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Datasheet for the decision of 27 September 2023

Case Number: T 0474/20 - 3.3.04

Application Number: 09785852.6

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Title of invention:
Hyaluronic acid-based gels including anesthetic agents

Patent Proprietor:
Allergan Industrie SAS

Opponents:
Farco-Pharma GmbH
Heineking, Nils
Merz Pharma GmbH & Co. KGaA
Teoxane SA
Laboratoires Vivacy
Nestlé Skin Health SA

Relevant legal provisions:
EPC Art. 56, 123(2)

Keyword:
Inventive step - (no)
Amendments - allowable (no) - Auxiliary request 6

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Case Number: T 0474/20 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 27 September 2023

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Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 11 December 2019 revoking European patent No. 2323617 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	R. Hauss
	R. Romandini

Summary of Facts and Submissions

I. European patent No. 2 323 617 was granted with a set of eight claims.

Claim 1 reads as follows:

> *1. A method of preparing a soft tissue filler composition, the method comprising the steps of:*
>
> *providing a hyaluronic acid component crosslinked with at least one crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane, or combinations thereof;*
>
> *adjusting the pH of said hyaluronic acid component to an adjusted pH above 7.2; and*
>
> *adding a solution containing at least one anesthetic agent to said hyaluronic acid component having said adjusted pH to obtain said soft tissue filler composition,*
>
> *wherein the at least one anesthetic agent is lidocaine HCl.*

II. Six oppositions were filed against the patent in suit. The patent 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. Opponents 2 and 4 subsequently withdrew their oppositions.

IV. The patent proprietor requested that the oppositions be rejected and the patent be maintained as granted. During the proceedings before the opposition division, it also filed amended sets of claims as auxiliary requests 1 to 5.

V. The documents cited in the proceedings before the opposition division included the following:

D1: WO 2005/112888 A2

D23: EP 1 701 981 B1

D35: Merck Index, 11th edn., 5359 "Lidocaine" (1989)

D48: Package insert Juvéderm® ULTRA3 (2007)

D58: Biotechnology Advances 25, 537-557 (2007)

D63: Synthesis of Soft Tissue Fillers with Lidocaine (May 2018)

D71: Allergan - Trial Report: Addition of Lidocaine in Juvéderm products: assessment of pH during manufacturing steps (September 2019)

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

VII. In the decision under appeal, the opposition division ruled, *inter alia*, the following.

(a) The subject-matter of claim 1 as granted was novel over the disclosure of document D1 (pages 3 to 5 and page 7, lines 3 to 10) (Articles 100(a), 52(1) and 54 EPC). It could not be inferred that "lidocaine" mentioned in D1 could only mean lidocaine HCl and nothing else, or that the lidocaine component was to be added subsequent to adjustment of the pH of the hyaluronic acid component to a value higher than 7.2.

(b) Starting from the technical teaching of document D1, the objective technical problem was the provision of an alternative method of preparing a crosslinked HA soft tissue filler comprising lidocaine HCl. In light of the teaching of the prior art, the selection of the HCl salt as well as the steps of the method according to claim 1 as granted were obvious solutions to this problem. Thus, the claims of the main request did not involve an inventive step (Articles 100(a), 52(1) and 56 EPC).

(c) None of the amendments provided with auxiliary requests 1 to 5 could overcome the objection of lack of inventive step.

VIII. The patent proprietor (appellant) appealed against this decision. Opponents 1, 3, 5 and 6 are respondents to the patent proprietor's appeal.

IX. With the statement setting out the grounds of appeal, the appellant requested that the decision under appeal be set aside and that the patent be maintained as granted. It furthermore filed six sets of claims as auxiliary requests 1 to 6. The claim sets of auxiliary requests 1 to 4 and 6 are identical to those of former auxiliary requests 1 to 5 considered in the decision under appeal.

The appellant also filed document D86 (H. Plötz: Kleine Arzneimittellehre, 7th edn. Springer 2017, ISBN 978-3-662-54418-1, chapter 25, 360).

Claim 1 of ***auxiliary request 1*** is identical to claim 1 as granted except that it specifies that the adjusted pH is "*above 7.5*" instead of above 7.2.

Claim 1 of ***auxiliary request 2*** is identical to claim 1 as granted.

Claim 1 of ***auxiliary request 3*** is identical to claim 1 of auxiliary request 1.

Claim 1 of ***auxiliary request 4*** is identical to claim 1 of auxiliary request 1 except that after the method step of adding a solution containing at least one anaesthetic agent, the further step "*and sterilizing the composition by autoclaving*" has been inserted.

Claim 1 of ***auxiliary request 6*** reads as follows (differences in comparison with claim 1 of the main request underlined by the board):

> *1. A method of preparing a soft tissue filler composition, the method comprising the steps of:*
>
> *providing a hyaluronic acid component crosslinked with at least one crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane, or combinations thereof;*
>
> *adjusting the pH of said hyaluronic acid component to an adjusted pH above 7.2; and*
>
> *adding a solution containing at least one anesthetic agent to said hyaluronic acid component having said adjusted pH to obtain said soft tissue filler composition;*
>
> *homogenizing the hyaluronic acid component during or after the step of adding said solution containing said anesthetic agent;*
>
> *wherein said step of providing a hyaluronic acid component comprises providing dry uncrosslinked sodium hyaluronate material and hydrating said dry*

uncrosslinked sodium hyaluronate material in an alkaline solution to obtain an alkaline, uncrosslinked sodium hyaluronate gel;

wherein the at least one anesthetic agent is lidocaine HCl; and

wherein said soft tissue filler composition is cohesive.

X. In a communication under Article 15(1) RPBA issued in preparation for oral proceedings and advising the parties of its preliminary opinion, the board mentioned, *inter alia*, that inventive step would be assessed starting from the disclosure of document D1. pH adjustment to a value above 7.2 was not considered to be a technical feature distinguishing the subject-matter of claim 1 as granted (main request) from the disclosure in D1. For claim 1 as granted, the objective technical problem could be defined as the provision of a method for preparing specific hyaluronic acid-based soft tissue fillers containing lidocaine (in implementation of the teaching of D1).

XI. Respondent-opponent 1 advised the board that it would not be attending the oral proceedings.

XII. Oral proceedings before the board were held on 27 September 2023 in the absence of respondent-opponent 1, in accordance with Article 15(3) RPBA and Rule 115(2) EPC. The debate focused on inventive step and, in the case of auxiliary request 6, compliance with Article 123(2) EPC. During the oral proceedings, the appellant withdrew auxiliary request 5.

XIII. The appellant's arguments may be summarised as follows.

Inventive step - main request

Document D48 was the closest prior art. If D1 was nevertheless to be used as the starting point for the assessment of inventive step, example 1, which did not involve the addition of lidocaine, should be selected as the starting point in D1.

The method defined in claim 1 differed from the disclosure in example 1 of D1 by the selection of lidocaine HCl as the anaesthetic and by the method step of adding the lidocaine HCl as a solution to the hyaluronic acid component of pH > 7.2.

With reference to example 7 in document D23, it was furthermore contested that the hyaluronic acid-based component in D1 would inevitably have a pH value of at least 7.4 after washing with phosphate-buffered saline (PBS) of pH 7.4. D23, for instance, reported that a similar gel that was washed with a PBS of pH 7.6 ended up with a pH of 7.2, i.e. lower than the pH of the buffer.

The technical effect provided by the claimed method was that the resulting compositions were not prone to degradation when treated by autoclaving.

This effect was attained by adding the lidocaine HCl to the compositions at a pH above 7.2. The alkaline pH compensated for the acidic pH of the lidocaine HCl solution.

While formulations representing D1 in a comparative test should, strictly, not contain lidocaine, the claimed method nevertheless solved the problem of degradation caused by the addition of lidocaine HCl to hyaluronic acid formulations.

The technical effect was demonstrated by the following comparative data:

- Example 4 in the patent in suit: samples 3 to 6, test 2 (lidocaine and pH adjustment, representative of the claimed invention) vs test 3 (no lidocaine, representative of example 1 in D1). Lower viscosity values and higher tan δ values (as shown in figures 4 to 6 and 8) were indicative of degradation.

  The reference to example 2 in paragraph [0110] of example 4 was unambiguous in making it clear that the pH in "Test 2" of example 4 had been adjusted to a value between 7.5 and 7.8. There could be no doubt to a reader that the value of 7.2 stated in example 4 was erroneous.

- D63, section 2: sample 3 (lidocaine and pH adjustment, representative of the claimed invention) vs sample 1 (no lidocaine, representative of D1)

- D71: samples 2 and 3 (representative of the claimed invention) vs sample 1 (control, no lidocaine)

The objective technical problem was the provision of a process for producing a soft tissue filler composition incorporating an anaesthetic agent which avoided degradation while maintaining the viscosity profile of the initial soft tissue filler composition during autoclaving.

Even if the objective technical problem were to be defined as providing a method for preparing specific hyaluronic acid-based soft tissue fillers containing lidocaine, the method defined in claim 1 as granted would not have appeared obvious to the person skilled in the art because incentives and pointers were lacking in the prior art. The features distinguishing the

claimed method from that disclosed in D1 were not self-evident choices, as different options existed for the choice of anaesthetic, the manner in which it was added to the compositions, the process stage when it was added and the pH at which it was added.

For instance, the lidocaine might conceivably be added as a dispersion rather than in solution, or it might be bound chemically to the gel component and, in that case, added before the washing step.

Inventive step - auxiliary request 1

In auxiliary request 1, the adjusted pH value above 7.5 was a further feature that distinguished the claimed method from the disclosure in D1.

The technical effect that rendered the claimed subject-matter inventive was the same as in the case of claim 1 of the main request, i.e. improved stability during autoclaving. This technical effect was, however, supported by different experimental data, namely:

- D71, page 4, table 1, sample 3 (representing the claimed invention) vs sample 2 (comparative sample, representative of D1)

This one data point was, in this case, sufficient as support of the alleged technical effect across the claimed scope, in particular in the absence of counter-evidence provided by the respondents.

The objective technical problem for claim 1 of auxiliary request 1 was the provision of a process for producing a soft tissue filler composition incorporating an anaesthetic agent which had improved stability.

The prior art in general taught that gels intended for injection into the human body should have a neutral pH between 6.5 and 7.5 to ensure physiological

compatibility. For this reason, the person skilled in the art would not have found it obvious to modify the process disclosed in D1 to result in a process according to claim 1.

Inventive step - auxiliary requests 2 to 4

The same inventive-step reasoning applied as set out for claim 1 of the main request and claim 1 of auxiliary request 1.

Amendments - auxiliary request 6

Claim 1 of auxiliary request 6 corresponded to claims 1, 2, 4 and 5 as granted.

XIV. The respondents' arguments may be summarised as follows.

Inventive step - main request

Document D1 constituted the closest prior art. The most appropriate starting point in D1 was the combination of technical features closest to the subject-matter of claim 1 derivable from the general disclosure in D1. Alternatively, example 1 in D1 could be considered in combination with the general embodiment (disclosed on the same page) according to which the gels could additionally contain lidocaine.

The required pH adjustment to a value above 7.2 was not a distinguishing technical feature of claim 1 since exhaustive buffer washing according to the method of D1 resulted in a hydrogel product saturated with PBS and, as a result, having a pH not lower than 7.4 (the pH of the buffer). In the context of the method taught in D1, it was also evident that the only technically sensible possibility for adding lidocaine would be after the

washing step, i.e. after pH adjustment to a value of at least 7.4.

In support of inventive step, the appellant relied on the experimental data in example 4 of the patent in suit and in documents D63 and D71. However, the alleged technical effect of improved stability during autoclaving was based on the pH adjustment step, which was not a distinguishing technical feature. Furthermore, the adjusted pH in example 4 was 7.2 (i.e. not "above" 7.2 as required in claim 1). In the further comparative tests provided by the appellant, the alleged improvement in stability had at most been shown for a pH value (before the addition of lidocaine HCl solution) above 10 but not for the lower end of the claimed pH range just above pH 7.2.

As a consequence, the appellant's experimental data and the alleged technical effect could not be pertinent to the formulation of the objective technical problem.

In any case, it was well known that hyaluronic acid could be degraded by acidic and alkaline hydrolysis (D58: page 543). It followed from this that the relevant pH value to be observed and controlled was the pH of the final formulation undergoing the autoclaving step, which should be substantially neutral to avoid degradation. The required neutral pH could be achieved by adjusting the pH either before or after the addition of the (acidic) lidocaine HCl solution. However, the pH in the intermediate process stage, as specified in claim 1, was not a meaningful parameter for the intended purpose if the amount of lidocaine HCl solution to be added was not specified. The importance of the final pH was indeed confirmed in paragraph [0077] of the patent in suit, which stated that the gels were kept neutral with a buffer or by adjustment with diluted NaOH in order that the final HA/lidocaine

composition would have a desired, substantially neutral, pH.

The only technical features distinguishing the claimed subject-matter from the disclosure of D1 were (1) that lidocaine was used in the form of the hydrochloride and (2) that the lidocaine was added as a solution.

No specific technical effect could be associated with these distinguishing technical features.

On this basis, the objective technical problem could be defined as either:

- the provision of an alternative method of preparing hyaluronic acid-based soft tissue fillers containing lidocaine (respondent-opponent 3)
- the provision of an alternative method of preparing a filler containing an anaesthetic (respondent-opponent 5)
- the provision of a method for preparing specific hyaluronic acid-based soft tissue fillers containing lidocaine in implementation of the teaching of D1 (respondent-opponent 6, agreeing with the objective technical problem as formulated by the board in its communication under Article 15(1) RPBA)

While D1 did not specify that lidocaine should be employed as a hydrochloride salt, lidocaine HCl was a commonly used commercially available form of lidocaine which was soluble in water (as confirmed by D35). Even if other options might have existed for implementing the teaching of D1, the person skilled in the art seeking to solve the objective technical problem would certainly have contemplated the obvious and convenient option of adding lidocaine HCl in an aqueous solution to the product prepared according to D1. A lidocaine-containing filler prepared in this way could reasonably

be expected to provide the intended effect of pain reduction upon application of the gel.

Inventive step - auxiliary request 1

Since D1 specified that there should be "one or more" washing cycles with a PBS buffer having a pH of 7.4, it encompassed embodiments with only a single washing cycle which might well result in a formulation still having a pH value above 7.5. This possibility was, therefore, covered by the teaching of D1.

The appellant had not provided conclusive evidence that any pH value above 7.5, including in the lower part of the range close to 7.5, could be associated with a technical advantage in comparison to pH values between 7.4 and 7.5 (also covered by D1).

It was contested that the data in D71 relied on by the appellant permitted extrapolation across the scope claimed, in particular considering that sample 2 in D71 (with an adjusted pH of 7.5) had not achieved the desired degree of stability.

Hence, the technical problem as formulated by the appellant was not solved across the entire scope claimed.

To solve the less ambitious technical problem of providing a specific composition or an alternative composition, no incentive would have been required for a slight pH modification. Furthermore, the final product was required to have, in order to be suitable for its intended use as an injectable hydrogel, a physiologically compatible pH between 6.5 and 7.5. It was also known that alkaline or acidic degradation could be an issue. It would therefore have been obvious to adjust the pH to a value above 7.5 before adding an

acidic component such as lidocaine HCl, which was bound to decrease the pH.

Inventive step - auxiliary requests 2 to 4

The same objections applied as set out for claim 1 of the main request and claim 1 of auxiliary request 1. Autoclaving as required in claim 1 of auxiliary request 4 was an obvious standard measure and was also explicitly disclosed in D1.

Amendments - auxiliary request 6

There was no basis in the application as filed for the combination of features defined in claim 1 of auxiliary request 6. Dependent claims in the application as filed which referred back only to claim 1 could not be combined. Features disclosed in the description as belonging to distinct embodiments could not be combined either.

XV. The appellant (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained as granted

or, in the alternative, that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of one of auxiliary requests 1 to 4 and 6, all filed with the statement setting out the grounds of appeal.

XVI. Respondent-opponent 1 did not present any request or substantive submission during the appeal proceedings.

XVII. Respondents-opponents 3, 5 and 6 requested that the appeal be dismissed. Respondents-opponents 3 and 6 also requested that document D86 not be admitted.

Reasons for the Decision

1. Oral proceedings, absence of respondent-opponent 1

In conformity with Article 15(3) RPBA and Rule 115(2) EPC, the oral proceedings before the board took place in the absence of respondent-opponent 1, which had been duly summoned and had not filed any request or substantive submission in writing (see points XI., XII. and XVI. above).

2. Inventive step - main request (Articles 100(a), 52 (1) and 56 EPC)

Patent in suit

2.1 The patent in suit relates to a method of preparing hyaluronic acid-based dermal and subdermal soft tissue fillers containing an anaesthetic agent (see the patent in suit, paragraph [0002]). The patent states that the envisaged compositions have enhanced stability relative to conventional hyaluronic acid-based compositions including, for example, lidocaine HCl, when subjected to sterilisation techniques such as autoclaving and/or when stored for long periods at ambient temperature (see paragraph [0014]).

2.2 With regard to the mandatory ("at least one") anaesthetic agent, claim 1 as granted is restricted to lidocaine HCl.

Starting point in the prior art

2.3 The parties were in disagreement about whether document D1 or document D48 should be considered the "closest" prior art. The appellant took the view that only D48 (a package insert relating to the dermal filler "Juvéderm® ULTRA3") could be the closest prior

art and that the disclosure of D1, favoured by the respondents, was more remote.

2.4 The board considered that establishing a relative degree of "closeness" of these alternative starting points was not crucial. If inventive step is to be acknowledged, the claimed subject-matter must be inventive starting from any starting point in the prior art. If a chosen starting point is too remote from the claimed subject-matter in terms of structural features and purpose, the problem-and-solution approach will simply not result in a finding of obviousness of the claimed subject-matter.

2.5 The board assessed inventive step starting from the disclosure of D1, as this was the approach chosen in the decision under appeal and pursued by the respondents. For the appeal to be allowed, the board must be convinced that the opposition division's assessment that the invention lacks inventive step based on the disclosure of D1 is wrong.

Content of D1

2.6 D1 relates to methods for making injectable polymer hydrogels, in particular injectable hyaluronan hydrogels (page 1, lines 21 to 22), with the technical background that injectable gels are often used for soft tissue augmentation (page 1, lines 10 to 12). The term "hyaluronan" refers to hyaluronic acid or its salts (see D1: paragraph bridging pages 3 and 4; see also the patent in suit: paragraph [0009]).

2.7 In the general part of the description (page 3, line 30 to page 7, line 10), D1 discloses a method that involves crosslinking hyaluronan in an alkaline medium

with a crosslinking agent such as, in particular, BDDE (page 4, line 3 to page 5, line 2).

The product thus obtained is exhaustively washed with phosphate-buffered saline (PBS) having a pH of 7.4 to remove residual crosslinking agent and unreacted hyaluronan, finally yielding a hydrated, highly swollen gel stabilised with PBS. This can take up to ten changes of PBS over a period of one to four days (D1: page 5, lines 3 to 19).

The purified swollen gel can then be homogenised (page 5, lines 6 to 11 and 19 to 20). The gel can be removed from the reaction vessel and packaged, e.g. in vials or syringes, before or after sterilisation, e.g. by autoclaving (page 5, lines 19 to 22).

The crosslinked gel may be useful for, *inter alia*, soft tissue augmentation (page 6, lines 28 to 29).

A further use for the injectable gels of D1 can be "in the delivery of therapeutically active agents including in any of the aforementioned applications" (page 7, lines 3 to 4). The therapeutically active agents may be anaesthetics, e.g. lidocaine, which is the only anaesthetic mentioned by name in D1 (see page 7, lines 5 to 8).

2.8 Example 1 of D1 further illustrates the generally disclosed method. Hyaluronan was crosslinked with BDDE. After 2.5 days of washing with six changes of fresh PBS, the gel was filtered to remove free PBS and stirred into an injectable gel by impeller stirring. The gel was filled into syringes for autoclaving (page 7, lines 15 to 25).

2.9 Thus, D1 discloses the combination of several of the method steps and features defined in claim 1 as granted.

2.9.1 The crosslinking reaction described in D1 provides a hyaluronic acid component crosslinked with BDDE. This corresponds to the first step of the claimed method.

2.9.2 On account of the washing/hydrating steps described in D1, in which a PBS buffer with a pH of 7.4 is used, the second step of adjusting the pH of the hyaluronic acid component to a value above 7.2 does not distinguish the claimed method from the disclosure in D1, either.

(a) Claim 1 as granted does not specify an initial pH value for the crosslinked hyaluronic acid component. The pH of the crosslinked hyaluronic acid component provided with the first method step can be any technically possible pH value. If the crosslinked hyaluronic acid component is provided at a pH above 7.2, this does not preclude pH adjustment to a (different) "adjusted pH above 7.2" in the second method step of claim 1.

(b) Since the crosslinking reaction in D1 is carried out in an alkaline medium, typically at a pH higher than 11 (page 4, lines 14 to 20; see also point 2.7 above), the starting pH is higher than that of the PBS buffer. Exhaustive washing of the crosslinked gel with PBS buffer of pH 7.4 (as required in the method of D1) will gradually adjust the pH to a value of 7.4 or above but cannot result in a pH lower than that of the buffer (i.e. 7.4.).

(c) Nevertheless, the appellant argued that washing with the PBS buffer according to D1 might also result in a pH of 7.2 or lower. According to the

appellant, this had been shown in document D23 (in example 7, paragraph [0069]), where the washing of crosslinked hyaluronic acid with a PBS buffer of 7.6 resulted in a pH of 7.2.

(d) This argument cannot succeed because the comparison with example 7 of D23 is not correct. In contrast to the situation in D1, the starting pH in example 7 of D23 was lower than that of the PBS buffer. The gel of D23 was first washed with hydrochloric acid, and a pH value of 2.8 was recorded (D23: line 42). The gel was then washed with neutral saline and after that with a PBS buffer having a pH of 7.6. Hence, in the case of D23, the pH before contact with the PBS buffer was in the acidic to neutral range. Washing with the slightly alkaline PBS buffer would have raised the pH but could not have resulted in a pH higher than that of the buffer (i.e. 7.6).

2.9.3 Since claim 1 is a "method of preparing a soft tissue filler composition", the composition provided by the method of claim 1 must be suitable as a soft tissue filler composition. While D1 mentions several possible applications of the crosslinked gels, soft tissue augmentation is explicitly identified both as a typical application (see page 1, line 10) and as being envisaged (see page 6, lines 27 to 29). There is no reason to assume that the product prepared by the method described in D1 (e.g. the injectable gel according to example 1) would not be suitable as a soft tissue filler composition. In any case, for inventive step to be acknowledged, the claimed subject-matter has to be inventive over any possible starting point in D1, and the embodiment that is suitable as a soft tissue

filler is in this case a more relevant starting point than embodiments suitable for other applications.

2.9.4 D1 also envisages that an anaesthetic such as lidocaine may be present in the final gel product as an agent to be delivered (see point 2.7 above).

Objective technical problem and solution

2.10 D1 does not disclose a specific method for adding the lidocaine to the formulation. Thus, the method defined in claim 1 differs from the disclosure in D1 by the following features:

- the selection of lidocaine HCl salt as the lidocaine component
- the method step of adding lidocaine HCl as a solution to the hyaluronic acid component of pH > 7.2

2.11 No specific technical effect or advantage has been associated with the selection of lidocaine HCl salt or with adding it in the form of a solution.

2.12 The appellant emphasised that D1 did not require the lidocaine HCl to be mixed with the PBS-treated gel. Thus, the process stage at which the anaesthetic was to be added was also a distinguishing feature - specifically, the requirement in claim 1 that the anaesthetic was to be added to the crosslinked hyaluronic acid component having an adjusted pH of above 7.2.

Still according to the appellant, this third method step defined in claim 1 provided a technical advantage based on the pH of the crosslinked hyaluronic acid component. The alkaline pH above 7.2 compensated for the acidic pH of the lidocaine HCl solution, and this

resulted in less degradation when the compositions were subjected to autoclaving.

In support of this alleged technical effect, the appellant relied on example 4 of the patent in suit (also in the application as filed) and further supplementary data in documents D63 and D71.

2.13 This line of argument cannot succeed for the following reasons.

2.13.1 The board acknowledges that D1 mentions, as a possible option, that the additional therapeutically active agents that may be present in the injectable gels *"may be bound, either physically or chemically, to the crosslinked gel using methods well known in the art"* (D1: page 7, lines 8 to 10).

2.13.2 It may, arguably, be doubted whether this remark was intended to refer also to lidocaine, which as an anaesthetic would be required to be readily available to reduce pain during/upon application (injection) of the filler composition.

2.13.3 In any case, however, the appellant did not provide any comparative evidence on methods according to which the lidocaine would end up bound to the gel. This means that no technical advantage of the claimed method was shown over this hypothetical embodiment.

2.13.4 On the other hand, the statement on page 7 of D1 does not rule out the other evident option of just adding the lidocaine without binding it to the crosslinked gel. As this embodiment comes closer to the claimed method, it is also the more relevant one for assessing inventive step, and comparative tests should appropriately be designed in relation to this embodiment of D1.

2.13.5 The board is of the view that in this latter embodiment, the process stage at which the anaesthetic is added does not distinguish the claimed method from the disclosure in D1.

D1 describes the preparation of a crosslinked hyaluronic acid gel that is washed repeatedly with a PBS buffer of pH 7.4. As the washing steps (which coincide with pH adjustment within the meaning of claim 1) are still part of the manufacturing process of the hyaluronic acid component, it is implicit that the anaesthetic would be added to the final product (having a pH of at least 7.4) only subsequent to these steps - in particular as it would have to be expected that any component added at an earlier stage of the process would be removed with the washing steps.

2.13.6 As a consequence, the appellant's comparative data, which are based on varying the pH of the hyaluronic acid component before the addition of lidocaine HCl, are not based on a distinguishing technical feature. For this reason alone, the alleged technical effect of improved stability during autoclaving cannot be used in the formulation of the objective technical problem.

2.14 Starting from the disclosure in document D1 and without evidence of a technical advantage, the objective technical problem is the provision of a method for preparing specific hyaluronic acid-based soft tissue fillers containing lidocaine in implementation of the teaching of D1.

2.15 The solution to this problem is the method defined in claim 1 as granted.

Obviousness of the solution

2.16 As mentioned above (see points 2.13.4 and 2.13.2), mixing the lidocaine with the crosslinked hyaluronic acid-based component after its completed preparation (which includes adjustment of the pH to a value of at least 7.4) is within the scope of D1, and this option would have suggested itself to the person skilled in the art as an appropriate and simple way of incorporating an anaesthetic intended to be delivered by the compositions.

2.17 It was not in dispute that lidocaine HCl was the predominantly used commercial form of lidocaine. Using a prevalent commercially available form of lidocaine would have been an obvious choice for the person skilled in the art to implement the teaching in D1 that the gel could contain an anaesthetic, for example, lidocaine.

2.18 As lidocaine HCl was known to be well soluble in water (see D35), adding it as a solution, e.g. an aqueous solution, would have been an obvious and convenient option for mixing the lidocaine with the gel.

2.19 While the appellant pointed out that a person skilled in the art might also have considered other options for adding lidocaine HCl to the formulations, the existence of alternative options cannot make an obvious option inventive.

2.20 For these reasons, the subject-matter of claim 1 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

3. Inventive step - auxiliary request 1

3.1 Claim 1 of auxiliary request 1 only differs from claim 1 of the main request in that the feature "adjusted pH above 7.2" was replaced by "adjusted pH above 7.5".

3.2 According to the method taught in D1, the pH of the hyaluronic acid-based component after washing with the PBS buffer cannot be lower than 7.4. It is not, however, required to be above 7.5. Thus, the adjusted pH is a further technical feature that distinguishes the claimed method from the disclosure in D1.

3.3 Since the description of the process in D1 does not rule out the possibility that the pH value after washing with the PBS buffer may remain above 7.5 (for example, it may be 7.6), the pH range "above 7.5" defined in claim 1 of auxiliary request 1 overlaps with the pH range encompassed by D1.

3.4 In support of the alleged technical effect of less degradation during autoclaving, the appellant referred to D71. This is a report on a study that examined the effect of the pH adjustment step on the compositions' rheology.

According to section 3.1 (Table 1) of D71, three samples were compared. The initial pH of all three was 7.45. In view of the one-decimal precision chosen in claim 1, this may be rounded to 7.5.

- The control sample (sample 1) did not undergo the second and third method steps in claim 1. Hence, without pH adjustment and addition of lidocaine HCl, the pH before autoclaving was 7.5.
- The pH of sample 2 (as mentioned above, this initial pH was 7.5) was not adjusted to a value

above 7.5 before the addition of lidocaine HCl, this resulting in a pH of 6.75 (rounded to 6.8) before autoclaving.

- The pH of sample 3 was adjusted with sodium hydroxide to a value of 10.54 (rounded to 10.5) before the addition of presumably the same amount of lidocaine HCl, this resulting in a pH of 7.13 (rounded to 7.1) before autoclaving.

According to the appellant, sample 3 in table 1 ("adjusted" intermediate pH = 10.5) represents the claimed invention, whereas sample 2 (intermediate pH = 7.5) represents D1.

The appellant contended that, as shown in section 3.2 of D71 for the parameters G' and viscosity, the rheological properties of sample 3 after autoclaving were about equivalent to those of the control sample, while the rheological properties of sample 2 had deteriorated, in comparison, to a larger extent.

The appellant also argued that the one data point obtained with sample 3 was sufficient in this case to support the alleged technical effect across the scope claimed, especially as the respondents had not provided any counter-evidence in the form of experimental data.

3.5 The board is not convinced by the appellant's arguments for the alleged technical effect for the following reasons.

3.5.1 According to the appellant, the claimed method provides better stability to the compositions in an autoclaving process, in comparison with the method taught in D1.

3.5.2 The burden of proof for this allegation lies with the appellant.

3.5.3 Thus, it must be examined whether the evidence provided by the appellant (in this case, the comparative test described in D71) is conclusive for acknowledging that the alleged technical effect is obtained across the scope claimed.

3.5.4 The board considers that D71 cannot demonstrate that the alleged effect of better stability during autoclaving is obtained across the pH range claimed because no sample with an "adjusted" pH closer to the lower limit of the pH range ("above 7.5") was tested. On the basis of the data provided in D71, it is not possible to verify how a sample with an "adjusted" intermediate pH of, for example, 7.6 (representative of claim 1) would have performed in comparison with a sample with an intermediate pH of 7.5 (representative of D1). Thus, the alleged advantage was not convincingly shown across the pH range claimed.

3.5.5 There is another, more fundamental reason why the alleged technical effect was not shown to be attained across the scope claimed. The appellant's premise that the stability of the filler compositions in an autoclaving process is linked to the "adjusted pH" parameter defined in claim 1 appears questionable.

It was not in dispute that the "adjusted pH" of claim 1 applies only temporarily in an intermediate method step as the pH will decrease when lidocaine HCl is added. While claim 1 does not, in fact, provide specifications for the lidocaine HCl solution, this can be based on the assumption that the solution is formed by dissolving lidocaine HCl in water, as described in paragraph [0077] of the patent in suit (see D35: the pH of a 0.5% aqueous solution of lidocaine HCl is 4.0 to 5.5, i.e. in the acidic range).

As pointed out by the respondents, it was common general knowledge that hyaluronic acid could be degraded by acidic or alkaline hydrolysis (see the research review paper D58: page 543, paragraph bridging columns).

Thus, the pH value likely to be relevant for stability during autoclaving is the pH of the formulation actually undergoing the autoclaving process, i.e. the pH attained after the addition of lidocaine HCl. This pH should be neutral to avoid acidic and alkaline hydrolysis.

The appellant merely chose, in the claimed method, to adjust the pH before, rather than after, the addition of lidocaine HCl - see paragraph [0077] of the patent in suit, which shows that the aim of this measure is still to achieve a final pH that is about neutral:

> *"The gels are kept neutral with a buffer or by adjustment with diluted NaOH in order that the final HA/lidocaine composition will have a desired, substantially neutral pH"*.

However, claim 1 does not specify a pH value or range for the filler composition after the addition of lidocaine HCl, and this feature is not implicit, either. The pH of the formulation after the addition of the lidocaine HCl solution depends on how much acidic solution is added relative to the alkaline hyaluronan formulation. Since this ratio cannot be derived from claim 1, it is not possible to correlate the intermediate ("adjusted") pH to the pH obtained after adding lidocaine HCl.

A general pH limitation is nevertheless provided by the claim feature specifying that the composition prepared by the claimed method is a soft tissue filler composition. This means that it must have a

physiologically acceptable pH (which may change slightly with subsequent autoclaving, see table 1 in D71). The implied requirement of a physiologically acceptable pH allows, however, for some variation and does not exclude compositions with a pH of 6.8 (as in sample 2 of D71, before and after autoclaving).

Thus, since claim 1 does not specify how much lidocaine HCl is added, the "adjusted pH" parameter cannot be correlated to the final pH, which is the relevant parameter for avoiding degradation.

Also because of this further aspect, it is not possible to infer that the alleged technical effect would be obtained across the scope of "adjusted pH" values claimed. For the sake of completeness, these considerations equally apply to the main request.

3.6 As a consequence, the alleged technical effect of improved stability during autoclaving cannot be taken into account in the formulation of the objective technical problem, which remains the same as defined for claim 1 of the main request, namely the provision of a method for preparing specific hyaluronic acid-based soft tissue fillers containing lidocaine in implementation of the teaching of D1.

3.7 With regard to the technical features that are also present in claim 1 of the main request, the claimed method would have been obvious to the person skilled in the art for the same reasons as set out for the main request in section 2 above.

3.8 Concerning the further requirement that the pH of the hyaluronic acid component be adjusted to a pH value above 7.5 rather than above 7.2, this possibility is covered by the method taught in D1 (see point 3.3 above). The general description of the method on page 5

of D1 provides that the crosslinked gel particles can be washed with one or more changes of PBS over a period of one to four days. There is no instruction or rationale provided in D1 according to which the gel should undergo washing until the pH is at most 7.5. In the absence of evidence of a specific technical effect, the choice to bring the pH down, by buffer washing, to a value that is still above 7.5 would be an arbitrary choice that does not depart from the general teaching in D1.

3.9 The appellant's argument that the person skilled in the art, to ensure the physiological acceptability of the formulations, would not have chosen a pH above 7.5 is not convincing because the value of "above 7.5" in claim 1 is the intermediate pH value before the addition of lidocaine HCl. The pH relevant for physiological acceptability is the final pH.

3.10 For these reasons, the subject-matter of claim 1 of auxiliary request 1 does not involve an inventive step within the meaning of Article 56 EPC.

4. Inventive step - auxiliary requests 2 to 4

4.1 Claim 1 of auxiliary request 2 is identical to claim 1 of the main request. The same reasoning applies as set out in section 2. above. As a consequence, the claimed subject-matter does not involve an inventive step within the meaning of Article 56 EPC.

4.2 Claim 1 of auxiliary request 3 is identical to claim 1 of auxiliary request 1. The same reasoning applies as set out in section 3. above. As a consequence, the claimed subject-matter does not involve an inventive step within the meaning of Article 56 EPC.

4.3 Claim 1 of auxiliary request 4 is identical to claim 1 of auxiliary request 1, except that it furthermore requires the composition to be sterilised by autoclaving after the anaesthetic has been added (see point IX. above).

This technical feature does not further distinguish the claimed subject-matter from the disclosure of D1, which discloses autoclaving in the general part of the description (page 5, lines 20 to 22: *"The gel can be removed from the vessel [...] and packaged [...] before or after sterilization, e.g. by autoclaving"*) as well as in example 1 (page 7, lines 23 to 25: *"The yield of gel was 55 grams, which was then used to fill syringes for autoclaving."*).

Since the appellant wished to rely on the alleged technical effect of reduced degradation during a subsequent autoclaving process, the assessment of inventive step for claim 1 of the main request and claim 1 of auxiliary request 1 was in any case based on the premise that the soft tissue filler composition undergoes autoclaving.

Thus, the additional feature cannot contribute anything to inventive step, and the same reasoning and conclusion apply as set out in section 3. above.

As a consequence, the subject-matter of claim 1 of auxiliary request 4 does not involve an inventive step within the meaning of Article 56 EPC.

5. Amendments - auxiliary request 6 (Article 123(2) EPC)

5.1 In its appeal submissions, the appellant merely indicated the correspondence of claim 1 with certain claims of the granted patent but failed to indicate any disclosure in the application as filed where the mandatory features of claim 1 of auxiliary request 6

are directly and unambiguously disclosed in combination.

5.2 Claims 1, 2, 6 and 8 in the application as filed read as follows:

1. A method of preparing a soft tissue filler composition, the method comprising the steps of:

providing a HA component crosslinked with at least one crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,4-bis(2,3-epoxypropoxy)butane, 1,4-bisglycidyloxybutane, 1,2-bis(2,3-epoxypropoxy) ethylene and 1-(2,3-epoxypropyl)-2,3-epoxy-cyclohexane, and 1,4-butanediol diglycidyl ether or combinations thereof;

adjusting the pH of said HA component to an adjusted pH above 7.2; and

adding a solution containing at least one anesthetic agent to said HA component having said adjusted pH to obtain said soft tissue filler composition.

2. The method of claim 1 wherein said soft tissue filler composition is cohesive.

6. The method of claim 1 further comprising the step of homogenizing the HA component during or after the step of adding said solution containing said anesthetic agent.

8. The method of claim 1 wherein said step of providing a HA component comprises providing dry uncrosslinked NaHA material and hydrating said dry uncrosslinked NaHA material in an alkaline solution to obtain an alkaline, uncrosslinked NaHA gel.

"HA" and "NaHA" are hyaluronic acid (also called hyaluronan) and sodium hyaluronate (see paragraphs [0008], [0009] and [0014] of the application as filed).

5.3 Claim 1 of auxiliary request 6 combines the features from claims 1, 2, 6 and 8 of the application as filed with "lidocaine HCl" as the mandatory anaesthetic agent, the latter feature being taken from the description (page 11, lines 22 to 23; page 14, line 16).

5.4 Each of claims 2, 6 and 8 as filed is dependent only on claim 1 as filed. Hence, the set of claims as filed does not directly and unambiguously support the combination of features defined in claim 1 of auxiliary request 6. The feature requiring the composition to be "cohesive" could be taken from claim 2 as filed, but based on the claim dependencies, claim 2 is not combinable with claims 6 and 8.

5.5 The features of claims 6 and 8 are also found in the text of the description as filed. Each is disclosed as a distinct embodiment, as follows:

- *"In another embodiment, the method further comprises the step of homogenizing the HA component during or after the step of adding the solution containing the at least one anesthetic agent."* (page 5, line 29 to page 6, line 2)

- *"In another embodiment, the step of providing a HA component comprises providing dry free NaHA material and hydrating the dry free NaHA material in an alkaline solution to obtain an alkaline, free NaHA gel."* (page 6, lines 5 to 8)

In the passage on page 6, the term "free" is used rather than the term "uncrosslinked" used in claim 8.

5.6 Thus, both in the claims and the description of the application as filed, the features of claims 2, 6 and 8 are disclosed separately, as embodiments distinct from one another. These distinct embodiments are not directly and unambiguously disclosed in combination.

5.7 For these reasons, the subject-matter of claim 1 of auxiliary request 6 extends beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

6. Admittance of document D86

6.1 The appellant filed document D86 to contest the opposition division's view that the data in D71 suggested that an intermediate pH adjustment to a value considerably higher than 7.2 would be required to provide a physiologically acceptable final tissue filler product (see point IX. above, decision under appeal: point 3.4.3, the appellant's grounds of appeal: point 2.2.4.3 on pages 33 and 34 and the appellant's letter dated 6 May 2021: point 2.2).

6.2 As the board does not rely on this argument in its reasoning on inventive step set out above, a decision on admittance of D86 was not required.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated