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Topical antimicrobial peptide omiganan recovers cutaneous dysbiosis but does not improve clinical symptoms in patients with mild to moderate atopic dermatitis in a phase 2 randomized controlled trial

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Background: Dysbiosis and colonization with *Staphylococcus aureus* is considered to play an important role in the pathogenesis of atopic dermatitis (AD). Recovering this dysbiosis may improve AD symptoms. Omiganan is a synthetic indolicidin analogue antimicrobial peptide with activity against *S aureus* and could be a viable new treatment option for AD.

Objective: To explore the tolerability, clinical efficacy, and pharmacodynamics of omiganan in mild to moderate AD.

Methods: Eighty patients were randomized to omiganan 1%, 1.75%, or 2.5% or vehicle twice daily for 28 days on all lesions. Weekly visits included clinical scores and microbiological and pharmacodynamic assessments of 1 target lesion.

Results: In all omiganan treatment groups, dysbiosis was recovered by reducing *Staphylococcus* species abundance and increasing diversity. A reduction of cultured *S aureus* was observed in all omiganan treatment groups, with a significant reduction for omiganan 2.5% compared to vehicle (-93.5%; 95% CI, -99.2 to -28.5%; P = .02). No significant clinical improvement was observed.

Conclusion: Topical administration of omiganan twice daily for up to 28 days in patients with mild to moderate AD led to a recovery of dysbiosis but without clinical improvement. Therefore, a monotreatment

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that selectively targets the microbiome does not appear to be a successful treatment strategy in mild to moderate AD. (J Am Acad Dermatol 2022;86:854-62.)

Key words: antimicrobial peptide; atopic dermatitis; dysbiosis; omiganan; pharmacodynamics; *Staphylococcus aureus*.

CAPSULE SUMMARY

- In this study, omiganan, a synthetic indolicidin analogue, was explored as a treatment option targeting dysbiosis in mild to moderate atopic dermatitis.
- Twice daily treatment recovered lesional dysbiosis but did not lead to clinical improvement. Our findings do not support the treatment of dysbiosis as monotherapy in mild to moderate atopic dermatitis.

The pathophysiology of atopic dermatitis (AD) is complex and incompletely understood. Genetic susceptibility, environmental factors, epidermal barrier abnormalities, immunologic disturbances, and dysbiosis of skin microbiota may explain the heterogeneous character of AD, and it remains hard to discern which of these are primary events, secondary events, or both.[1]

Staphylococcus aureus is an important player regarding dysbiosis in AD.[2,3] Colonization with this pathogen and a lower overall microbial diversity is apparent in approximately 70% of the lesional skin of patients with AD.[4] A deficiency in antimicrobial peptides (AMPs) related to a T helper 2 response may partially account for the susceptibility to *S aureus* colonization.[5,6] After adhesion, *S aureus* may directly cause or increase ongoing inflammation by binding of its superantigens to MHCII molecules, which induces excessive production of T-cell cytokines.[7-9] In addition, its superantigens may serve as conventional allergens and will generate a specific immunoglobulin E response.[9]

Based on the hypothesis that dysbiosis plays an important role in the pathogenesis of mild to moderate AD, the microbiome and, more specifically, *S aureus* might be an important target for novel therapies.[6,9-11] A potential novel topical treatment from this perspective is omiganan, a synthetic indolicidin analogue. This short AMP from the cathelicidin family has shown in vitro and in vivo antimicrobial activity against *S aureus* without the development of bacterial resistance.[12-14] We previously investigated the efficacy and tolerability of omiganan 1% topical gel, 2.5% topical gel, or vehicle gel that was applied once daily to 1 antecubital fossa (target lesion) affected by AD.[15] We observed a statistically significant shift from the lesional to nonlesional microbiome profile with both omiganan 1% and 2.5% gel, whereas there was no change in the vehicle group. Moreover, we found a statistically significant improvement of the target lesion according to local objective Scoring Atopic Dermatitis (oSCORAD) and patient-reported itch scores. Although clinical effects were small, these results suggested a dose-response relationship, and therefore, we hypothesized that an increased dosing frequency of omiganan twice daily to all AD lesions would lead to a better clinical response.

The objective of this study was to investigate the tolerability, safety, clinical efficacy, microbiological, and pharmacodynamic effects of omiganan 1%, 1.75%, and 2.5% applied to all lesions twice daily in patients with mild to moderate AD.

MATERIALS AND METHODS

The Declaration of Helsinki was the guiding principle for trial execution. The independent medical ethics committee "Medisch Ethische Toetsingscommissie van de Stichting Beoordeling Ethiek Biomedisch Onderzoek" (Assen, the Netherlands) approved the study before any study activity. All patients provided written informed consent before participation. The study was conducted from March 2017 to December 2017 at the Centre for Human Drug Research, Leiden, the Netherlands.

Study characteristics, patients, and treatments

This was a randomized, double-blind, placebo-controlled, monocenter, phase 2 study in 80 patients with mild to moderate AD. Patients with confirmed mild to moderate AD (Eczema Area and Severity Index score between 1.1 and 21.0 and body surface area of 2%-20%) present for at least 1 year before study participation were included. There was a washout period for any AD medication. Patients with any other clinically significant condition were excluded. Health status was verified by taking a detailed medical history, a complete physical examination, vital signs, 12-lead electrocardiography (ECG), and laboratory tests (including hepatic and renal panels, complete blood count, chemistry panel, virology, and urinalysis). Eligible patients were randomized 1:1:1:1 to omiganan 1%, 1.75%, or 2.5% or vehicle gel by an independent statistician.

Abbreviations used:

AD:	atopic dermatitis
AE:	adverse event
AMP:	antimicrobial peptide
CI:	confidence interval
ECG:	electrocardiography
EOT:	end of treatment
IL:	interleukin
oSCORAD:	objective Scoring Atopic Dermatitis
qPCR:	quantitative polymerase chain reaction

Vehicle gel served as placebo, with an identical appearance to omiganan gel. The study drug was applied to all eczema lesions twice daily for 28 consecutive days. Bland emollients (Unguentum leniens) were supplied to use as maintenance therapy. Triamcinolon 0.1% was provided as rescue medication when discussed with the study physician. The full study protocol can be found in the Supplemental Material ("Clinical Study Protocol"; available via Mendeley at https://doi.org/10.17632/822gpnyv4j.1).

Microbiome and microbiology

For microbiome analysis and *S aureus* quantitative polymerase chain reaction (qPCR) quantification, skin swab samples of lesional and nonlesional skin were collected. Procedures and conditions are described in detail in the Supplemental Material ("Clinical Study Protocol," section 7.5, pp 44-46). The analysis was performed as described by van den Munckhof et al.[16] For *S aureus* cultures, sterile swabs (Puritan [Guilford, ME] Sterile Polyester-Tipped Applicators, REF 25-806-1PD) were taken of lesional and nonlesional skin and transported to the microbiology department of the Alrijne Hospital, the Netherlands. Cultures were performed on blood agar plates.

Efficacy and patient-reported outcomes

Efficacy was evaluated by the Eczema Area and Severity Index score, oSCORAD score, and Investigator Global Assessment. Patient-reported outcomes consisted of weekly Patient-Oriented Eczema Measure and Dermatology Life Quality Index questionnaires and daily numeric rating scale itch scores.

Target lesion pharmacodynamics

One AD lesion, preferably of the antecubital fossa, was assigned as target lesion, opposed to a part of healthy skin that served as negative control (nontarget lesion). Erythema and roughness were assessed by 3-dimensional photo analysis (Antera 3D, Miravex, Ireland). Skin barrier status of lesional and nonlesional skin was assessed by transepidermal water loss assessment (AquaFlux AF200 system, Biox, London, UK). Skin surface biomarkers interleukin (IL) 10, interferon (IFN) γ, IL-13, IL-6, eotaxin 3, and IL-31 were assessed with transdermal analysis patches (FibroTx, Tallinn, Estonia) and qualitatively and quantitatively analyzed by spot enzyme-linked immunosorbent assay. At day 0 (predose) and day 28 (end of treatment [EOT]), 3-mm skin punch biopsy samples were collected from lesional and nonlesional skin. RNA extraction and real-time qPCR analysis was performed by the Erasmus Medical Centre, Rotterdam, the Netherlands, for the following biomarkers: IFN-α, IFN-γ, IL-31, IL-6, IL-13, and eotaxin 3. Details of the procedures and conditions are described in the Supplemental Material ("Clinical Study Protocol," section 7.5, pp 44-46).

Treatment compliance, safety, and tolerability

Treatment compliance was recorded with a mobile e-diary app including a notification and photo capture function to enable documentation. Safety and tolerability were evaluated by adverse events monitoring, physical examination, vital signs, 12-lead ECG, and laboratory tests.

Statistical analysis

All calculations were performed by using SAS for windows V9.4 (SAS Institute, Cary, NC). No formal power calculation was performed given the exploratory character of this study. Efficacy/pharmacodynamic endpoints were analyzed with a mixed model analysis of variance by using treatment, time, and treatment by time as fixed factors and subject as the random factor. Analyses were conducted in all patients who applied the study medication for at least 21 days and completed the EOT visit. Estimates of the difference, 95% confidence intervals (CIs), least square means, and *P* values were generated. Analyses of messenger RNA expression levels in the biopsy samples incorporated normalization for the housekeeping gene *GAPDH* and incorporated the values from nonlesional skin to correct for the high variability. For the organization and visualization of microbiome data, Python 3.5.2 (Python Software Foundation, Wilmington, DE) was used. The Supplemental Material ("Microbiome Report"; available via Mendeley at https://doi.org/10.17632/822gpnyv4j.1) includes the methodology for the microbiome analysis.

RESULTS

Patient disposition and baseline characteristics

Eighty patients were enrolled in the study, of whom 72 (90%) completed the study. For the participant flow, see the Supplemental Material ("*Staphylococcus* Abundance Over Time"; available via Mendeley at https://doi.org/10.17632/822gpnyv4j.1). For the baseline characteristics of patients in all treatment groups, see Table I.

Microbiome

Microbiome composition of lesional skin was dominated by *Staphylococcus* and exhibited a low diversity index in general. After omiganan treatment, abundance of *Staphylococcus* was reduced in all active treatment groups (Supplemental Material, "*Staphylococcus* Abundance Over Time"). This reduction was statistically significant in the omiganan 1% and 2.5% treatment versus vehicle group (-15.1; 95% CI, -28.6 to -1.7; $P = .03$ and -17.2; 95% CI, -30.4 to -4.1; $P = .01$, respectively). After treatment discontinuation, *Staphylococcus* abundances in the 1.75% and 2.5% treatment groups returned to predose levels and remained low in the omiganan 1% treatment group. The diversity index increased in all omiganan treatment groups. This was statistically significant for omiganan 1% versus vehicle (0.15; 95% CI, 0.03-0.26; $P = .01$) and omiganan 2.5% versus vehicle (0.15; 95% CI, 0.04-0.27; $P = .01$). A summary of the changes in *Staphylococcus* abundance and diversity data is depicted in Fig 1. See the Supplemental Material ("Microbiome Report") for the full microbiome report with individual plots.

Microbiology

A reduction in *S aureus* in the cultures was observed in all active treatment groups, which was most pronounced and statistically significant in the omiganan 2.5% group compared to vehicle at EOT (Table II). In the omiganan 1% and 1.75% treatment groups, a substantial, but not statistically significant, numeric mean reduction was observed. After cessation of treatment, *S aureus* culture values increased up to the end of the study. For the qPCR *S* aureus data, a nonsignificant decrease was observed in all omiganan treatment groups.

Pearson correlation coefficients of the relation between *S aureus* in culture and the relative abundance of the genus *Staphylococcus* by 16S ribosomal RNA gene profiling using next-generation sequencing were 0.46, 0.33, 0.10, and 0.38 for vehicle and omiganan 1%, 1.75%, and 2.5%, respectively. For the relation between *S aureus* qPCR and the relative abundance of the genus *Staphylococcus* by next-generation sequencing, correlation coefficients were 0.60, 0.68, 0.55, and 0.78 for vehicle and omiganan 1%, 1.75%, and 2.5%, respectively (Figs 2 and 3).

Efficacy and patient-reported outcomes

Clinical efficacy showed no significant improvements in the active treatment groups compared to vehicle. The omiganan 1.75% group exhibited a small but significant clinical worsening (see Table II.) Patient-Oriented Eczema Measure scores showed a similar pattern, in line with the clinical efficacy scores. Daily numeric rating scale itch scores were highly variable, and no statistically significant changes occurred in any of the treatment groups.

Biomarkers

Based on 3-dimensional photography of the target lesion, erythema and roughness slightly worsened (Table II). Transepidermal water loss significantly differed between lesional and nonlesional skin at baseline (32.27; 95% CI, 28.31-36.24; $P < .0001$), but no significant changes were observed after omiganan and vehicle treatment (Table II and Supplemental Material, "Transepidermal Water Loss"; available via Mendeley at https://doi.org/10.17632/822gpnyv4j.1). Biopsy biomarker data were highly variable in general. At baseline, a significant difference between lesional and nonlesional skin was found for IL-13 only (0.99; 95% CI, 0.83-1.14; $P < .0001$). Nonsignificant differences were observed between lesional and nonlesional skin for eotaxin and IL-31 (0.1; 95% CI, -0.01 to 0.21; $P = .08$ and -0.08; 95% CI, -0.18 to 0.01; $P = .09$, respectively) (Fig 3). Although there were no significant differences between lesional and nonlesional skin at baseline for IL-6, a significant reduction was observed in the omiganan 1% and 2.5% groups. In the vehicle and omiganan 1.75% groups no significant changes were observed. For all other biopsy biomarkers, no significant changes occurred. Transdermal analysis patches showed no differences in any of the biomarkers between lesional and nonlesional skin at baseline nor after any of the treatments. Serum thymus and activation-regulated chemokine increased significantly, with 26.4% in the omiganan 1.75% group, parallel to the small increase in clinical severity scores. The other serum biomarkers showed no notable changes.

Treatment compliance and safety

Overall treatment compliance ranged from 90% to 98% across the treatment groups. Average use of study medication per day ranged from 1.1 to 2.0 mg per cm^2. No serious adverse events (AEs) or deaths

Table I. Baseline characteristics

Characteristics	All patients (N = 80)	Omiganan 1% (n = 20)	Omiganan 1.75% (n = 20)	Omiganan 2.5% (n = 20)	Vehicle (n = 20)
Patients dosed, n (%)	80 (100)	20 (100)	20 (100)	20 (100)	20 (100)
Patients completed, n (%)	72 (90)	19 (95)	16 (80)	19 (95)	18 (90)
Age, y					
Mean (SD)	24.4 (6.5)	24.5 (8.4)	25.9 (8.2)	23.6 (3.5)	23.5 (4.5)
Median	23.5	22.5	23.0	24.0	22.0
Min, max	18, 49	18, 49	18, 48	18, 31	18, 33
Sex					
Female, n (%)	44 (55.0)	11 (55.0)	11 (55.0)	11 (55.0)	11 (55.0)
Male, n (%)	36 (45.0)	9 (45.0)	9 (45.0)	9 (45.0)	9 (45.0)
oSCORAD					
Mean (SD)	19.9 (4.6)	19.3 (4.1)	20.7 (4.3)	20.8 (5.4)	18.8 (4.4)
Min, max	10.9, 29.8	10.9, 25.4	14.4, 29.8	10.9, 28.8	10.9, 28.5
EASI					
Mean (SD)	3.8 (2.0)	3.8 (1.6)	3.8 (2.2)	4.1 (2.3)	3.5 (2.1)
Min, max	1.1, 9.8	1.4, 5.8	1.4, 9.8	1.2, 9.3	1.1, 8.1
POEM					
Mean (SD)	16.9 (4.4)	18.0 (3.9)	15.9 (5.6)	16.9 (4.3)	16.8 (3.5)
Min, max	6, 26	10, 25	6, 26	6, 24	10, 22
Serum TARC					
Mean (SD)		146.3 (122.9)	190.1 (87.3)	140.1 (125.2)	140.4 (85.4)
Fitzpatrick skin type, n (%)					
1	7 (8.8)	2 (10.0)	1 (5.0)	3 (15.0)	1 (5.0)
2	39 (48.8)	8 (40.0)	12 (60.0)	7 (35.0)	12 (60.0)
3	20 (25.0)	7 (35.0)	4 (20.0)	6 (30.0)	3 (15.0)
4	9 (11.3)	2 (10.0)	2 (10.0)	3 (15.0)	2 (10.0)
5	4 (5.0)	0 (0)	1 (5.0)	1 (5.0)	2 (10.0)
6	1 (1.3)	1 (5.0)	0 (0)	0 (0)	0 (0)
Filaggrin mutation present, patients with mutation present/total patients that consented for optional polymorphism analysis (%)	12/73 (16)	4/17 (24)	3/19 (16)	4/18 (22)	1/19 (5)
Staphylococcus aureus colonization lesional skin	50 (63)	11 (55)	16 (80)	11 (55)	12 (60)
CFU/ml, mean (SD)*	933,503 (±5,650,793)	908,232 (±5,637,456)	744,972 (4,560,153)	856,325 (±5,371,280)	933,503 (±5,650,793)

CFU, Colony-forming unit; *EASI*, Eczema Area and Severity Index; *max*, maximum; *min*, minimum; *oSCORAD*, objective Scoring Atopic Dermatitis; *POEM*, Patient-Oriented Eczema Measure; *SD*, standard deviation; *TARC*, thymus and activation-regulated chemokine.
*Of *Staphylococcus aureus*–positive patients.

occurred during the study. Eight patients discontinued because of a significant increase in AD symptoms not related to the study drug. Most frequently occurring AEs were application site AEs (n = 13), headache (n = 14), and influenza-like illnesses (n = 8). All treatment-emergent AEs were of mild or moderate severity and were self-limiting. There were no clinically significant changes in any of the safety laboratory parameters, vital signs, and ECG recordings.

DISCUSSION

In this study, we observed that treatment of AD skin with the topical AMP omiganan led to a recovery of lesional skin dysbiosis across all active treatment groups. The statistically significant reduction of *S aureus* in culture, a decrease of the *Staphylococcus* genus in the microbiota, and an increase in the diversity index of the microbiota profile did not translate into clinical efficacy or significant improvement of molecular biomarkers.

We observed a similar recovery of dysbiosis in our previous study evaluating a single target lesion using oSCORAD.[15] The results of the current study, however, indicate that BID administration to all AD lesions does not lead to a significant improvement of clinical symptoms. First, this could be explained by the absence of a linear dose-response pharmacology of omiganan. Second, the effects on the target lesion oSCORAD of the previous QD study might have been a coincidence, and with a greater variability of the measurement in this study, no effects

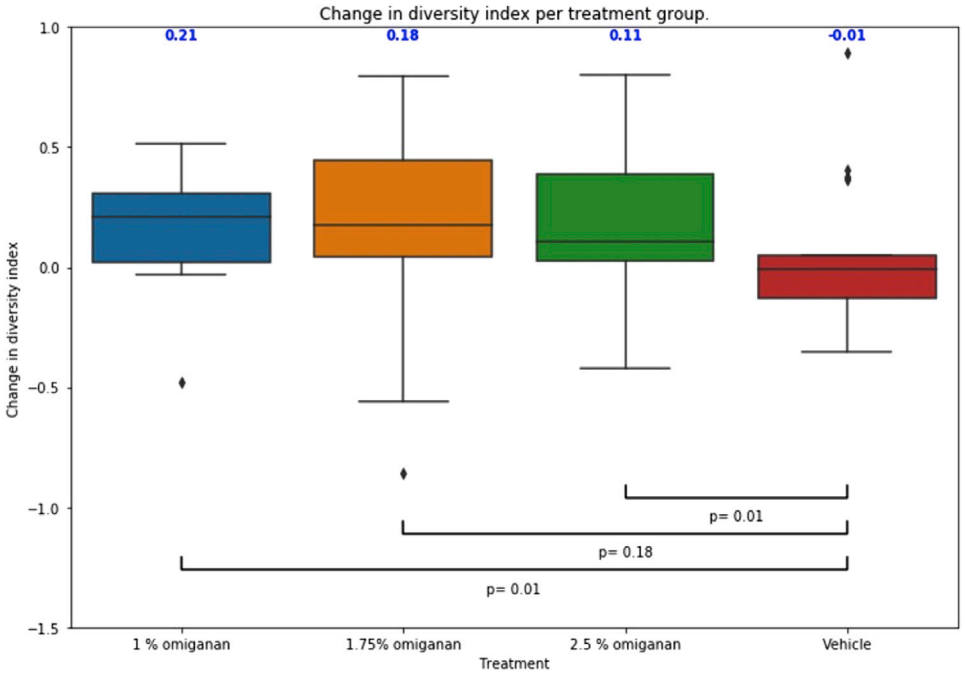

Fig 1. Mild to moderate AD. Summary of the change in diversity index of the target lesion, showing boxplots and medians (blue text). The whiskers indicate differences between the the boxplots with the corresponding significance levels. *AD*, Atopic dermatitis.

could be observed. Finally, cationic peptides, including omiganan, are suggested to have proinflammatory effects, which might interfere with the anti-inflammatory properties.[17,18] However, for omiganan, the proinflammatory capacities are triggered only by a viral costimulus, which is not relevant in patients with AD.[19]

Whether microbial skin dysbiosis is a primary or secondary factor in the pathogenesis of AD remains uncertain. Kobayashi et al[20] highlighted the microbiota-host immunity axis as a potential target for future AD treatment in their study in which Adam17 (fl/fl)Sox9-(Cre) mice developed eczematous dermatitis with dysbiosis similar to the dysbiosis observed in AD. Mice were treated with targeted antibiotics against *S aureus*, *Corynebacterium mastitidis*, and *Corynebacterium bovis* species, which recovered dysbiosis and eliminated skin inflammation clinically and in the (biopsy) biomarkers.[20] Our study focused on this axis with the strong antimicrobial capacity of omiganan against the species involved in the dysbiosis of AD.[12,14] Our findings of reversed dysbiosis, without improvement of clinical scores, seem to suggest that dysbiosis is more likely to be a secondary effect in the pathogenesis of AD, by susceptibility for *S aureus* colonization through a deficient barrier related to T helper 2—skewed immune dysregulation. This hypothesis is supported by the observed dysbiosis recovery after corticosteroids and coal tar treatments, which do not have any specific antimicrobial properties.[2,21] Apparently, by suppressing inflammation, the epidermal barrier will heal and the susceptibility to *S aureus* colonization will decrease, leading to a normalization of the microbiota profile.

Baseline data of the current study did show numeric differences between lesional and nonlesional skin but no statistically significant differences for the proximal. *aureus*-associated downstream biomarkers, in spite of the fact that *S aureus* is known to activate the TLR-2 pathway and to produce staphylococcal enterotoxin B, which can induce the production of a variety of cytokines, including IL-6, IFN-ɣ, IL-31, and eotaxin.[7,8] However, with active treatment, we did observe a statistically significant decrease of IL-6, but in general, the *S aureus* reduction did not yield a clear signal of the downstream markers.

The relatively short duration and the monotherapy approach are potential limitations of this study. However, a recently published study showed no corticosteroid-sparing effect with an antimicrobial endolysin specifically targeting *S aureus*.[22] Another limitation could be that our patient population could have been mixed in terms of *S aureus* colonization, because this was based on 1 single culture and may have benefitted less from omiganan treatment than a population with abundantly colonized or infected AD lesions.

Table II. Analysis results: Intention-to-treat analysis

	Omiganan 1% versus vehicle			Omiganan 1.75% versus vehicle			Omiganan 2.5% versus vehicle		
Outcome	**Estimated difference**	**95% CI**	***P* value**	**Mean**	**95% CI**	***P* value**	**Mean**	**95% CI**	***P* value**
oSCORAD	2.0	0.52 to 4.51	.12	3.83	1.3 to 6.36	.003	2.52	0.0 to 5.04	.05
EASI	0.2	−0.8 to 1.19	.69	1.36	0.35 to 2.36	.008	0.57	−0.41 to 1.55	.25
POEM	0.66	−2.07 to 3.39	.63	4.31	1.59 to 7.02	.002	2.68	−0.01 to 5.38	.05
NRS itch, first half of the day	−0.4	−10.3 to 9.4	.93	3.4	−6.5 to 13.3	.49	4.7	−5.2 to 14.6	.35
NRS itch, second half of the day	1.2	−8.2 to 10.5	.80	4.9	−4.5 to 14.3	.30	3.7	−5.6 to 13.1	.43
Erythema target lesion by 3D photography	5.5	−5.93 to 16.92	.34	17.84	6.44 to 29.24	.003	1.02	0.04 to 2.0	.04
Roughness target lesion by 3D photography	0.19	−0.78 to 1.16	.7	1.35	0.37 to 2.33	.008	1.02	0.04 to 1.99	.04
TEWL flux, $g/m^2/h$	−0.49	−8.25 to 7.27	.90	5.57	−2.27 to 13.41	.16	4.0	−3.91 to 11.91	.32
IFN-α biopsy, mRNA relative to ABL, %	−15.9	−80.4 to 261.3	.81	−35.9	−85.1 to 175.3	.54	46.6	−65.4 to 521.1	.60
IFN-γ biopsy, mRNA relative to ABL, %	−51.8	−87.4 to 83.8	.28	−33.2	−82.2 to 150.6	.54	−30.6	−81.2 to 156.1	.58
IL-6 biopsy, mRNA relative to ABL, %	−80.5	−94.8 to −26.9	.02	−30.6	−81.5 to 160.3	.58	−71.3	−92.2 to 5.9	.06
IL-31 biopsy, mRNA relative to ABL, %	−16.1	−76.9 to 204.1	.79	25.4	−66.3 to 366.1	.73	−48.2	−85.7 to 87.9	.31
Eotaxin biopsy, mRNA relative to ABL, %	−8.4	−62.4 to 122.9	.84	24.8	−48.7 to 203.8	.62	−4.7	−60.4 to 129.4	.91
IFN-γ TAP, ng/ml, %	64	0 to 169.2	.05	33.1	−18.6 to 117.5	.25	25.1	−22.6 to 102.3	.36
IL-10 TAP, ng/ml, %	15.3	−25.7 to 79.0	.52	−9.5	−42 to 41.2	.66	−11.5	−43.2 to 37.8	.58
IL-13 TAP, ng/ml, %	20	−45.5 to 164.3	.65	7.7	−51.4 to 138.8	.85	20	−45.7 to 165.3	.65
IL-31 TAP, ng/ml, %	75	−30 to 337.4	.23	24.3	−50.6 to 212.4	.64	18.4	−51.6 to 189.4	.71
IL-6 TAP, ng/ml, %	−7.6	−58.8 to 107.1	.85	−20.6	−65.3 to 81.7	.58	−17.7	−62.6 to 81.2	.62
Eotaxin TAP, ng/ml, %	−17.1	−52.7 to 45.4	.51	−24.1	−56.7 to 33.1	.33	8.6	−36.8 to 86.8	.76
IFN-α serum, pg/ml, %	−4.8	−15.1 to 6.8	.40	−3.7	−14.2 to 8.0	.51	−4.7	−15 to 5.9	.41
IFN-γ serum, pg/ml, %	−7.1	−38 to 39.2	.72	13.8	−24.4 to 71.2	.53	21.9	−19 to 83.6	.34
TARC serum, pg/ml, %	−7.4	−27.3 to 18.1	.53	26.4	−1.7 to 62.7	.07	2.7	−19.5 to 30.9	.83
IL-31, pg/ml, %	−9.3	−28.3 to 14.8	.41	−12	−31.2 to 12.5	.30	−13.8	−32.5 to 10.0	.23
Eotaxin, pg/ml, %	5.5	−2.6 to 14.3	.19	−4.1	−11.7 to 4	.31	−1.2	−8.8 to 7.1	.77
Staphylococcus aureus in culture, CFU/ml, %	−84.3	−98.4 to 51.6	.11	−83.6	−98.3 to 61.9	.12	−92.5	−99.2 to −28.5	.02
qPCR *Staphylococcus aureus*, copies/μl, %	−70.5	−96 to 119.7	.23	−53.8	−94.2 to 265.4	.46	−63.2	−95.2 to 184.9	.34

3D, 3-Dimensional; *CFU*, colony-forming units; *CI*, confidence interval; *EASI*, Eczema Area and Severity Index; *IFN*, interferon; *IL*, interleukin; *mRNA*, messenger RNA; *NRS*, numeric rating scale; *oSCORAD*, objective Scoring Atopic Dermatitis; *POEM*, Patient-Oriented Eczema Measure; *qPCR*, quantitative polymerase chain reaction; *TAP*, transdermal analysis patches; *TARC*, thymus and activation-regulated chemokine; *TEWL*, transepidermal water loss assessment.

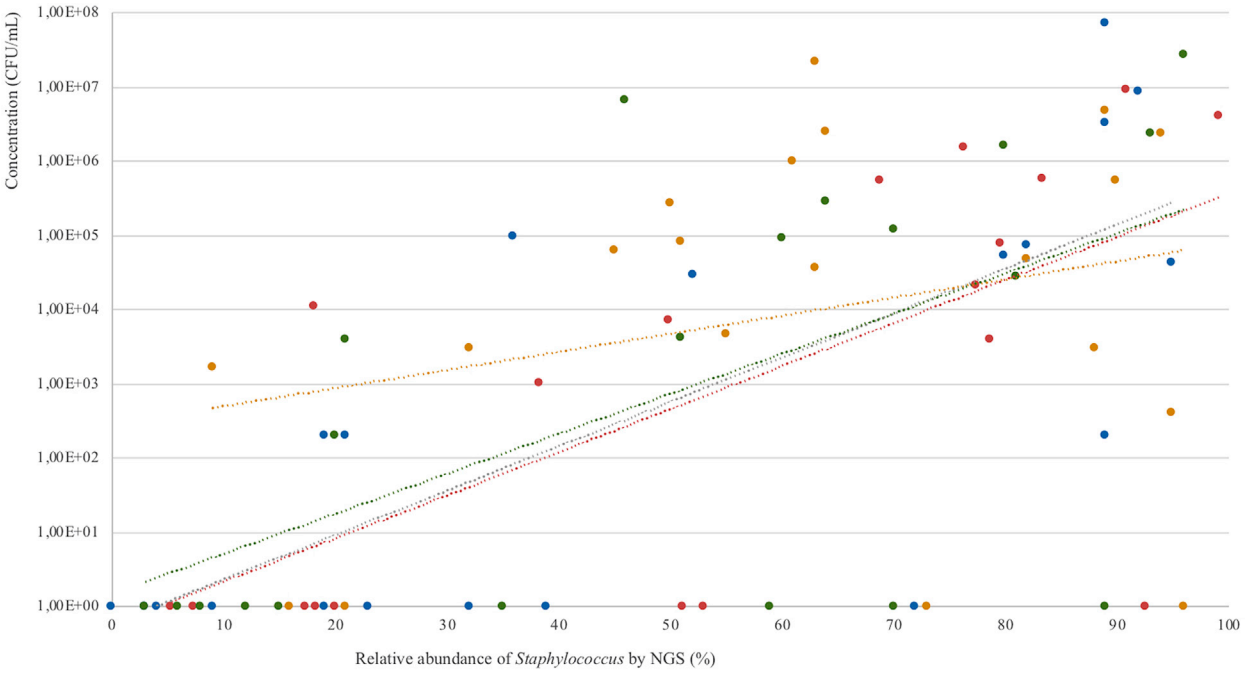

Fig 2. Mild to moderate atopic dermatitis. Presence of *Staphylococcus aureus* based on culture or qPCR in relation to the relative abundance of *Staphylococcus* species determined by next-generation sequencing at baseline of the target lesion of each patient. Red indicates vehicle, blue indicates omiganan 1%, orange indicates omiganan 1.75%, and green indicates omiganan 2.5%. *CFU*, Colony-forming units.

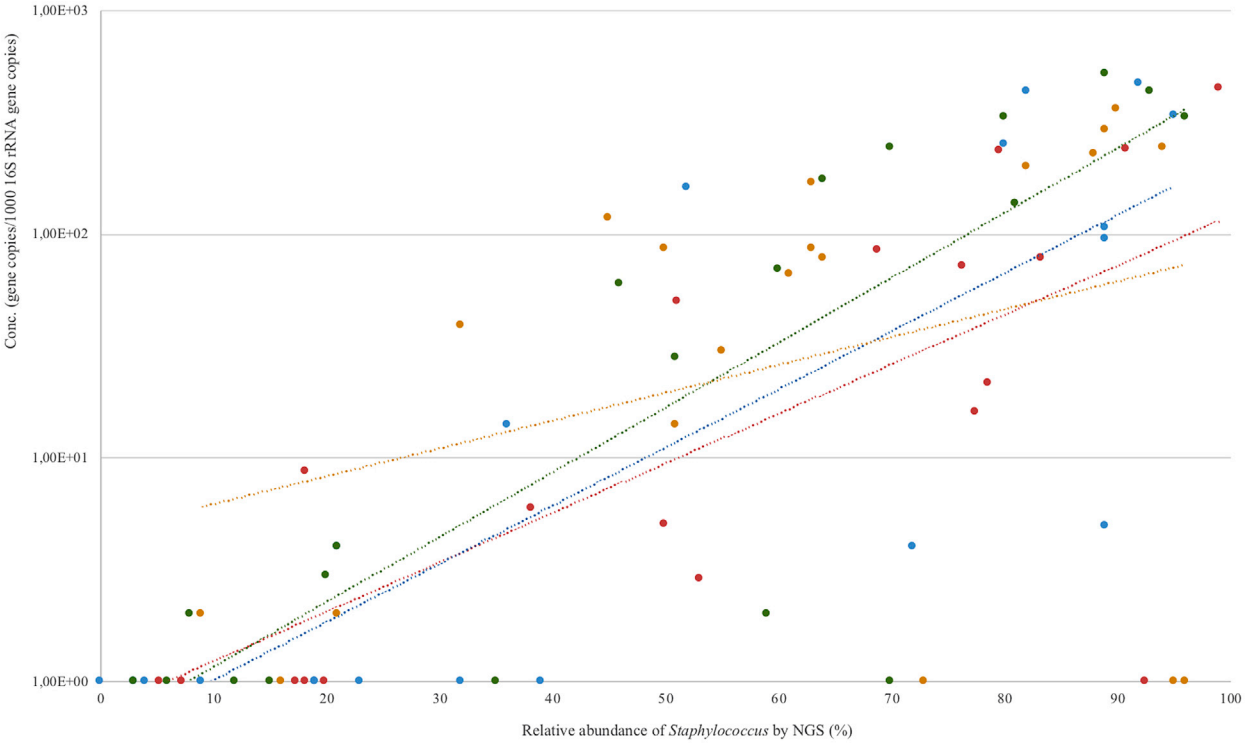

Fig 3. Mild to moderate AD. Presence of *Staphylococcus aureus* based on quantitative polymerase chain reaction in relation to the relative abundance of *Staphylococcus* species determined by next-generation sequencing at baseline of the target lesion of each patient. Red indicates vehicle; blue indicates omiganan 1%; orange indicates omiganan 1.75%; and green indicates omiganan 2.5%. *AD*, Atopic dermatiti; *rRNA*, ribosomal RNA.

Based on our results, the future development of omiganan may be focused on diseases where *S aureus* plays a more central role; for example, in superinfected AD, a nonantibiotic drug like omiganan may reduce the need for oral antibiotics that are increasingly associated with bacterial resistance. A clear clinical benefit was shown in a case series of 3 patients with *S aureus*–related dermatoses who were treated with a topical bacteriophage-derived endolysin.[23] Omiganan might also have clinical utility in the eradication of multidrug-resistant *S aureus* strains in long-term carriers, where it might replace the long-term use of oral antibiotics.

In conclusion, this study showed that topical administration of omiganan twice daily for up to 28 days in patients with mild to moderate AD led to a recovery of dysbiosis, but without clinical improvement. Our findings do not support dysbiosis as a viable monotherapy drug target in mild to moderate AD, and they indirectly suggest that *S aureus may* play a less prominent role in the pathogenesis of mild to moderate AD.

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