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

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.

Funding

This work was supported by a grant from the National Key R&D Program of China (No. 2023YFC2508200).

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.

References

1. Neagu N, Conforti C, Agozzino M, Marangi GF, Morariu SH, Pellacani G, *et al*. Melasma treatment: A systematic review. J Dermatolog Treat 2022;33:1816–1837. doi: 10.1080/09546634.2021.1914313.
2. Kligman AM, Willis I. A new formula for depigmenting human skin. Arch Dermatol 1975;111:40–48. doi: 10.1001/archderm.1975.01630130042004.

How to cite this article: Zhang L, Geyao Xu GY, Liu QZ, Pan WL, Liu LF, Li LF, Wang JY, Cheng H, Ji C, Pan M, Gao XH. 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. Chin Med J 2026;139:947–948. doi: 10.1097/CM9.0000000000003718