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Datasheet for the decision of 27 May 2025

Case Number: T 1207/23 - 3.3.04

Application Number: 14747994.3

Publication Number: 3019185

IPC: A61K38/16, A61K38/21, A61K31/56, A61K31/573, A61K45/06, A61P17/00, A61K38/47

Language of the proceedings: EN

Title of invention:
Combination treatment for atopic dermatitis

Patent Proprietor:
Micreos Human Health B.V.

Opponent:
SONN Patentanwälte OG

Headword:
Endolysin/corticosteroid combination/MICREOS HUMAN HEALTH

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

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Decisions cited:
G 0002/21

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Case Number: T 1207/23 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 27 May 2025

Appellant: (Opponent)	SONN Patentanwälte OG Riemergasse 14 1010 Wien (AT)
Representative:	SONN Patentanwälte GmbH & Co KG Riemergasse 14 1010 Wien (AT)
Respondent: (Patent Proprietor)	Micreos Human Health B.V. Bankaplein 2 2585 EV Den Haag (NL)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 20 April 2023 concerning maintenance of the European Patent No. 3 019 185 in amended form**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	B. Rutz
	R. Romandini

Summary of Facts and Submissions

I. The appeal by the opponent (appellant) lies from the decision of the opposition division that European patent No. 3019185, entitled "*Combination treatment for atopic dermatitis*", met the requirements of the EPC in its amended form according to auxiliary request 1 (originally filed as auxiliary request 4).

II. The patent had been opposed on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and of Article 100(b) and (c) EPC.

III. In the decision under appeal, the opposition division found that the subject-matter of claim 1 of auxiliary request 1 was inventive when starting from the disclosure of document D4 as the closest prior art.

IV. In its reply to the appeal, the respondent relied on the set of claims of the patent as maintained (auxiliary request 1 in the decision under appeal) and the sets of claims of auxiliary requests 2 and 3, which had been filed during the opposition proceedings as auxiliary requests 5 and 6.

V. The board summoned the parties to oral proceedings, as requested, and informed them of its preliminary opinion in a communication under Article 15(1) RPBA.

VI. With a letter dated 27 March 2025, the respondent resubmitted auxiliary requests 2 and 3 and a document that had first been filed during examination, dated 20 March 2013 and entitled "*How does Gladskin*

work?" (D9).

VII. With a letter dated 25 April 2025, the appellant indicated that it withdrew its request for oral proceedings and would not be attending.

VIII. Claim 1 of auxiliary request 1 (upheld in the decision under appeal) reads as follows.

"1. A composition comprising a first and a second compound, wherein said first compound is a corticosteroid and said second compound is a compound specifically targeting *Staphylococcus* and comprises at least one cell wall binding domain specifically binding the peptidoglycan cell wall of said *Staphylococcus*, wherein said second compound further comprises one or more enzymatic active domains exhibiting target bond specificity, wherein said target bond is an essential bond in a peptidoglycan layer of said *Staphylococcus*, and wherein said second compound is a polypeptide that has at least 80% identity with SEQ ID NO: 2, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 76, 78, 80, 82, 84, 86, 88, 90, 92, or 94; and/or said cell wall binding domain has at least 80% identity to any of SEQ ID NO: 4, 6 or 8; and/or wherein said one or more enzymatic active domains has at least 80% identity to any of SEQ ID NO: 10, 12, 14, 16, 18, 98 or 100."

Claim 1 of auxiliary request 2 differs from claim 1 of auxiliary request 1 in the following passages (differences underlined): "a polypeptide that has at least 80% <u>sequence</u> identity <u>over its entire length</u> with SEQ ID NO: 2, ..." and "said one or more enzymatic active domains has at least 80% <u>sequence</u> identity to any of SEQ ID NO: 10, ...".

Claim 1 of auxiliary request 3 reads as follows:

"1. A composition comprising a first and a second compound, wherein said first compound is a corticosteroid and said second compound is a compound specifically targeting *Staphylococcus* and comprises at least one cell wall binding domain specifically binding the peptidoglycan cell wall of said *Staphylococcus*, wherein said second compound further comprises one or more enzymatic active domains exhibiting target bond specificity, wherein said target bond is an essential bond in a peptidoglycan layer of said *Staphylococcus*, and wherein said second compound is a polypeptide that has at least 80% sequence identity over its entire length with SEQ ID NO: 84."

IX. The oral proceedings took place in the absence of the appellant, which was treated as relying on its written submissions (Rule 115(2) EPC and Article 15(3) RPBA). At the end of the oral proceedings the chairwoman announced the board's decision.

X. The following documents are referred to in this decision.

D4 K. L. Hon et al., "*Combined Antibiotic/ Corticosteroid Cream in the Empirical Treatment of Moderate to Severe Eczema: Friend or Foe?*", Journal of Drugs in Dermatology 11(7), 2012, 861-864

D6 WO 2012/150858 A1

D9 Anonymous, "*Bacterial skin balance*", 20 March 2013, https://web.archive.org/web/20130320002931/http://www.gladskin.com/content/HowItWorks

XI. The appellant's submissions are summarised as follows.

Auxiliary request 1 (upheld in the decision under appeal)
Inventive step (Article 56 EPC) - claim 1

The difference between the cream (i.e. a composition) disclosed in document D4 and the subject-matter of claim 1 was that D4 relied on an antibiotic (fucidin) while the opposed patent used recombinant antibacterial enzymes which were generated by shuffling domains of specific endolysins or bacteriocins.

In the decision under appeal, the opposition division had acknowledged in point 44 that there was no direct comparative evidence on file comparing treatment results obtained according to the alleged invention and those obtained by the treatment disclosed in document D4.

The technical problem had to be formulated on the basis of an effect resulting from the difference between document D4 and the claimed invention (see decision G 2/21, point 24 of the Reasons). However, there was no evidence on file which would suggest that using the claimed polypeptides instead of fucidin would make it possible to reduce the use of corticosteroid.

The example in the patent stated that some of the patients had reported that they needed "less" corticosteroids ([0139]). It was not clear from the patent what "less corticosteroids" was compared with, such as a standard treatment regimen, previous treatments, the same corticosteroid, the same disease, etc. Moreover, it was not clear that "less

corticosteroids" was less of the same corticosteroid when given alone. The "less need" was merely a "report" from the patients, and thus subject to the individual perception of each patient, and not the result of objective scientific monitoring.

There was no documented effect associated with using the claimed second compound rather than fucidin, as disclosed in document D4. The initial burden of proof of an effect to support inventive step resided with the respondent. This burden of proof had not been met by the study in the patent.

The objective technical problem to be solved by the present invention was therefore the provision of an alternative to the composition of document D4.

The claimed solution was obvious to the skilled person. The selection of the claimed second compound was entirely arbitrary, and consequently not based on an inventive step. The domains and polypeptides claimed in the opposed patent were for the most part already disclosed in document D6.

SEQ ID NO: 84 of the present application corresponded to SEQ ID NO: 29 in document D6. The polypeptide of SEQ ID NO: 29 encoded by the nucleic acid of SEQ ID NO: 9 (see Table 1) was even one of the compounds exemplified in more detail in document D6 (see Fig. 4) and was thus merely one of several straightforward options for the skilled person.

All of the sequences and sequence combinations claimed in claim 1 were simply straightforward options for the skilled person who was trying to find an alternative to the cream disclosed in document D4. This applied all

the more in view of the concern regarding "... *emergence of fucidin-resistant S. aureus*" in document D4 (Abstract, Conclusions, last line).

Auxiliary requests 2 and 3
Inventive step (Article 56 EPC) - claim 1

The same argument applied as that for auxiliary request 1.

XII. The respondent's submissions are summarised as follows.

Auxiliary request 1 (upheld in the decision under appeal)
Inventive step (Article 56 EPC) - claim 1

The difference between document D4 and the subject-matter of the claim was that an endolysin was used instead of an antibiotic. The effect of the difference was that less corticosteroids could be used, thus decreasing the chance or degree of side effects induced by the corticosteroids.

It seemed that the appellant wanted to apply the standards for obtaining market authorisation for a pharmaceutical to the assessment of inventive step. However, there was no requirement under the EPC to conduct a clinical trial to demonstrate a technical effect.

The experiment in the application as filed was guided by a physician. In two out of eight patients, no corticosteroids were required any more; in three out of eight patents, less corticosteroids could be used; and in one out of eight patients, less corticosteroids could be used until a relapse occurred. This clearly

demonstrated a surprising effect, since this effect was not suggested anywhere in the prior art.

The appellant questioned the outcome of the experiment disclosed in the application as filed. In such a case, the appellant should provide evidence by verifiable facts, e.g. by submitting experimental data itself.

Auxiliary requests 2 and 3
Inventive step - claim 1

The claim included as a second compound a polypeptide that had at least 80% sequence identity over its entire length with SEQ ID NO: 84. The argument submitted in relation to auxiliary request 1 applied.

XIII. In its written submission, the appellant (opponent) requested that the decision under appeal be set aside and that the European patent be revoked.

The respondent (patent proprietor) requested that:
- the appeal be dismissed and the decision to maintain the patent in amended form be upheld;
- auxiliarily, that the patent be maintained based on the sets of claims of auxiliary request 2 or 3, filed on 20 January 2023 during the opposition proceedings as auxiliary requests 5 and 6 and resubmitted on 27 March 2025.

Furthermore, it requested that a document by Micreos entitled "*How does Gladskin work? Bacterial skin balance*", dated 20 March 2013, which had been cited in the International Search Report (ISR) and submitted with the letter of 27 March 2025, be admitted into the appeal proceedings.

Reasons for the Decision

Admission of document D9 (Article 13(2) RPBA)

1. Document D9 was cited in the International Search Report (ISR) but was not (apparently) relied upon during the opposition proceedings (see consolidated list annexed to the decision under appeal). It was submitted by the respondent during the appeal only after notification of a communication under Article 15(1) RPBA by the board, thereby constituting an amendment to the appeal case. Its admittance is thus subject to Article 13(2) RPBA.

2. The respondent referred to the document during oral proceedings as further evidence that Staphefekt™, the active ingredient of Gladskin, was publicly known and available at the relevant date. As the board did not question this and assumed that Staphefekt™ was identical to the polypeptide of SEQ ID NO: 84 (see point 5. below), and ultimately found no comparative data in the document, it considered the document to be irrelevant for assessing inventive step. Its admission was therefore not decided upon.

Auxiliary request 1 (upheld in the decision under appeal)
Inventive step - claim 1

Closest prior art

3. In the decision under appeal, inventive step was assessed starting from document D4 (see point 40 there), which discloses the use of the antibiotic fucidin in combination with the corticosteroid betamethasone valerate for the treatment of atopic

eczema (see Abstract and page 861, right-hand column, first paragraph). Fucidin targets *S. aureus*, which is considered the most prevalent organism in moderate to severe eczema (see document D4, Abstract). The parties agreed that document D4 was to be used as the starting point for assessing inventive step.

Difference, effect and objective technical problem

4. The parties also agreed that the difference between the claimed subject-matter and the disclosure of document D4 lay in the presence of a different bactericide in the combination, namely the polypeptides listed in the claim, in particular "a polypeptide that has at least 80% identity with SEQ ID NO: [...] 84". The question of what effect resulted from this difference was in dispute between the parties.

5. In addressing this question, the board assumes, in the respondent's favour, that the compound Staphefekt™ tested in the application as filed (see Table 1) is identical to the polypeptide with the amino acid sequence of SEQ ID NO: 84 (see Table 2 and Sequence Listings).

6. The application as filed states that "*corticosteroid use and symptom relief was monitored in eight patients, of whom the treatment of several kinds of dermatitis with Staphefekt™ was guided and observed by a physician*" and "*patients reported less need of corticosteroids anamnestically*" (page 44, lines 23 to 27). The board concludes from this statement that the patients received only corticosteroid before the treatment with Staphefekt™ and that the "*reported less need*" was by comparison with corticosteroid alone. This was not disputed by the respondent. A comparison with

the combination treatment in document D4 is thus lacking in the application as filed.

7. The opposition division stated in its decision that "[w]*hile there is no direct comparative evidence comparing treatment results obtained according to the invention with those that would be obtained by D4, it would seem that the Patent puts forward experimental evidence making it at least plausible that corticosteroid usage in certain patients (*S. aureus *carriers) could be reduced when combining with active endolysins comprising both an enzymatically active domain and a cell wall binding domain at least plausible* [sic]" (point 44 of the Reasons). The opposition division concluded that "*combining an active endolysin with a corticosteroid would provide a treatment for dermatitis/eczema where corticosteroid use could be reduced in at least some patients who have* S. aureus *or who may be exposed to this pathogen*" (point 45 of the Reasons). Finally, the opposition division reasoned that "[s]*ince document D4 does not disclose any reduction in corticosteroid use it cannot be assumed that this is an effect inherently arising from the use of any antibacterial. Although it could be postulated that antibiotic use would lead to a corresponding reduction in corticosteroid use this has to be regarded as speculative*" (point 46 of the Reasons).

8. The opposition division thus considered that a reduction in corticosteroid use was made plausible in the application as filed, while such an effect had not been disclosed in document D4 and would be "speculative". It then formulated the objective technical problem to be solved as "*the provision of a*

treatment for dermatitis/eczema where corticosteroid use could be reduced".

9. The board does not agree with the opposition division on this technical effect and resulting objective technical problem. In the problem-solution approach, it is necessary to determine the technical effect(s) or result(s) achieved by and linked specifically to the distinguishing feature(s) over the prior art (see decision G 2/21, point 24 of the Reasons). If the patent proprietor relies on an effect when formulating the objective technical problem, it must show that the effect is indeed achieved, and if necessary provide comparative tests (see Case Law of the Boards of Appeal of the EPO, 10th edition 2022, I.D.4.3.1. and 4.3.2). An effect not tested in a comparison with a prior art composition cannot simply be assumed to result from the difference between the claimed composition and that prior art.

10. The opposition division also erred in requiring the opponent to provide "*evidence which would negate this evidence*" (point 45 of the Reasons). Since the application as filed does not provide any comparative evidence, this evidence cannot be negated. Nor is it for the opponent to show that the closest prior art does not achieve the alleged effect. On the contrary, to rely on the effect it would have been for the patent proprietor to show that the treatment disclosed in document D4 did not lead to a reduction in corticosteroid use, or required more corticosteroid than the claimed treatment.

11. The board agrees with the respondent that clinical trials are not always required to establish inventive step under the EPC. However, in the present case, it is

the absence of comparative data of any sort that prevents the board from taking the alleged effect into account when formulating the objective technical problem.

12. In conclusion, an effect resulting from the difference to the closest prior art D4 has not been shown in the application as filed or by any other evidence on file. The objective technical problem is therefore formulated as the provision of an alternative combination treatment for eczema in patients who carry *S. aureus* on their skin.

Obviousness

13. The skilled person looking for alternative combination treatments would have found an indication in document D4 that the antibiotic used in the disclosed combination treatment had drawbacks for reducing bacterial load. The authors of document D4 find that "*the percentage of fucidin-resistant* S. aureus *increased from 8% to 58%*" (page 862, left-hand column) and conclude that "*long-term impact of resistance development of* S. aureus *in this group of patients* [receiving combined treatment] *will need to be carefully weighed*" (page 863, right-hand column). Document D4 also stresses that "[t]*he most prevalent organism in moderate to severe eczema was* S. aureus" (page 864, left-hand column, second full paragraph).

14. The skilled person therefore had a motivation to look for alternative agents which specifically target *S. aureus* to be combined with a corticosteroid to treat atopic eczema.

15. Document D6 also mentions the problem of antibiotic resistance by stating that "Staphylococcus aureus *is a major human pathogen frequently implicated in several serious infectious diseases and food poisoning. Its treatment becomes more and more difficult because of emerging antibiotic resistant strains. Endolysins from phages infecting* Staphylococcus aureus *have been shown to potentially control these pathogens*" (page 1, lines 16 to 20).

16. Document D6 discloses "*retrofitted*" chimeric enzymes against *S. aureus* (page 1, last paragraph and page 2, first paragraph; Figures 4 and 5; Table 1), including "*M23-LST_Ami2638_CBD2638*", which combines an N-terminal M23 endopeptidase domain (from lysostaphin of *S. simulans*), a central amidase domain of phage Φ2638 and a C-terminal cell-wall-binding domain of phage Φ2638 (see Table 1; SEQ ID NOs: 9 (nucleic acid sequence) and 29 (amino acid sequence) and paragraph bridging pages 5 and 6) for the treatment of skin infections (see page 15, lines 4 to 11; claims 8 and 13). The fact that SEQ ID NO: 29 of document D6 is identical to SEQ ID NO: 84 listed in the present claim has not been disputed.

17. The construct of SEQ ID NO: 9 is "[e]*ven more preferred*" in document D6 (see page 5, lines 30 to 33) as it "*demonstrated at least 20% increased lytic activity as compared to* S. aureus *bacteriophage Φ2638a endolysin while the lytic activity is maintained after lyophilisation and reconstitution*" (page 6, lines 10 to 12 and Figures 4 and 5). The nucleic acid molecule with SEQ ID NO: 9 is also the subject of dependent claim 8 of document D6.

18. The respondent has not argued that the skilled person would be dissuaded from replacing the antibiotic used in document D4 with one of the chimeric endolysins used in document D6. Nor has the respondent argued that there would have been no reasonable expectation of success when combining corticosteroids with the chimeric endolysins of document D6 to achieve a therapeutic effect in eczema patients.

19. In any case, the board does not see any teaching in the prior art that would have dissuaded or prevented the person skilled in the art from replacing the antibiotic used in document D4 with a chimeric endolysin (e.g. of SEQ ID NO: 29) disclosed in document D6. The board further finds that there would have been a reasonable expectation that the chimeric endolysin of SEQ ID NO: 29 disclosed in document D6 could achieve effective control of *S. aureus* (see examples in document D6) and would thus be suitable for replacing fucidin in the combination treatment disclosed in document D4.

20. It would thus have been obvious to the skilled person to replace the antibiotic in document D4 with the chimeric endolysin of SEQ ID NO: 29 disclosed in document D6.

21. The subject-matter of claim 1 lacks an inventive step (Article 56 EPC).

Auxiliary requests 2 and 3
Inventive step - claim 1

22. Claim 1 of these requests includes as the second compound a polypeptide that has at least 80% sequence identity over its entire length with SEQ ID NO: 84.

23. The same considerations apply as for the main request (see points 3. to 20. above).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated