

Efficacy and safety of the triple combination cream in Chinese patients with moderate to severe melasma: A multi-center, randomized, double-blind, three-arm, parallel-group, placebo-controlled clinical trial

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To the Editor: Melasma is a chronic, acquired, and hyperpigmentation disease in which patients present with facial pigmented patches, affecting 8.8% to 40% of the population worldwide.^[1] Currently, the mainstay treatment for the condition is the application of topical agents, among which the triple combination cream (TCC) (Tri-Luma, Galderma) comprising fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05%, a modification of the Kligman–Willis formula first proposed in 1975,^[2] was approved by Food and Drug Administration in 2002. This cream has shown promising efficacy in Caucasian and other races. However, its efficacy has not been proved in Chinese patients, and there are no approved formulations in the Chinese market. In the proposed phase III trial (ChiCTR2100043798), we aimed to investigate the efficacy and safety profile of TCC using a double-blind, placebo-controlled design.

The study was approved by the Ethics Committee of the First Hospital of China Medical University (No. 2020YL026), and informed consent was obtained from all patients. The inclusion criteria were: Patients of 18–60 years old, with moderate or severe facial melasma (Melasma Severity Score [MSS] [0–3, four-point scale] ≥ 2). Pregnant women and patients with facial skin conditions that would interfere with the diagnosis of melasma were excluded. The patients were recruited between October 14, 2020, and August 18,

2021. The enrolled participants ($n = 320$) were randomized (2:2:1) to receive Tri-Luma, the generic formulation (the same TCC manufactured by Zhejiang Fonow Medicine Co., Ltd.), or placebo [Supplementary file, <http://links.lww.com/CM9/C646>]. In all patients, the creams were applied at least 30 min before bedtime, once daily for 8 weeks. During the trial, the occurrence of adverse events (AEs) and the systemic absorption of the three active ingredients were monitored.

The primary efficacy was determined based on the proportion of patients who achieved at least a two-point reduction in MSS compared to baseline at 4- and 8-week visits. The secondary efficacy variable was the percentage of patients with a reduction of not less than 50% in the Melasma Area and Severity Index (MASI).

Before the trial, investigators and participants received standardized training to minimize assessment bias. Per-protocol analysis was conducted using PASS version 14.0 (Power Analysis and Sample Size, NCSS, Kaysville, Utah, USA), with between-group comparisons performed via Pearson's chi-squared test. Demographic factors were compared among the three groups using the Kruskal–Wallis test and the One-way analysis of variance test. A P -value ≤ 0.05 was considered statistically significant.



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Table 1: Efficacy outcomes of three study groups in Chinese patients with moderate to severe melasma.

Items	N	Methods	Average score of efficacy variable			Efficacy (%)	P values
			Baseline	4-week	8-week		
Tri-Luma	104	MSS	2.452	1.635	1.394	35.6	0.408*; <0.001†
		MASI	13.886	7.068	5.741	59.6	0.759*; <0.001†
Generic formulation	107	MSS	2.523	1.617	1.336	41.1	<0.001‡
		MASI	13.142	7.255	5.475	61.7	<0.001‡
Placebo	56	MSS	2.500	2.143	2.070	7.1	–
		MASI	12.566	10.271	9.289	17.9	–

*Tri-Luma *vs.* generic formulation; †Tri-Luma *vs.* Placebo; ‡Generic formulation *vs.* Placebo. MSS: (0) Cleared (melasma lesions approximately equivalent to surrounding normal skin or with a minimal residual hyperpigmentation); (1) mild (melasma lesions slightly darker than the surrounding normal skin); (2) moderate (melasma lesions moderately darker than the surrounding normal skin); (3) severe (melasma lesions markedly darker than the surrounding normal skin). MASI: MASI = 0.3(Df + Hf)Af + 0.3(Drm + Hrm)Arm + 0.3(Dlm + Hlm)Alm + 0.1(Dc + Hc)Ac, where D represents darkness, H = homogeneity, A = area, f = forehead, rm = right malar, lm = left malar, and c = chin, with co-efficiencies of 0.3, 0.3, 0.3, and 0.1, respectively. –: Not applicable.

A total of 293 patients completed the 8-week treatment, among whom 267 were eligible to undergo per-protocol set (PPS) analysis. Notably, there was no significant difference ($P > 0.05$) in MSS and MASI assessment among the three groups at the baseline. Similarly, patient demographics, including age, gender, height, weight, or ethnicity, were comparable among the three groups.

Overall, it was observed that the efficacy rates for MSS after the 8-week treatment were 35.6% (37/104) for Tri-Luma, 41.1% (44/107) for the generic formulation, and 7.1% (4/56) for the placebo group, indicating that both treatment groups had higher efficacy compared to placebo (both $P < 0.001$). However, there was no significant difference in efficacy between the generic formulation and Tri-Luma groups ($P = 0.408$). In addition, clinically meaningful improvements were observed within the first 4 weeks in both treatment groups [Table 1].

The analysis showed that the efficacy rates for MASI were 59.6% (62/104), 61.7% (66/107), and 17.9% (10/56) for Tri-Luma, the generic formulation, and the placebo group, respectively. This indicated that the generic formulation had equivalent efficacy to Tri-Luma ($P = 0.759$), and both treatments had significantly superior efficacy to placebo ($P < 0.001$).

In the assessment of the systemic absorption for the active ingredients, hydroquinone and fluocinolone acetonide were not detected or below the limit of quantification in plasma in any of the three groups. Tretinoin levels remained within normal physiological ranges throughout the study, with no significant fluctuations observed pre- and post-treatment. The incidence of AEs was significantly higher in both treatment groups compared with the placebo group. The most frequent AEs were erythema (88/233, 37.8%), application site pain (87/233, 37.3%), and desquamation (72/233, 31.0%, 233 is the total number of patients in triluma and generic group who have completed this trial, excluded the withdrawn). The majority of recorded AEs were mild to moderate in severity, and no serious AEs related to the investigational drugs occurred during the trial.

In previous clinical studies, 37.9% of patients treated with Tri-Luma achieved at least a two-point decrease

in MSS scores, which is consistent with the results of our trial. This pharmacodynamic concordance between distinct races confirms the high treatment efficacy of the triple-combination formulation, laying a strong foundation for its widespread clinical application.

This trial confirms that the generic formulation exhibits comparable efficacy and safety to Tri-Luma in the short-term management of melasma in Chinese patients. However, given that the treatment was evaluated for 8 weeks, we could not assess the long-term tolerability, prolonged efficacy, or recurrence rates, which have been previously associated with triple combination therapies. Extended trials are warranted to evaluate optimal maintenance regimens and recurrence mitigation strategies in Chinese patients with melasma.

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Conflicts of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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