Research letter

A novel proof-of-concept study assessing the lightening effects and safety of malassezin for treatment of facial hyperpigmentation

To the Editor: Disorders of hyperpigmentation are often disfiguring and can have a profoundly negative impact on one's quality of life. Therefore, there remains an unmet need for new, efficacious, and safe topical treatments.

Tinea versicolor is a quintessential skin disorder caused by *Malassezia furfur* and other *Malassezia* species. Malassezin is a natural indole compound produced by *M furfur*, reported to induce melanocyte apoptosis, dose-dependent induction of apoptotic markers, and decreased melanin synthesis in melanocyte cultures.[1,2] Our preliminary in vitro, ex vivo, and in vivo investigations have documented the ability of malassezin to suppress melanogenesis and decrease skin pigmentation.[3] Hence, the primary objective of this seminal and first proof-of-concept, double-blind, dose-ranging study was to investigate the efficacy and safety of malassezin for mild, moderate, and severe facial hyperpigmentation secondary to photodamage or melasma.

This study enrolled 20 subjects (14 on active drug and 6 on placebo) who underwent treatment for 14 weeks with an additional 8-week observation period. The patient characteristics and key inclusion and exclusion criteria are presented in Table I. The subjects were randomized in a 1:1:1:1 ratio into 4 groups: 3 groups received 1 mL of topical natural malassezin in an oil-in-water emulsion applied twice daily to the full face (0.1% [increased to 1% after 10 weeks], 0.5%, and 1%, each), and the fourth group received 1 mL of a placebo applied twice daily to the full face. Morning application was followed by the application of a sheer zinc sunscreen with a sun protection factor of 50. The primary endpoint was a lightening effect of the malassezin treatment compared with that of the placebo at week 14. The secondary endpoints included global improvement in overall facial skin, change in pigment severity, and changes in the melasma severity index score for subjects with melasma. This hypothesis-generating study was not powered to achieve statistically significant outcomes. However, according to the analysis plan, the dosage groups could be combined and compared with the placebo group if there were no significant between-dose differences. Therefore, the groups were combined for the overall analysis.

The primary endpoint was achieved with significantly increased lightening with malassezin (0.1%, 0.5%, and 1% combined) compared with that with the placebo at week 14 (2.85 vs 1.40, respectively, $P = .0007$), with significance evident by week 4 (2.31 vs 0.33, respectively, $P = .0001$) (Table II and Supplementary Figs 1 and 2, available via Mendeley at https://doi.org/10.17632/n65436ctw7.4). All the subjects maintained the lightening effects during the 8-week observation period, and none of the subjects experienced relapse.

Table I. Baseline patient demographics and clinical characteristics*

Characteristics	Malassezin (n = 14)	Placebo (n = 6)
Female sex, n (%)	13 (92.9)	6 (100)
Mean age, (range), y	51.8 (30-65)	49.8 (34-56)
Skin type, n (%)		
Fitzpatrick skin type 3	6 (46.2)	2 (33.3)
Fitzpatrick skin type 4	4 (30.8)	1 (16.7)
Fitzpatrick skin type 5	3 (23.1)	3 (50.0)
Diagnosis, n (%)		
Melasma	7 (50.0)	3 (50.0)
Photodamage	7 (50.0)	3 (50.0)
Severity, n (%)		
Mild	2 (14.3)	3 (50.0)
Moderate	10 (71.4)	2 (33.3)
Severe	2 (14.3)	1 (16.7)

*The patients were aged 30-65 years, in good general health, had Fitzpatrick skin types 2-5, with mild, moderate, or severe facial hyperpigmentation due to melasma or photodamage. Subjects using any brightener, lightener, hydroquinone, retinoid, glycolic acid, or agents that impact pigmentation for at least 6 weeks prior to study enrollment were excluded. Subjects with Fitzpatrick skin types 1 and 6 and pregnant women were also excluded.

Trends consistent with significant lightening and improvement were observed with all the other secondary endpoints (Table II), including melasma severity index score (Supplementary Table I, available via Mendeley at https://doi.org/10.17632/n65436ctw7.4). Adverse events were minimal, with mild erythema in 14.7% and dryness or scaling in 8.4% of the subjects.

Malassezin is a highly active agonist of the aryl hydrocarbon receptor with key homeostasis functions that may impact the mechanism of pigmentation reduction,[4] as shown by in vitro testing demonstrating that malassezin is not a tyrosinase inhibitor. The major strength of this investigation is the early onset of lightening visible at weeks 2 and 4 and the maintenance of improvement for 8 weeks after treatment, an outcome that has been rarely reported in other clinical trials.[5] A limitation of this study is the small sample size. These results support the need for larger randomized clinical trials.

Table II. Primary and secondary efficacy outcomes

Outcomes	Malassezin (n = 14) Mean (SEM)	Placebo (n = 6) Mean (SEM)	*P* value
Lightening effect			
Week 2	0.43 (0.17)	0.17 (0.17)	.3748
Week 4	2.31 (0.17)	0.33 (0.21)	.0001
Week 8	2.77 (0.17)	1.20 (0.49)	.0011
Week 14	2.85 (0.15)	1.40 (0.40)	.0007
Week 18	2.92 (0.18)	1.60 (0.25)	.0009
Week 22	2.92 (0.18)	1.80 (0.20)	.0026
Global improvement			
Week 2	0.50 (0.20)	0.17 (0.17)	.3287
Week 4	2.39 (0.14)	0.33 (0.21)	.0001
Week 8	2.77 (0.17)	1.20 (0.49)	.0011
Week 14	2.92 (0.14)	1.40 (0.40)	.0003
Severity, percent change from baseline			
Week 2	-1.79 (6.682)	0.00 (0.00)	.5274
Week 4	-25.00 (18.63)	-4.17 (10.206)	.0211
Week 8	-30.13 (15.04)	-16.67 (23.57)	.1646
Week 14	-26.92 (21.02)	-21.67 (21.73)	.6438

SEM, Standard error of the mean.

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Conflicts of interest

Dr Grimes is a consultant, investigator, and shareholder of Versicolor Technologies LLC and a consultant and investigator for Incyte, L'Oreal, Arcutis, and Sun Pharmaceutical. Dr Bhawan is an investigator for Versicolor Technologies LLC. Dr Howell is an employee and stockholder at DermTech and a consultant advisor and stockholder of Versicolor Technologies LLC. Dr Desai is a consultant for Versicolor Technologies LLC and a consultant and investigator for Pfizer, L'Oréal, Lilly, LEO Pharma, and Galderma. Dr Coryell is a consultant and stockholder for Versicolor Technologies LLC and an employee at Skin Science Advisors LLC. Authors Einziger and Simpson are founders and stockholders and own intellectual property rights in Versicolor Technologies LLC. Dr Yaroshinsky is a consultant for Versicolor Technologies LLC. Dr Mc Craw is a consultant, investigator, and stockholder of Versicolor Technologies LLC and is the founder of Skin Science Advisors LLC. Author Nashawati has no conflicts of interest to declare.

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