Lack of improvement after short-term topical antistaphylococcal endolysin SA.100 therapy in patients with mild-to-moderate atopic dermatitis: results from a randomized, vehicle-controlled trial

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SHORT COMMUNICATION

Lack of improvement after short-term topical antistaphylococcal endolysin SA.100 therapy in patients with mild-to-moderate atopic dermatitis: Results from a randomized, vehicle-controlled trial

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Abstract

Atopic dermatitis (AD) is a chronic immune-mediated inflammatory skin disease. An overgrowth of *Staphylococcus aureus (S. aureus)* and decreased microbial diversity is apparent in 70%–90% of AD patients. SA.100 is a recombinant endolysin targeting *S. aureus* that might be a novel treatment for patients with mild-to-moderate AD. To test safety, pharmacodynamics and efficacy of SA.100 a double-blind, randomized, vehicle-controlled trial in 53 subjects with mild-to-moderate AD was performed. Patients were randomized equally to topical SA.100 or vehicle with stratification for *S. aureus* positivity. SA.100 was safe and well tolerated. No reduction of *S. aureus* and no changes in microbiome features were seen after 2 weeks of treatment. Additionally, no statistically significant changes in clinical or patient-reported outcomes were observed compared to vehicle. In conclusion, topical SA.100 was safe and well tolerated in patients with mild-to-moderate AD, but our findings do not support short-term clinical use.

KEYWORDS
atopic dermatitis, endolysin, microbiome, SA.100, *Staphylococcus aureus*

The authors confirm that Robert Rissmann was the principal investigator for this study and Mariette E. van Poelgeest had direct medical responsibility for the patients.

Clinical trial registration number: NL71660.056.19

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic immune-mediated inflammatory skin disease. Immune dysregulation in AD is mainly T-cell driven, with strong Th2 immune activation.[1] Dysbiosis of the skin, with overgrowth of *Staphylococcus aureus (S. aureus)* and decreased microbial diversity, is apparent in 70%–90% of AD patients and is associated with a higher disease severity.[2] *S. aureus* contributes to skin inflammation through the production of toxins and superantigens, disruptions of the epidermal barrier and modulation of host immune responses, promoting a type 2 inflammation.[3] The skin microbiome and more specifically *S. aureus* might therefore be a target for novel antimicrobial therapies for this patient population.[4,5]

SA.100 is a recombinant endolysin targeting *S. aureus*.[6] A cetomacrogol cream containing SA.100 is available in Europe as a medical device for the treatment of inflammatory skin conditions. Successful treatment of chronic *S. aureus*-related dermatoses with SA.100 was reported in a case series.[7] An open label, single treatment-arm study with topical SA.100 monotherapy showed significant improvement of AD symptoms and quality-of-life.[8] In the only published randomized controlled trial, SA.100 in AD had no topical corticosteroid-sparing effect compared to vehicle cream.[9] To date, no randomized controlled trial has been performed with SA.100 as monotherapy and current evidence regarding the standalone efficacy and impact on the skin's microbiome is lacking.

Therefore, we performed a randomized controlled trial from December 2019 to September 2020 to evaluate the efficacy, safety, *S. aureus* load and changes in skin microbiome after short term treatment with SA.100 compared to vehicle cream in patients with mild-to-moderate AD.

What is already known about this subject

- Atopic dermatitis is a chronic immune mediated inflammatory skin disease, with dysbiosis of the skin and an overgrowth of *Staphylococcus aureus*
- There is a medical need for novel non-steroidal topical treatments for mild-to-moderate atopic dermatitis patients
- Targeting *S. aureus* might be a novel treatments strategy

What does this study adds

- This study demonstrates that short-term clinical use of SA.100 neither improves symptoms of mild-to-moderate atopic dermatitis patients nor reduces the *S. aureus* load on the skin

2 | METHODS

The Declaration of Helsinki was the guiding principle for this trial execution. All patients provided written informed consent prior to participation. In this double-blind, randomized, vehicle-controlled trial, 53 subjects with mild-to-moderate AD were randomized to SA.100 or vehicle treatment. Mild-to-moderate AD was defined by an Investigator's Global Assessment (IGA) score of 2 or 3 and diagnosed according to Hanifin criteria. All eligible patients had an Eczema Area and Severity Index (EASI) score ≥4, ≥5% body surface area (BSA) affected and a target lesion of ≥1% BSA with at least mild erythema and induration. Key exclusion criteria included other clinically significant skin conditions, recent tanning and use of prohibited AD treatments. A stratified randomization was performed for *S. aureus* positive and negative patients. Each treatment group consisted of at least 20 subjects colonized with *S. aureus*, that is, two out of three swabs had to be positive for *S. aureus* in the semiquantative cultures taken from two lesional sites and the nose at one point in time during the screening period. All patients underwent a wash-out period before treatment induction. Treatment was applied by the patients to all lesions twice daily for 14 consecutive days. Treatment compliance was monitored with a mobile e-diary.

SA.100 was applied in its commercially available concentration, as registered for use as a Class I medical device. In vitro data showed minimally inhibitory concentration concentration (MIC) for the *S. aureus* strain of 32 μg/mL (data on file). SA.100 also rapidly reduced turbidity for methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), indicating effective killing of planktonic *S. aureus* within 60 min, while *S. epidermidis* remained unaffected (data on file). Twice-daily application was chosen to maintain continuous exposure, consistent with standard practice for topical AD treatments. The treatment period of 2 weeks was selected as a short-term proof-of-mechanism to evaluate microbiome and clinical changes rather than to establish dose–response relationships or long-term proof-of-concept. To assess clinical efficacy, Eczema Area and Severity Index (EASI), (local) objective SCORing Atopic Dermatitis (oSCORAD) and Investigator Global Assesment (IGA) scores and patient reported outcomes (Patient-Oriented Eczema measure (POEM), Dermatology Life Quality Index (DLQI) and Numeric Rating Scale [NRS]) were recorded. Standardized swab samples were taken from a target lesion for semi-quantative *S. aureus* culture and 16S DNA microbiome analysis. In addition, pharmacodynamic measurements of the target lesion were performed (multispectral imaging, trans epidermal water loss, laser speckle contrast imaging and biopsy biomarkers). Adverse events were monitored.

Sample size was estimated based on assumptions for EASI and *S. aureus* reduction. For EASI, 25 participants per group provided 80% power to detect a mean difference of 1.4 points (SD = 1.7), and for *S. aureus* reduction, 18 participants per group provided 80% power to detect a 97% difference (SD = 3.7 log CFU), using a two-sided *t*-test at $\alpha = 0.05$.

2.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are

permanently archived in the Concise Guide to PHARMACOLOGY 2025/26.[10]

3 | RESULTS

Baseline characteristics were similar between groups (Table 1), with 69.8% of patients having a positive *S. aureus* culture of the target lesion. At baseline, we observed a clear distinction between lesional and nonlesional skin in the microbiome analysis, mainly due to a higher *S. aureus* load at the lesional site. Following 14-day treatment, we found no reduction of *S. aureus* in the cultures when comparing SA.100 to vehicle (Table S1.B) and no changes in the microbiome features (alpha-diversity and abundances of taxa, specifically *S. aureus*). Also, no statistically significant changes in clinical or patient-reported outcomes were observed compared to vehicle (Figure 1 and Table S1.A). In the pharmacodynamic endpoints, a slight improvement in erythema by multispectral imaging of the target lesion when comparing SA.100 to vehicle (−0.14, 95% CI −0.26 to −0.02, $p = 0.02$) (corrected for nonlesional skin) and an improvement in transepidermal

TABLE 1 Baseline characteristics.

	All subjects ($N = 53$)	Vehicle ($N = 26$)	SA.100 ($N = 27$)
Sex			
Female	30 (56.6%)	11 (42.3%)	19 (70.4%)
Male	23 (43.4%)	15 (57.7%)	8 (29.6%)
Age, years			
Mean (SD)	25.1 (6.3)	25.1 (5.1)	25.0 (7.4)
BSA (%)			
Mean (SD)	16.20 (9.25)	18.71 (9.87)	13.78 (8.07)
EASI total score			
Mean (SD)	9.67 (4.42)	10.73 (4.96)	8.65 (3.64)
SCORAD total body			
Mean (SD)	26.88 (6.72)	28.51 (7.48)	25.31 (5.59)
IGA			
2	29 (54.7%)	12 (46.2%)	17 (63.0%)
3	24 (45.3%)	14 (53.8%)	10 (37.0%)
S. aureus culture inclusion (*N* - %)			
Negative 0/3	6 (11.3%)	2 (7.7%)	4 (14.8%)
Negative 1/3	7 (13.2%)	4 (15.4%)	3 (11.1%)
Positive 2/3	8 (15.1%)	5 (19.2%)	3 (11.1%)
Positive 3/3	32 (60.4%)	15 (57.7%)	17 (63.0%)
S. aureus culture nose (*N* - %)			
+	33 (62.3%)	17 (65.4%)	16 (59.3%)
++	12 (22.6%)	5 (19.2%)	7 (25.9%)
+++	1 (1.9%)	1 (3.8%)	0 (0%)
–	7 (13.2%)	3 (11.5%)	4 (14.0%)
S. aureus culture (TL) (*N* - %)			
+	19 (35.8%)	8 (30.8%)	11 (40.7%)
++	14 (26.4%)	10 (38.5%)	4 (14.8%)
+++	4 (7.5%)	2 (7.7%)	2 (7.4%)
–	16 (30. 2%)	6 (23.1%)	10 (37.0%)
S. aureus culture (NTL) (*N* - %)			
+	23 (43.4%)	13 (50.0%)	10 (37.0%)
++	9 (17.0%)	2 (7.7%)	7(25.9%)
+++	5 (9.4%)	2 (7.7%)	3 (11.1%)
–	16 (30.2%)	9 (34.6%)	7(25.9%)

Abbreviations: BSA, body surface area; EASI, eczema area and severity index; IGA, Investigators Global Assessment; oSCORAD, objective SCORing Atopic Dermatitis; SD, standard deviation; *S .aureus*, *Staphylococcus aureus*.

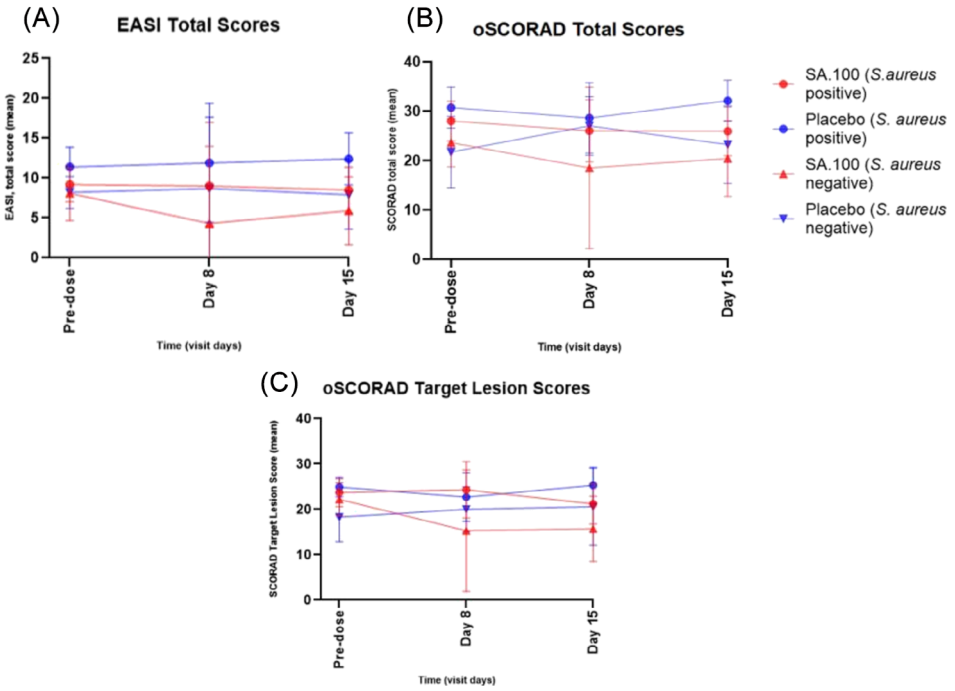

FIGURE 1 AD clinical severity scores (EASI, oSCORAD total score and oSCORAD target lesion) Red indicates SA.100, blue indicates placebo. D15 is EOT. (a) Mean EASI total score on different timepoints. (b) Mean oSCORAD total score on different timepoints. (c) Mean oSCORAD target lesion. Error bars represent 95% CI interval; lower limits are truncated for visual clarity. Graph is generated using GraphPad Prism (GraphPad Software, San Diego, CA, USA).

water loss (TEWL) of the target lesion when comparing SA.100 to vehicle (−10.04, 95% CI −18.40 to −1.67, $p = 0.02$) were observed. However, when corrected for nonlesional skin, the TEWL difference was not statistical significant (−9.68, 95% CI −21.24–1.87, $p = 0.1$). There were no significant treatment-emergent adverse events.

4 | DISCUSSION

Despite the effective killing of *S. aureus* by SA.100 in vitro, we found no significant decreases in *S. aureus* load or 16S microbiome composition between SA.100 and vehicle after 2 weeks of treatment. Translational differences between in vitro and in vivo settings might explain this absence of a significant antimicrobiological effect in our study. SA.100 is a large protein (MW 56 kDa) that acts after binding to **the bacerial cell wall** of *S. aureus*. Based on its size and its physicochemical properties, it is not expected to penetrate deeply into the skin to reach *S. aureus* in all layers of the skin. However, the limited treatment duration, unkown bioavailability of SA.100 in less accessible skin niches, recolonization from the nose or the environment and the bias from DNA still present from killed *S. aureus* bacteria could have influenced the in vivo microbiological effect and read out. Furthermore, an MIC value of 32 μg/mL could not be sufficient to disrupt or penetrate the *S. aureus* biofilm, and as the study was not designed to assess dose–response relationships, we cannot exclude that a higher application frequency, higher dose strength, or longer treatment duration would be requiered to achieve measurable reduction in *S. aureus* load.

Consistent with the microbiological results, we observed no statistically significant change in clinical scores after 2 weeks of treatment compared to vehicle, in contrast to the open label, single arm study that showed a significant reduction compared to baseline of AD severity after 2 weeks of SA.100 monotherapy.[8] In the open-label study, no microbiological analysis was performed, precluding a comparison between the two studies. Previously in another study, no corticosteroid-sparing effect or effect on the clincial scores was found, in line with the results of the current study.[11] However, it should be noted that in the previous study, patients were allowed to use corticosteroids and the corticosteroid induction therapy prior to starting SA.100 decreased AD severity to a level where little corticosteroids were needed, precluding a possible effect on both outcome parameters. Furthermore, we can speculate that there was an improvement in skin barrier, as shown by uncorrected TEWL flux on lesional skin of SA.100 compared to vehicle hinting towards positive effects on skin barrier restoration. This effect might be attributable to the emollient base of the cream. However, this improvement did not translate into better patient-reported or clinical outcomes and is not robust, as the analysis was not corrected for nonlesional skin (corrected version was not significantly different) and is more prone to be effected to variability of measurements. The question remains whether short term anti-*S. aureus* monotherapy could actually lead to clinically relevant improvement in populations with mild disease, as we previously found a significant reduction of *S. aureus* after treatment with an antimicrobial peptide but without clinical improvement in a similar AD cohort.[12,13]

In conclusion, topical SA.100 was safe and well tolerated in patients with mild-to-moderate AD. We found no change in *S. aureus* load or microbiome composition after 2 weeks of monotherapy. Consequently, we found no clinical relevant improvement of clinical scores, patient-reported or pharmacodynamic outcomes compared to vehicle, apart from a possible improvement in skin barrier as measured by TEWL. Our findings therefore show that SA.100 does not support clinical benefit in patients with mild-to-moderate AD upon short-term treatment.

CONFLICT OF INTEREST STATEMENT

Laura W. J. van der Meulen: Investigation; formal analysis; writing—original draft; writing—review and editing. **Menthe E. Bergmans:** Investigation; writing—review and editing. **Salma Assil:** Investigation; writing—review and editing. **Ismahaan Abdisalaam:** Investigation; writing—review and editing. **Rianne Rijneveld:** Investigation; writing—review and editing. **Erica S. Klaassen:** Formal analysis; writing—review and editing. **Alexa J. Tibboel:** Formal analysis; writing—review and editing. **Thorsten Brach:** Microbiome analysis; writing—review and editing. **Bjorn L. Herpers:** Conceptualization; writing—review and editing. **Johan Frieling:** Conceptualization; writing—review and editing. **Benthe Freyee:** Conceptualization; writing—review and editing. **Karin Platenkamp:** Investigation; writing—review and editing. **Mariette E. van Poelgeest:** Supervision; writing—review and editing. **Robert Rissmann:** Conceptualization; supervision; writing—review and editing. **Martijn B. A. van Doorn:** Conceptualization; supervision; writing—review and editing. **Tessa Niemeyer – van der Kolk:** Conceptualization; supervision; writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

L.W.J.v.d.M., M.E.B., T.N.-v.d.K., E.S.K., A.J.T. and R.R. are employees of the Centre for Human Drug Research which received funding from Micreos Human Health B.V. to conduct this study. S.A., I.A., R.R. and M.E.v.P. were employees of Centre for Human Drug Research during the study conduct. B.L.H. is a consultant to Micreos Human Health B. V. B.F. and J.F. were employees of Micreos Human Health B.V. at study conduct. J.F. and B.L.H. have stock options of Micreos Human Health B.V.

DATA AVAILABILITY STATEMENT

Authors elect not to share.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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