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ORIGINAL RESEARCH

Efficacy and Safety of a Fixed-Dose Combination Gel with Adapalene 0.1% and Clindamycin 1% for the Treatment of Acne Vulgaris (CACTUS): A Randomized, Controlled, Assessor-Blind, Phase III Clinical Trial

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ABSTRACT

Background: Combination therapy is required for the treatment of moderate acne vulgaris. However, patient compliance in applying multiple topical formulations is poor.
Objective: To assess the efficacy and safety of a fixed-dose combination gel with adapalene 0.1% and clindamycin 1% (adapalene-clindamycin) relative to adapalene 0.1% monotherapy and clindamycin 1% monotherapy in patients with moderate facial acne vulgaris.
Methods: This was a randomized, controlled, assessor-blind, phase III study conducted in patients with moderate facial acne vulgaris.
Results: A total of 1617 patients were enrolled. At week 12, patients in the adapalene–clindamycin gel treatment group showed a significant reduction in the percentage change from baseline in total lesion count (– 66.85%), compared with adapalene alone (– 50.82%) or clindamycin gel alone (– 57.61%). The difference in the least square means of the adapalene–clindamycin gel group and adapalene group, or clindamycin gel group was – 16.08% (95% CI – 19.95%

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to −12.21%) and −9.38% (95% CI −13.25% to −5.51%;), respectively. At week 12, 19.28% of participants who received adapalene–clindamycin gel achieved at least 2-grade improvement in IGA, versus 7.74% with adapalene gel (OR 3.05, 95% CI 1.93, 4.80) and 14.77% with clindamycin gel (OR 1.42, 95% CI 0.97, 2.07). The study also achieved all its secondary endpoints. Adverse event rates were mostly mild to moderate and comparable across the three treatment groups.

Conclusion: Adapalene 0.1%–clindamycin 1% combination gel is well tolerated and demonstrated superior efficacy over 0.1% adapalene gel monotherapy and 1% clindamycin gel monotherapy for the treatment of moderate acne vulgaris.

Trial Registration: ClinicalTrials.gov identifier NCT03615768.

Keywords: Acne vulgaris; Adapalene–clindamycin combination gel; Adapalene; Clindamycin

Key Summary Points

Fixed-dose combination therapy of antibiotics and retinoids are recommended in guideline because they can target multifactorial pathogenesis of acne vulgaris.

This is the largest randomized, controlled, assessor-blind, phase III study to evaluate the efficacy and safety of a fixed-dose combination (FDC) of adapalene 0.1% and clindamycin 1% gel in patients 12 years and older with moderate facial acne vulgaris in China.

Adapalene 0.1%–clindamycin 1% combination gel demonstrated superior efficacy over 0.1% adapalene gel monotherapy and 1% clindamycin gel monotherapy in the treatment of moderate acne vulgaris, with statistical different in both two co-primary endpoints and all secondary endpoints.

Adapalene–clindamycin combination gel was safe and well tolerated.

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INTRODUCTION

Acne vulgaris is one of the most prevalent diseases in the world. It is particularly common in teenagers and young adults [1, 2]. It affects patients both mentally and physically and could have detrimental effects on their quality of life [3, 4]. The pathogenesis of acne vulgaris is multifactorial, characterized by excess sebum production, microbiome dysbiosis, hyperkeratinization, and release of inflammatory mediators in the skin [5, 6]. Treatment of acne vulgaris should target these known pathogenic factors.

According to the US and Chinese acne treatment guidelines, retinoids, benzoyl peroxide, and antibiotics recommended for mild-to-moderate acne treatment [7, 8]. Retinoids are the first-line topical therapy for the treatment and maintenance of mild acne owing to their dual comedolytic and anti-inflammatory effects; topical antibiotics are not recommended as the standard treatment for acne because of the potential risk of resistance [7, 8]. But, antibiotics are recommended when combined with retinoids [7]. Studies have revealed that fixed-dose combination therapy might be more effective than monotherapy for the treatment of acne [9, 10]. Moreover, superior efficacy of combinations of retinoids, benzoyl peroxide, and antibiotics has been observed in numerous studies [9, 11–14]. The combinations might provide a synergistic effect by acting on different pathogenic factors, and effectively reduced both inflammatory and non-inflammatory acne lesions with a rapid onset of action.

When the two monotherapies of adapalene and clindamycin are used in combination, it might lead to side effects including increasing the likelihood of resistance because of uneven application and poor patient compliance because of the inconvenience. Furthermore, adapalene has been shown to increase follicular penetration of clindamycin [15]. To date, several fixed-dose combinations including adapalene and clindamycin in nano-emulsion gel formulations have been approved in some countries like India and their efficacy and safety have been widely verified [16–19], but, adapalene and clindamycin gel is not available in China [19]. To improve patient compliance and lower the possibility of antibiotic resistance, a new combination gel of adapalene and clindamycin hydrochloride (adapalene–clindamycin gel) has been developed using patented technology, to minimize skin irritation and improve adherence to acne treatment.

The preliminary efficacy and safety of the combination of adapalene 0.1% and clindamycin 1% fixed-dose combination (FDC) were validated in a previous phase Ib + IIa study (CTR20140593) (data unpublished). In the current phase III trial, we further evaluated the efficacy and safety of adapalene 0.1% and clindamycin 1% FDC gel vs adapalene 0.1% monotherapy vs clindamycin 1% monotherapy in patients with moderate facial acne vulgaris.

METHODS

Study Design

This study was a multicenter, randomized, assessor-blind, controlled, parallel-group phase III comparison study of the efficacy and safety of adapalene–clindamycin gel. This study was conducted in 28 sites across China from August 14, 2018 to June 15, 2020. The study was approved by the ethics committees and institutional review boards of all study sites.

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and/or their parents or guardians. Male or female patients from 12 to 40 years old, whose facial acne scored as II or III with the Modified Pillsbury Acne Grading Scale were enrolled in this study.

Key exclusion criteria included use of topical acne therapies within 2 weeks and use of systemic retinoids or antibiotics within 4 weeks. Patients who have known hypersensitivity to adapalene, clindamycin hydrochloride, clindamycin phosphate, lincomycin, or any ingredient of the study drug, or of allergic constitution were not enrolled in this study. Individuals with secondary acne, such as occupational acne or drug-induced acne, were also excluded. In addition,

patients with a dermatological condition of the face that could interfere with the clinical evaluations, such as sunburn, psoriasis, seborrheic dermatitis, or eczema, were excluded. Patients with a history of Crohn's disease, ulcerative colitis or antibiotic-associated colitis, or history of serious heart disease or hypertension, serious liver or kidney disease, aspartate transaminase (AST) or alanine transaminase (ALT) more than twice the upper limit of normal, or creatinine (Cr) above normal, serious endocrine, hematologic, or psychiatric disease, known immunocompromised conditions, or requiring long-term steroids or immunosuppressants were excluded. Women who are pregnant, lactating, or not willing to use effective contraception were not enrolled. Patients with drug or alcohol abuse, those who used any topical acne treatment within 2 weeks, or used any systemic retinoid, antibiotic, or other acne treatment were excluded. Patients who used any investigational drugs or device within 3 months or concurrently enrolled in another clinical trial were not enrolled. Patients who the investigator deemed to be unsuitable for any reason were also excluded.

Participants were randomized (1:1:1) into three groups and received the allocated treatment for 12 weeks. Subjects in the adapalene–clindamycin gel group received once daily adapalene–clindamycin gel at night, subjects in the adapalene gel group received once daily adapalene gel at night, and subjects in the clindamycin gel group received twice daily (at morning and night) clindamycin gel. Only investigators delegated as outcome assessors were blinded to treatment allocation.

Safety Assessment

The safety set included all participants who were randomized, received the study medication at least once, and had their safety assessed after receiving the study medication. The full analysis set (FAS) included all participants who were randomized and received the study medication at least once. The per protocol (PP) set included participants in the FAS who completed the study without any significant protocol deviations. The safety analysis was conducted on the safety set. The efficacy analysis was conducted on the FAS and PP set, with FAS as the primary set for statistical analysis.

At each visit, manual counting of inflammatory and noninflammatory lesions and Investigator Global Assessment (IGA) score was performed by the blinded assessor. Vital signs, local skin reactions, and adverse events were assessed at each visit. The local skin reactions (erythema, scaling, itchiness, stinging, and burning) were assessed by a four-point scale (0, none; 1, mild; 2, moderate; 3, severe).

Investigators also assessed participants' treatment compliance by analyzing treatment diaries. The compliance rate is calculated as (number of days the participant used the study medication/number of days the participants was scheduled to use the study medication) × 100%. Non-compliance was defined as a compliance rate lower than 80% or higher than 120%.

The two co-primary endpoints were the percentage change at week 12 from baseline in total lesion count and the proportion of participants achieving two-grade improvement in IGA. To reduce variability, each patient was matched with a specific assessor for the duration of the study.

Secondary efficacy endpoints included the following observations at week 12: (i) percentage change from baseline in inflammatory lesion and noninflammatory lesion counts; (ii) absolute change in inflammatory, noninflammatory, and total lesion counts; (iii) change in IGA score; and (iv) treatment success rate. Treatment success was defined as an IGA score of clear (0) or almost clear (1); however, if the score at baseline was 2, success was only achieved with a score of 0 at week 12. Safety endpoints included adverse events, local skin reactions, vital signs, physical examinations, and laboratory tests.

Statistical Analysis

The trial was designed so that both co-primary endpoints were expected to demonstrate statistical difference. The trial would be considered to have met its primary endpoint if either one of the co-primary endpoints demonstrated superiority with statistical difference of $p < 0.025$ (two-sided).

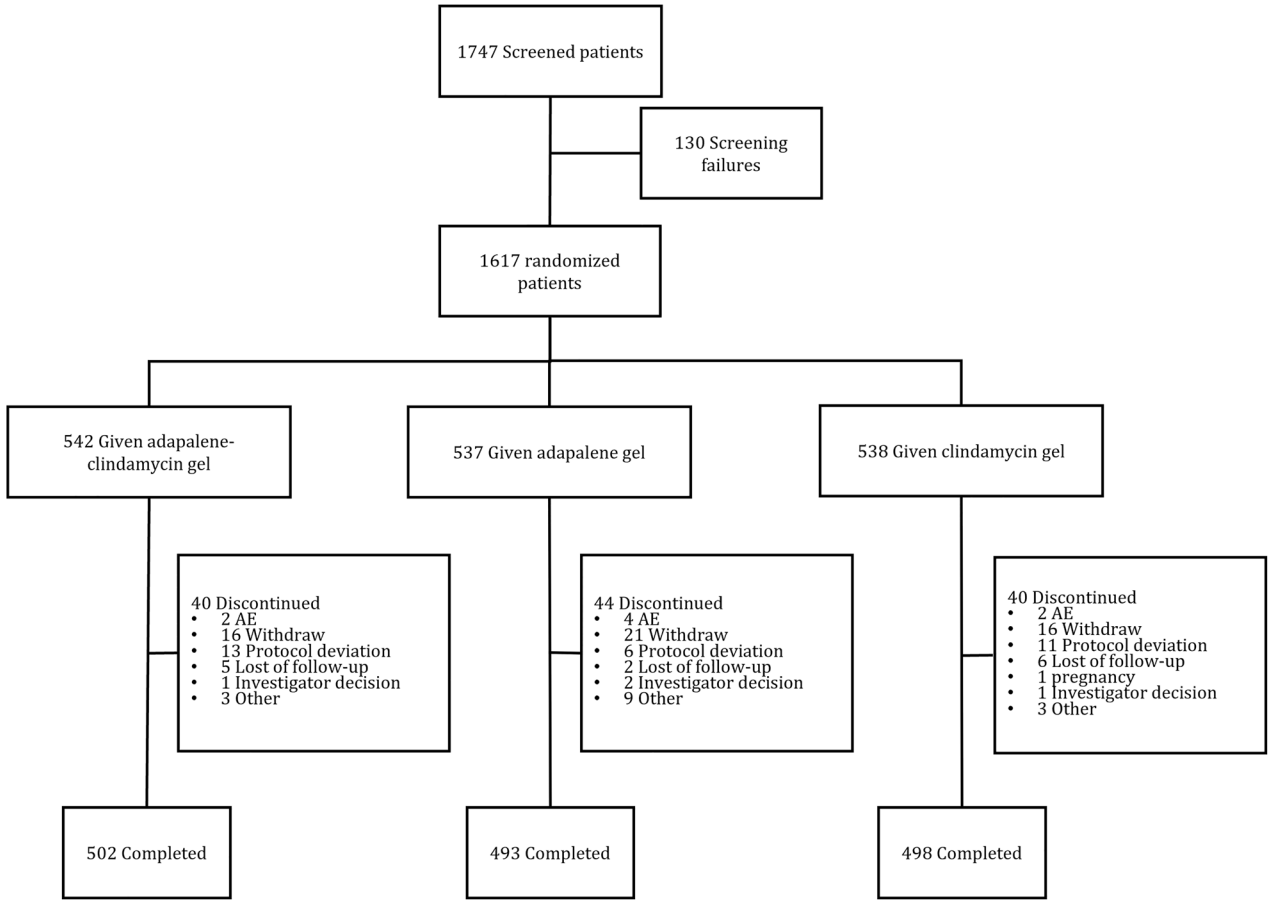

Fig. 1 CONSORT diagram. The enrollment outcome of 1747 patients with acne. Patients were screened for study inclusion and a total of 1617 patients were randomized 1:1:1 in three treatment groups, receiving combination adapalene–clindamycin gel, adapalene, or clindamycin

Table 1 Patient demographic and baseline characteristics (FAS)

Characteristic	Patients aged 12–40				Patients aged 12–18			
	Adapalene–clindamycin gel	Adapalene gel	Clindamycin gel	All	Adapalene–clindamycin gel	Adapalene gel	Clindamycin gel	All
	(*N* = 534)	(*N* = 530)	(*N* = 535)	(*N* = 1599)	(*N* = 31)	(*N* = 37)	(*N* = 27)	(*N* = 95)
Age								
Mean (SD)	22.1 (3.77)	22.2 (3.89)	22.2 (3.75)	22.2 (3.80)	15.3 (1.72)	15.2 (1.62)	14.9 (1.72)	15.2 (1.67)
Median	21	22	22	22	16	15	15	15
Age group, *n* (%)								
< 18	31 (5.8%)	37 (7.0%)	27 (5.0%)	95 (5.9%)	NA	NA	NA	NA
≥ 18	503 (94.2%)	493 (93.0%)	508 (95.0%)	1504 (94.1%)	NA	NA	NA	NA
Sex								
Male	189 (35.4%)	196 (37.0%)	219 (40.9%)	604 (37.8%)	14 (45.2%)	15 (40.5%)	19 (70.4%)	48 (50.5%)
Female	345 (64.6%)	334 (63.0%)	316 (59.1%)	995 (62.2%)	17 (54.8%)	22 (59.5%)	8 (29.6%)	47 (49.5%)
IGA score								
2	135 (25.3%)	127 (24.0%)	99 (18.5%)	361 (22.6%)	7 (22.6%)	11 (29.7%)	7 (25.9%)	25 (26.3%)
3	372 (69.7%)	372 (70.2%)	400 (74.8%)	1144 (71.5%)	22 (71.0%)	25 (67.6%)	17 (63.0%)	64 (67.4%)
4	27 (5.1%)	31 (5.8%)	36 (6.7%)	94 (5.9%)	2 (6.5%)	1 (2.7%)	3 (11.1%)	6 (6.3%)
Total lesion count, mean (SD)	51.9 (18.46)	53.1 (18.81)	55.5 (19.69)	53.5 (19.04)	58.0 (17.12)	56.4 (20.74)	60.1 (20.10)	58.0 (19.30)
Inflammatory lesion count, mean (SD)	20.6 (10.49)	21.5 (11.46)	22.0 (10.99)	21.4 (10.99)	20.1 (8.52)	22.4 (11.38)	22.1 (12.76)	21.5 (10.90)

Table 1 continued

Characteristic	Patients aged 12–40				Patients aged 12–18			
	Adapalene–clindamycin gel	Adapalene gel	Clindamycin gel	All	Adapalene–clindamycin gel	Adapalene gel	Clindamycin gel	All
	(*N* = 534)	(*N* = 530)	(*N* = 535)	(*N* = 1599)	(*N* = 31)	(*N* = 37)	(*N* = 27)	(*N* = 95)
Non-inflammatory lesion count, mean (SD)	31.3 (15.69)	31.6 (15.86)	33.5 (16.72)	32.2 (16.12)	37.9 (16.43)	34.0 (16.04)	38.1 (18.08)	36.4 (16.70)

FAS full analysis set, *N* number of patients, *SD* standard deviation, *IGA* Investigator Global Assessment, *NA* not applicable

On the basis of the results from the unpublished phase Ia + IIb study, we estimated that at least 431 patients in each treatment group were required to provide 90% power. To account for a potential dropout rate of 20%, a total of 1617 patients were recruited. No interim analyses were planned. The statistical analysis was performed using SAS, version 9.4 (SAS Institute).

The analysis of the percentage change in total lesion count at week 12 was performed with an analysis of covariance (ANCOVA) model, with percentage change in total lesion count at week 12 as dependent variable, treatment group as independent variable, and total lesion count at baseline as covariate. Least square means with associated 97.5% CIs of difference from the analysis of covariance were analyzed. If both lower bounds of the 97.5% CI were less than 0%, it could be concluded that adapalene–clindamycin is superior to both control groups.

To compare the proportion of patients achieving two-grade IGA improvement at week 12, a Cochran–Mantel–Haenszel test, stratified by center, was used to analyze the odds ratio and the corresponding 97.5% CIs, between adapalene–clindamycin group and the two control groups.

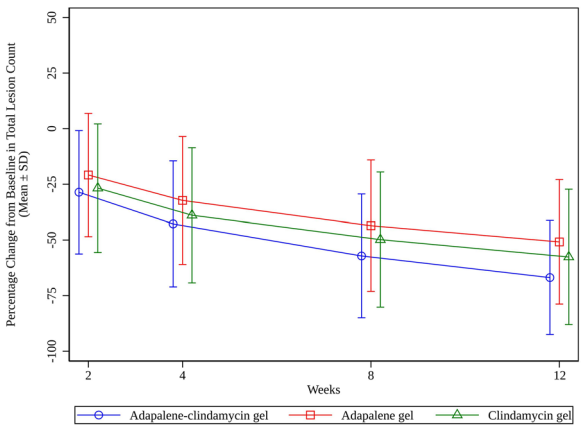

Fig. 2 Total lesion count changes (FAS). At weeks 2, 4, 8, and 12, reductions in total lesion count were measured in the adapalene–clindamycin combination gel, adapalene gel, or clindamycin gel group, respectively. Data are expressed as mean ± SD

RESULTS

Patients and Exposure

A total of 1617 patients were include and randomized 1:1:1 to receive three treatment: (i) 542 in the adapalene–clindamycin gel group, 534 participants (98.5%) had used the drug at least once; (ii) 537 in the adapalene gel group and 530 participants (98.7%) had used the drug at least once; and (iii) 538 in clindamycin gel group and

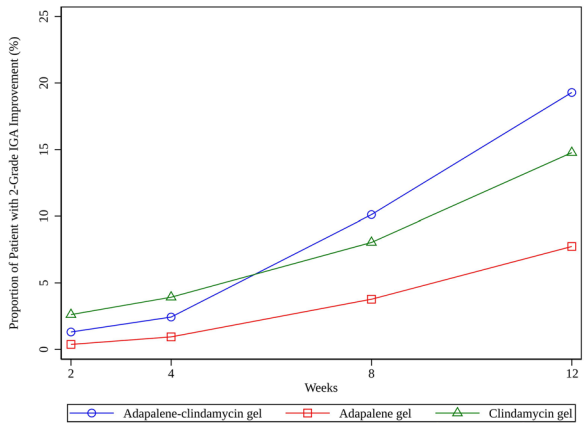

Fig. 3 Proportion of patients achieving two-grade IGA improvement (FAS). At weeks 2, 4, 8, and 12, numbers of patients achieving two-grade improvement in IGA in the adapalene–clindamycin combination gel group, adapalene gel group, and clindamycin gel group, respectively, were evaluated

535 participants (99.4%) had used the drug at least once. Figure 1 shows the enrollment outcome of the study. Table 1 shows the patient demographics and baseline characteristics. All characteristics were balanced across groups.

Overall, 99.4% patients demonstrate good compliance rate to the treatment. Only 10 (0.6%) patients had a compliance rate lower than 80%.

Efficacy

The primary efficacy endpoint was met. At week 12, the percentage change from baseline in total lesion count was 66.85% (SD 25.59%), 50.82% (SD 27.93%), and 57.61% (SD 30.40%) in the adapalene–clindamycin gel group, adapalene group, and clindamycin group, respectively (Fig. 2). The difference between adapalene–clindamycin gel group and adapalene group was −16.08% (97.5% CI −19.95% to −12.21%), $P<0.0001$. The difference between

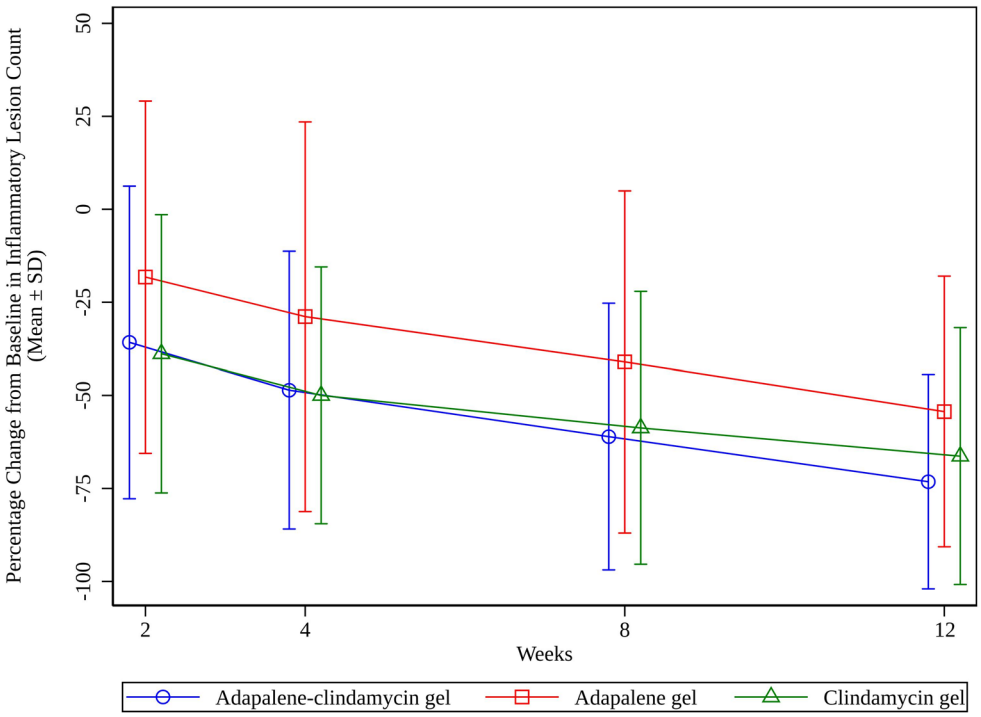

Fig. 4 Percentage change from baseline in inflammatory lesion count (FAS). At weeks 2, 4, 8, and 12, the percentage change from baseline in inflammatory lesion count was measured in the adapalene–clindamycin combination gel, adapalene gel, or clindamycin gel group, respectively. Data are expressed as mean ± SD

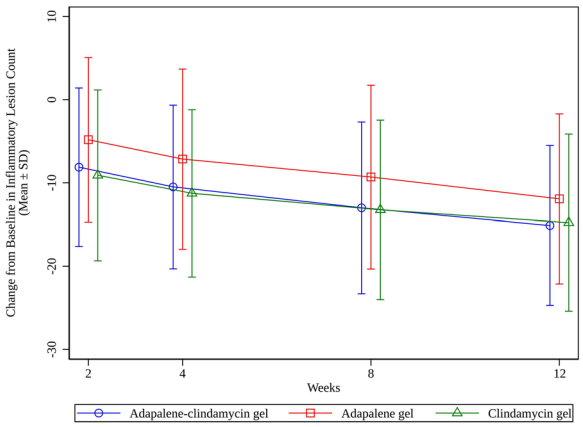

Fig. 5 Change from baseline in inflammatory lesion count (FAS). At weeks 2, 4, 8, and 12, the change from baseline in inflammatory lesion count was measured in the adapalene–clindamycin combination gel, adapalene gel, or clindamycin gel group, respectively. Data are expressed as mean ± SD

adapalene–clindamycin group and clindamycin group was −9.38% (97.5% CI −13.25% to −5.51%), $P<0.0001$. The lower bounds of 97.5% CI were both lower than 0%, which demonstrated that adapalene–clindamycin gel was superior to both adapalene gel and clindamycin gel in percentage change of total lesion count at week 12. At week 12, 103 (19.28%) patients in the adapalene–clindamycin gel group achieved two-grade improvement in IGA, whereas 41 (7.74%) and 79 (14.77%) achieved two-grade improvement in IGA in the adapalene gel group and clindamycin gel group, respectively (Fig. 3). The odds ratio between the adapalene–clindamycin gel group and adapalene group was 3.05 (97.5% CI 1.93 to 4.80), $P<0.0001$. The odds ratio between adapalene–clindamycin gel group and clindamycin gel group was 1.42 (97.5% CI 0.97 to 2.07), $P=0.039$. The 97.5% lower bound of the odds ratio between adapalene–clindamycin gel and adapalene gel was higher than 1, which showed that adapalene–clindamycin gel was superior to adapalene gel in achieving two-grade IGA improvement at week 12. This was not the case between adapalene–clindamycin and clindamycin, since the lower bound of their odds ratio was lower than 1.

The study also met its secondary endpoint. At week 12, the percentage change from baseline in inflammatory lesion was −73.20%, −54.33% ,and −66.33% in the adapalene–clindamycin gel, adapalene gel, and clindamycin gel group, respectively (Fig. 4). The adapalene–clindamycin gel group demonstrated statistically significant difference in reducing inflammatory lesion counts when compared with the adapalene gel

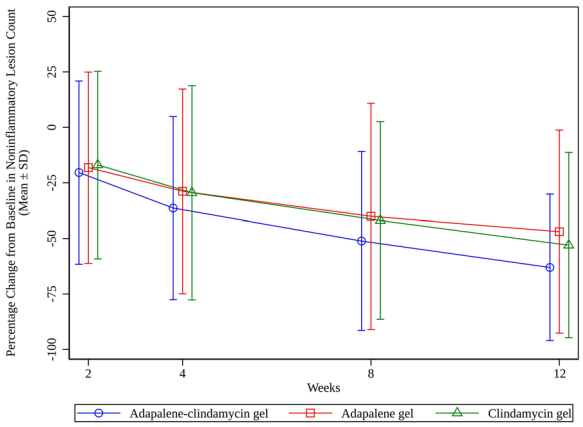

Fig. 6 Percentage change from baseline in noninflammatory lesion count (FAS). At weeks 2, 4, 8, and 12, the percentage change from baseline in noninflammatory lesion count was measured in the adapalene–clindamycin combination gel, adapalene gel, or clindamycin gel group, respectively. Data are expressed as mean ± SD

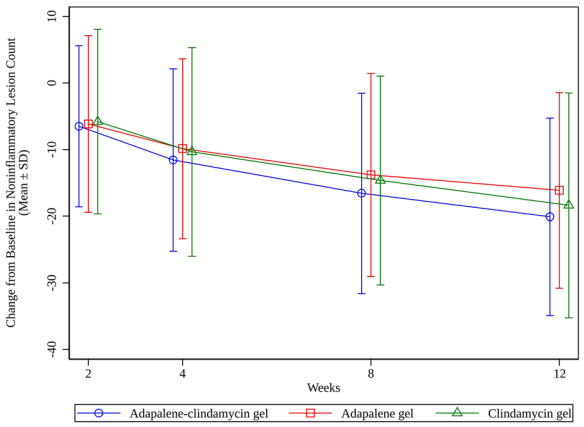

Fig. 7 Change from baseline in noninflammatory lesion count (FAS). At weeks 2, 4, 8, and 12, the change from baseline in noninflammatory lesion count was measured in the adapalene–clindamycin combination gel, adapalene gel, or clindamycin gel group, respectively. Data are expressed as mean ± SD

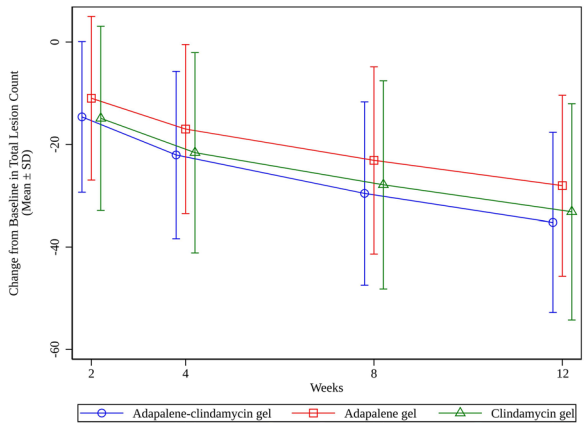

Fig. 8 Change from baseline in total lesion count (FAS). At weeks 2, 4, 8, and 12, the change from baseline in total lesion count was measured in the adapalene–clindamycin combination gel, adapalene gel, or clindamycin gel group, respectively. Data are expressed as mean ± SD

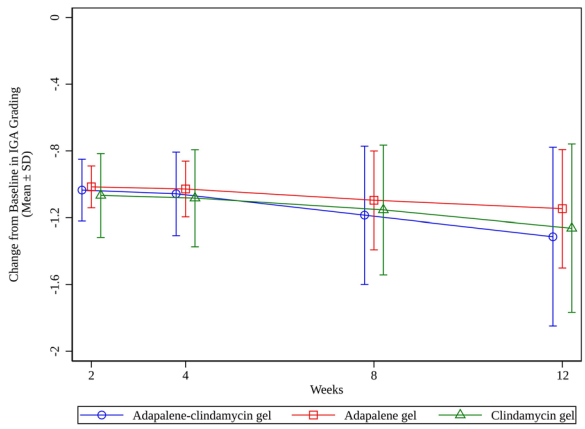

Fig. 9 Change from baseline in IGA grading (FAS). At weeks 2, 4, 8, and 12, the change from baseline in IGA grading was measured in the adapalene–clindamycin combination gel, adapalene gel, or clindamycin gel group, respectively. Data are expressed as mean ± SD

and clindamycin gel group; the least squares mean difference and 95% CI were −19.03% (−23.17%, −14.90%, $p<0.0001$) and −7.17% (−11.31%, −3.04%, $P=0.0007$), respectively. The absolute changes in inflammatory lesion counts were −15.1 (9.60), −11.9 (10.21), and −14.8 (10.63) in the adapalene–clindamycin gel, adapalene gel, and clindamycin gel group, respectively (Fig. 5), when compared with the adapalene gel and clindamycin gel group; the least squares mean difference and 95% CI were −3.8 (−4.6, −2.9, $p<0.0001$) and −1.4 (−2.3, −0.6, $P=0.0022$), respectively.

At week 12, the percentage change from baseline in noninflammatory lesion was −63.04%, −46.93%, and −53.02% in the adapalene–clindamycin gel, adapalene gel, and clindamycin gel group, respectively (Fig. 6). The adapalene–clindamycin gel group demonstrated statistically significant difference in reducing noninflammatory lesion counts when compared with the adapalene gel and clindamycin gel group; the least squares mean difference and 95% CI were −16.40% (−21.38%, −11.41%, $p<0.0001$) and −10.74% (−15.72%, −5.75%, $P<0.0001$), respectively. The absolute change in noninflammatory lesion counts was −20.1 (14.82), −16.1 (14.67), and −18.4 (16.87) in the adapalene–clindamycin gel, adapalene gel, and clindamycin gel group, respectively (Fig. 7), when compared with the adapalene gel and clindamycin gel group, the least squares mean difference and 95% CI were −4.6 (−6.0, −3.1, $p<0.0001$) and −3.1 (−4.5, −1.6, $P<0.0001$), respectively.

The absolute change in total lesion counts was −35.2 (17.58), −28.1 (17.66), and −33.1 (21.11) in the adapalene–clindamycin gel, adapalene gel, and clindamycin gel group, respectively (Fig. 8), when compared with the adapalene gel and clindamycin gel group; the least squares mean difference and 95% CI were −8.2 (−10.1, −6.4, $p<0.0001$) and −4.4 (−6.2, −2.5, $P<0.0001$), respectively.

The change from baseline in IGA score at week 12 was −1.3 (0.54), −1.1 (0.35), −1.3 (0.50) in the adapalene–clindamycin gel, adapalene gel, and clindamycin gel group, respectively (Fig. 9). Figure 10 shows photos of patients before and after treatment in the three groups. Among the three groups, the adapalene–clindamycin gel group demonstrated the highest treatment success rate at week 12, with a success rate of 16.5%, followed by the clindamycin phosphate gel group (success rate of 11.6%), and the lowest success rate was in the adapalene gel group (success rate of 4.3%), the difference between groups was statistically significant (vs adapalene gel, $P<0.0001$; vs clindamycin gel, $P=0.0213$) (Fig. 11).

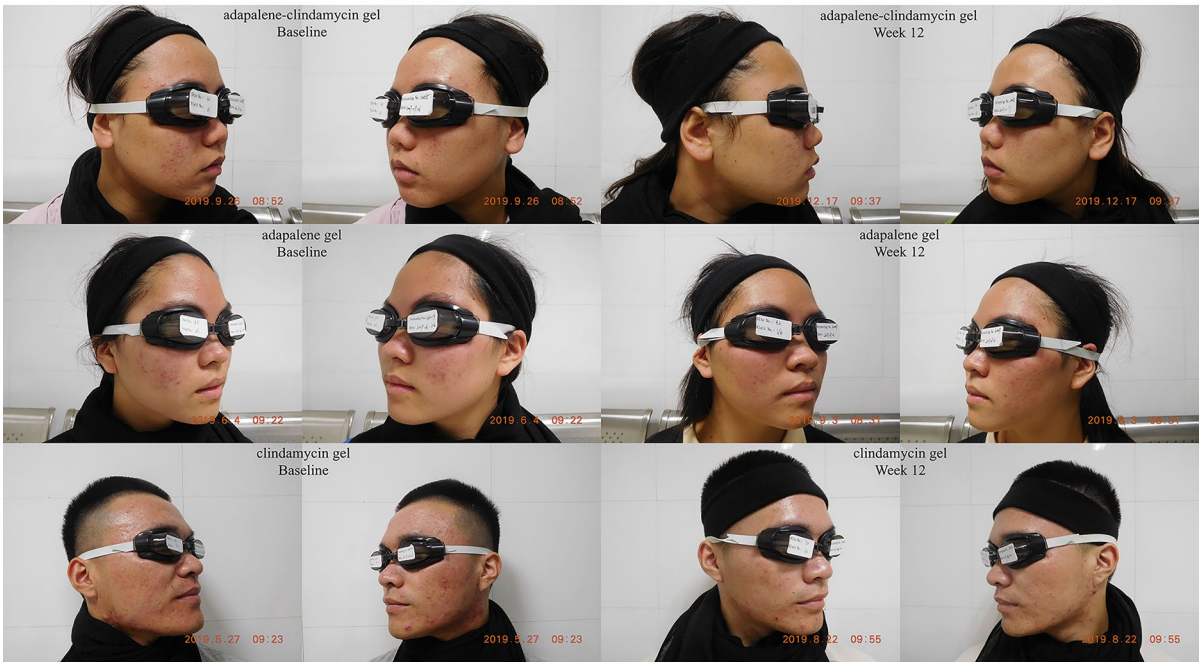

Fig. 10 Photos of patients prior to and after 12 weeks of treatment in the three groups

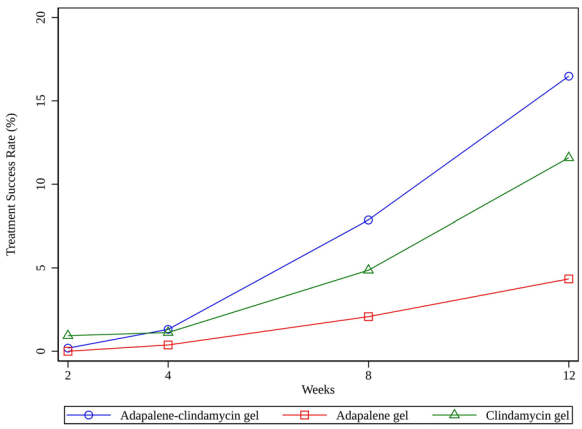

Fig. 11 Treatment success rate in the three groups (FAS). At weeks 2, 4, 8, and 12, the treatment success rate was calculated in the adapalene–clindamycin combination gel, adapalene gel, or clindamycin gel group, respectively

Safety

Overall, adapalene–clindamycin gel was safe and well tolerated and the combination of the two active ingredients did not cause any additional adverse reactions; 238 (44.74%) patients in the adapalene–clindamycin gel group, 235 (44.51%) patients in the adapalene gel group, and 207 (38.69%) patients in the clindamycin gel group reported treatment-emergent adverse events (TEAE). Most TEAE were considered mild or moderate. The most common TEAE reported for all treatment groups was upper respiratory tract infection, with 40 (7.52%) patients in the adapalene–clindamycin gel group, 39 (7.39%) in the adapalene gel group, and 53 patients (9.91%) in the clindamycin gel group reporting such an event. Drug-related TEAE occurred in 83 (15.60%) patients in the adapalene–clindamycin gel group, 69 (13.07%) patients in the adapalene gel group, and 18 (3.36%) patients in the clindamycin gel group in which dry skin was the most frequently reported. Severe TEAE occurred in 5 (0.94%), 9 (1.70%), and 2 (0.37%) patients in the adapalene–clindamycin gel, adapalene gel, and clindamycin gel group, respectively. TEAEs that caused study drug discontinuation were reported in 48 (9.02%), 38 (7.20%), and 9 (1.68%) subjects in the adapalene–clindamycin gel, adapalene gel, and clindamycin gel groups, respectively. Four subjects (0.8%) in the adapalene–clindamycin gel

Table 2 Adverse event summary (SS)

Event	Patients aged 12–40			Patients aged 12–18		
	Adapalene–clindamycin gel	Adapalene gel	Clindamycin gel	Adapalene–clindamycin gel	Adapalene gel	Clindamycin gel
	(*N* = 532)	(*N* = 528)	(*N* = 535)	(*N* = 30)	(*N* = 35)	(*N* = 22)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
TEAE	238 (44.7%)	235 (44.5%)	207 (38.7%)	19 (63.3%)	13 (35.1%)	7 (25.9%)
Drug-related TEAE	83 (15.6%)	69 (13.1%)	18 (3.4%)	5 (16.7%)	3 (8.1%)	0
Most frequently reported drug-related TEAE (≥ 3% in any group)						
Dry skin	28 (5.3%)	29 (5.5%)	5 (0.9%)	1 (3.3%)	1 (2.7%)	0
Skin stripped	28 (5.3%)	29 (5.5%)	5 (0.9%)	2 (6.7%)	2 (5.4%)	0
Pruritus	6 (1.1%)	7 (1.3%)	0	2 (6.7%)	1 (2.7%)	0
Erythema	13 (2.4%)	5 (0.9%)	1 (0.2%)	1 (3.3%)	0	0
Paresthesia	13 (2.4%)	4 (0.8%)	1 (0.2%)	3 (10.0%)	0	0
Peri-orbit swollen	0	0	0	1 (3.3%)	0	0
Serious adverse event	5 (0.9%)	4 (0.8%)	1 (0.2%)	0	0	0
Drug-related SAE	0	0	0	0	0	0

SS safety set, *TEAE* treatment-emergent adverse effect, *N* number of patients enrolled, *n* number of event

group, 5 subjects (0.9%) in the adapalene gel group, and 1 subject (0.2%) in the clindamycin gel group reported TEAEs that led to permanent discontinuation of the study drug. Serious adverse events (SAE) occurred in 5 (0.94%, 1 case each of congenital aural fistula, congenital cerebral cysts, infectious pneumonia, nasal septal deviation, and threatened abortion) patients in the adapalene–clindamycin gel group, 4 (0.76%, 1 case each of biochemical pregnancy, spontaneous abortion, fibroadenoma breast, and hyperplasia of mammary glands) patients in the adapalene gel group and 1 (0.19%, 1 case of vascular and lymphatic diseases) patient in the clindamycin gel group. No drug-related SAE was reported. Safety of patients aged 12–18 years old was similar to the overall study population. Table 2 shows a summary of the adverse events of this study.

The proportions of patients with local skin reactions were similar in all treatment groups. The reported local skin reactions were mostly mild or moderate. The proportions of patients who experienced severe local skin reaction were similar in all treatment groups. No substantial changes in laboratory values, vital signs, physical examinations, and ECG were observed in all treatment groups.

DISCUSSION

The current study is designed as a randomized, controlled, assessor-blind phase III clinical trial to evaluate the efficacy and safety of adapalene–clindamycin gel. It has enrolled total 1617 patients, making it the largest dermatology clinical trial in China. The results showed that the study met the primary endpoint and demonstrated that adapalene–clindamycin gel applied once daily for 12 weeks was superior to

adapalene gel monotherapy and clindamycin gel monotherapy, in reducing total lesion counts in patients with moderate facial acne. Although monotherapy, such as adapalene and clindamycin, can be applied separately to patients with acne vulgaris, the possibly uneven localized coat on the skin might increase the risk of developing bacterial resistance [20]. In addition, applying multiple drugs frequently will reduce patient compliance. Hence, the new combination gel containing adapalene and clindamycin hydrochloride developed using a patented unique formulation minimizes skin irritation and optimizes adherence for acne treatment. The mean treatment compliance in this study is 98.37% (SD 4.72); only 5 (0.94%), 1 (0.19%), and 4 (0.75%) patients in the adapalene–clindamycin gel, adapalene gel, and clindamycin gel group showed a compliance rate lower than 80%, respectively. The unique and stable formulation of adapalene–clindamycin (once-daily) has demonstrated significant improvement in patient compliance.

Patients who used adapalene–clindamycin gel for 12 weeks achieved a mean reduction of 66.85% in their total lesion count. The result was consistent with previous studies using adapalene 0.1% gel and clindamycin 1% lotion in combination, with mean reduction ranging from 46.7% to 75.1% [18–20]. Although there was no significant difference in the proportion of patients achieving a two-grade IGA improvement between adapalene–clindamycin combination gel group and clindamycin group, more patients in the combination gel group reached the endpoint than those applying either adapalene 0.1% gel (q.n.) (103 vs 41) or clindamycin 1% (b.i.d.) (103 vs 79). In this study, the sample size is powered to detect the statistically significant difference in total lesion count, which could explain the failure to see statistical difference between combination gel and clindamycin in two-grade IGA improvement. The dosage of clindamycin in the adapalene–clindamycin combination group was half of that in the clindamycin monotherapy group, indicating that the adapalene–clindamycin gel with low dose of clindamycin might also be sufficient to achieve similar effects in treating inflammatory lesions. Moreover, adapalene has been shown to increase follicular penetration of clindamycin, which might further reduce the effective dosage of clindamycin in the combination compared with the monotherapy [15]. The overuse of topical antibiotics like clindamycin and erythromycin has been reported to increase the risk of bacterial resistance by developing cross-resistant strains of Propionibacteria [21]. The guideline for treating acne in China and the USA has recommended not prescribing antibiotics as the monotherapy and reducing the possibility of antibiotic resistance [7, 8]. The long-term use of high-dose antibiotics has been recognized to develop resistance to antibiotics [21]. In fact, studies have shown that the clindamycin-resistant strains were frequently isolated from patients with moderate-to-severe acne [22, 23]. Reduction in selection pressure, interference with the transmission of problematic genotypes, and multidrug approaches have been recommended as effective approaches to reduce bacterial resistance [22]. The low dosage of clindamycin in the combination gel might reduce the risk of developing resistance by reduction of the selection pressure.

The results of the current phase III trial have also indicated that the adapalene–clindamycin combination gel is safe and well tolerated. The adapalene–clindamycin combination gel did not cause additional adverse reactions beyond those of the monotherapy. No drug-related serious adverse event was reported. Though the adverse event rate of the adapalene–clindamycin gel group (44.74%) was higher than that of the clindamycin gel group (38.69%), the adverse event rate was comparable to that of the adapalene gel group (44.51%). The rate of drug-related TEAE was also higher in the adapalene–clindamycin gel group (15.60%) and adapalene gel group (13.07%) than that of the clindamycin gel group (3.36%). The drug-related TEAEs reported were similar in the adapalene–clindamycin gel group and adapalene gel group. Although clindamycin gel appears to have fewer adverse effects, it is also less efficacious in the treatment of moderate acne vulgaris than the adapalene–clindamycin combination gel. Moreover, clindamycin is generally not recommended as a monotherapy for the treatment of acne because of potential development

of antibiotic resistance. More importantly, acne usually occurs in adolescence and, therefore, the safety of adapalene–clindamycin gel is also important [2, 7]. The clinical data showed that no SAE or drug-related SAE was reported in the patients aged 12–18 years old, indicating that the fixed-dose adapalene–clindamycin gel is also safe in adolescent patients. Taken together, by incorporating clindamycin into a fixed-dose combination with adapalene, the combination gel is more efficacious than using the individual drugs alone, while having a similar safety profile to the already marketed adapalene gel.

There are some limitations in this study. As a result of differences in the drug appearance and dosing frequency between adapalene–clindamycin gel and the two comparators, the patients and the investigators could not be blinded. By blinding the assessor, the possibility of bias in outcome assessment was reduced; however, there might be bias in the safety assessment. In theory, treatment compliance should be higher for patients using adapalene–clindamycin gel, as compared with using the two individual drugs at the same time. This study, however, only compared the compliance of using adapalene–clindamycin gel with adapalene or clindamycin monotherapy. The true compliance advantage of the once-daily administration in the real world was not determined in this study. Finally, the number of patients under 18 years old is small, limiting the statistical analysis of this subgroup of patients.

CONCLUSIONS

This study evaluated the efficacy and safety of adapalene–clindamycin gel in patients 12 years and older with moderate facial acne vulgaris. Our results show that the fixed-dose combination with adapalene 0.1% and clindamycin 1% is more efficacious than using adapalene monotherapy or clindamycin monotherapy. The combination does not cause additional adverse reactions beyond those of the individual components. The less frequent once-daily administration of a single gel product will increase convenience and further improve patient compliance. In summary, the adapalene–clindamycin combination gel provides multiple advantages over conventional treatments in the fight against acne vulgaris.

Author Contributions. Kun Chen, Heng Gu and Benjamin Xiao Yi Li conceived and designed the study and were responsible for administrative, technical, or material support. Wen Lin Yang, Jia Wen Yin, Lie Hua Deng, Bin Chen, Hong Wei Liu, Shou Min Zhang, Jian De Han and Zhi Jun Liu conducted the study, including acquisition, analysis, or interpretation of data. Chao Luan and Xiang Rong Dai were responsible for statistical analysis. Chao Luan, Kun Chen, Heng Gu, Qiu Ju Yin and Xiao Hui Yu drafted the manuscript. All authors critically revised the manuscript. All authors gave final approval of the manuscript. Kun Chen, Heng Gu and Benjamin Xiao Yi Li contributed equally to this work and are the joint corresponding authors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Dr. Benjamin Xiao Yi Li is the Chairman & CEO of Zhaoke Ophthalmology Limited, and Director of Zhaoke Pharmaceutical (Hefei) Company Limited and Lee's Pharmaceutical (Hong Kong) Limited. Xiang Rong DAI, and Xiao Hui YU are the staffs employed by Zhaoke Pharmaceutical (Hefei) Company Limited. Qiu Ju YIN is the staff employed by Zhaoke (Guangzhou) Ophthalmology Pharmaceutical Limited; The other authors declare no conflict of interest.

Ethics Approval. The trial was conducted in accordance with the Good Clinical Practice guidelines and complies with the Declaration of Helsinki. The protocol and informed consent form were reviewed and approved by a properly constituted institutional review board/independent ethics committee/research ethics board before study commencement. The names of the approving ethics committees are listed in Supplementary Table 1.

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