Title
Use of an alternative method to evaluate erythema severity in a clinical trial: difference in vehicle response with evaluation of baseline and postdose photographs for effect of oxymetazoline cream 1·0% for persistent erythema of rosacea in a phase I...

Permalink
https://escholarship.org/uc/item/73f0m5r5

Journal
The British journal of dermatology, 180(5)

ISSN
0007-0963

Authors
Eichenfield, LF
Del Rosso, JQ
Tan, JKL
et al.

Publication Date
2019-05-01

DOI
10.1111/bjd.17462

Peer reviewed
Use of an alternative method to evaluate erythema severity in a clinical trial: difference in vehicle response with evaluation of baseline and postdose photographs for effect of oxymetazoline cream 1·0% for persistent erythema of rosacea in a phase IV study

L.F. Eichenfield,1,2 J.Q. Del Rosso,3 J.K.L. Tan,4 A.A. Hebert,5 G.F. Webster,6 J. Harper,7 H.E. Baldwin,8 L.H. Kirck,9,10 L. Stein-Gold,11 A. Kaoukhov12 and N. Alvandi12

1University of California, San Diego, CA, U.S.A.
2Rady Children’s Hospital, San Diego, CA, U.S.A.
3JDR Dermatology Research/Thomas Dermatology, Las Vegas, NV, U.S.A.
4Windor Clinical Research Inc., Windsor, ON, Canada
5UTHealth McGovern Medical School, Department of Dermatology, Houston, TX, U.S.A.
6Webster Dermatology, P.A., Hockessin, DE, U.S.A.
7Dermatology and Skin Care Center of Birmingham, Birmingham, AL, U.S.A.
8The Acne Treatment and Research Center, Morristown, NJ, U.S.A.
9DermResearch, PLLC, Louisville, KY, U.S.A.
10Icahn School of Medicine at Mount Sinai, New York, NY, U.S.A.
11Henry Ford Health System, West Bloomfield, MI, U.S.A.
12Allergan plc, Irvine, CA, U.S.A.

Linked Comment: Tangielli. Br J Dermatol 2019; 180:978.

Summary

Background Once-daily topical oxymetazoline cream 1·0% significantly reduced persistent facial erythema of rosacea in trials requiring live, static patient assessments. Objectives To evaluate critically the methodology of clinical trials that require live, static patient assessments by determining whether assessment of erythema is different when reference to the baseline photograph is allowed. Methods In two identically designed, randomized, phase III trials, adults with persistent facial erythema of rosacea applied oxymetazoline or vehicle once daily. This phase IV study evaluated standardized digital facial photographs from the phase III trials to record ≥1-grade Clinician Erythema Assessment (CEA) improvement at 1, 3, 6, 9 and 12 h postdose.

Results Among 835 patients (oxymetazoline n = 415, vehicle n = 420), significantly greater proportions of patients treated with oxymetazoline vs. vehicle achieved ≥1-grade CEA improvement. For the comparison between phase IV study results and the original phase III analysis, when reference to baseline photographs was allowed while evaluating post-treatment photographs, the results for oxymetazoline were similar to results of the phase III trials (up to 85.7%), but a significantly lower proportion of vehicle recipients achieved ≥1-grade CEA improvement (up to 29.7% [phase 4] vs. 52.3% [phase 3]; P<0.001). In the phase IV study, up to 80·2% of patients treated with oxymetazoline achieved at least moderate erythema improvement vs. up to 22·9% of patients treated with vehicle. The association between patients’ satisfaction with facial skin redness and percentage of erythema improvement was statistically significant.

Conclusions Assessment of study photographs, with comparison to baseline, confirmed significant erythema reduction with oxymetazoline on the first day of application. Compared with the phase III trial results, significantly fewer vehicle recipients attained ≥1-grade CEA improvement, suggesting a mitigated vehicle effect. This methodology may improve the accuracy of clinical trials evaluating erythema severity.

© 2018 The Authors. British Journal of Dermatology published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
Reduction of persistent facial erythema, which is the most common and bothersome sign of rosacea, is an important objective in the clinical management of rosacea.1–4 This clinically evident manifestation of rosacea is associated with a substantial burden of illness,5,6 and rosacea therapies that offer immediate, visible erythema reduction may lead to better patient-reported outcomes and quality of life. Topical α-adrenergic receptor agonists, which target vascular mechanisms involved in the development of erythema associated with rosacea,7 can significantly reduce persistent facial erythema, according to published clinical trials.8–10

Once-daily topical oxymetazoline hydrochloride cream 1–0% (oxymetazoline; Rhofade, Allergan plc, Dublin, Ireland) is an α1A-adrenoceptor agonist approved to treat persistent facial erythema associated with rosacea in adults.11 Two previously published, identically designed, pivotal, phase III, vehicle-controlled trials (REVEAL)8,9,12 demonstrated that oxymetazoline applied once daily for 29 days significantly improved moderate-to-severe persistent facial erythema compared with vehicle. Efficacy assessments were performed using the Clinician Erythema Assessment (CEA) scale with photumeric guide, which provided a static assessment of overall facial erythema based on the actual appearance of the face on the day of evaluation without relying on prior memory, perception, or assessment of change from previous assessments, in accordance with guidelines issued by the U.S. Food and Drug Administration.13–15 Thus, in assigning a CEA score to patients’ facial erythema during efficacy assessments, investigators did not refer to photographs taken at baseline or during other study visits.

A phase IV study was conducted to determine whether allowing investigators to refer to baseline photographs while evaluating post-treatment photographs from the two phase III trials would yield differences in CEA score assessment for the post-treatment time points, and to quantify the magnitude of erythema improvement via assessment of percentage of erythema reduction. The CEA scale is well suited for this use because it was developed in consultation with dermatologists specializing in rosacea, and was designed to detect readily apparent and clinically different degrees of facial erythema (data on file, Allergan plc, Irvine, CA, U.S.A.).

**Patients and methods**

**Phase III trials**

The methods of the phase III trials from which the photographs were obtained have been published previously; they are briefly summarized here.8,9 The studies were approved by the Quorum Review institutional review board and were conducted in accordance with the ethical standards of the review board and with the Declaration of Helsinki.

Two identically designed, phase III, randomized, multicentre, double-blind, parallel-group, vehicle-controlled trials were conducted in the U.S.A., namely REVEAL trial 1 (ClinicalTrials.gov identifier NCT02131636) and REVEAL trial 2 (ClinicalTrials.gov identifier NCT02132117). The studies enrolled adults aged 18 years and older with moderate-to-severe persistent facial erythema associated with rosacea.8,9 Patients in both studies were randomized 1 : 1 to topical application of oxymetazoline or vehicle cream once each morning. They were instructed to apply a pea-sized amount of medication in a thin layer covering the entire face.

CEA was assessed in patients predose and 1, 3, 6, 9 and 12 h postdose at study visits. Standardized digital photographs (Canfield Scientific, Inc., Parsippany, NJ, U.S.A.) were obtained at each time point after assessments were completed.

**Phase IV study**

The present study included treated patients who had a complete set of photographs and data for all assessment time points.
points on day 1 in the phase III trials and consented in writing to the use of their photographs for research purposes.

Image review

A total of 10 highly experienced board-certified dermatologists participated in a consensus training session on the use of the CEA with a photo guide using sample photographs before study evaluations occurred. Physicians provided their evaluations of the sample photographs and training was repeated, if necessary, until they achieved consensus. Upon completion of training, the investigators independently reviewed a unique set of patient photographs from day 1 before treatment application (baseline) and postdose at 1, 3, 6, 9 and 12 h. Investigators were blinded to the treatment received by patients in the photographs and to the postdose time points. A high-resolution monitor (Canfield Scientific, Parsippany, NJ, U.S.A.) displayed the baseline photograph for initial assessment, then displayed the baseline photograph alongside each postdose photograph (Fig. S1; see Supporting Information). Investigators entered assessments for each photograph using a touchscreen tablet.

Efficacy assessments

The primary efficacy analysis was the proportion of patients who achieved at least a 1-grade improvement on the 5-point CEA scale with photonumeric guide (0, clear; 1, almost clear; 2, mild erythema; 3, moderate erythema; 4, severe erythema) from baseline at 1, 3, 6, 9, and 12 h postdose (Table S1; see Supporting Information). In addition, investigators compared the erythema severity between the baseline photograph and the post-treatment photographs and determined the percentage of erythema reduction using the following scale: 0, none; ~25%, mild; ~50%, moderate; ~75%, marked; ~95%, complete clearing.

Additional analyses

Patient satisfaction

In the phase III trials, patient satisfaction with the appearance of facial skin redness was assessed using item 1 of the validated 10-item Satisfaction Assessment for Rosacea Facial Redness (SAT-RFR) questionnaire at 3, 6, 9 and 12 h postdose. The patients responded using a 5-point scale that ranged from 0 (very dissatisfied) to 4 (very satisfied). The present analysis examined the association between the patients’ satisfaction with the appearance of their facial skin redness in the phase III trials and the investigator-assessed percentage improvement in erythema in the phase IV study.

Fitzpatrick skin phototype

CEA improvement of at least one grade was assessed using Fitzpatrick skin phototypes I–III and IV–VI.

Worsening of erythema

The number and proportion of patients in the photographic assessments who had ≥1-grade CEA increase (worsening) with either oxymetazoline or vehicle were evaluated.

Statistical analysis

Pairwise analyses between postdose time points and the day-1 predose time point (baseline) were conducted on the per-protocol population, which consisted of patients with complete datasets for all time points. The data were summarized using descriptive statistics. P-values were adjusted for multiple comparisons using the Hochberg method to control the family-wise error rate.16

For comparative and correlational analyses between the phase III and the phase IV datasets, these datasets were relationally merged (merged population). No imputation of missing data was utilized. Correlations between percentage improvement categories and SAT-RFR item 1 were conducted on the per-protocol sample based on the Spearman rank correlation coefficient. Comparisons between treatment arms in the phase IV study and the phase III trials were calculated using the McNemar paired test. All analyses were performed using R version 3.4.3 or greater (The R Foundation for Statistical Computing).

Results

Patients

A total of 835 patients (oxymetazoline n = 415, vehicle n = 420) were included. The mean age was 49.9 years, and the majority of patients were female (79.8%) and had Fitzpatrick skin phototype II (50.4%) or III (30.1%) (Table S2; see Supporting Information). The merged population assessed in comparisons and correlations between the phase IV and phase III datasets comprised 814 patients (oxymetazoline, n = 407; vehicle, n = 407). Baseline characteristics of the patients in the phase III trials (trial 1, N = 440; trial 2, N = 445; combined N = 885) have been published previously.8,9

Efficacy

In the photographic assessments, a significantly greater proportion of patients treated with oxymetazoline than those treated with vehicle achieved at least a 1-grade CEA improvement from baseline (P < 0.001 for the comparison with vehicle at all postdose time points. Fig. S2; see Supporting Information). At 1 h, these proportions were 54.9% of patients in the oxymetazoline group compared with 17.9% of patients in the vehicle group; at 3 h, 85.3% vs. 26.7%; at 6 h, 84.1% vs. 28.8%; at 9 h, 74.7% vs. 29.8% and at 12 h, 65.3% vs. 27.6%. There was up to a 58.6 percentage-point difference...
between the oxymetazoline and vehicle groups in the proportion of patients who achieved this milestone.

The proportion of patients in the oxymetazoline arm who achieved at least a 1-grade CEA improvement from baseline in the phase IV study, in which investigators were allowed to refer to the baseline photograph while evaluating post-treatment photographs, was not significantly different from that in the phase III trials, which required live, static assessments (Fig. 1). However, a significantly lower proportion of patients treated with vehicle had at least a 1-grade CEA improvement when reference to the baseline photograph was allowed compared with the proportion when live, static assessments were required ($P < 0.001$ for 1 h and 12 h; $P < 0.0001$ for 3 h, 6 h and 9 h).

Figure 2 shows representative photographs of patients evaluated in this study. The patient treated with oxymetazoline (Fig. 2a) achieved at least a 1-grade CEA improvement from baseline, whereas the patient treated with vehicle (Fig. 2b) did not. The CEA ratings for the patient treated with oxymetazoline were consistent regardless of the investigator’s ability to see the baseline photograph, whereas the apparent treatment effect in the patient who received vehicle was not noted when reference to the baseline photograph was allowed.

At least a moderate improvement (~50% or greater) in persistent erythema was noted in a significantly higher proportion of patients treated with oxymetazoline than those who received vehicle ($P < 0.001$) (Fig. S3; see Supporting Information). At 1 h, these proportions were 45.8% of patients in the oxymetazoline group compared with 9.8% of patients in the vehicle group; at 3 h, 80.2% vs. 19.5%; at 6 h, 74.5% vs. 22.9%; at 9 h, 63.4% vs. 21.4% and at 12 h, 54.2% vs. 17.9%. At least a marked (~75% or greater) erythema reduction was achieved in up to 43.6% of patients treated with oxymetazoline vs. 7.1% for those treated with vehicle. Figure 3 shows photographs of a patient from the oxymetazoline group who achieved moderate (~50%) or marked (~75%) reduction or complete clearing (~95%) in erythema at different time points.

The percentage erythema reduction scores had a strong negative correlation with the CEA scores (Spearman rank correlation $-0.7084$; $P < 0.001$), indicating a high level of agreement between these methods of assessment. The majority of photographs rated as showing ~95% erythema improvement compared with baseline were assigned CEA scores of 0 or 1 (93.1%, 148 of 159). Similar observations were made for photographs showing ~75% erythema improvement [CEA scores of 1 or 2 (90.8%, 484 of 533)], ~50% improvement [CEA scores of 2 or 3 (85.9%, 869 of 1012)], ~25% improvement [CEA scores of 2 or 3 (87.1%, 758 of 870)] and no improvement [CEA scores of 3 or 4 (93.5%, 1497 of 1601)].

Correlation with patient satisfaction

Patient satisfaction levels with their facial skin redness in the phase III trials correlated with the percentage of erythema improvement from the phase IV study (Fig. 4). This association was statistically significant for patients treated with oxymetazoline (Spearman rank correlation 0.1824; $P < 0.001$) and for patients treated with vehicle (Spearman rank correlation 0.0623; $P = 0.01$). Of 136 patients in the oxymetazoline group who had ~95% erythema improvement, approximately 40% (54 patients) were satisfied (47 patients) or very satisfied (seven patients), and 36% (49 patients) reported their satisfaction level as acceptable. In contrast, only eight patients in the vehicle group had ~95% erythema improvement and 25%

---

**Fig 1.** Proportions of patients with rosacea with at least a 1-grade Clinician Erythema Assessment (CEA) improvement in the phase IV study compared with the phase III trials for patients in the oxymetazoline group and the vehicle group (merged population). CEA scale: 0, clear; 1, almost clear; 2, mild erythema; 3, moderate erythema; 4, severe erythema. $^bP < 0.001$ for the comparison between phase IV and phase III data. $^aP < 0.0001$ for the comparison between phase IV and phase III data.
(two patients) reported being very satisfied. Among each sub-
set of patients treated with vehicle whose percentage of ery-
thera improvement was ~75% or less, more than half
consistently reported dissatisfaction with their facial skin red-
ess. In general, in the oxymetazoline group, as the percent-
age of erythema improvement with oxymetazoline increased,
so did the satisfaction levels of patients.

Fitzpatrick skin phototype analysis
As in the overall study population, the proportions of patients
who achieved at least a 1-grade CEA improvement in the Fitz-
patrick skin phototype subgroups I–III and IV–VI were signifi-
cantly greater in the oxymetazoline group than in the vehicle
group (Fig. 5). In the subgroup of patients with Fitzpatrick skin
phototype I–III, the proportion of patients achieving at least
a 1-grade CEA improvement was significantly greater in the
oxymetazoline group compared to the vehicle group (Fig. 5).

Fig 2. Representative photographs of a patient with rosacea from the oxymetazoline group (a) and a patient from the vehicle group (b). The Clinician Erythema Assessment (CEA) improvements for the patient treated with oxymetazoline were the same in both trials. Although the CEA assessments for the patient in the vehicle group demonstrated improvement in the phase III trial, they showed no improvement when the investigator was able to refer to the baseline photograph while evaluating post-treatment photographs (phase IV). CEA scale: 0, clear; 1, almost clear; 2, mild erythema; 3, moderate erythema; 4, severe erythema. •, CEA ≥ 1-grade improvement.

Fig 3. Photographs of a patient with rosacea from the oxymetazoline group with representative percentage improvements in erythema from baseline on day 1. Percentage improvement scale for reduction in erythema: 0, none; ~25%, mild; ~50%, moderate; ~75%, marked; ~95%, complete clearing.
phototype I–III, up to 85·1% of patients in the oxymetazoline group had at least a 1-grade CEA improvement compared with 27·8% of patients in the vehicle group (P < 0·001). Similarly, in the subgroup of patients with skin phototype IV–VI, up to 91·9% of patients treated with oxymetazoline achieved this level of improvement in CEA, compared with 25·5% of patients treated with vehicle (P < 0·001).

Worsening of erythema

On day 1, fewer than 1% of patients (0·72%, three of 415) in the oxymetazoline group were assessed as having at least a 1-grade increase in CEA, indicating worsening erythema, compared with 5·48% (23 of 420) in the vehicle group. When reference to the baseline photograph was not allowed, the proportion of patients who were considered to have at least a 1-grade CEA increase was 2·47% (11 of 446) in the oxymetazoline group and 5·24% (23 of 439) in the vehicle group.

Discussion

In this photographic study of topical once-daily oxymetazoline 1·0% cream, investigators evaluated erythema severity in photographs from the REVEAL pivotal phase III trials, with reference to the baseline photograph. More than 60% of patients achieved at least a 1-grade CEA improvement that persisted at least 12 h after application of oxymetazoline. Notably, the proportions of patients achieving the same outcome with reference to the baseline photograph was not allowed, the proportion of patients who were considered to have at least a 1-grade CEA increase was 2·47% (11 of 446) in the oxymetazoline group and 5·24% (23 of 439) in the vehicle group.
vehicle were substantially lower when investigators were allowed to refer to the baseline photograph than in the phase III trials, in which live, static assessments were made (up to 43-2% lower). The introduction of a baseline photograph into the methodology for evaluating erythema severity resulted in an apparent mitigation of the vehicle effect, perhaps allowing better visualization of lack of improvement. At the same time, the use of photography in the CEA assessments did not distort the results for oxymetazoline; proportions of patients who achieved at least a 1-grade improvement in CEA from baseline with oxymetazoline remained consistent between the trials.

The lack of access to the baseline photographs during the live patient assessments in the phase III trials may have inflated the results for vehicle. Improvements with vehicle treatment have been a documented limitation of randomized controlled clinical trials investigating new drugs for dermatological diseases, including rosacea.17–21 Raters, blinded to the study treatment, may seek out the expected effects of the active drug treatment from the vehicle treatment, artificially identifying a response to vehicle where none exists.22 The vehicle control is inherent to the design of clinical trials to support new rosacea drug approvals by the U.S. Food and Drug Administration, as is the live, static assessment of efficacy measures, i.e. assessment based on physical examination of patients at study visits with no reference to other time points in the study, such as baseline.13–15 This study has demonstrated that the review of photography – in particular, reference to a baseline photograph – may enhance the evaluation of the efficacy of a topical treatment for persistent erythema of rosacea, potentially resulting in more accurate assessments for vehicle.

Randomized controlled clinical trials of therapies for other dermatological conditions also may include evaluation of patient photographs to assess efficacy. In trials of topical, oral, and laser treatments for hair loss, efficacy has been evaluated through review of standardized baseline and post-treatment photographs.23–27 This global approach to photographic assessment is also used in the study of therapies for scarring and hyperpigmentation.28–30 The results of this study suggest that similar methodology should be incorporated into the design of clinical trials to support approval for treatments of persistent facial erythema.

Another consequence of the lack of access to baseline photographs in the REVEAL trials may have been differences in the proportions of patients who had at least a 1-grade increase in CEA, indicating worsening erythema. The same number of patients treated with vehicle experienced this increase in CEA, but fewer patients treated with oxymetazoline were deemed to have worsening erythema when reference to the baseline photograph was allowed. These observations underscore the importance of the comparison to baseline in the accuracy of assessments of erythema severity.

A limitation of this study is that it analysed only frontal facial photographs, neglecting assessment of the lateral aspect of the cheeks. In photographs, it may be more difficult to distinguish the telangiectasia of rosacea from background erythema, which may result in underestimating the level of erythema improvement. Other factors that could affect the appearance of the patient in a photograph include photographic filters, lighting in the room and the patient’s physical state. Additionally, worsening of erythema may have been more difficult to assess in patients with severe erythema at baseline, because the CEA scale does not allow a higher rating for erythema beyond fiery redness.

Whether darker skin pigment contributed to the poorer assessments for vehicle in this study is one concern, as erythema may be less detectable in darker skin.31 However, the results in patients with Fitzpatrick skin phototype subgroups (I–III and IV–VI) echoed the findings in the overall phase IV study population. The percentage of patients who had at least a 1-grade improvement in CEA was substantially lower with vehicle than with oxymetazoline, regardless of phototype. The data were consistent with unpublished analyses indicating that efficacy of topical oxymetazoline cream in patients with persistent erythema of rosacea was similar in subgroups of patients with Fitzpatrick skin phototypes I–III and those with types IV–VI (data on file, Allergan plc). The visible improvement in facial erythema even in patients with darker skin colour that was noted in these studies is encouraging, as effective treatment of rosacea in patients with skin of colour is needed.

In this study, a greater percentage of patients achieved improvement in persistent facial erythema of rosacea from baseline on the first day of application with oxymetazoline than with vehicle when investigators were allowed to reference the patient’s baseline photograph while evaluating post-treatment photographs to assess erythema severity over time. The results were similar to those in the oxymetazoline arms of the phase III trials, but there was a significantly less pronounced vehicle effect. These observations suggest that this methodology, which allows for comparison to baseline photographs, may improve the accuracy of clinical trials that evaluate erythema severity.

Acknowledgments

The authors wish to acknowledge Regina Kelly of Peloton Advantage ( Parsippany, NJ, U.S.A.), for writing support and Marc Schwartz of MS Biostatistics, LLC for support with the statistical analysis. Writing and editorial assistance was provided to the authors by Peloton Advantage and was funded by Allergan plc, Dublin, Ireland. All authors meet the International Committee of Medical Journal Editors authorship criteria.

References

1 Del Rosso JQ. Advances in understanding and managing rosacea: part 2: the central role, evaluation, and medical management of diffuse and persistent facial erythema of rosacea. J Clin Aesthet Dermatol 2012; 5:26–36.
2 Lee WJ, Lee YJ, Lee MH et al. Prognosis of 234 rosacea patients according to clinical subtype: the significance of central facial erythema in the prognosis of rosacea. J Dermatol 2016; 43:526–31.
3 Tan J, Blume-Peytavi U, Ortonne JP et al. An observational cross-sectional survey of rosacea: clinical associations and progression between subtypes. Br J Dermatol 2013; 169:555–62.
Additional Supporting Information may be found in the online version of this article at the publisher’s website:

**Fig S1.** Monitor and data capture set-up. Investigators were blinded to the sequence of presentation of photographs.

**Fig S2.** Proportions of patients with rosacea with at least a 1-grade Clinician Erythema Assessment (CEA) scale improvement (per-protocol population). 0, clear; 1, almost clear; 2, mild erythema; 3, moderate erythema; 4, severe erythema. \( p < 0.001 \) for the comparison to vehicle.

**Fig S3.** Proportion of patients with erythema improvement of \(~< \)50%, \(~\leq \)50% and/or \(~< \)95% at each time point (per-protocol population). Percentage improvement scale for reduction of erythema: 0, none; \(~< \)25%, mild; \(~\leq \)50%, moderate; \(~< \)75%, marked; \(~\leq \)95%, complete clearing. \( p < 0.001 \) for the comparison to vehicle.

**Table S1** Clinician Erythema Assessment (CEA) scale and percentage of erythema improvement scale descriptions.

**Table S2** Patient demographics and baseline clinical characteristics (per-protocol population).

---

4 Del Rosso JQ, Tanghetti EA, Baldwin HE et al. The burden of illness of erythematotelangiectatic rosacea and papulopustular rosacea: findings from a web-based survey. J Clin Aesthet Dermatol 2017; 10:17–31.

5 Harper J, Del Rosso JQ, Ferrusi IL. Cross-sectional survey of the burden of illness of rosacea by erythema severity. J Drugs Dermatol 2018; 17:150–8.

6 Fowler J, Tan J, Jackson JM et al. Treatment of facial erythema in patients with rosacea with topical brimonidine tartrate: correlation of patient satisfaction with standard clinical endpoints of improvement of facial erythema. J Eur Acad Dermatol Venereol 2015; 29:474–81.

7 Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical presentation, and new therapeutics. Exp Dermatol 2017; 26:659–67.

8 Kiricik LH, DuBois J, Draelos ZD et al. Pivotal trial of the efficacy and safety of oxymetazoline cream 1.0% for the treatment of persistent facial erythema associated with rosacea: findings from the first REVEAL trial. J Drugs Dermatol 2018; 17:97–105.

9 Baumann L, Goldberg DJ, Stein-Gold L et al. Pivotal trial of the efficacy and safety of oxymetazoline cream 1.0% for the treatment of persistent facial erythema associated with rosacea: findings from the second REVEAL trial. J Drugs Dermatol 2018; 17:290–8.

10 Fowler J Jr, Jackson M, Moore A et al. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, and vehicle-controlled pivotal studies. J Drugs Dermatol 2013; 12:650–6.

11 Rosade [package insert]. Irvine, CA: Allergan, 2017.

12 Tanghetti EA, Dover JS, Goldberg DJ et al. Clinically relevant reduction in persistent facial erythema of rosacea on the first day of treatment with oxymetazoline cream 1.0%. J Drugs Dermatol 2018; 17:621–6.

13 Food and Drug Administration. Draft guidance on tivermectin. U.S. Food and Drug Administration, 2017. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM573031.pdf (last accessed 22 February 2018).

14 Food and Drug Administration. Draft guidance on brimonidine tartrate. U.S. Food and Drug Administration, 2015. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM460927.pdf (last accessed 22 February 2018).

15 Food and Drug Administration. Draft guidance on azelaic acid. U.S. Food and Drug Administration, 2012. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm212602.pdf (last accessed 22 February 2018).

16 Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988; 75:800–2.

17 Czarnecki T, Linkner RV, Suarez-Farriñas M et al. An investigator-initiated, double-blind, vehicle-controlled pilot study: assessment of tachyphylaxis to topically occluded halobetasol 0.05% ointment in the treatment of psoriasis. J Am Acad Dermatol 2014; 71:954–9 e1.

18 Garshick MK, Chang AL, Kimball AB. Only skin deep: optimism and public self-consciousness did not associate with the placebo response in a dermatology clinical trial. J Drugs Dermatol 2014; 13:719–22.

19 Torre K, Shahriari M. Clinical trials in dermatology. Int J Womens Dermatol 2017; 3:180–3.

20 Grosshans E, Michel C, Arcade B et al. [Rilmenidine in rosacea: a double-blind study versus placebo]. Ann Dermatol Venereol 1997; 124:687–91 (in French).

21 Chiou WL. Low intrinsic drug activity and dominant vehicle (placebo) effect in the topical treatment of acne vulgaris. Int J Clin Pharmacol Ther 2012; 50:434–7.

22 Geers AL, Weiland PE, Koshab K et al. Goal activation, expectations, and the placebo effect. J Pen Soc Psychol 2005; 89:143–59.

23 Olsen EA, Whiting DA, Savin R et al. Global photographic assessment of men aged 18 to 60 years with male pattern hair loss receiving finasteride 1 mg or placebo. J Am Acad Dermatol 2012; 67:379–86.

24 McCoy J, Goren A, Kovacevic M, Shapiro J. Minoxidil dose response study in female pattern hair loss patients determined to be non-responders to 5% topical minoxidil. J Br Reg Mbasmt Agmo 2016; 30:1153–5.

25 Jimenez JJ, Wikramanayake TC, Bergfeld W et al. Efficacy and safety of a low-level laser device in the treatment of male and female pattern hair loss: a multicenter, randomized, sham device-controlled, double-blind study. Am J Clin Dermatol 2014; 15:115–27.

26 Huang Y, Zhuo F, Li L. Enhancing hair growth in male androgenetic alopecia by a combination of fractional CO2 laser therapy and hair growth factors. Laser Med Sci 2017; 32:1711–18.

27 Eun HC, Kwon OS, Yeon JH et al. Efficacy, safety, and tolerability of dutasteride 0.5 mg once daily in male patients with pattern hair loss: a randomized, double-blind, placebo-controlled, phase III study. J Am Acad Dermatol 2010; 63:252–8.

28 Kim DY, Kang SW, Kim DS et al. Preventive effect of human aecellular dermal matrix on post-thyroideotectomy scars and adhesions: a randomized, double-blind, controlled trial. Dermatol Surg 2015; 41:812–20.

29 Uaboonkul T, Nakakes A, Ayuthaya PK. A randomized control study of the prevention of hyperpigmentation post Q-switched Nd:YAG laser treatment of Horii nevus using topical fucidic acid plus betamethasone valerate cream versus fucidic acid cream. J Cosmet Lasers Surg 2016; 14:1153–1159.

30 Alster TS, Lewis AB, Rosenbach A. Laser scar revision: comparison of CO2 laser vaporization with and without simultaneous pulsed dye laser treatment. Dermatol Surg 1998; 24:1299–302.

31 Alexis AF. Rosacea in patients with skin of color: uncommon but not rare. Cutis 2010, 86:60–2.