BJD
British Journal of Dermatology

A treatment for severe nodular acne: a randomized investigator-blinded, controlled, noninferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs. oral isotretinoin

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Summary

Background Oral isotretinoin (ISO) is the gold standard for severe nodular acne. However, as some patients are unwilling or unable to take, or are intolerant to, ISO, other options are needed.

Objectives To compare efficacy and safety of oral ISO vs. doxycycline 200 mg plus adapalene 0·1%/benzoyl peroxide 2·5% gel (D+A/BPO) in severe nodular acne over 20 weeks.

Methods This was a multicentre, randomized, controlled, noninferiority investigator-blinded study involving 266 subjects.

Results D+A/BPO showed a significantly earlier onset of action in reducing nodules, papules/pustules and total lesions at week 2. ISO was superior in reducing nodules (95·6% vs. 88·7%), papules/pustules (95·2% vs. 79·6%) and total lesions (92·9% vs. 78·2%; all $P < 0·01$) at week 20. Half as many subjects for D+A/BPO compared with ISO had treatment-related, medically relevant adverse events (33 events in 18·0% of subjects vs. 73 in 33·8% of subjects, respectively). D+A/BPO was noninferior to ISO in the intent-to-treat population [95% confidence interval (CI) −2·7 to 20·8 ($P = 0·13$); 63·9% vs. 54·9% of subjects, respectively] and per-protocol population [95% CI 3·9–28·6 ($P = 0·01$); 74·3% vs. 58% of subjects, respectively), based on the composite efficacy/safety end point.

Conclusions D+A/BPO showed a favourable composite efficacy/safety profile compared with ISO. This combination is an alternative to ISO in patients intolerant to, or unable or unwilling to take, oral ISO, and is an option for treatment of severe nodular acne.

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Accepted for publication
8 June 2014

Funding sources
This study was funded by Galderma.

Conflicts of interest
J.T., S.H., R.V., B.B., M.G. and C.L. received investigator fees for the study. N.K. and F.A. are employees of Galderma. J.T. has served as an advisor (advisory board), consultant, investigator and speaker for Galderma. S.H. and R.V. have served as advisors (advisory board), speakers and investigators for Galderma. B.B. is a speaker for Galderma. M.G. is an investigator and speaker for Galderma. C.L. has served as an advisor (advisory board), consultant and investigator for Galderma.

ClinicalTrials.gov identifier: NCT01474590

DOI 10.1111/bjd.13191

What's already known about this topic?

- Oral isotretinoin (ISO) is the gold standard for treatment of severe nodular acne.

What does this study add?

- Oral doxycycline plus adapalene/benzoyl peroxide (D+A/BPO) gel was efficacious and safe in the treatment of severe nodular acne over 20 weeks.
- D+A/BPO is an option for the treatment of severe nodular acne and may offer an alternative for patients unable or unwilling to take, or intolerant of, oral ISO.

Isotretinoin (ISO) has been the standard of treatment for severe nodular acne and, since its introduction more than 30 years ago, has been transformative for many of those afflicted. However, not all patients are able or willing to take this medication, and some may need to discontinue because of side-effects. ISO is well known to be associated with a spectrum of idiosyncratic and dose-dependent adverse reactions, including cutaneous eruptions, hepatitis, pancreatitis, ocular changes and enteric disturbances. Furthermore, owing to the teratogenicity of ISO, pregnancy prevention programmes and monitoring are required for women of childbearing potential.[1–3]

Comparative effectiveness and safety information on alternative treatment regimens in severe nodular acne are crucial for clinical decision making. Adapalene 0·1%/benzoyl peroxide (BPO) 2·5% gel (Epiduo®, Galderma S.A., Lausanne, Switzerland) (A/BPO) is an antibiotic-free, fixed-dose combination of a topical retinoid possessing anticomedogenic, comedolytic and anti-inflammatory properties,[4–7] and a potent bactericidal agent against *Propionibacterium acnes* (*P. acnes*).[8–12] Adapalene and BPO (A/BPO) is efficacious in mild and moderate acne,[9–11] which may be owing to the synergistic effect of A/BPO when used in a fixed-dose formulation.[13,14] Furthermore, a prior study in severe acne (without nodules) demonstrated a significant increase in efficacy when A/BPO was added to doxycycline hyclate 100 mg daily, resulting in a fourfold increase in treatment success compared with the oral antibiotic alone.[15]

The objective of this study was to compare the effectiveness and safety of ISO (0·5–1·0 mg kg^{-1} daily) to that of doxycycline hyclate (200 mg daily) with A/BPO (D+A/BPO) in severe nodular acne over a 20-week period.

Materials and methods

Study design

This phase IIIb, noninferiority, multicentre, randomized, investigator-blinded, controlled, parallel group study recruited subjects of any race, aged 12–35 years, with a minimum of severe facial acne vulgaris [investigator global assessment (IGA) ≥ 4, ≥ 20 papules/pustules and ≥ 5 nodules] and meeting specific eligibility criteria. Study drug treatment duration was 20 weeks. Subjects attended visits for screening and baseline, and at weeks 2, 4, 8, 12, 16 and 20.

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices, and in compliance with local regulatory requirements. It was approved by institutional review boards, and all subjects provided written informed consent prior to study procedures.

Treatments administered

Eligible subjects received once-daily D+A/BPO or once-daily oral ISO (0·5 mg kg^{-1} daily for the first 4 weeks with an escalation to 1 mg kg^{-1} daily for the subsequent 16 weeks) plus vehicle gel. Subjects receiving ISO were to receive a mean cumulative dose of 126 mg kg^{-1} over the 20-week treatment period. A moisturizing lotion and lip balm were provided for use as required for skin and lip dryness/irritation. Skin cleanser and sunscreen (sun protection factor 50) were provided for use prior to application of study treatment or outdoor activities, respectively.

Efficacy end points

Efficacy end points were the percentage change from baseline in facial nodules, papules/pustules and total lesion counts (sum of comedones, papules/pustules and nodules), and IGA success rate (defined as improvement of at least two grades from baseline) at each postbaseline visit. IGA was evaluated using a scale from 0 ('clear' – residual hyperpigmentation and erythema may be present) to 5 ('very severe' – highly inflammatory acne covering the face, with nodules present).

Atrophic acne scar counts were conducted on half the face, and the presence of *P. acnes* was also assessed by ultraviolet fluorescence photography (VISIA® system; Canfield Scientific, Inc., Fairfield, NJ, USA). The presence of *P. acnes* has been shown to correlate with the intensity of orange–red fluorescence from its metabolites (coproporphyrin III).[16] As few centres are equipped with this system, this test was performed on only 40 subjects.

Safety end points

Safety end points included depression monitoring (Major Depression Inventory, International Classification of Diseases-10) and incidence of adverse events (AEs) observed by the investigator or reported by the subject. Standard laboratory tests were performed at screening and at weeks 4, 16 and 20.

Composite efficacy/safety end point

The study objective was to compare the efficacy/safety ratio of D+A/BPO to that of ISO. To achieve this objective, a composite end point strategy was devised. Composite end points are useful in 'real-world' clinical trials to assess the net effect of interventions with different risk profiles.[17]

A composite end point (composite success) was based on prespecified efficacy and safety criteria. The composite end point was developed and predefined based on the precedent of nodule counts as a standard efficacy measure for oral ISO clinical trials and the safety criteria based on consultation with study investigators. Composite success was achieved in those attaining an efficacy outcome of ≥ 75% reduction in the number of nodules at the end of treatment, and the safety outcome of absence of safety issues. Criteria for treatment-related safety issues were predefined and are shown in Table 1.

This end point is experimental and *post hoc* sensitivity analyses were performed to assess if more stringent definitions of parameters could alter study conclusions. For the efficacy end point, two-grade improvements in IGA, and 90% and 100%

Table 1 Treatment-related safety issues

1	Serious AE
2	Severe AE
3	AE leading to treatment discontinuation
4	AE requiring prescription of concomitant systemic medication
5	Depression
6	Phototoxicity
7	Clinically significant laboratory test changes
8	Inability to escalate ISO treatment dose to 1 mg kg^{-1} daily
9	Downward dose adjustment (for both oral treatments)
10	Study termination owing to subject's request (if motivated by treatment concern)
11	AE requiring prescription of concomitant topical medication
12	Mucocutaneous AE (if very bothersome for > 1 month)
13	Gastrointestinal AE (for at least 2 weeks)
14	Headache (for at least 2 weeks)
15	Myalgia, arthralgia (for at least 2 weeks)
16	Vulvovaginal mycotic infection

AE, adverse event; ISO, isotretinoin.

nodule reduction, in addition to the predefined 75% reduction, were also tested. Moreover, 75% nodule reduction data were also analysed in concert with seven of the safety categories considered to be the most clinically relevant for severity (Table 1; categories 1–7).

Sample size, randomization and blinding

Sample size determination was based on an estimated composite success rate of 75% at the last evaluable time point, a power of 80% and a noninferiority margin of 15%. It was calculated that a total sample size of 262 subjects (131 per group) were required.

Prior to the start of the study, the randomization list was generated by a statistician. The RANUNI routine of SAS (SAS Institute Inc., Cary, NC, U.S.A.) was used for the kit number generation. Subjects were randomized in a 1 : 1 ratio for each group. The randomization list was secured in a locked cabinet and in an electronic file with restricted access to only the designated personnel directly responsible for labelling and handling the study treatments until the study database was locked and unblinded.

Investigators did not have access to the randomization list and study treatments were dispensed by the designated study drug dispenser – someone other than the investigator/rater. Both study drug dispenser and subject were instructed not to discuss the study treatments with the investigator/rater.

Statistical analysis

Three study populations were analysed: safety, intent-to-treat (ITT) and per-protocol (PP) populations. The last observation carried forward method was used to impute missing efficacy values. For the composite end point, missing values were considered as unsuccessful.

In the composite efficacy/safety end point, noninferiority of D+A/BPO to ISO was to be demonstrated by showing that the 95% confidence interval (CI; using normal approximation) of the between-treatment difference, in terms of proportion of success, excluded 15% of the PP and ITT populations.

Efficacy end points were analysed using Cochran–Mantel–Haenszel statistics on the ITT population. *P. acnes* and safety assessments were descriptively analysed.

Results

Baseline characteristics and subject disposition

Demographic and baseline disease characteristics were similar in the two treatment groups (Table 2). Two hundred and sixty-six subjects were randomized and included in the ITT population across 29 centres in Canada from November 2011 to July 2013. Of those, 217 (81·6%) were included in the PP analysis. An equal number of subjects was randomized to receive D+A/BPO (n = 133) or ISO (n = 133). The majority of subjects completed the study; discontinuations are described in Figure 1. The percentage discontinuation difference between groups was unrelated to study treatment.

Efficacy

Percentage changes from baseline in lesion counts (nodules, papules/pustules and total) and IGA success rate are shown in Figure 2. At week 2, D+A/BPO showed an earlier onset of action and was more efficacious at that time point than ISO in the reduction of nodules (40·4% vs. 24·2%; $P < 0·01$), papules/pustules (26·8% vs. 14·3%; $P < 0·01$), comedones (12·5% vs. 6·1%; $P = 0·06$) and total lesions (22·7% vs. 10·6%, respectively; $P < 0·01$). IGA success (two-grade improvement) at week 4 was 27·1% vs. 17·3%, respectively ($P = 0·03$). At week 20, ISO was superior to D+A/BPO in the reduction of nodules (95·6% vs. 88·7%), papules/pustules (95·2% vs. 79·6%), comedones (92·3% vs. 75·9%) and total lesions (92·9% vs. 78·2%, respectively) (all $P < 0·01$). In the D+A/BPO group, 96·0% had ≥ 75% reduction in nodules compared with 98·0% for ISO. ISO was superior to D+A/BPO for IGA success (90·2% vs. 73·7%, respectively; $P < 0·01$).

The mean number of total atrophic acne scars assessed at baseline for each half of the face was approximately 16 in each group (Fig. 3). After 20 weeks of treatment, no change in acne scar counts was observed in either group. Figure 4 illustrates typical responses to the studied treatments.

Reduction in *P. acnes* fluorescence was detectably different at week 2 in the D+A/BPO treatment group (Fig. 5), with a median percentage change of −30·2% vs. 14·1% in the ISO treatment group. At week 20, reduction in *P. acnes* fluorescence was in favour of ISO (52·7% vs. 44·0%).

Table 2 Baseline characteristics

	D+A/BPO (n = 133)	ISO (n = 133)	Total (n = 266)
Sex (%)			
Male	115 (86·5)	112 (84·2)	227 (85·3)
Female	18 (13·5)	21 (15·8)	39 (14·7)
Age (years)	19·5 ± 5·0 (12·0–41·0)	19·3 ± 4·5 (12·0–36·0)	19·4 ± 4·8 (12·0–41·0)
Skin phototype, n (%)			
I	8 (6·0)	8 (6·0)	16 (6·0)
II	35 (26·3)	45 (33·8)	80 (30·1)
III	57 (42·9)	55 (41·4)	112 (42·1)
IV	26 (19·5)	20 (15·0)	46 (17·3)
V	4 (3·0)	4 (3·0)	8 (3·0)
VI	3 (2·3)	1 (0·8)	4 (1·5)
Total lesion counts	104·2 ± 56·4 (30·0–365·0)	109·6 ± 64·9 (41·0–430·0)	106·9 ± 60·8 (30·0–430·0)
Nodule counts	8·0 ± 3·6 (5·0–25·0)	7·6 ± 2·5 (5·0–17·0)	7·8 ± 3·1 (5·0–25·0)
Papule/pustule counts	40·1 ± 22·5 (17·0–167·0)	43·4 ± 35·3 (13·0–365·0)	41·7 ± 29·6 (13·0–365·0)
Comedone counts	56·1 ± 46·8 (0–261·0)	58·6 ± 52·4 (0–388·0)	57·4 ± 49·6 (0–388·0)
IGA, n (%)			
4 (severe)	118 (88·7)	115 (86·5)	233 (87·6)
5 (very severe)	15 (11·3)	18 (13·5)	33 (12·4)
Total atrophic acne scar counts	15·9 ± 16·3 (0–93·0)	15·5 ± 14·5 (0–80·0)	15·7 ± 15·4 (0–93·0)

Values given as mean ± SD (range) unless otherwise indicated. D+A/BPO, doxycycline hyclate + adapalene/benzoyl peroxide; ISO, isotretinoin; IGA, investigator global assessment.

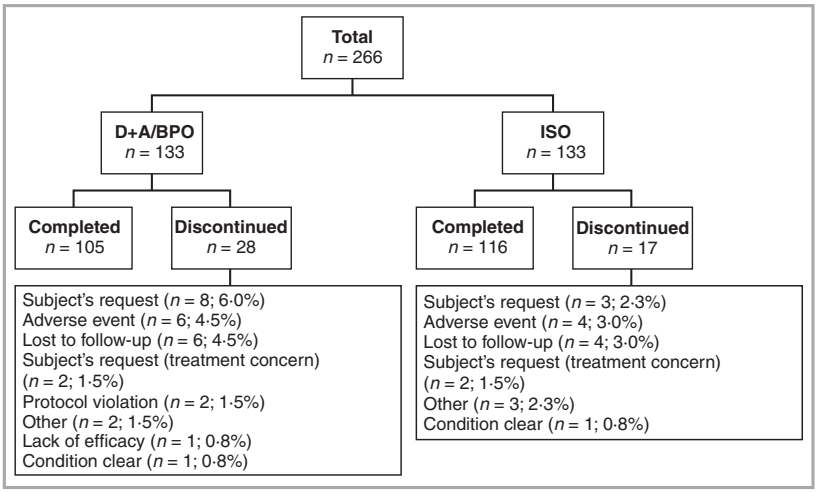

Fig 1. Subject disposition. D+A/BPO, doxycycline hyclate + adapalene/benzoyl peroxide; ISO, isotretinoin; AEs, adverse events.

Safety

One hundred and eighty-seven (70·0%) subjects in both treatment groups experienced 441 treatment-related AEs. Treatment-related AEs were reported less frequently in the D+A/BPO group. In the D+A/BPO group, 70 (53·0%) subjects experienced 142 treatment-related AEs compared with 117 (88·0%) subjects with 299 AEs in the ISO group.

For treatment-related AEs, 35·0% of subjects receiving ISO were prescribed at least one concomitant treatment compared with 9·0% of subjects in the D+A/BPO group. The most frequently prescribed treatments, aside from moisturizers and emollients, were oral nonsteroidal anti-inflammatory drugs, topical midpotency corticosteroids, topical antibacterial and topical antifungal drugs. The most frequently reported treatment-related AEs, for the D+A/BPO vs. ISO groups, respectively, were mucocutaneous and gastrointestinal (GI) disorders, including dry lip (6·8% vs. 49·6%), dry skin (16·5% vs. 32·3%), cheilitis (1·5% vs. 24·1%), vomiting (7·5% vs. 0·8%) and nausea (6·8% vs. 2·3%).

No severe or serious treatment-related AE was reported in the D+A/BPO group, while five treatment-related severe AEs (i.e. dry lips, fatigue and acne flare), including one related serious AE (Stevens–Johnson syndrome requiring hospitalization 24 days following initiation of treatment), were reported in the ISO group.

Four subjects in each group discontinued treatment owing to treatment-related AEs. In the D+A/BPO group, three subjects discontinued for GI disorders (vomiting, diarrhoea, dyspepsia) and one for skin and subcutaneous tissue disorders (skin reaction); in the ISO group, two subjects discontinued for nondepressive psychiatric disorders (depressed mood,

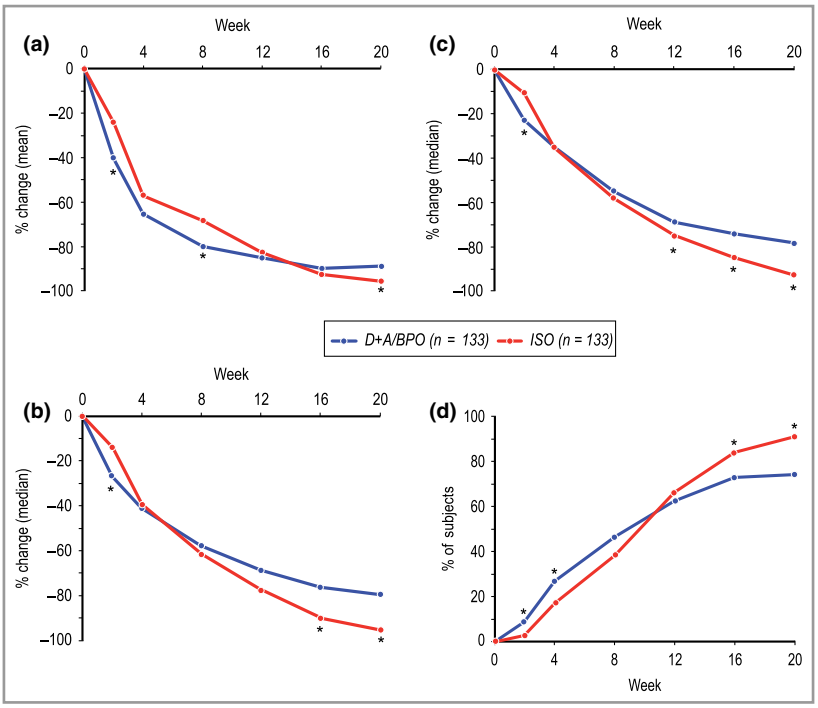

Fig 2. Percentage change in (a) nodule, (b) papules/pustules and (c) total lesion counts from baseline. (d) Percentage of subjects with investigator global assessment success. *P < 0·05. D+A/BPO, doxycycline hyclate + adapalene/benzoyl peroxide; ISO, isotretinoin.

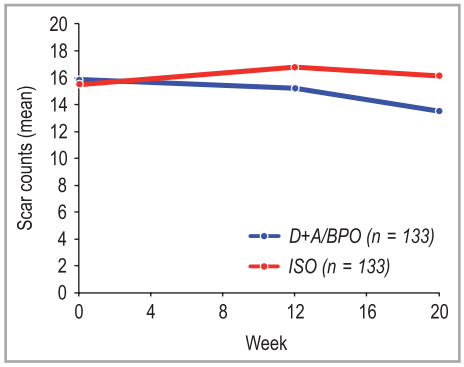

Fig 3. Change in atrophic acne scar counts. D+A/BPO, doxycycline hyclate + adapalene/benzoyl peroxide; ISO, isotretinoin.

insomnia, hallucination) and one for decreased appetite. Two subjects in each group discontinued the study owing to treatment concerns.

Only one treatment-related AE (hypercholesterolaemia) due to clinically significant laboratory abnormalities was reported in the D+A/BPO group, while six AEs (increased triglycerides, alanine aminotransferase and aspartate aminotransferase) were reported in the ISO group. Owing to tolerance issues, doses of oral study treatments had to be decreased for four (3·0%) subjects in the D+A/BPO group vs. seven (5·3%) in the ISO group.

Composite efficacy/safety end point (composite success)

Subjects who did not achieve composite success in the ITT population are described in Table 3.

For the safety criteria, almost twice as many subjects in the ISO group compared with the D+A/BPO group were unsuccessful (37·6% vs. 20·3%, respectively). From the 441 treatment-related AEs reported during the study, 106 were deemed as not meeting the composite success definition. They were reported less frequently in the D+A/BPO group than in the ISO group: 33 events in 18·0% of subjects vs. 73 events in 33·8% of subjects, respectively.

Composite success was achieved by 63·9% in the D+A/BPO group compared with 54·9% in the ISO group. Within the 15·0% margin, D+A/BPO was noninferior to ISO in the ITT population (63·9% vs. 54·9%, respectively; 95% CI −2·7 to 20·8; P = 0·13) and the PP population (74·3% vs. 58%, respectively; 95% CI 3·9–28·6%; P = 0·01).

In all *post hoc* sensitivity analyses, D+A/BPO remained noninferior to ISO within the 15·0% margin (all 95% CIs between −13·61 and −4·21) (Table 4).

Discussion

This study compared the efficacy and safety of oral ISO with a fixed-dose combination of topical retinoid/BPO plus oral antibiotic in the treatment of severe nodular acne over 20 weeks of therapy. There are few previous studies of ISO compared with an oral antibiotic, in combination with a topical treatment or as monotherapy.[18–21]

D+A/BPO showed efficacy in reducing nearly 90% of nodules and 80% of papules/pustules in those with severe and very severe acne. ISO showed a superior efficacy to D+A/BPO after 20 weeks of treatment, and the difference in percentage reduction of different acne lesions varied from 7% to 15% for nodules and total lesions, respectively. However, D+A/BPO was significantly faster in reducing inflammatory lesions at week 2. This rapid onset of effect may be clinically relevant

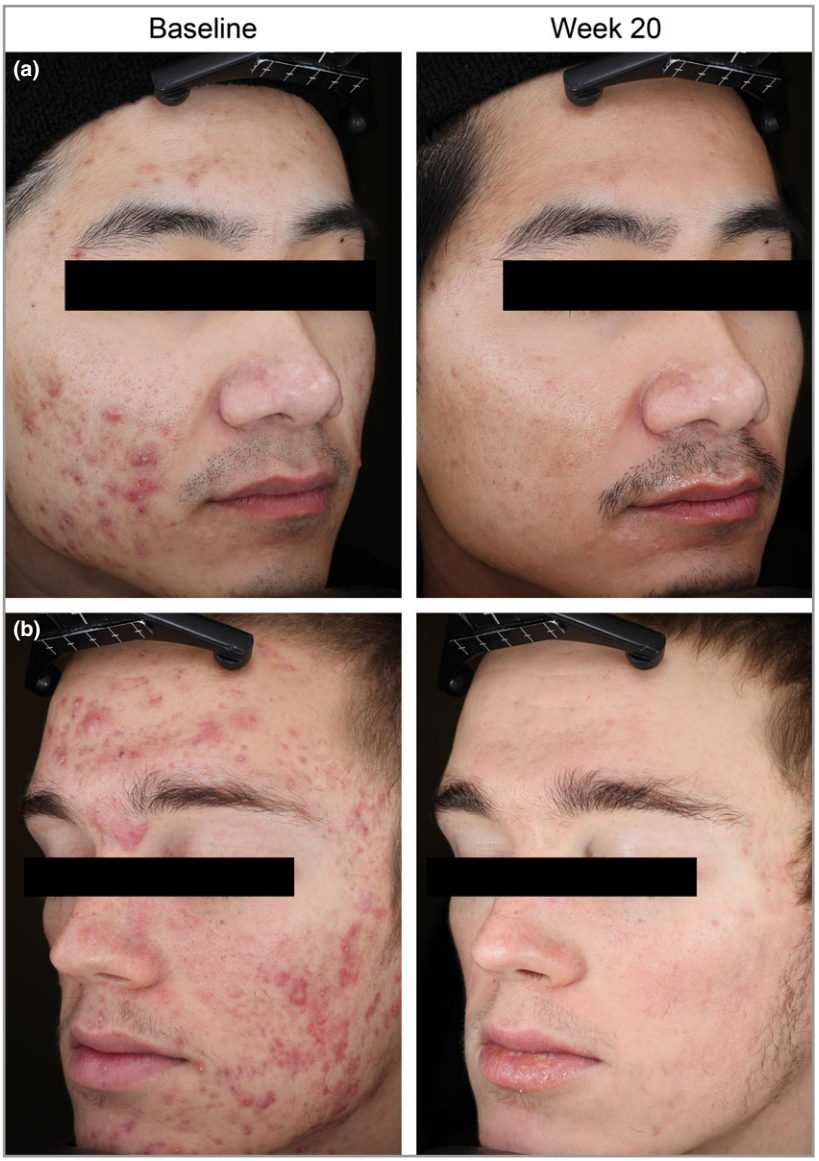

Fig 4. Subject photographs before/after treatment with (a) doxycycline hyclate + adapalene/benzoyl peroxide and (b) vehicle gel + isotretinoin.

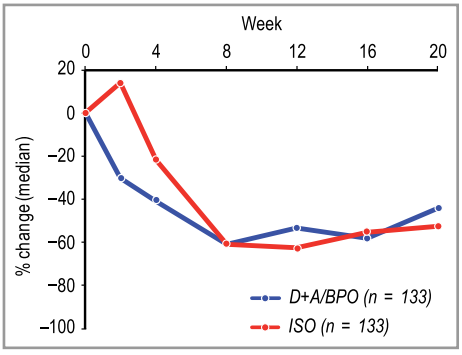

Fig 5. Reduction of *Proprionibacterium acnes* based on percentage change of fluorescence intensity. D+A/BPO, doxycycline hyclate + adapalene/benzoyl peroxide; ISO, isotretinoin.

by reducing inflammation and may encourage adherence to treatment.

In this trial, neither ISO nor D+A/BPO treatments led to an increase in acne scars. In severe acne populations, increased acne scar numbers are expected with resolution of primary acne lesions. The absence of this finding suggests that both treatments may abrogate scar development.

As observed in other trials, almost 90% of ISO-treated subjects had treatment-related AEs.[22,23] The mucocutaneous AEs were the most common but least severe, with the majority managed with topical emollients and moisturizing nasal and eye drops. However, 45 (33·8%) subjects receiving ISO presented with medically important treatment-related AEs requiring medical intervention or treatment adjustment.

Table 3 Efficacy and safety reasons for not achieving success

	D+A/BPO (n = 133)		ISO (n = 133)	
	Event (n)	Subject (n, %)	Event (n)	Subject (n, %)
At least one reason	64	48 (36·1)	105	60 (45·1)
Missing value	17	17 (12·8)	8	8 (6·0)
Efficacy outcome (nodule reduction < 75%)	4	4 (3·0)	2	2 (1·5)
Safety outcome	43	27 (20·3)	95	50 (37·6)
Reason owing to related AEs	33	24 (18·0)	73	45 (33·8)
Any related serious AE	0	0	1	1 (0·8)
Any related severe AE	0	0	5	5 (3·8)
Any related AE leading to discontinuation of treatment	5	4 (3·0)	5	4 (3·0)
Any related AE requiring prescription of a systemic medication	6	5 (3·8)	7	5 (3·8)
Depression	0	0	0	0
Phototoxicity	1	1 (0·8)	1	1 (0·8)
Clinically significant laboratory abnormality	1	1 (0·8)	6	4 (3·0)
Downward dose adjustment	4	4 (3·0)	2	2 (1·5)
Inability to escalate to 1 mg kg^{-1} daily at week 4 for ISO	–	–	5	5 (3·8)
Subject treatment concern leading to discontinuation of treatment	2	2 (1·5)	2	2 (1·5)
Any related AE requiring prescription of a local/topical medication	3	3 (6·0)	27	23 (20·3)
Other relevant related AEs	23	18 (13·5)	41	26 (19·5)

D+A/BPO, doxycycline hyclate + adapalene/benzoyl peroxide; ISO, isotretinoin; AE, adverse event.

Table 4 *Post hoc* analyses: overall success

Worst-case population[a]	D+A/BPO	ISO	Difference (D+A/BPO) − (ISO)	95% CI[b]	P-value[c]
Initial definition of safety issue					
Nodule 100%[e]					
n (%)	133 (100·0)	133 (100·0)		−9·62 to 14·13	
Success	78 (58·6)	75 (56·4)	2·26		0·74
Failure	55 (41·4)	58 (43·6)			
Nodule 90%[f]					
n (%)	133 (100·0)	133 (100·0)		−4·21 to 19·25	
Success	85 (63·9)	75 (56·4)	7·52		0·21
Failure	48 (36·1)	58 (43·6)			
IGA − two grades[g]					
n (%)	133 (100·0)	133 (100·0)	3·01	−8·82 to 14·84	0·63
Success	80 (60·2)	76 (57·1)			
Failure	53 (39·8)	57 (42·9)			
New definition of safety issue[d]					
Nodule 75%[h]					
n (%)	133 (100·0)	133 (100·0)		−13·61 to 6·09	
Success	102 (76·7)	107 (80·5)	−3·76		0·45
Failure	31 (23·3)	26 (19·5)			

D+A/BPO, doxycycline hyclate + adapalene/benzoyl peroxide; ISO, isotretinoin; IGA, investigator global assessment. [a]All missing values were considered as overall 'failure'. [b]95% confidence interval (CI) in proportion of success using normal approximation. [c]P-value for between treatment difference, by Cochran–Mantel–Haenszel test based on ridit scores stratified by analysis centre. [d](i) Serious adverse event (AE); (ii) severe AE; (iii) attributable AE leading to discontinuation of treatment; (iv) AE requiring prescription treatments – only systemic medications, not for vaginal candidiasis; (v) depression; (vi) phototoxicity; (vii) clinically significant laboratory test changes. [e]Change from baseline in nodule lesion count < 100% considered as efficacy 'failure'. [f]Change from baseline in nodule lesion count < 90% considered as efficacy 'failure'. [g]Improvement of at least two grades from baseline based on IGA. [h]Change from baseline in nodule lesion count < 75% considered as efficacy 'failure'.

From an efficacy/safety perspective, D+A/BPO treatment is not inferior to ISO (74·3% vs. 58·0% of success, respectively).

An innovative feature of this study was the use of a composite end point to compare efficacy/safety profiles of ISO against a combination of D+A/BPO. Composite end

points are outcome measures in ongoing development with regulatory, clinical and practical importance. However, these tools are in ongoing evaluation and are limited by challenges in use, interpretation, and in the relevance and number of chosen end points.[24] In our study, we selected a reduction in acne nodules of 75% for efficacy and 16 different potential treatment-related AE categories for safety issues, and conducted a statistical analysis based on those predefined efficacy/safety end points. Despite more stringent definitions (IGA success of two-grade improvement, 90% or 100% nodule reduction, and seven safety categories considered as the most clinically relevant for severity), these *post hoc* sensitivity analyses showed the same trend of noninferiority.

We acknowledge the following shortcomings of this study. The potential for lip and facial skin dryness, potential indicators of oral ISO therapy, may bias raters to subjects randomized to this treatment. However, administrative and operational measures were established for an investigator-blinded study (experimental medications were administered by pharmacy staff and not by study investigator/raters, and lip and facial moisturizers were provided to all subjects). Nevertheless, this bias may be more likely reflected as greater profile of efficacy/safety, not lesser, of those subjects thought to be on oral ISO. Another limitation of our study was the predominantly male cohort (85·0%). This may be owing to the pregnancy prevention measures as a prerequisite of trial entry. Accordingly, the overall findings of this study may not be generalizable to the female population. Furthermore, we used doxycycline (200 mg daily) for a prolonged period of time to match the recommended period of ISO treatment (5 months). The dose of 200 mg daily is at the higher spectrum of recommended dosing for doxycycline and was selected owing to the potential for greater efficacy in severe acne. The early onset of action of D+A/BPO observed in our study after 1 month of treatment suggests that the dose and treatment duration of doxycycline can be adjusted depending on the clinical outcome. Finally, this study is limited to comparative efficacy at 20 weeks. While long-term remission is an important and recognized additional potential benefit of oral ISO, this study is aimed at addressing the issue of acute control of severe nodular acne.

Based on the results of this study, the combination of D+A/BPO may be a reasonable treatment option in severe nodular acne.

Treatment selection in severe acne depends on multiple factors, including acne history, prior treatment, psychosocial impact, medical history, and patient preferences and values. Such decisions are facilitated by comparative evidence on relative efficacy and safety of available treatment options. We show that D+A/BPO is noninferior to ISO in efficacy/safety over 20 weeks in the treatment of severe nodular acne. This combination may provide an alternative for severe acne patients unable or unwilling to take, or intolerant to, oral ISO, and may serve as a reasonable treatment option for severe nodular acne.

Acknowledgments

We would like to thank the other study investigators: David N. Adam, Lorne Albrecht, Kirk Barber, Vincent Bertucci, Sam Cammisuli, Wayne Carey, Isabelle Delorme, Lyne Giroux, Eric Goldstein, Peter Hull, Arnon Katz, Rodion Kunynetz, Ian Landells, Richard Langley, Catherine Maari, Kamal Ohson, Kim Papp, Yves Poulin, Mani Raman, Sheetal Sapra, John Toole, Norman R. Wasel and Derek Woolner. We also thank Galadriel Bonnel and Sotirios Georgantopoulos for editorial assistance.

References

1 Strauss JS, Krowchuk DP, Leyden JJ *et al.* Guidelines of care for acne vulgaris management. *J Am Acad Dermatol* 2007; **56**:651–63.
2 Dréno B, Bettoli V, Ochsendorf F *et al.* An expert view on the treatment of acne with systemic antibiotics and/or oral isotretinoin in the light of the new European recommendations. *Eur J Dermatol* 2006; **16**:565–71.
3 Layton AM, Dreno B, Gollnick HP, Zouboulis CC. A review of the European Directive for prescribing systemic isotretinoin for acne vulgaris. *J Eur Acad Dermatol Venereol* 2006; **20**:773–6.
4 Gollnick H, Schramm M. Topical drug treatment in acne. *Dermatology* 1998; **196**:119–25.
5 Brogden RN, Goa KL. Adapalene: a review of its pharmacological properties and clinical potential in the management of mild to moderate acne. *Drugs* 1997; **53**:511–19.
6 Michel S, Jomard A, Demarchez M. Pharmacology of adapalene. *Br J Dermatol* 1998; **139**(Suppl. 52):3–7.
7 Shroot B, Michel S. Pharmacology and chemistry of adapalene. *J Am Acad Dermatol* 1997; **36**:S96–103.
8 Leyden JJ. Current issues in antimicrobial therapy for the treatment of acne. *J Eur Acad Dermatol Venereol* 2001; **15**(Suppl. 3):S51–5.
9 Thiboutot DM, Weiss J, Bucko A *et al.* Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicentre, randomized double-blind, controlled study. *J Am Acad Dermatol* 2007; **57**:791–9.
10 Gollnick HP, Draelos Z, Glenn MJ *et al.* Adapalene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients. *Br J Dermatol* 2009; **161**:1180–9.
11 Gold LS, Tan J, Cruz-Santana A *et al.* A North American study of adapalene-benzoyl peroxide combination gel in the treatment of acne. *Cutis* 2009; **84**:110–16.
12 Pariser DM, Westmoreland P, Morris A *et al.* Long-term safety and efficacy of a unique fixed-dose combination gel of adapalene 0.1% and benzoyl peroxide 2.5% for the treatment of acne vulgaris. *J Drugs Dermatol* 2007; **6**:899–905.
13 Tan J, Gollnick HP, Loesche C *et al.* Synergistic efficacy of adapalene 0.1%-benzoyl peroxide 2.5% in the treatment of 3855 acne vulgaris patients. *J Dermatolog Treat* 2011; **22**:197–205.
14 Feldman SR, Tan J, Poulin Y *et al.* The efficacy of adapalene-benzoyl peroxide combination increases with number of acne lesions. *J Am Acad Dermatol* 2011; **64**:1085–91.
15 Gold LS, Cruz A, Eichenfield L *et al.* Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. *Cutis* 2010; **85**:94–104.
16 Lee WL, Shalita AR, Poh-Fitzpatrick MB. Comparative studies of porphyrin production in *Propionibacterium acnes* and *Propionibacterium granulosum*. *J Bacteriol* 1978; **133**:811–15.

17 Ferreira-González I, Alonso-Coello P, Solà I *et al.* Composite endpoints in clinical trials. *Rev Esp Cardiol* 2008; **61**:283–90.
18 Gollnick HP, Graupe K, Zaumseil RP. Comparison of combined azelaic acid cream plus oral minocycline with oral isotretinoin in severe acne. *Eur J Dermatol* 2001; **11**:538–44.
19 Oprica C, Emtestam L, Hagstromer L, Nord CE. Clinical and microbiological comparisons of isotretinoin vs. tetracycline in acne vulgaris. *Acta Derm Venereol* 2007; **87**:246–54.
20 Pigatto PD, Finzi AF, Altomare GF *et al.* Isotretinoin versus minocycline in cystic acne: a study of lipid metabolism. *Dermatologica* 1986; **172**:154–9.
21 Lester RS, Schachter GD, Light MJ. Isotretinoin and tetracycline in the management of severe nodulocystic acne. *Int J Dermatol* 1985; **24**:252–7.
22 Strauss JS, Leyden JJ, Lucky AW *et al.* Safety of a new micronized formulation of isotretinoin in patients with severe recalcitrant nodular acne: a randomized trial comparing micronized isotretinoin with standard isotretinoin. *J Am Acad Dermatol* 2001; **45**:196–207.
23 Center for Drug Evaluation and Research. FDA Clinical review 21-951 Cipher Pharmaceuticals Inc. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/021951Orig1s000MedR.pdf (last accessed 21 January 2014).
24 Ross S. Composite outcomes in randomized clinical trials: arguments for and against. *Am J Obstet Gynecol* 2007; **196**:119e1–6.