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Datasheet for the decision of 4 July 2024

Case Number: T 0668/22 - 3.3.04

Application Number: 11770786.9

Publication Number: 2629769

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Language of the proceedings: EN

Title of invention:
Cysteine and ageing-associated anorexia

Patent Proprietors:
Société des Produits Nestlé S.A.
INRA

Opponent:
Fresenius Kabi Deutschland GmbH

Relevant legal provisions:
EPC Art. 83

Keyword:
Sufficiency of disclosure - (yes)

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0668/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 4 July 2024

Appellant: (Patent Proprietor 1)	Société des Produits Nestlé S.A. Entre-deux-Villes 1800 Vevey (CH)
Appellant: (Patent Proprietor 2)	INRA 147 Rue de l'Université 75338 Paris (FR)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Opponent)	Fresenius Kabi Deutschland GmbH Else-Kröner-Str. 1 61352 Bad Homburg (DE)
Representative:	Fresenius Kabi Deutschland GmbH Patent Department Pharmaceuticals Division Borkenberg 14 61440 Oberursel (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 14 January 2022 revoking European patent No. 2629769 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. European patent No. **2 629 769** (patent in suit) was granted with a set of eight claims.

Claim 1 as granted reads as follows:

1. Cysteine, provided in the form of a nutritional composition, wherein the nutritional composition contains a protein fraction comprising at least 3.0 weight-% cysteine, for use in the prevention of ageing-associated anorexia, to be administered to an elderly subject in a daily dose in the range of 0.03 to 0.15 g/kg body weight.

II. The patent in suit was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

III. The documents cited in the proceedings included the following:

D1: Am J Clin Nutr 66, 760-773 (1997)

D2: International Journal of Obesity 39, 447-455 (2015)

D13: FASEB J. 22, 659-661 (2007)

D14: A. Amin, "The effect of L-cysteine on appetite in humans", Thesis, Imperial College London, 2013

D17: FDA Guidance for Industry, Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 2005

IV. The decision under appeal is the opposition division's decision revoking the patent in suit.

It is based on the patent proprietors' main request that the opposition be rejected and the patent be maintained as granted and on eight amended sets of claims of auxiliary requests 1 to 8, as identified in point XVIII of the decision.

V. The decision under appeal includes the following findings.

(a) The ground for opposition under Article 100(c) EPC did not prejudice the maintenance of the patent as granted.

(b) There were serious doubts, based on verifiable facts, that the cysteine composition defined in claim 1 as granted was suitable for attaining the claimed prevention of ageing-associated anorexia. As a consequence, the ground for opposition under Article 100(b) EPC (insufficiency of disclosure) prejudiced the maintenance of the patent as granted.

(c) The same objection for insufficiency of disclosure applied to claim 1 of each of auxiliary requests 1 to 7 (Article 83 EPC).

(d) Auxiliary request 8 was not allowable under Article 123(3) EPC.

VI. The patent proprietors (appellants) filed an appeal against this decision. They requested that the decision revoking the patent be set aside and that the case be remitted to the opposition division for examination of the remaining grounds for opposition on the basis of the main request (i.e. the patent as granted) or,

alternatively, the claims of one of auxiliary requests 1 to 7 submitted with the grounds of appeal.

VII. With their statement setting out the grounds of appeal, the appellants submitted the following documents:

D19: Perception & Psychophysics 17(2), 140-146 (1975)

D20: Eur J Nutr 53, 963-971 (2014)

VIII. In a communication under Article 15(1) RPBA issued in preparation for oral proceedings, the board addressed the issue of claim construction. A point for discussion was whether the use for the prevention of ageing-associated anorexia recited in claim 1 was exclusively a medical use (see points 1.3 to 1.5 of the board's communication dated 5 June 2024). A further question was whether claim 1, as it no longer qualified anorexia as a "disorder", extended beyond the content of the application as filed (see point 2.4 of the board's communication).

IX. By letter dated 26 June 2024, the appellants filed a set of auxiliary claim requests designated as "main request A" and auxiliary requests 1A, 2A, 3A, 4A, 5A, 6A and 7A.

X. **Claim 1 of main request A** reads as follows (differences in comparison with claim 1 of the main request marked in bold by the board):

1. Cysteine, provided in the form of a nutritional composition, wherein the nutritional composition contains a protein fraction comprising at least 3.0 weight-% cysteine, for use in the prevention of ***a disorder related to malnutrition, wherein the disorder is*** *ageing-associated anorexia, to be*

administered to an elderly subject in a daily dose in the range of 0.03 to 0.15 g/kg body weight.

XI. Oral proceedings before the board took place on 4 July 2024. During the oral proceedings, the board admitted the request entitled "main request A". The appellants withdrew their main request and auxiliary requests 1 to 7. At the close of the oral proceedings, the board announced its decision remitting the case to the opposition division for further prosecution.

XII. The board's decision set out below is based on the claims of main request A. Claim 1 is the only independent claim of that request.

XIII. The appellants' arguments pertinent to main request A may be summarised as follows.

Admittance of main request A (Article 13(2) RPBA)

Main request A responded to the board's objection that claim 1 as granted might not be restricted to a medical use and consequently did not find support in the application as filed. The fact that this issue was raised for the first time in the board's communication under Article 15(1) RPBA constituted an exceptional circumstance within the meaning of Article 13(2) RPBA that justified admitting main request A.

Amendments (Article 84 EPC)

"Ageing-associated anorexia" designated a therapeutic indication. As this term was present both in claim 1 as granted and in claim 1 of main request A, it was not open to objection for lack of clarity in opposition appeal proceedings.

Moreover, the explicit characterisation as a "disorder related to malnutrition" in claim 1 of main request A

left no doubt that only pathological ageing-associated anorexia was intended.

The product form of a nutritional composition, as exemplified in claim 8, was suitable for delivering cysteine and - contrary to the respondent's view - did not give rise to any inconsistency with the therapeutic use defined in claim 1.

Amendments (Articles 100(c) and 123(2) EPC)

Claim 1 of main request A was based on claims 1, 5, 6, 8 and 9, together with page 2, lines 22 to 24 and page 12, lines 5 to 6 of the application as filed.

Claim 1 as filed related to the treatment and/or prevention of malnutrition and/or disorders related to malnutrition. Claim 5 and the passage on page 4, lines 17 to 22 of the description as filed confirmed that anorexia was a disorder related to malnutrition.

The person skilled in the art would understand that the term "anorexia" encompassed ageing-associated anorexia. It was also readily apparent from the context and general disclosure in passages of the description as filed that ageing-associated anorexia was the relevant pathological disorder to be addressed by the claimed invention.

Sufficiency of disclosure (Article 83 EPC)

The setup of the experiment described in the Examples section of the patent in suit (and identically in the application as filed) was correct. The experiment showed, in a rodent model, that the food intake of ageing rats did not decrease with cysteine supplementation, which was better than what would have been expected. This favourable result providing proof of concept was obtained independently of any comparison with alanine supplementation. If converted into a human

equivalent, the dosage used in the Examples section would fall within the range specified in claim 1. The appellants had thus discharged their burden of proof by rendering the therapeutic use of claim 1 credible, and it was for the respondent to prove its objections of insufficient disclosure. The respondent had failed to do this. The data presented in the post-published documents D2 and D14 were not directly relevant and did not give rise to serious doubt about the credibility of the claimed therapeutic use.

XIV. The respondent's arguments pertinent to main request A may be summarised as follows.

Admittance of main request A (Article 13(2) RPBA)

Main request A was an amendment to the appellants' case that was not justified by exceptional circumstances. Admitting this new request would be contrary to procedural economy as it would re-introduce the term "disorder" that had been deleted in the claims as granted. Beyond the purpose of overcoming an issue under Article 100(c) EPC, the wording of main request A might also affect the assessment of novelty and inventive step.

Amendments (Article 84 EPC)

The subject-matter of claim 1 of main request A lacked clarity because the amendment that qualified ageing-associated anorexia as a disorder created a contradiction in terms. This was because a disorder was implicitly pathological, whereas ageing-associated anorexia was not by itself pathological. "Anorexia" merely meant a decreased sensation of appetite, and this did not have to have pathological consequences.

As a consequence of the amendment, it was not clear what patient group should be treated and whether claim 1 of main request A addressed only those in whom ageing-associated anorexia was linked to a pathology. Other disorders might be considered to be included, such as cachexia in an elderly person or any condition that made swallowing difficult (e.g. in post-operative patients with oesophageal cancer).

The nutritional compositions listed in dependent claim 8 included typical food products. It was inconsistent with therapeutic treatment that claim 8 was not limited to pharmaceutical products.

Amendments (Articles 100(c) and 123(2) EPC)

The combination of technical features in claim 1 of main request A was not disclosed directly and unambiguously in the application as filed as it could only be reached with more than one selection step.

Sufficiency of disclosure (Article 83 EPC)

The suitability of cysteine for the claimed therapeutic use was not rendered credible in the application as filed for the following reasons.

The use of claim 1 encompassed the administration of cysteine to humans. The probative value of the single experiment described in the Examples section was questionable since an investigation of food intake and changes in body weight in an animal model, in this case a rat model, could provide no insight on how the relevant parameter in anorexia, namely the subjective sensation of appetite, might progress (especially in human subjects).

In contrast, post-published data based on feedback from human subjects as reported in D2 and D14 suggested that cysteine actually had an anorectic effect, i.e.

that it reduced appetite, in adult humans. The suitability of cysteine for the claimed therapeutic application was also called into question by the disclosure of D19 that the taste of L-cysteine was "distinctly obnoxious" (see D19, Table 1) and of D2 that it decreased food intake in rodents (see D2, page 449, Figure 1).

The rat experiment described in the application as filed did not reflect the administration regimen of claim 1 but instead provided a daily cysteine intake higher than the dosage range defined in claim 1. Nor did the application disclose a basis for dosage conversion from rats to humans.

Furthermore, the experiment described in the application as filed lacked a valid control. This was because alanine supplementation, as used for the control diet, had not been ruled out as a possible factor that might cause a decrease in food intake, for instance because of an aversion of the rats to the taste of the alanine-supplemented control diet.

Considering that the use defined in claim 1 was not restricted to rats or human subjects, the suitability of cysteine for the claimed therapeutic use in other animals, such as elderly pets, had not been rendered credible.

In addition, the claimed upper limit of the daily dosage of 0.15 g/kg was 15 times higher than the recommended daily intake for an adult human and was likely to be too high for human subjects due to adverse side effects (see D14: page 55, last paragraph, which mentioned the occurrence of adverse effects at a dose of 0.07 g/kg).

Moreover, the scope of claim 1 with regard to the patient group could not be determined on the basis of the ill-defined term "elderly subject".

XV. The appellants (patent proprietors) requested that the decision under appeal be set aside and that the case be remitted to the opposition division for examination of the remaining grounds for opposition on the basis of the request entitled "main request A", or, alternatively, on the basis of the claims of one of auxiliary requests 1A to 7A, all filed by letter dated 26 June 2024.

XVI. The respondent (opponent) requested that the appeal be dismissed and that document D20 not be admitted.

Reasons for the Decision

1. Admittance - main request A (Article 13(2) RPBA)

1.1 The appellants amended their appeal case by filing new sets of claims after filing their grounds of appeal. As main request A was filed only after the board issued a summons to oral proceedings and a communication under Article 15(1) RPBA, the provisions of Article 13(2) RPBA apply for its admittance.

1.2 The board noted in its communication under Article 15(1) RPBA that the parties held different views on whether anorexia, specifically ageing-associated anorexia, was always pathological. Also, claim 1 as granted did not qualify anorexia as a disorder, in contrast to the claims in the application as filed. As a consequence, it might be doubted, firstly, that claim 1 as granted was limited to a

medical use and, secondly, that its wording found a basis in the application as filed (see point VIII. above and points 1.3 to 1.5 and 2.4 of the board's communication).

1.3 The appellants filed main request A to address these points.

1.4 The board's comments in the communication under Article 15(1) RPBA represent the first time in the opposition and appeal proceedings that the construction of the use defined in claim 1 ("for use in the prevention of ageing-associated anorexia") was addressed with regard to a possible extension of the claimed subject-matter beyond the content of the application as filed (Article 100(c) EPC).

1.5 Previously, the respondent had not presented a consistent view on claim construction.

Regarding the issue of sufficiency of disclosure, the respondent read claim 1 as a claim in the format according to Article 54(5) EPC restricted to a further medical use and argued that the claimed therapeutic efficacy had not been rendered credible (see section 3 of the reply to the grounds of appeal).

Regarding the issue of novelty, the respondent argued, in contrast, that the claimed subject-matter was not restricted to a further medical use (see point 4.1 of the reply to the grounds of appeal). Claim 1 should accordingly be construed as relating to cysteine-containing nutritional compositions that were inherently suitable for the claimed use if they fulfilled all compositional requirements mentioned in the claim.

But the respondent did not rely on this latter approach to claim construction in its objections under Article 100(c) EPC (see section 2 of the reply to the grounds of appeal).

1.6 In the decision under appeal, the opposition division did not address the problem of diverging approaches to claim construction and did not even provide a reasoned opinion on claim construction before turning to the assessment of the substantive objections.

1.7 In view of this case history, the board acknowledged that main request A was presented due to exceptional circumstances. Certain consequences of claim construction for the assessment of the ground for opposition under Article 100(c) EPC had been pointed out for the first time in the board's communication under Article 15(1) RPBA. Since the issue had not been raised before by the respondent or by the opposition division, the appellants had no obligation to file a claim request addressing it at an earlier stage of the proceedings.

1.8 As the objection in question was based on the absence of the term "disorder" in claim 1 as granted, the amended main request A, on account of re-introducing the term "disorder" into claim 1, is suitable for overcoming this objection (see points X. and 1.2 above).

1.9 For these reasons, the board found it appropriate to admit main request A under Article 13(2) RPBA.

2. Claim construction

2.1 Article 54(5) EPC provides that the patentability of a substance or composition comprised in the state of the art, for any specific use in a method referred to in

Article 53(c) EPC, is not excluded, provided that such use is not comprised in the state of the art.

2.2 While ageing-associated anorexia is typically mentioned in connection with its negative impact on the health of the subjects concerned, a distinction has also been made in the scientific literature between physiologic and pathologic anorexia of ageing (see D1: title). Even if it might be debatable on this basis whether ageing-associated anorexia would in every case be considered a pathological state, it was not in dispute that the term "disorder", according to its usual meaning in the medical field, would be understood to designate a pathological state, i.e. a condition necessitating therapeutic treatment.

2.3 So the use defined in claim 1 of main request A:

for use in the prevention of a disorder related to malnutrition, wherein the disorder is ageing-associated anorexia

is considered a therapeutic use in a method under Article 53(c) EPC, at least for the reason that ageing-associated anorexia is further qualified as a "disorder related to malnutrition", which may be regarded as a limiting feature.

2.4 Claim 1 of main request A is thus directed to a further medical use drafted in the claim format provided by Article 54(5) EPC.

2.5 As a consequence, the therapeutic use, which involves attaining therapeutic efficacy, has to be regarded as a technical feature of the claim.

2.6 In line with the established case law of the boards, where a therapeutic application is claimed in the format provided in Article 54(5) EPC (as is the case for current claim 1), attaining the claimed therapeutic

effect is regarded as a functional technical feature of the claim. As a consequence, such a feature may establish novelty (see Case Law of the Boards of Appeal of the European Patent Office, 10th edn. 2022, I.C.7.2.1; G 2/08, OJ 2010, 456, Reasons 5.10.9). It also has to be taken into account in the assessment of sufficiency of disclosure (see G 1/03, OJ EPO 2004, 413, Reasons 2.5.2).

3. Clarity (Article 84 EPC)

3.1 As mentioned above (see point 2.2), the parties were in agreement that the term "disorder" related to a pathological condition.

3.2 According to the respondent, however, the claims of main request A lacked clarity for the following reasons.

(a) The amendment inserting the phrase "a disorder related to malnutrition, wherein the disorder is" into claim 1 was inconsistent with the fact that ageing-associated anorexia encompassed non-pathological conditions. It could not limit the use defined in claim 1 to the prevention of pathological ageing-associated anorexia.

(b) Nor was it clear what patient group should be treated. Other disorders related to malnutrition might be considered to be included, such as cachexia in an elderly person or any condition that made swallowing difficult.

(c) Dependent claim 8, which listed examples of nutritional compositions, gave rise to a further lack of clarity since the product types mentioned in claim 8 were not limited to pharmaceutical products but also included food products. This was

inconsistent with the allegedly therapeutic indication in claim 1.

3.3 These objections cannot succeed for the following reasons.

(a) As set out in the section on claim construction (see point 2.2 above), the term "ageing-associated anorexia" may arguably encompass a non-pathological condition in addition to pathological ageing-associated anorexia (see, for instance, D1, which distinguishes between physiologic and pathologic anorexia of ageing). But the feature "for use in the prevention of disorders related to malnutrition, wherein the disorder is ageing-associated anorexia" is clear in that:

(i) it is limited to the prevention of ageing-associated anorexia

(ii) it excludes any embodiment of ageing-associated anorexia that is not a disorder related to malnutrition

(b) Claim 1 of main request A does not restrict the patient group, except for the feature that the patients are "elderly" and, therefore, are at risk of ageing-associated anorexia, which is to be prevented. Thus, the respondent's objection regarding the uncertainty about the targeted patient group has no basis in any technical feature of the claim. The term "elderly" itself was present in claim 1 as granted. It is consequently not open to objection under Article 84 EPC in opposition appeal proceedings, in accordance with the principle established by the Enlarged Board in decision G 3/14 (OJ EPO 2015, A102).

(c) The product form of a nutritional composition, as recited in claim 1 and exemplified in claim 8 of main request A, was unchanged from claims 1 and 8 as granted. It is not apparent how the product form could be in conflict with an intended therapeutic use, seeing that it is the definition of the therapeutic indication which determines that there is a therapeutic use, irrespective of the product form employed for administering the cysteine.

3.4 In conclusion, the respondent's objections under Article 84 EPC failed to convince the board that the claims of main request A lacked clarity due to an amendment of the claims as granted.

4. Amendments (Articles 100(c) and 123(2) EPC)

4.1 Claims 1, 5, 8 and 9 of the application as filed read as follows:

1. Cysteine for use in the treatment and/or prevention of malnutrition and/or disorders related thereto.

5. Cysteine for use in accordance with claim 1, wherein the disorder related to malnutrition is selected from the group consisting of anorexia, anorexia nervosa, cachexia, inflammatory diseases associated with decreased food intake, or combinations thereof.

8. Cysteine for use in accordance with one of the preceding claims, wherein the cysteine is provided in the form of a nutritional composition.

9. Cysteine for use in accordance with one of the preceding claims, wherein the nutritional composition contains a protein fraction comprising at least 3.0 weight-% cysteine, and/or wherein the cysteine

is administered in a daily dose in the range of about 0.03 to 0.15 g/kg body weight.

4.2 Claim 9 is linked to claim 8, which is the first claim to mention a nutritional composition, by back-reference and by further defining the nutritional composition. Claim 9 as filed, in combination with claims 8 and 1, provides direct disclosure of most of the features of claim 1 of main request A in combination, with the exception of the use in the prevention of ageing-associated anorexia and administration to an elderly subject.

4.3 Ageing-associated anorexia is not mentioned in the claims as filed. It is, however, mentioned twice in the description as filed (on pages 2 and 12), in passages that attribute an anti ageing-associated anorexia property to cysteine. Pointers to ageing-associated anorexia or malnutrition are also found in the application as filed in the Examples section (see pages 10 to 12), in the introductory background section (page 1, line 9 to page 2, line 8) and in the summary of the invention (page 2, lines 18 to 26).

4.3.1 The background section sets out that anorexia is often present in the ageing population. Ageing-associated anorexia may have substantial adverse effects as it predisposes to pathological weight loss and malnutrition. Marked weight loss in the elderly drives morbidity and increased mortality, has a negative impact on quality of life, and contributes to frailty. As known medicaments may have unwanted side effects, there is a need for a natural way to treat and/or prevent malnutrition and disorders related thereto without unwanted side effects, in particular in the elderly (see page 1, lines 16 to 29).

4.3.2 The description then sets out that the inventors, striving to solve this problem, had found that cysteine can be used as part of a composition for enteral nutrition or a food product, to maintain or improve food intake, for example, in the elderly. The inventors found that cysteine exhibits a beneficial effect on food intake and has "an anti-anorexic property, for example an anti ageing-associated anorexia property* (see page 2, lines 18 to 24).

4.3.3 The example in the application as filed describes an animal experiment carried out with ageing rats that permitted drawing conclusions on the effect of a cysteine-supplemented diet on ageing-associated anorexia (see page 12, lines 3 to 6).

4.4 On this basis, it can be acknowledged that the use defined in claim 1, i.e. the use in the prevention of a disorder related to malnutrition, where the disorder is ageing-associated anorexia, does not go beyond the content of the application as filed.

4.5 Administration to the elderly (i.e. those at risk of ageing-associated anorexia) fits in this context and is explicitly mentioned in claim 6 and on page 5, lines 3 to 4. Providing a cysteine-rich diet or adding cysteine to a food product is suggested as a measure to counteract the decrease in food consumption that occurs in the elderly (see the paragraph bridging pages 2 and 3 in the application as filed).

4.6 Thus, administration to the elderly is both technically linked to the concept of preventing ageing-associated anorexia and generally disclosed.

4.7 The respondent objected that anorexia had to be selected from a list of pathologies listed as disorders in claim 5 as filed and that it required further

selections to qualify this as ageing-associated anorexia and to select prevention as the purpose of the envisaged treatment.

4.8 This argument is not convincing for the following reasons.

4.8.1 Based on the description passages summarised in point 4.3 above, it is apparent that ageing-associated anorexia is the focus of the invention as a preferred disorder. So it can be considered generally disclosed in the application as filed.

4.8.2 The restriction to prevention, which is one of the two alternatives (treatment or prevention) in claim 1 as filed, does not create new combinations of features or new technical information and cannot be regarded as extending beyond the content of the application as filed.

4.9 For these reasons, the subject-matter of claim 1 of main request A meets the requirements of Article 123(2) EPC.

5. Sufficiency of disclosure (Article 83 EPC)

5.1 The requirement of sufficiency of disclosure must be satisfied at the effective date of the patent, i.e. on the basis of the information provided in the patent application together with the common general knowledge then available to the skilled person (see T 609/02, Reasons 8). Subsequently filed evidence cannot be used to establish sufficiency of disclosure on its own.

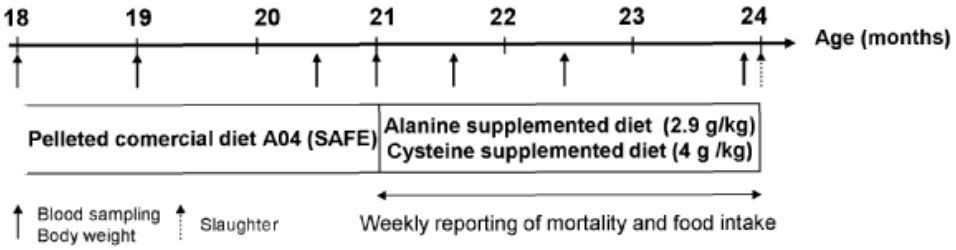
5.2 As set out above (see point 2.5), the therapeutic use, which involves attaining therapeutic efficacy, has to be regarded as a technical feature of the claim.

5.3 In the case in hand, the question to be answered on sufficiency of disclosure was whether the suitability of cysteine for preventing a disorder related to malnutrition that was ageing-associated anorexia was rendered credible by the information presented in the application as filed and common general knowledge.

Evidence provided in the application as filed

5.4 The content of the Examples section of the patent in suit on experimental data (paragraphs [0051] to [0058], including Tables 1 and 3, and Figures 1 to 4) is identical to that of the corresponding passage in the application as filed (page 9, line 17 to page 12, last line of Table 3, and Figures 1 to 4).

5.5 In the experiment described, two groups of rats were fed differently supplemented commercial diets for 14 weeks, starting at the age of 21 months. The amino acid composition of the commercial diet is provided in Table 1, and the experimental design is shown in Figure 1 of the application as filed:



5.6 The cysteine diet was supplemented with 4.0 g/kg of L-cysteine. To provide an iso-nitrogenous control, the control diet was supplemented with 2.9 g/kg of L-alanine (see page 10, lines 14 to 21 of the application as filed).

The results reported include the following.

- Cysteine supplementation did not change the mortality rate.
- Food intake significantly decreased by 0.96% per week in the alanine group but was unchanged in the cysteine group (see also Figure 4).

The conclusion drawn from the last point was that the cysteine diet blunted the decrease in food intake that occurred when rats were about 22.5 months old, suggesting that cysteine exhibited an anti ageing-associated anorexia property (see page 12, lines 3 to 6).

Objections relating to the experimental set-up

5.7 The experimental approach described in the Examples section of the application as filed appears to be suitable for providing evidence on the efficacy of cysteine in the claimed therapeutic indication. The following considerations are relevant.

5.7.1 The respondent never actually disputed that ageing-associated anorexia or a phenomenon corresponding to it is also observed in rats, which presumably was the technical basis for the use of this animal model.

5.7.2 Also, the rats in the experiment were not reported to suffer from any other condition, apart from ageing, that might have caused reduced food intake.

5.7.3 The colloquial understanding of anorexia in its broadest sense as a "lack of appetite", on which the respondent based its argument that animal models are fundamentally unsuitable, is too general. The health issues resulting from ageing-associated anorexia are linked to insufficient food intake due to anorexia, which is the relevant factor, rather than the

associated lack of appetite. Thus, animal models are not necessarily unsuitable, and it is appropriate to observe food intake in the rat model.

5.7.4 The data reported in the application as filed show that with the cysteine-supplemented diet, there was no decrease in food intake in ageing rats (see point 5.6 above and Figure 4 of the application as filed).

5.7.5 The alanine-supplemented diet was used as a control to confirm that this effect was indeed caused by cysteine supplementation and not by some other ingredient of the commercial diet. To rule out the possibility that the effect might be due to the overall amount of protein, the control diet had to be iso-nitrogenous, which was achieved by adding alanine instead of cysteine in an appropriate concentration. According to the appellants, alanine was chosen for being a non-essential amino acid that had no effect on the function tested.

5.7.6 The respondent's speculative argument that the alanine-supplemented diet might not be a suitable control cannot succeed.

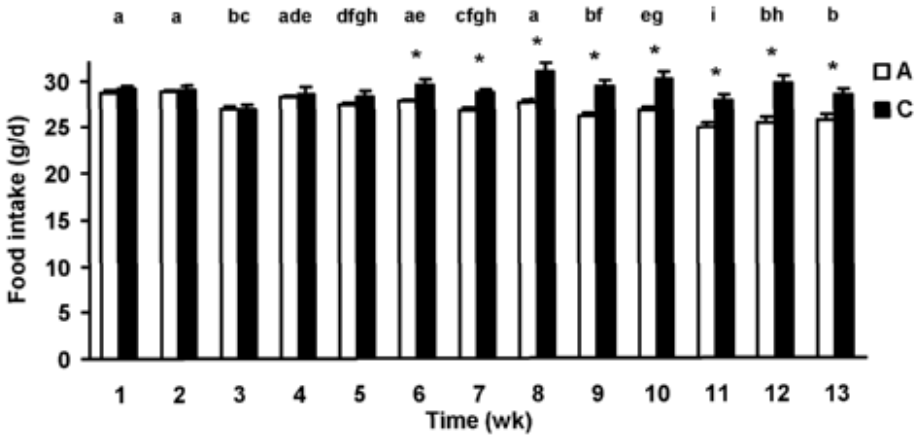
The fact that glycine was used for the negative control in rodent experiments reported in D2 (see page 448, left-hand column, fifth paragraph) and in studies with human volunteers reported in D14 (page 25, last paragraph and page 26, first paragraph) does not speak against the suitability of alanine.

In the experiment reported in the application as filed, food intake decreased in the alanine group towards the end of the experiment, which corresponds to the usual decrease in food intake that the person skilled in the art would have expected to see in ageing subjects.

The respondent's argument that rats might have an aversion to the taste of alanine and of the alanine-

supplemented diet was not supported by any evidence. It is indeed disproved by Figure 4 in the application as filed, which shows that in the initial weeks of the experiment, food intake was the same in animals receiving the alanine-supplemented diet ("A") and in those receiving the cysteine-supplemented diet ("C").

Figure 4 :



In conclusion, the alanine-supplemented diet is considered an appropriate control diet since there is no adequately substantiated reason for doubting its suitability.

5.7.7 The finding that food intake did not decrease in the test cohort receiving the cysteine-supplemented diet whereas it ultimately decreased in the control cohort speaks in favour of the efficacy of cysteine in the claimed therapeutic indication.

Objections based on evidence in D2, D14 and D19

5.8 The respondent argued that the evidence in D2, D14 and D19 raised doubt about the credibility of the therapeutic effect. The board did not arrive at the same conclusion for the following reasons.

5.8.1 D2 is a post-published journal article on the effect of L-cysteine on appetite in rodents and humans (see D2: title). It reports that L-cysteine reduced food intake in rodents and hunger in a small-scale study in humans (see D2: page 451, right-hand column, Discussion). The respondent contended that this appeared to contradict the data provided in the application as filed. The respondent also relied on Figure 1a of D2 to argue that the experiment in the application as filed was flawed since alanine and cysteine both acted to reduce food intake.

5.8.2 However, based on statements in D2 itself, the findings of D2 on rats cannot call those in the application as filed into question.

D2 notes that, according to prior findings reported in reference [36], cysteine supplementation had been found to lessen the age-related decline in food intake in rats, suggesting an appetite-stimulating effect in older animals. This corresponds to the teaching of the application as filed.

But the authors of D2 did not consider their own rodent data to be in contradiction to the findings in reference [36]. Instead, D2 points out that the test animals used, though adult, were still growing, and that this might also influence their response to L-cysteine. As further specified in D2 (see page 447, right-hand column, Materials and Methods, Animals) the rats were in fact 8 to 10 weeks old. With regard to the studies of D2 and reference [36], D2 concludes that "[c]ollectively, these studies suggest that cysteine may have different effects on food intake dependent on the nutritional status and age of the animals" (see D2: page 453, right-hand column, first paragraph beneath Figure 5).

This conclusion also applies to the data presented in Figure 1a of D2, which shows the acute effect of different amino acids on food intake in rodents at 1h after administration (see D2: page 448, first paragraph; page 449, first paragraph). Moreover, it has not been established whether the acute effect would contribute to the prevention of ageing-associated anorexia - in other words, whether it is relevant to the therapeutic indication of claim 1.

In conclusion, the rodent data in D2 cannot raise serious substantiated doubt about the efficacy of cysteine in the claimed therapeutic indication, nor about the suitability of an alanine-supplemented diet as the control diet in the rat experiment of the application as filed.

5.8.3 D2 also reports that cysteine reduced hunger in a small-scale study in humans (see also D2: Figure 5). This is found similarly in D14, which is a post-published thesis by one of the authors of D2. The experimental set-up, once more, focused on effects observed immediately (i.e. in an interval up to 2.5 hours) after a single administration of cysteine (in comparison with vehicle control or glycine). This does not permit any direct conclusions to be drawn on efficacy in preventing ageing-associated anorexia (see D2: page 448, right-hand column, Clinical studies, Study design and D14: page 25, last paragraph to page 26, first paragraph; page 31, Figure 2.3; page 35, Figure 2.5).

5.8.4 The respondent also relied on D19 (filed by the appellants, see point VII. above), which disclosed that cysteine had an unpleasant taste. According to the respondent, this suggested that cysteine would discourage food consumption. However, the taste

reported in Table 1 of D19 was that of powdered reagent-grade cysteine HCl as such (see D19: page 141, left-hand column, Methods). This does not permit drawing any conclusion about the likely taste of a nutritional composition as defined in claim 1 containing cysteine in admixture with at least a protein component. Thus, the respondent's argument does not amount to substantiated doubt regarding the credibility of the therapeutic efficacy of cysteine.

Objections relating to dosage and to claim breadth

5.9 Based on a cysteine content of 6.84 g/kg in the cysteine-supplemented test diet (see Table 1), a daily food intake of 27 g (Figure 4) and a body weight of the rats of about 650 g (Figure 3), it can be calculated that the daily dose of cysteine used in the example of the application as filed was about 0.28 g/kg body weight.

5.10 The respondent argued that the example did not render therapeutic efficacy credible for the dosage range recited in claim 1 of 0.03 to 0.15 g/kg body weight. This line of argument was not found convincing for the following reasons.

5.10.1 As set out above (see point 5.7.7), the rat experiment described in the Examples section of the application as filed provides the necessary proof of concept. The dosage used in the Example being higher than the upper limit of the dosage range recited in claim 1 does not invalidate the experiment as there is no reason to assume there would be no effect observed in rats at, for instance, a daily dosage of 0.15 g/kg body weight.

5.10.2 According to the appellants, when the rat dosages are converted into human equivalent dosages, these also

fall within the claimed range. The board accepts this for the following reasons.

Dosage translation from animals to humans may be considered a matter of common general knowledge. The person skilled in the art would have been aware of the body surface area (BSA) normalisation method and its use in determining the human equivalent dose (HED), which had been endorsed by the FDA (see D17: III, third paragraph; V, step 2A, Table 1; Appendix D). Since D17 is an FDA "Guidance for Industry" document, it may be regarded as being representative of the skilled person's common general knowledge. There is thus no need for it to be referenced in the application as filed to be taken into consideration.

The respondent's argument that the principles of dosage conversion according to D17 do not apply to proteinogenic amino acids such as cysteine has no basis in fact.

As shown in Table 1 of D17 and explained in D13 (page 660, right-hand column), the species-dependent k_m factor, which is body weight (kg) divided by BSA (m^2), is used to convert an mg/kg dose to an mg/m^2 dose. The formula for dose translation based on BSA is HED (mg/kg) = animal dose (mg/kg) multiplied by (animal k_m/human k_m).

On this basis, using the factors 37 for human k_m and 6 for rat k_m (as disclosed in Table of D13 and Table 1 of D17), the appellants calculated an HED of 0.047 g/kg based on the rat data of the example in the application as filed. This falls within the claimed range for daily dosage.

The respondent objected to this on the ground that the k_m conversion factor is not a constant for any species, but increases within a species as body weight

increases. According to the respondent, the factor k_m = 6 was only correct for rats with a body weight of about 150 g (see D17, Appendix B and Table 3), whereas the rats used in the example had been much larger, namely 650 to 660 g.

However, D17 teaches that standardised factors may nevertheless be used for each species as they still permit a reasonable estimate (see D17: page 6, last paragraph), implying that the deviation would not be large. The conversion factors in Table 1 of D17 are therefore recommended, regardless of actual weight, including k_m = 6 for rats.

D17 also provides an alternative HED calculation for cases where the weight of the animal is different to the weight used for the standardised k_m value (see D17, Appendix B, Table 3, index b). The respondent did not contest the appellants' calculation, according to which the HED value based on the alternative formula and a body weight of 660 g for the rats would still be within the claimed range.

Thus, the objection raised by the respondent cannot refute the appellants' argument that HED values calculated on the basis of the rat experiment in the application as filed are within the claimed range.

5.11 The respondent also argued that the entire dosage range of claim 1 (i.e. 0.03 to 0.15 g/kg or 30-150 mg/kg) exceeded the recommended daily intake for adult humans of 10 mg/kg body weight (see the patent in suit, paragraph [0017]) and that the dosage was too high in view of possible toxicity and adverse effects. According to the respondent, this was supported by D14, which stated that a 0.07 g/kg (or 70 mg/kg) dose of cysteine induced adverse effects (see D14: page 55, last paragraph).

5.12 However, this argument was not found convincing since the cited passage in D14 is not conclusive evidence of what dosage might be too high. The clinical studies reported in D14 used cysteine dosages of 0.04 g/kg and 0.07 g/kg body weight. D14 mentions that the 0.07 g/kg dose induced minor adverse effects (dizziness) in one study participant. This finding is not statistically significant nor indicative of a dose-limiting toxicity.

5.13 Anorexia of ageing also occurs in older animals (see D1: Abstract, lines 9 to 10). The respondent did not substantiate its objection with regard to efficacy of the envisaged treatment in further animal species (e.g. aged pets).

5.14 The respondent's further objection as to the delimitation of the scope of the term "elderly" is, in fact, an objection for lack of clarity rather than insufficiency. It was addressed in point 3.3(b) above.

Conclusion

5.15 For these reasons, the board concluded that the subject-matter claimed in main request A is sufficiently disclosed.

6. Documents presented during the appeal proceedings

6.1 D20 is a post-published document that the appellants presented for the first time at the appeal stage as supplementary evidence of the credibility of the data in the patent in suit (see the appellants' letter of 8 December 2022, point (6)). The board did not take the document and the arguments related thereto into account since the evidence reported in the patent and application as filed was deemed sufficient. A decision on the admittance of D20 was, therefore, not required.

6.2 The respondent did not object to the admittance of D19. Both parties relied on Table 1 of D19 for their reasoning on the possible influence of taste on food intake. Since Table 1 only reports the taste of powdered, reagent-grade alanine and powdered, reagent-grade cysteine HCl as observed by a panel of human testers, this does not permit drawing any conclusion on the taste of nutritional compositions supplemented with these amino acids, such as the composition of claim 1, or on the taste of the diets fed in the rat model as perceived by rats (see also point 5.8.4 above). For this reason, the board concluded that the parties' arguments based on D19 were irrelevant.

7. Remittal (Article 111(1) EPC)

7.1 The decision under appeal concerns only the objections raised under Article 100(c) EPC and under Articles 100(b)/83 EPC. The opposition division did not rule on the objections under Article 100(a) EPC concerning lack of novelty and inventive step.

7.2 In view of its finding that main request A met the requirements of Articles 123(2) and 83 EPC, the board considered it appropriate to remit the case to the opposition division for further prosecution, in accordance with the appellants' request. The respondent did not oppose this request and stated at the oral proceedings that it did not wish to comment on the appellants' request for remittal.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division for further prosecution.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated