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Original Article

Efficacy and safety of cysteamine-isobionicamide complex in postinflammatory hyperpigmentation: A 16-week, randomized, double-blinded, vehicle-controlled trial

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Abstract

Background: Postinflammatory hyperpigmentation (PIH) is a prevalent acquired hyperpigmentation disorder with significant psychosocial implications. Cysteamine has demonstrated notable efficacy and safety in treating hyperpigmentation disorders. This study conducted a double-blinded, randomized clinical trial to evaluate the efficacy and safety of the cysteamine-isobionicamide complex in managing PIH. **Objectives:** The objective was to assess the cysteamine-isobionicamide complex's efficacy for PIH treatment through comprehensive clinical and imaging evaluations. **Methods:** Forty patients with PIH were recruited at a tertiary medical center from 2021 to 2022 and randomized into the cysteamine-isobionicamide complex treatment group and placebo-vehicle control group. Dermatological assessments, investigator and patient global assessments, and quality of life scores were collected at baseline, week 4, week 8, and week 16. Quantitative evaluation of skin type and lesion pigmentation was performed with the Mexameter®, VISIA skin analyzer, and cellular resolution optical coherence tomography (OCT). **Results:** At week 8, the cysteamine-isobionicamide complex treatment group exhibited marked advancement in dermatological assessments, melasma area and severity index (MASI), total postacne hyperpigmentation index, and life quality score compared with the placebo-vehicle control group. Furthermore, melanin index and erythema index scores from Mexameter® and VISIA analysis exhibited significant improvement for brown spots at week 16. Cellular resolution OCT imaging revealed decreased melanosome capping and fewer hyperreflective melanophages. **Conclusion:** This study demonstrated the clinical effectiveness and safety of the cysteamine-isobionicamide complex through comprehensive dermatological assessments, imaging techniques, and patient-reported outcomes. The complex emerges as a promising therapeutic option for PIH, offering potential relief to individuals affected by this hyperpigmentation disorder.

Key words: Cysteamine, isobionicamide, optical coherence tomography, postinflammatory hyperpigmentation
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Introduction

Postinflammatory hyperpigmentation (PIH) is defined as an acquired, reactive hypermelanosis in response to cutaneous

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inflammation.[1-3] The enhanced synthesis and deposition of melanin in skin cells lead to an uneven distribution of dark and flattened spots on the body. PIH can be detrimental to one's self-confidence and can have a negative impact on the quality of life (QoL) and social/emotional functioning.[4] Common endogenous causes of PIH include acne vulgaris, psoriasis, lichen planus, and atopic dermatitis. Excessive exposure to ultraviolet lights, inappropriate laser procedures, chemical peels, and nonionizing radiation are classified as exogenous stimuli.[1-3,5] Although there is no significant difference in the incidence of PIH among age and gender, it is well established that PIH affects skin-of-color patients with higher frequency and severity (Fitzpatrick skin types IV through VI).[2,6-8]

The pathogenesis of PIH is complicated.[3] A variety of inflammatory mediators, such as prostaglandins, numerous cytokines, and reactive oxygen species (ROS), are involved in triggering melanocyte activity and transferring pigment to surrounding keratinocytes.[3,9,10] For instance, the literature demonstrates that leukotrienes C4 and D4, prostaglandins E2 and D2, thromboxane-2, interleukin (IL)-1, IL-6, tumor necrosis factor-α, and epidermal growth factor exert melanocyte-stimulating properties.[3,8-12] Moreover, injury to basal keratinocytes causes release of melanin into the dermis, which in turn, is phagocytosed by melanophages, leading to further dermal deposition of pigmentation.[10,13,14]

Management of PIH primarily involves impeding deterioration by photoprotection in conjunction with the use of agents to disperse melanin builtup in the skin.[3,15] Among current topical depigmenting agents, the preferred first-line treatment is hydroquinone or a triple combination cream containing 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide, which is also known as modified Kligman's formula (mKF).[3,16-19] Hydroquinone acts as a melanocytotoxic agent after being metabolized by the enzymes tyrosinase and peroxidase within melanocytes, causing the destruction of hyperactive melanocytes.[20] However, hydroquinone is also known to cause contact dermatitis and paradoxical darkening of the skin, especially in long-term or excessive use.[3] Other possible adverse events include nail discoloration, transient halo hypochromia, and abnormal skin repigmentation. The side effect profile of hydroquinone raises many potential concerns in its long-term application.[3,16,17]

Cysteamine is a small aminothiol metabolite derivatized during coenzyme A degradation in mammals.[19,21-23] It possesses prominent antioxidant properties by suppressing ROS generation and enhancing intracellular glutathione.[24-28] The application of cysteamine has been proven to be safe, well tolerated, and effective in treating hyperpigmentation disorders including melasma and lentigines.[29-32] Numerous studies have demonstrated the efficacy of topical cysteamine in melasma to be comparable to triple combination cream and intradermal tranexamic acid injections.[19,21,22] A recently introduced novel compound, isobionicamide, derived from the pyridine family of molecules, acts as a melanosomal transfer inhibitor. Isobionicamide is theorized to act in synergy with cysteamine to inhibit multiple melanogenesis pathways and impede epidermal pigmentation (personal communication with Dr. B. Kasraee). A proprietary product comprised mainly of the cysteamine isobionicamide complex has recently been released. The efficacy and safety of this novel topical agent, however, have not been investigated in patients with PIH. We conducted a double-blinded, randomized, and placebo-vehicle controlled clinical trial to investigate the effectiveness of this product in treating PIH.

Materials and Methods

Trial design and recruitment

This double-blinded, randomized, placebo-vehicle controlled clinical trial evaluated the efficacy and safety of treatment with cysteamine isobionicamide complex in patients with PIH. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by our institutional ethical committee (Ethics Committee of Chang Gung Memorial Hospital, IRB no: 202101456A3). The IRB approves the waiver of the participants' consent.

Patients presenting to our dermatology clinic, based at an academic tertiary care institution, with the chief complaint of PIH were screened, and eligible participants were recruited. Patients who were over 20 years old in age and had experienced more than 12 weeks of acquired hyperpigmentation following acne or laser therapy were eligible for enrollment. The exclusion criteria were as follows: (a) patients with ongoing inflammatory symptoms, and/or under anti-inflammatory medications, (b) pregnant patients, (c) patients undergoing hormone therapy and/or oral contraceptives, (d) patients presenting with dermal hyperpigmentation without epidermal involvement, and (e) patients with a known history of allergic reactions to the product. A total roster of 40 patients with PIH were recruited between September 2021 and September 2022. Recruited subjects were required to cease the use of topical hydroquinone, oral tranexamic acid, and/or other skin whitening agents at least 8 weeks before participation.

Patients were randomized using computer-generated random numbers with a 1:1 random allocation ratio. Both participants and researchers were blinded to avoid bias. Patients were allocated to one of two groups: the treatment arm (cysteamine-isobionicamide-complex, $n = 20$) and the placebo vehicle-controlled arm ($n = 20$). The study design of the trial is outlined in Supplement Figure 1.

Outcome and measures

To quantify the severity of target lesions, a multimodality subjective scoring system was adopted, which included (a) overall disease severity assessment: scale 1–8 (1 normal and 8 severe); (b) pigmentation intensity score: scale 1–5 (1 normal and 5 severe); (c) involved area of hyperpigmented lesion: scale 0–5 (0; 1 [1%–10%]; 2 [11%–25%]; 3 [26%–40%]; 4 [41%–50%]; and 5 [>50%]); (d) investigator global assessment score: scale 0–5 (0; 1 [1%–10%]; 2 [11%–25%]; 3 [26%–40%]; 4 [41%–50%]; and 5 [>50%]), and (e) patient

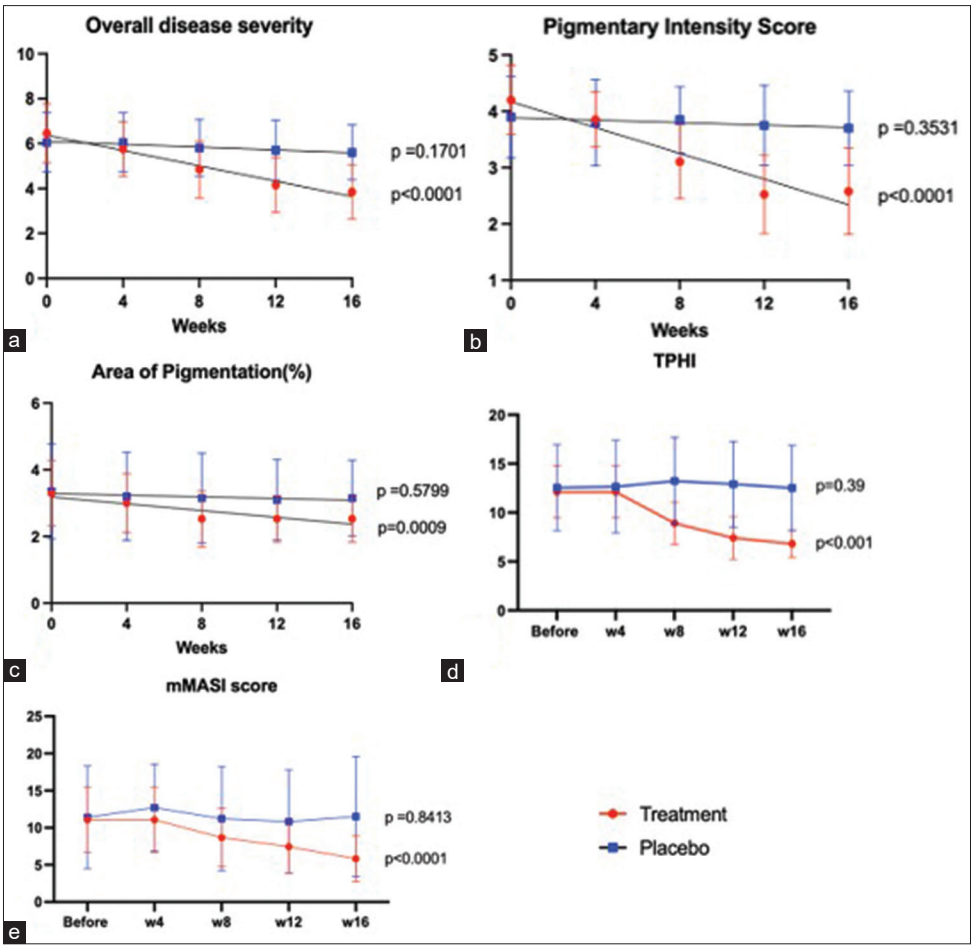

Figure 1: Subjective evaluation results of cysteamine-isobionicamide complex in patients with postinflammatory hyperpigmentation. (a) Overall disease severity, (b) pigmentary intensity score, (c) area of pigmentation (%) (d) Total postacne hyperpigmentation index, (e) modified MASI score. TPHI: Hyperpigmentation index, mMASI: Modified MASI.

global assessment score: scale 0–5 (0; 1 [1%–10%]; 2 [11%–25%]; 3 [26%–40%]; 4 [41%–50%]; and 5 [>50%]). The Melasma Area and Severity Index (MASI) score was used for the evaluation of postlaser hyperpigmentation lesions, whereas the total postacne hyperpigmentation index (TPHI) score was used to evaluate those experiencing hyperpigmentation after acne inflammation. Patients were also asked to fill in a self-assessment and QoL questionnaires.

For objective evaluation, we used the Mexameter® (Courage + Khazaka electronic GmbH, Köln, Germany) to analyze the melanin index and erythema index of lesional and nonlesional skin. Digital high-resolution images were obtained at every clinic visit with the VISIA skin analyzer (Canfield Scientific, New Jersey, USA). A cellular resolution optical coherence tomography (OCT) (Apollo Medical Optics, Taipei, Taiwan) was also utilized to evaluate the melanin content of select patients in both groups at baseline and week 16 of treatment.

Intervention (topical agent application)

Patients were allocated to two different groups based on the randomization plan. The treatment arm was provided with a three-product system (Cyspera® Intensive system) involving three different products which are used sequentially. To ensure integrity of the blinding process, both the treatment and placebo vehicle-control arms received three products with equivalent labeling and secondary packaging. The three-product system consisted of (1) a short-contact product, (2) a rinse-off cleanser, and (3) a leave-on product. In the treatment arm, the short-contact product (Cyspera® Intensive™) contained the cysteamine isobionicamide complex and alpha (AHA); the rinse-off cleanser (Cyspera® Neutralize™) contained AHA and L-Arginine complex; and the leave-on product (Cyspera® Boost™) contained isobionicamide complex and retinol. All three products in the placebo vehicle-control arm were devoid of any active ingredients, including cysteamine, isobionicamide, AHA, and retinol.

Participants were instructed to apply a thin layer of the first short-contact product on the entire face once per day in the morning and leave for 15 min of exposure. They were then instructed to rinse thoroughly with water and cleanse with the second rinse-off cleanser. The last step was application of a thin layer of the third leave-on product on the whole face. All patients were advised to apply broad-spectrum sunscreen and avoid prolonged sun exposure during the treatment period.

Statistical analysis

The randomization process was performed through a random number generator by GraphPad Prism 9 (Graph Pad Software, California, USA). Continuous variables are expressed as the mean (± standard deviation) or median (quartiles) and as count (percentage) for discrete variables. Paired *t*-test was used to compare the two groups, and Wilcoxon test was performed to compare each visit with the baseline. The Chi-square test was utilized for the investigator and patient global assessment analysis. All statistical analysis was performed with GraphPad Prism 9 software. $P < 0.05$ was considered statistically significant.

Results

Demographics and baseline characteristics

Forty patients with acquired PIH were enrolled and randomized into the treatment group or control group. The mean age was 41.3 ± 9.77 years in the treatment group and 39.8 ± 10.34 in the control group. Most recruited subjects were female (treatment group male/female = 2/18 and control group male/female = 3/17). All patients were of Asian ethnicity with Fitzpatrick skin types III and IV. The mean duration of PIH before treatment based on the patients' description was 9.95 ± 3.1 weeks in the treatment group and 10.05 ± 3.27 weeks in the placebo group ($P = 0.92$). Overall impact of PIH on patients' QoL before treatment was high in both groups (Dermatology life Quality Index [DLQI] score, treatment group: 6.53 ± 3.63 and control group: 6.1 ± 3.24, $P = 0.72$). No statistical difference regarding pigmentary intensity and area of hyperpigmented lesions was seen between the two groups at baseline. Demographic data, clinical characteristics, and baseline hyperpigmentation severity are summarized in Table 1.

Efficacy

During the 16-week trial, the investigator global assessment of both groups was recorded and is shown in Figure 1. Subjective evaluation scores including overall disease severity, pigmentary intensity score, and area of hyperpigmented lesions significantly improved in the treatment group compared to the control group ($P < 0.05$). The treatment group had a 26% reduction at week 8 and a 43% reduction at week 16 in TPHI score from baseline. Notable improvement in MASI score was also seen in the treatment group, with 21.5% reduction at week 8% and 47.3% reduction at week 16 from baseline. Both TPHI and MASI score improvement in the treatment group reached statistical significance when compared with the control group.

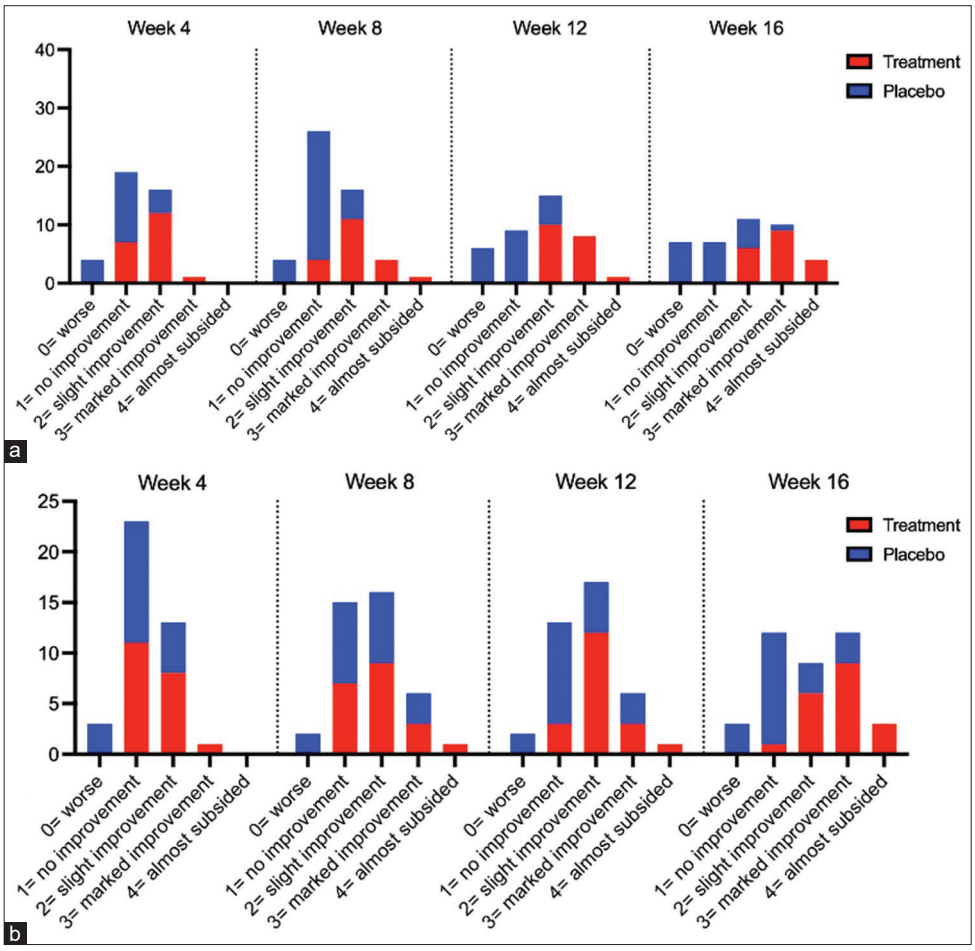

Figure 2: (a) Investigator global assessment. A significant improvement in postinflammatory hyperpigmentation was found for week 4 of treatment (week 4, $P < 0.05$, week 8, $P < 0.001$). (b) Patient Global Assessment. A significant improvement in postinflammatory hyperpigmentation was found for week 12 of treatment (week 12, $P < 0.05$, week 8, $P < 0.001$).

Both investigator and patients completed global assessment questionnaires during each visit to evaluate the improvement of PIH after treatment [Table 2 and Figure 2]. At week 16, 21% ($n = 4/19$) of patients in the treatment group were scored by the investigator as almost resolved, 47% ($n = 9/19$) as marked improvement, and 32% ($n = 6/19$) as slight improvement, and no one ($n = 0/19$) as no improvement [Table 2]. In the control group, 5% ($n = 1/20$) of patients were scored as marked improvement; 25% ($n = 5/20$) as slight improvement, 35% ($n = 7/20$) as no improvement, and 35% ($n = 7/20$) as worse [Table 2]. These results were comparable in both investigator and patient assessment, showing an interobserver agreement with kappa coefficient of moderate-to-high consistency (Investigator global assessment = 0.82, Patient global assessment = 0.69, $P < 0.0001$). Moreover, the DLQI score of the treatment group also decreased significantly compared with the control group during the experiment (treatment group: baseline: 6.5 ± 3.63, week 16: 2.157 ± 2.19 and control group: baseline: 6.1 ± 3.24, week 16: 6.55 ± 3.3, $P < 0.001$).

Table 1: Clinical characteristics and demographics of the study population

	Treatment	Placebo	*P*
Age, mean±SD	41.3±9.77	39.8±10.34	0.54
Gender (male/female)	2/18	3/17	
Skin phototypes (III/IV)	8/12	9/11	
Duration of PIH (weeks), mean±SD	9.95±3.1	10.05±3.27	0.92
Life quality (DLQI), mean±SD	6.53±3.63	6.1±3.24	0.72
Overall disease severity, mean±SD	6.45±1.31	6.05±1.32	0.34
Pigmentary intensity of hyperpigmented lesions, mean±SD	4.2±0.61	3.9±0.72	0.16
Area of hyperpigmented lesions, mean±SD	3.9±0.97	3.2±1.39	0.79

SD: Standard deviation, DLQI: Dermatology life quality index, PIH: Postinflammatory hyperpigmentation

Aside from subjective evaluations, quantitative measurements also demonstrated significant improvement in the treatment group. The melanin index of the treatment group showed significant decrease at weeks 8 and 16 compared with the control group [$P < 0.001$, Figure 3]. Erythema index showed improvement in both treatment and control groups [Figure 3]. Cellular resolution OCT skin imaging was obtained in five patients in both groups: only subjects in the treatment group revealed a significant reduction in hyperreflective melanophages and decreased melanosome capping in the dermal–epidermal junction compared with normal skin after 16 weeks of treatment [Figure 4]. Clinical photographs of patients exhibiting hyperpigmentation resulting from both acne and laser interventions were captured before and following cysteamine-isobionicamide complex treatment, which also revealed visible improvements [Figure 5].

Tolerability

Only mild adverse events, without resulting in discontinuation, were noted after treatment and are shown in Table 3. There were no significant differences in both groups concerning paresthesia, malodor, and skin peeling after application of the products

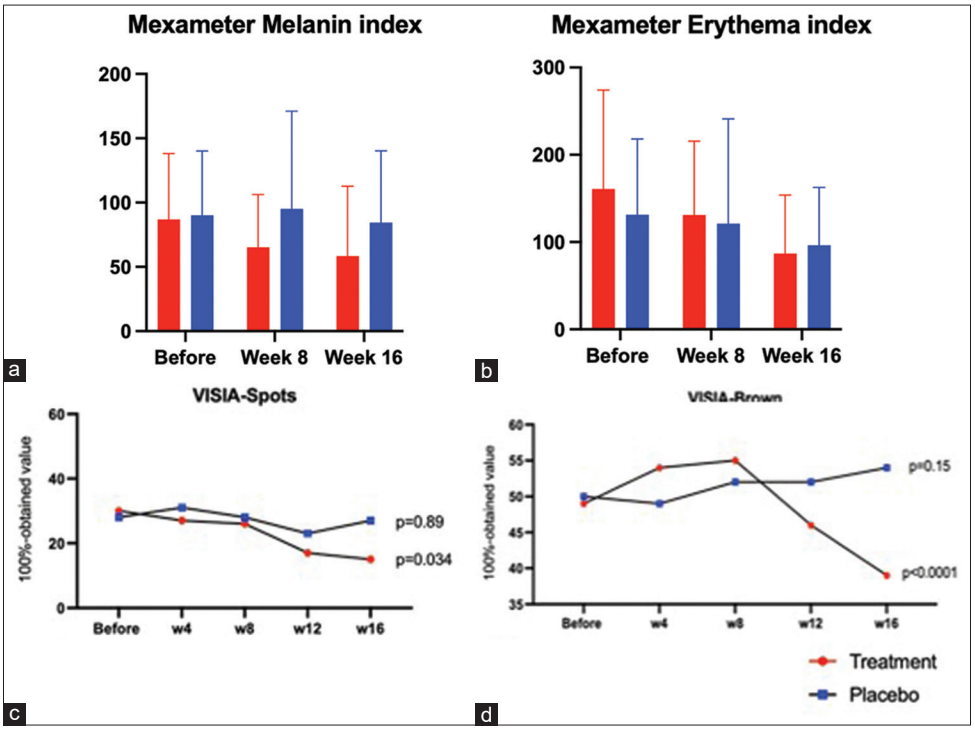

Figure 3: Mexameter® and skin imaging analysis (VISIA skin analyzer) for the efficacy of cysteamine-isobionicamide complex in patients with postinflammatory hyperpigmentation (a) Mexameter melanin index; (b) Mexameter erythema index; (c) VISIA skin analysis – surface spots absolute scores; (d) VISIA skin analysis – brown spots absolute scores.

Table 2: Investigator global assessment and patient global assessment

	Week 4			Week 8			Week 12			Week 16		
	Treatment	Placebo	*P*	Treatment	Placebo	*P*	Treatment	Placebo	*P*	Treatment	Placebo	*P*
IGA, percentage (*n*)												
0=Worse	-	20 (4/20)	0.0014	-	20 (4/20)	<0.0001	-	30 (6/20)	<0.0001	-	35 (7/20)	<0.0001
1=No improvement	35 (7/20)	60 (12/20)		20 (4/20)	55 (22/20)		-	45 (9/20)		-	35 (7/20)	
2=Slight improvement	60 (12/20)	20 (4/20)		55 (11/20)	25 (5/20)		53 (10/19)	25 (5/20)		32 (6/19)	25 (5/20)	
3=Marked improvement	5 (1/20)	-		20 (4/20)	-		42 (8/19)	-		47 (9/19)	5 (1/20)	
4=Almost subsided	-	-		5 (1/20)	-		5 (1/19)	-		21 (4/19)	-	
PGA, percentage (*n*)												
0=Worse	-	15 (3/20)	0.0482	-	10 (2/20)	0.201	-	10 (2/20)	0.018	-	15 (3/20)	<0.0001
1=No improvement	55 (11/20)	60 (12/20)		35 (7/20)	40 (8/20)		16 (3/19)	50 (10/20)		5 (1/19)	55 (11/20)	
2=Slight improvement	40 (8/20)	25 (5/20)		45 (9/20)	35 (7/20)		63 (12/19)	25 (5/20)		32 (6/19)	15 (3/20)	
3=Marked improvement	5 (1/20)	-		15 (3/20)	15 (3/20)		16 (3/19)	15 (3/20)		47 (9/19)	15 (3/20)	
4=Almost subsided	-	-		5 (1/20)	-		5 (1/19)	-		16 (3/19)	-	

Treatment group, one patient lost to follow-up week 12 (allergic reaction). IGA: Investigator global assessment, PGA: Patient global assessment

or placebo. One patient in the treatment group and six in the control groups experienced acne eruption; three patients in the treatment group suffered allergic dermatitis after application.

Discussion

PIH is a common issue in individuals with skin of color, and the disease course is often refractory.[33] mKF (4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide) has been the treatment of choice for PIH since the 1970s.[19] However, various long-term side effects limit its clinical use for long-term maintenance of hyperpigmentation disorders. One of the main components, hydroquinone, the most widely used depigmenting topical agent, can cause a plethora of adverse reactions including skin irritation, exogenous ochronosis, and unwanted melanocytotoxic or mutagenic effects.[19,21,34] Topical retinoic acid has a side effect profile of inducing skin peeling, erythema, and xerosis. Prolonged exposure to corticosteroids contained in mKF may also inevitably result in skin atrophy. Hence, the recommended application of mKF in PIH is limited to 8 weeks. Therefore, there has always been a demand to development a safer, more effective, durable regimen as an alternative treatment option for hyperpigmentation disorders. The efficacy of cysteamine used in the treatment of epidermal melasma has been confirmed in multiple randomized, double-blind, controlled clinical trials.[21,23,35-37] We present the first trial to study the efficacy and safety of a novel topical agent, cysteamine-isobionicamide complex, in PIH.

Cysteamine is a natural aminothiol metabolite with an excellent safety profile. Its oral form has been established in the use of treating the inherited metabolic disease cystinosis, and very few side effects have been reported.[38,39] In its stabilized topical form, cysteamine has shown promising results in tackling various hyperpigmentation disorders including melasma and lentigines. Pathways behind the potent antipigmentation properties of cysteamine include inhibiting tyrosinase and peroxidase formation, increasing glutathione, an intracellular antioxidant, removing the pigment precursor, dopaquinone, and regulating the chelation of iron and copper involved in melanin synthesis pathways.[20,40-42] In addition, isobionicamide, which is an isoform of niacinamide (Vitamin B3), has shown to exert higher activity than niacinamide in inhibiting melanosomal transfer in early *in vitro* models (personal communication Dr. R. Sfriso, unpublished data). A compound product of cysteamine and isobionicamide (Cyspera® Intensive™) has

Table 3: Adverse skin reactions in the study population

	Percentage (*n*)	
	Treatment group (*n*=20)	Control group (*n*=20)
Paresthesia	10 (2/20)	10 (2/20)
Malodor	15 (3/20)	5 (1/20)
Peeling skin	10 (2/20)	5 (1/20)
Acne eruption	5 (1/20)	30 (6/20)
Dermatitis	15 (3/20)	0 (0/20)

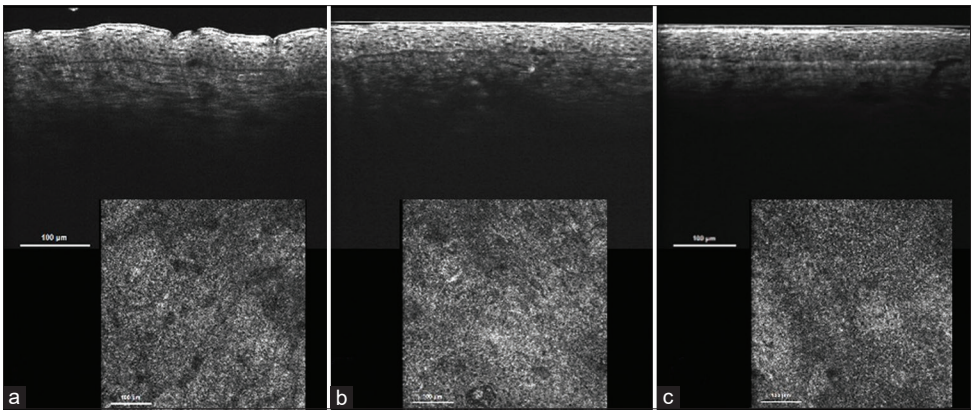

Figure 4: Dynamic evaluation of postinflammatory hyperpigmentation lesions with optical coherence tomography. Significant reduction in hyperreflective melanophages and decreased melanosome capping in the dermal–epidermal junction compared with normal skin. (a) Normal skin, (b) Postinflammatory hyperpigmentation-before treatment (c) Postinflammatory hyperpigmentation-after treatment (week 16).

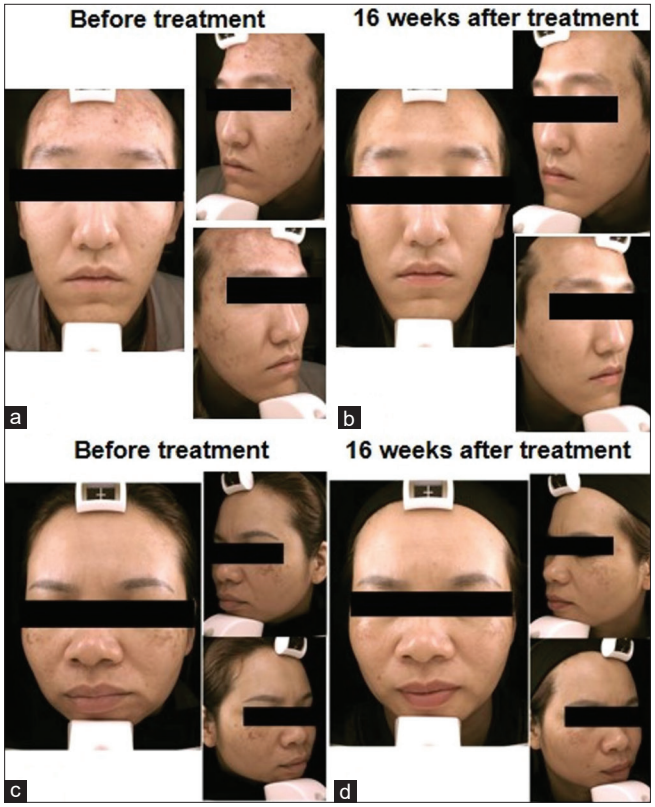

Figure 5: Clinical images prior to cysteamine-isobionicamide complex treatment and after treatment. A 20 year-old male with postacne hyperpigmentation for 1 year (a) before treatment and (b) 16 weeks after treatment; a 40-year-old female with postlaser hyperpigmentation for 6 months (c) before treatment and (d) 16 weeks after treatment.

recently been introduced in a three-part product system and is the main focus of this study. After the administration of cysteamine-isobionicamide complex treatment, there was a subtle increase in the incidence of hypersensitivity-like adverse events when compared to the carefully controlled group. This observation prompted an extensive examination of prior research to delve deeper into the identification of potential causal factors, with similar phenomena having been reported in the existing literature. It is hypothesized that the active ingredient, cysteamine, might be responsible for peeling skin and dermatitis.[19,21,23,43] Furthermore, the presence of malodor associated with cysteamine is likely due to its metabolic conversion into dimethyl sulfide, a well-known malodorous compound.[23,44,45] Future research and product development endeavors will be focused on optimizing formulation, concentrations, and application protocols to minimize adverse events while simultaneously preserving therapeutic efficacy and enhancing product stability.

Conclusion

In this study, we found that the cysteamine-isobionicamide complex is effective for treating PIH, specifically postlaser and postacne hyperpigmentation. Improvement of MASI score, TPHI score, and subjective evaluations was noted after 8 weeks into treatment. Global assessment scores evaluated by both patients and investigators confirmed the effectiveness of cysteamine-isobionicamide complex versus the placebo control. Furthermore, quantitative evaluation with the Mexameter®, VISIA skin imaging, and cellular resolution OCT all confirmed an improvement in the treatment group compared to the vehicle control group. This trial suggests that the cysteamine-isobionicamide complex presents as a viable treatment option for PIH. Prolonged studies with a larger population are needed to further assess the long-term effects and safety profile of the current formulation. For forthcoming investigations, it may be prudent to contemplate the utilization of a split-face design, wherein both control groups receive treatment on separate sides of the face. This modification holds the potential to augment the validity of direct comparisons and to facilitate a more comprehensive evaluation of potential contact dermatitis and associated side effects.

Acknowledgment

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Data availability statement

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

Financial support and sponsorship

This work was supported by the Scientis Pharma (XMRPG3L2181).

Conflicts of interest

Chau Yee Ng is a global advisory board member and principal investigator of Scientis Pharma. The other authors declare that the research was conducted without any commercial or financial relationships that could be constructed as a potential conflict of interest.

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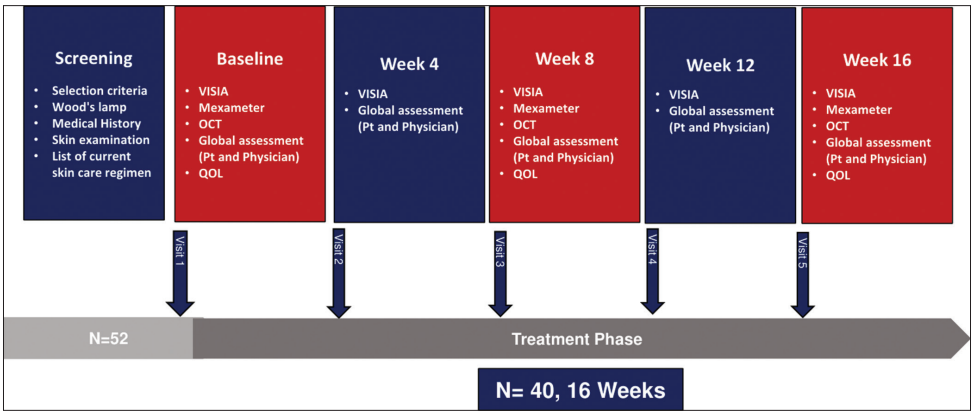
Supplementary Material



Supplement Figure 1: Study design. Fifty-two patients acquired postinflammatory hyperpigmentation were initially screened by dermatologists; the qualified patients (n = 40) were enrolled and randomized into the cysteamine-isobionicamide complex treatment group and placebo-vehicle control group. At the trial's onset, participants underwent subjective evaluations and received diagnostic imaging documentation using Mexameter®, VISIA skin analyzer, and optical coherence tomography. Subsequent assessments were recorded at week 4, week 8, and week 16. OCT: Optical coherence tomography, QoL: Quality of life.