates are similar within each subscale, no one item or group of items seems to be dominant. These findings suggest that an IRT-based scoring algorithm (or any algorithm that would differentially weight the items) is not likely to improve the precision of these measurements substantially. Because a more complex algorithm might also discourage the use of the Acne-QoL, it is recommended that the current scoring algorithm continue to be utilized.

In summary, the results of this study confirm previous psychometric evaluations of the Acne-QoL and demonstrate that the questionnaire is sufficiently responsive to assess the humanistic impacts of facial acne in a randomized clinical trial of a therapeutic intervention for acne vulgaris.

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