

M89, A DERMOCOSMETIC COMBINING 89% VICHY VOLCANIC MINERALIZING WATER AND HYALURONIC ACID DOES NOT MODIFY CUTANEOUS PENETRATION OF TOPICAL IVERMECTIN EX VIVO

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INTRODUCTION

Rosacea is a chronic inflammatory dermatosis with an unpredictable course and characteristic features of persistent erythema associated with periodic intensification or 'flares'.¹⁻³

Clinical trials with ivermectin 1% cream have demonstrated greater rapidity and overall superiority in decreasing inflammatory lesions when compared to vehicle in papulopustular rosacea.^{1,4}

M89 (Mineral 89, Laboratoires Vichy) contains 89% of Vichy volcanic mineralizing water (VVMW) a volcanic mineralizing water, and 0.4% hyaluronic acid (HA), an extracellular matrix component with viscoelastic and hygroscopic properties, and is able reinforce skin barrier and improve signs and symptoms in rosacea among other indications.⁵

VVMW is highly enriched in minerals which strengthen the skin's natural defenses, e.g. restoring the skin barrier, and enhancing innate immunity.⁵⁻⁹ In vitro and in vivo studies showed that VVMW induced a statistically significant increase ($p < 0.05$) in catalase enzyme activity.¹⁰ These primary antioxidant enzymes convert 2 potentially harmful reactive oxygen species: superoxide and hydrogen peroxide, to water.^{6, 11} It has also been shown to have anti-inflammatory activity.^{8, 12}

In vitro and in vivo studies on VVMW have confirmed its potential to reinforce skin barrier function and even accelerate skin barrier recovery.¹³ Salsberg *et al.* showed that M89 was very well tolerated, with no reported safety issues and was very much appreciated by subjects with sensitive skin and investigators.¹⁴

Moreover, results from a large, international observational study showed that M89 significantly improves skin signs and symptoms after 4 weeks of continued use with no tolerance issues in subjects with dermatological conditions such as rosacea, sensitive and reactive skin, as well as in subjects who had recently undergone esthetic procedures. M89 was well-tolerated and had high subject satisfaction.¹⁵

AIM

This *ex vivo* assay assessed the skin absorption and distribution in the skin of ivermectin 1% applied before or after M89 application.

METHODS

The assay was conducted using full thickness human skin samples from 3 donors (2 women, 1 man), who underwent abdominal plastic surgery. Subcutaneous fat was removed before storage of the skin samples at -20°C . The skin was thawed at room temperature and cleaned with distilled water. Transepidermal water loss (TEWL) was measured after about one hour of setting on Franz cells and was between 0.5 and 5 g/m²/h confirming skin barrier integrity. Skin surface temperature was maintained at $32 \pm 1^{\circ}\text{C}$ using a water bath connected to the diffusion cells. The application area was 2 cm² and the receptor compartment contained 7 mL of PBS 0.01M pH 7.4 + 0.25% Tween[®] 80 as receptor fluid. Receptor fluid was stirred continuously during the assay. Each formulation was spread on the skin sample using a glass rod and with a 30 second-massage.

The experimental design is given in Table 1.

Each condition was tested on 2 replicates for the 3 skin donors under non-occlusive conditions. Twenty-four hours after application, formulations that remained on the skin surface were removed with 2 kimwipes (2 x 2 cm) wetted with PEG 400 / ethanol (70/30 v/v) and skin surface was dried with 3 kimwipes (2 x 2 cm). Cells were dismantled, receptor fluid was sampled, and *stratum corneum* was collected by tape-stripping. Skin corresponding to the application area was collected. Samples were stored at -80°C until analysis. Samples were analyzed using an HPLC method with MS/MS detection.

RESULTS

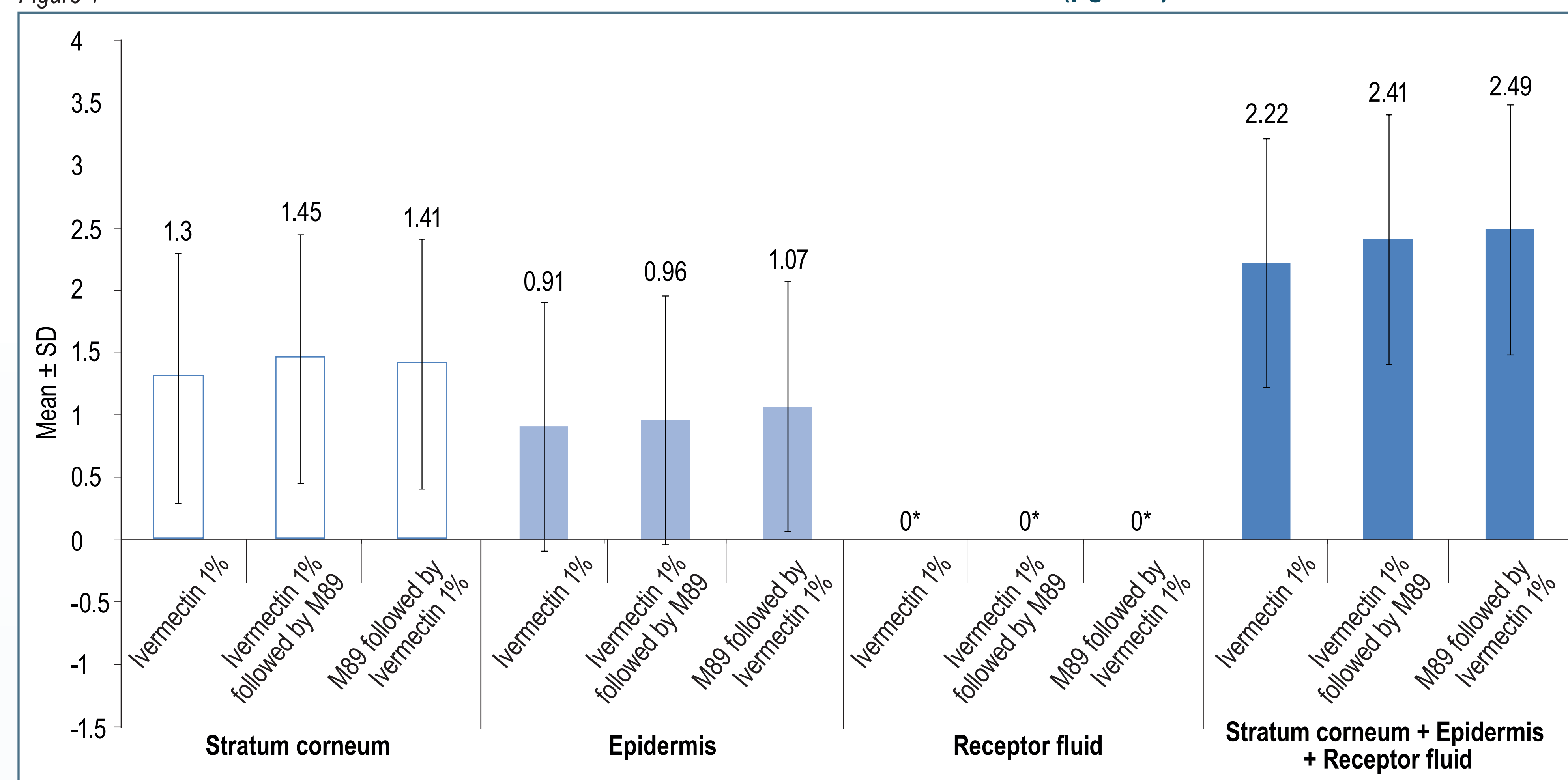
Ivermectin was not detected in the receptor fluid (LOD 1.5 ng/mL) and mainly found in the stratum corneum.

The mean total ivermectin amount in the stratum corneum, skin and receptor fluid was 2.22 $\mu\text{g}/\text{cm}^2$ (representing 4.15% of the applied dose) after application of ivermectin alone, 2.41 $\mu\text{g}/\text{cm}^2$ (4.54%) after application of ivermectin followed by M89 and 2.49 $\mu\text{g}/\text{cm}^2$ (4.83%) after application of M89 followed by ivermectin (Figure 1).

Condition	• Application of ivermectin 1% cream	• Application of ivermectin 1% cream • 20-minutes delay between applications • Application of M89	• Application of M89 • 20-minutes delay between applications • Application of ivermectin 1% cream
Total amount of ivermectin 1%/cm ²	5 mg		
Total amount of M89/cm ²	none	5 mg	
Skin thickness	Full skin thickness		
Number of cells per donor	2	2	2
Number of donors	3	3	3
Total number of cells	18	18	18
Receptor fluid	PBS 0.01M pH7.4 (data given by the supplier) + 0.25% tween 80		
Receptor fluid sampling	total volume of receptor fluid : 7 mL; collected after 24 hours		
Washing and dismantling of cells	24h		
Washing of formulations	2 kimwipes (2 x 2 cm) wetted with PEG 400 / EtOH (70/30 v/v) and 3 dried kimwipes (2 x 2 cm) or equivalent		
Strips	20* strips Polypropylene adhesive tape roll 3M (Sensitive [®]) size 19*5mm were performed on each skin. Strips were pooled by 4 (1-4, 5-8, 9-12, 13-16, 17-20).		
RCD extraction solvent	MeOH		

Figure 1

CUTANEOUS DISTRIBUTION OF IVERMECTIN ($\mu\text{g}/\text{cm}^2$)



*Concentration of ivermectin in the receptor fluid was below the limit of detection - Number of Franz cells per application condition: 6

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Conflict of interest: J. Tan is a consultant for Vichy Laboratoires, D. Kerob is an employee of Vichy Laboratoires. I. Durand, S. Gregoire and L. Roussel-Berlier are employees of l'Oréal Research and Development and M. Breisse, E. Raynaud and N. Merle are employees of Eurofins ADME bioanalyses and performed the assay for Vichy Laboratoires.

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CONCLUSION : Cutaneous absorption of topical ivermectin is not impacted by the application of M89