Clinical Efficacy of the Human Tyrosinase Inhibitor Thiamidol (isobutylamido thiazolyl resorcinol) in Melasma

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Abstract

Thiamidol (isobutylamido thiazolyl resorcinol) was the most potent inhibitor of human tyrosinase identified out of 50,000 screened substances. *In vivo*, it was well tolerated and improved melasma significantly. This was the first 24-week, randomized, double-blind, vehicle-controlled, cosmetic clinical study to assess the efficacy and tolerability of Thiamidol in moderate-to-severe melasma in phototype III-V subjects with subsequent regression phase. Females allocated to the Thiamidol treatment group (n=23), applied daily Thiamidol-based Serum followed either by a Thiamidol cream with SPF 30 in the morning or by Thiamidol cream without SPF in the evening. The vehicle group (25 females) followed the same skin care routine using the corresponding vehicle formulations. Subjects returned for a follow-up visit 13-20 weeks after treatment (regression phase). Assessments included clinical photography, Melasma Area and Severity Index (MASI), skin lightness, quality of life, and tolerability. Baseline demographics and hyperpigmentation were well balanced across all treatment groups. Clinical photography and MASI improved significantly with Thiamidol versus baseline ($p < 0.001$) and vehicle ($p < 0.001$-0.043) at all time points up to treatment end. At follow-up, MASI was still significantly lower than at baseline but similar for treatment and vehicle groups. Skin lightness and quality of life improved significantly versus baseline without significant differences between treatment and vehicle groups. This study demonstrated that Thiamidol is well tolerated and superior in improving melasma compared to baseline and vehicle over a treatment period of 24 weeks.

Materials and Methods

Clinical Study Design

This randomized, vehicle-controlled, double-blind clinical trial was conducted in a study center in Mauritius (CIDP Ltée, Biopark, Socota Phoenicia, Phoenix, Mauritius). In the 24-week treatment phase, the subjects returned every 4 weeks for assessments and between 13 and 20 weeks after treatment discontinuation for a 1-day regression phase visit. The study was conducted following the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines as applicable to cosmetic products. All subjects provided written informed consent before inclusion. Subject anonymity in the study documentation was maintained by pseudonymization.

Study Population and Treatment

Healthy, female subjects, aged 18-65 years, with Fitzpatrick skin phototypes III-V, demonstrating moderate-to-severe (30-50% severe) melasma according to Melasma Area and Severity Index (MASI) score (MASI score 10-20 as moderate and >20 as severe melasma), willing and capable to follow the study rules including avoidance of sun exposure for the duration of the study, and undergoing stable dose hormonal treatment/contraception for at least 6 months before study onset were eligible for the trial.

For 24 weeks, the subjects allocated to the Thiamidol group applied twice daily (morning and evening) on their face a Thiamidol-based serum, followed by a Day Care cream containing Thiamidol and SPF 30 in the morning, and a Night Care cream with Thiamidol in the evening. The vehicle group applied the same skin care routine using the Thiamidol-free vehicle formulations. The vehicle formulations did not contain other substances that could improve melasma. In the washout period of approximately 3 days before baseline and during the entire study, the subjects were not allowed to use any skin care product on the face (including care-providing cleansers, soaps, or shower oils) other than the products provided by the sponsor. The first application of the study products was performed at baseline in the study center under supervision by trained personnel. During the 24 hours preceding each scheduled measurement, subjects had to refrain from intensive sports and visits to saunas and swimming pools. No sunscreen was allowed in the washout period and subjects had to refrain from ultraviolet exposure.

Assessments

The primary outcome of the study was the evaluation of the hyperpigmentation-reducing effect of the test products through MASI score at each of the eight visits (baseline, Weeks 4, 8, 12, 16, 20, and 24, and regression), and through skin pigmentation (individual typology angle [ITA°] measurements with Chromameter® Minolta CR400) and digital standardized clinical photography with Facial Imaging System VISIA CR and the lighting modes standard 2 and cross-polarized (Canfield Imaging Systems) at all visits except the regression visit. In addition, subjects completed a quality-of-life questionnaire at baseline, Week 12, and Week 24 with 10 questions on a 7-point scale (1 = no discomfort, 7 = always discomfort). Before any measurements, the subjects acclimatized under controlled room conditions (24 ± 2°C, 40-60% relative humidity) for 30 minutes.

The secondary outcome was the skin tolerability as assessed by the subjects and the investigator (baseline, Weeks 12 and 24).Treatment adherence was controlled by weighing the products at each of the visits (1-7).

Statistical Analysis

Statistical analyses of efficacy variables were based on the full analysis set (FAS) consisting of all randomized subjects having completed the study without any major protocol deviation. Tolerability analyses were based on the tolerability set (TAS), which included all subjects who applied the products at least once. Quantitative variables, or those that can reasonably be treated as such, were summarized using the mean, minimum, maximum, standard deviation, and variation coefficient. Qualitative variables were summarized using counts and percentages. Data normality for each comparison was tested using a Shapiro-Wilk test at 5% significance. The null hypothesis (rejected for $p \leq .05$) was that there is no difference between the treatment groups or the time points compared. For instrumental measurements, the significance of the difference between two groups at baseline was investigated using the independent samples t-test, and the evolution across time was investigated with Student's paired t-test.

Results

TABLE 1. Demographics and Baseline Characteristics of the Randomized Subjects.

Characteristic	Group A (vehicle) (n = 26)	Group B (Thiamidol) (n = 25)
Age, years	54 (1)	52 (1)
Phototype, n		
III	1	1
IV	18	16
V	7	8
Race, n		
Caucasian	1	–
Mixed race	17	19
Indian	8	8
Skin type, n		
Normal	16	16
Combination	5	2
Dry	1	2
Very dry	–	1
Oily	4	4
Melasma severity, *n* (%)		
Moderate (MASI score 10–20)	19 (73)	18 (72)
Severe (MASI score > 20)	7 (27)	7 (28)
Melasma duration before study start, years	8.2 (4.7)	9.8 (6.7)

Abbreviation: MASI, Melasma Area and Severity Index.
[a]Data are presented as mean (standard deviation) unless otherwise stated.

FIGURE 1. Representative Clinical Photography of Subjects. Images of two subjects at baseline and after 24 weeks of treatment with either the Thiamidol-containing skin regimen or the corresponding vehicles.

FIGURE 2. Changes of Melasma Area and Severity Index (MASI) Score. MASI score (mean ± standard error of the mean) versus baseline at every time point measured after treatment with Thiamidol-containing regimen or vehicle. Significant improvement in comparison to baseline for Thiamidol-treated group and vehicles at all points in time. Significant differences between Thiamidol treated group and vehicle as indicated (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). After 13-20 weeks of cessation of all treatment (regression), including sunscreen use, there was a significant difference for both treatments compared to baseline ($p < 0.005$).

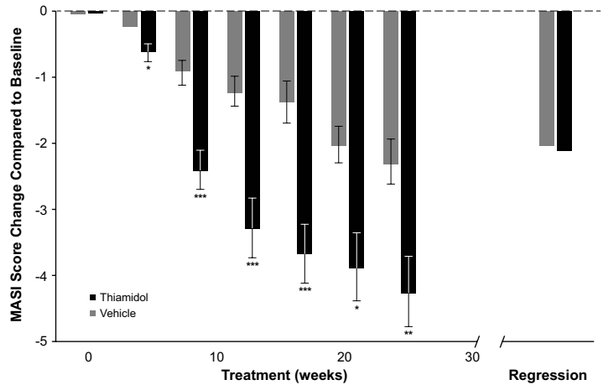


FIGURE 3. Significant Improvement in Skin Lightness in Thiamidol Treated Subjects. Significant improvement of skin lightness (individual typology angle, ITA°) of hyperpigmented spots and normal skin in Thiamidol (●) and vehicle (●) treated subjects in comparison to baseline.

Significant improvement as marked: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Between-group comparisons were not significant.

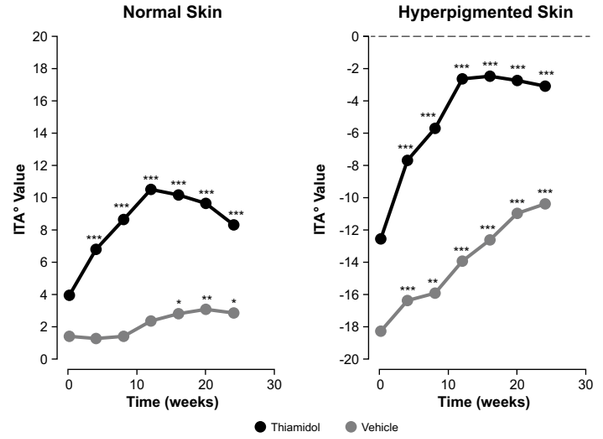
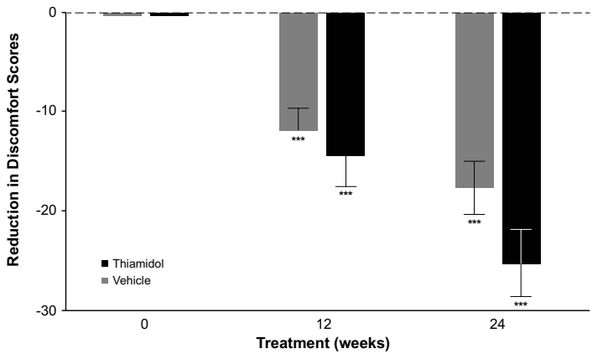


FIGURE 4. Significant Improvement in Quality of Life in Thiamidol Treated Subjects. Significant improvement (***$p < 0.001$) in quality of life in Thiamidol and vehicle treated subjects in comparison to baseline (mean difference ± standard error of the mean). The difference between the two groups was not significant.



Summary and Conclusions

- This was the first reported randomized, double-blind, controlled clinical study to evaluate the efficacy and tolerability of a Thiamidol-based skin care regimen for 24 weeks compared to vehicle control in subjects (Fitzpatrick skin types III-V) with moderate-to-severe melasma
- Significant improvement in MASI score and clinical photography compared to baseline was observed for both treatment groups, with significantly superior improvement over the 24-week period for the Thiamidol-containing regimen group
- This single-center, randomized, double-blind, vehicle-controlled, parallel-group study demonstrated that Thiamidol, applied as a three-product skin care regimen, is well tolerated, and reduced significantly long-lasting, moderate-to-severe melasma
- These findings suggest that Thiamidol is safe for at least 24 weeks of use and should be considered as a part of an overall regimen for the treatment of hyperpigmentation associated with moderate-to-severe melasma

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