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Datasheet for the decision of 30 October 2025

Case Number: T 1739/23 - 3.3.07

Application Number: 17160312.9

Publication Number: 3246017

IPC: A61K9/08, A61K38/08, A61P5/00, A61P3/14

Language of the proceedings: EN

Title of invention:
STABLE LIQUID FORMULATION OF AMG 416 HCL (ETELCALCETIDE)

Patent Proprietor:
Amgen Inc.

Opponents:
Fresenius Kabi Deutschland GmbH
Adalvo Ltd.
STADA Arzneimittel AG
Synthon BV

Headword:
Formulation of AMG 416 HCl / AMGEN

Relevant legal provisions:
EPC Art. 100(a), 54, 56

Keyword:
Novelty - main request (yes)
Inventive step - main request (yes)

Decisions cited:
G 0002/21, T 2342/19

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Beschwerdekammern

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Case Number: T 1739/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 30 October 2025

Appellant: (Opponent 3)	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Respondent: (Patent Proprietor)	Amgen Inc. One Amgen Center Drive Thousand Oaks California 91320 (US)
Representative:	Dörries, Hans Ulrich df-mp Patentanwälte Rechtsanwälte PartG mbB Theatinerstraße 16 80333 München (DE)
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Party as of right: (Opponent 2)	Adalvo Ltd. Malta Life Science Park, Building 1 Level 4, Sir Temi Zammit Buildings, San Gwann Industrial Estate, San Gwann, SGN 3000 (MT)
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Party as of right: (Opponent 4)	Synthon BV Microweg 22 6503 GN Nijmegen (NL)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 3 August 2023 rejecting the opposition filed against European patent No. 3246017 pursuant to Article 101(2) EPC.**

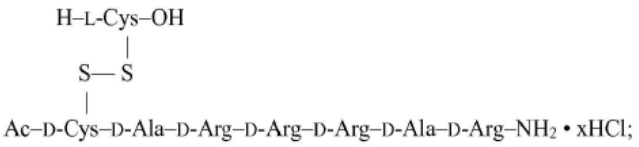
Composition of the Board:

Chairman	E. Duval
Members:	J. Lécaillon
	A. Jimenez

Summary of Facts and Submissions

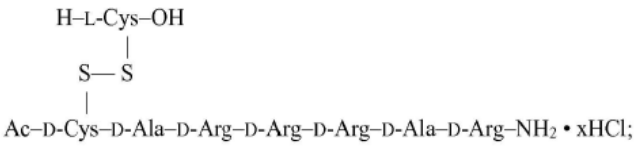
I. European patent 3 246 017 (hereinafter "the patent") was granted on the basis of 15 claims. The independent claims of the patent as granted read as follows:

"1. A pharmaceutical formulation comprising AMG 416 hydrochloride:



in aqueous solution, wherein the formulation has a pH of 2.0 to 5.0."

"15. A formulation comprising 2 mg/mL to 20 mg/mL of AMG 416 hydrochloride:



in aqueous solution, a succinate buffer that maintains the formulation at a pH of about 3.0 to 3.5, and a sufficient concentration of sodium chloride for the formulation to be approximately isotonic."

II. Four oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the (parent) application as originally filed.

III. The opposition division took the decision to reject the oppositions.

IV. The decision of the opposition division, posted on 3 August 2023, cited *inter alia* the following documents:

D1: Walter *et al.*, J Pharmacol Exp Ther, 2013 Aug; 346(2):229-240
D1a: JPET Fast Forward, Walter *et al.*, Published on May, 14, 2013, DOI: https://doi.org/10.1124/jpet.113.204834
D1b: Website pages of J Pharmacol Exp Ther with information regarding the publication of the article with DOI: https://doi.org/10.1124/jpet.113.204834
D6: WO 2012/170955 A1
D10: Wang *et al.*, Journal of Parenteral Science and Technology, Vol. 42, Number 2S, supplement, S4-S23, 1988
D15: Aulton's Pharmaceutics, 3rd Edition, Elsevier, 2007, pages 8, 368, 369, 616 - 620
D31: PhD thesis of C. Avanti, 2012. Chapters 1 and 2
D32: Textbook "Pharmaceutical Dosage Forms", Parenteral Medications, 3rd Edition, Volume 1 - Formulation and Packaging, 2010, Informa Healthcare, chapter 9
D33: Textbook, "Pharmazeutische Technologie", 1993, 4th Edition, Georg Thieme Verlag, pages 225-228
D35: WO 2011/014707 A2
D37: Experimental data from Amgen concerning the stability of aqueous solutions comprising AMG 416
D40: Chang *et al.*, "Lyophilized Biologics" in "Lyophilized Biologics and Vaccines", Springer, 2015, pages 93-119

V. The opposition division decided in particular as follows:

(a) The grounds of opposition under Article 100(b) and 100(c) EPC did not prejudice the maintenance of the patent.

(b) The right to priority was validly claimed.

(c) D1a was considered to have been made available to the public before the priority date. It did not anticipate the claimed subject-matter.

(d) The claimed subject-matter involved an inventive step starting from either D1a or D6.

VI. Opponent 3 (appellant) lodged an appeal against the above decision of the opposition division.

VII. With its reply to the appellant's statement setting out the grounds of appeal the patent proprietor (respondent) defended its case on the basis of the patent as granted as the main request, and on the basis of auxiliary requests 1 to 40 filed during the opposition proceedings on 29 July 2022 (auxiliary requests 1 to 16) and 14 June 2023 (auxiliary requests 17 to 40).

VIII. Summons to attend oral proceedings on 27 October 2025 were sent to the parties on 19 July 2024. The Board issued a communication pursuant to Article 15(1) RPBA on 28 May 2025. The Board provided therein their preliminary opinion that the appeal was likely to be dismissed.

IX. The parties as of right (opponents 1, 2 and 4) indicated with their respective letters dated 19 August 2024 (opponent 2), 15 October 2024 (opponent 1) and 11 June 2025 (opponent 4) that they would not attend the oral proceedings. With the letter dated 8 October 2025, the appellant also indicated that they would not attend the oral proceedings.

X. On 13 October 2025, the parties were informed that oral proceedings were cancelled.

XI. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

XII. The respondent requested that the appeal be dismissed and the patent be maintained as granted, or, as an auxiliary measure, that the patent be maintained on the basis of one of auxiliary requests 1 to 40 filed during the opposition proceedings on 29 July 2022 (auxiliary requests 1 to 16) and 14 June 2023 (auxiliary requests 17 to 40).

XIII. Opponents 1, 2 and 4 (parties as of right) did not make any substantial submissions during the appeal proceedings.

XIV. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) D1a was published online on 14 May 2013 and was hence publicly available before the priority date of the patent. D1a disclosed on page 10 lines 10 to 13 a formulation comprising AMG 416 in a vehicle comprising glycine, trehalose and succinate buffer with a pH 5.0. It was unambiguous that this formulation was an aqueous solution. Furthermore,

the final solution would have a pH of 5.0 due to excellent buffering capacity of the succinate buffer. Finally, the choice of the HCl salt disclosed on page 8 would hence be implicit. Therefore D1a anticipated the subject-matter of granted claim 1.

(b) The subject-matter of the granted claims did not involve an inventive step. D1a represented the closest prior art, since it disclosed a concrete formulation of a pharmaceutical composition of AMG 416. As explained in the context of novelty, there was no distinguishing feature between the claimed subject-matter and the formulation disclosed in D1a. However, to the extent that any distinguishing feature was to be acknowledged, it would have resided in AMG 416 being present in the form of its HCl salt. The use of the hydrochloride salt of AMG 416 in the claimed composition represented an arbitrary choice, unsupported by any technical rationale in the patent, and thus lacked inventive step. Furthermore, D1a already disclosed an aqueous solvent system with a specific pH, and given AMG 416's solubility at pH 5, formulating it as a solution would have been an obvious next step for a skilled person. Consequently, the claimed subject matter was obvious either from D1a alone or in combination with common general knowledge.

XV. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) D1a had not been made available to the public before the priority date of the patent. Furthermore, the subject-matter of the claims of the main request was novel over D1a, because D1a

fails to unambiguously disclose a formulation of AMG 416 (i) in the form of an aqueous solution and (ii) wherein AMG 416 is present as its HCl salt.

(b) The subject-matter of the granted claims involved an inventive step. D6 represented the closest prior art, since it disclosed the intravenous administration of AMG 416 to humans. The claimed formulation differed from the subject-matter of D6 in that it was (i) in the form of an aqueous solution (ii) having a pH of 2.0 to 5.0, and (iii) wherein AMG 416 was present in the form of its HCl salt. The underlying objective technical problem resided in the provision of a formulation comprising AMG 416 (formulated as AMG 416 HCl) which was convenient, reliable, safe to use, well tolerated and at the same time exhibited sufficient stability suitable for use as a commercial "ready-to-use" pharmaceutical, wherein the claimed formulation exhibited a high degree of stability for an extended period of time, such that the degradation was less than 10% in the liquid (refrigerated) state over 2 years. There was no suggestion in the prior art to prepare a formulation as claimed in order to solve the problem posed. A similar line of reasoning applied when starting from D1a as the closest prior art, as the claimed subject-matter differed from D1a in the same distinguishing features as when starting from D6.

Reasons for the Decision

Main request - patent as granted

1. Amendments and sufficiency of disclosure

The appellant did not pursue in the appeal stage the objections under Article 100(b) EPC and Article 100(c) EPC. The Board is satisfied that the main request fulfils the requirements of these articles as stated in the impugned decision.

2. Novelty

2.1 The appellant maintained that the claimed subject-matter was not novel over D1a.

2.2 The respondent contested that D1a had been made available to the public before the priority date of the patent.

The Board considers that D1a, D1 and D1b substantiate that D1a was publicly available on 14 May 2013. Considering the Board's finding that D1a is not prejudicial to the patentability of the claimed subject-matter (see below), it is not necessary to provide detailed reasons on this point.

2.3 According to the appellant, a formulation comprising AMG 416 in a vehicle comprising glycine, trehalose and succinate buffer with a pH 5.0 would be disclosed on page 10 lines 10 to 13 of D1a. They argued that, as pH values without reference standard value were only meaningful for aqueous phases, it would be directly and unambiguously disclosed that the formulation was aqueous. Furthermore, since all the excipients listed

as well as AMG 416 were soluble in water, the formulation would necessarily be an aqueous solution. Moreover, it would be directly and unambiguously disclosed that the final solution had a pH of 5.0, in particular because the succinate buffer was known to have excellent buffering capacity so that neither the excipients nor the active agent would change the pH. Finally, a hydrochloride (HCl) salt would be disclosed in a one-dimensional list on page 8 of D1a and would provide acceptable solubility in view of the administration dose disclosed on page 10. The choice of HCl would hence be implicit.

2.4 As argued by the respondent, there is no unambiguous disclosure of the medium in which AMG 416 is administered in the embodiment disclosed on page 10 of D1a. Said embodiment indeed discloses that "AMG 416 (0.3, 1 or 3 mg/kg) **OR** vehicle (18 mg/mL glycine, 9 mg/mL trehalose, 2.4 mg/mL succinate, pH 5.0) was administered as s.c. bolus injection [...]" (emphasis added). While the same vehicle may have been used to formulate AMG 416, this does not appear unambiguous. It follows that the formulation of AMG 416 in said embodiment is unspecified.

2.5 Furthermore, as further brought forward by the respondent, it cannot be considered that the unspecified formulation of AMG 416 in said embodiment would necessarily be in the form of an aqueous solution merely because water is a commonly used vehicle or because the formulation is for subcutaneous (sc) injection. Indeed also suspensions or emulsions may be used for parenteral injections (see D33, page 225, left column, 2nd paragraph; D32, page 231, 4th full paragraph; D15, page 8, right column, 1st full

paragraph; D6, paragraph [085]; D35, paragraph [00169]).

2.6 Moreover, contrary to the opinion of the appellant, there is no direct and unambiguous disclosure in D1a that the administered AMG 416 was in a salt form. The preparation of the peptide disclosed on page 8, first paragraph of D1a mentions a purification in acetate, trifluoroacetate or hydrochloride salt form by high performance liquid chromatography. However, there is no indication that AMG 416 used to prepare the formulation for injection was still in said salt forms. There is indeed no direct link between the passages on page 8 and 10 and no reference to any salt in the remaining parts of D1a.

2.7 Accordingly, the embodiment of D1a relied upon by the appellant does not directly and unambiguously disclose an aqueous solution comprising AMG 416 HCl, let alone wherein the formulation has a pH of 2.0 to 5.0.

2.8 The subject-matter of the claims of the main request is therefore novel over D1a (Article 100(a) EPC in combination with Article 54 EPC).

3. Inventive step

3.1 Closest prior art

3.1.1 The patent relates to a liquid formulation of AMG 416 HCl, a peptide agonist of the calcium sensing receptor (CaSR) useful in the treatment of secondary hyperparathyroidism (SHPT) (see paragraphs [0001] and [0003]). The purpose of the patent is to provide a liquid formulation thereof which remains nevertheless

stable upon storage for an extended period of time (see paragraph [0005]).

3.1.2 The parties disagreed regarding the choice of the closest prior art document. The appellant considered that D1a represented the best starting point while the respondent considered that D6 should be chosen.

3.1.3 D1a presents the results of preclinical studies on the administration of AMG 416 as CaSR agonist as subcutaneous (sc) or intravenous (iv) bolus injection to normal or renally compromised rats. The parathyroid hormone (PTH) levels were studied (see Abstract, pages 21-23, page 10 lines 10-13). As discussed under novelty, D1a does not unambiguously disclose the actual formulation of the peptide nor its actual form (free base or salt). The hydrochloride salt of AMG 416 is merely generally mentioned in a list on page 8, lines 3 to 7.

3.1.4 D6 discloses inter alia the present peptide (see Ac-c(C)arrrar-NH_2 (SEQ ID N0:3)), for use in the treatment of secondary hyperparathyroidism in dialysis patients (see for example paragraphs [001], [021], [028], [033], [084]). In particular examples 1 and 2 of D6 describe the intravenous administration of AMG 416 to human patients but do not provide any information regarding the actual formulation of the peptide (solution or suspension, aqueous solvent or not, specific pH,...) nor its actual form (free base or salt). The hydrochloride salt of AMG 416 is merely generally mentioned in a list in paragraph [085].

3.1.5 Both documents relate to the study of AMG 416 as CaSR agonist in the treatment of SHPT. None of the documents unambiguously disclose the actual formulation of the

peptide which was administered. D6 relates to the administration to humans while D1a is limited to rats, so that D6 might be considered closer to the subject-matter of the patent. Nevertheless, D1a represents also a realistic starting point.

3.1.6 It is established case law that, "if the skilled person has a choice of several workable routes, *i.e.* routes starting from different documents, which might lead to the invention, the rationale of the problem-solution approach requires that the invention be assessed relative to all these possible routes, before an inventive step can be acknowledged", see Case Law of the Boards of Appeal, 11th Edition, 2025, I.D.3.3.

3.1.7 In the present case, non-obviousness must therefore be established starting from each one of D1a and D6 before an inventive step could be acknowledged.

3.2 Distinguishing features and associated technical effects

3.2.1 The claimed formulation differs from D1a (see above under novelty) and D6 in the same features, namely:

(i) AMG 416 is specifically formulated as an aqueous solution having a pH of 2.0 to 5.0, and

(ii) AMG 416 is present in the form of its HCl salt.

3.2.2 The appellant considered that, if some distinguishing features would be acknowledged over D1a, their choice would be either arbitrary or the result of routine optimisation.

3.2.3 The respondent argued *inter alia* that the claimed pH range resulted in liquid formulations having a higher degree of storage stability over an extended period of time. Furthermore, the respondent considered that the use of the HCl salt rendered the formulations well tolerated because they would be less resistant to neutralisation in the body.

3.2.4 Regarding the storage stability, the Board observes that the experimental data provided in table 5 of the patent substantiate that solutions having a pH of 2 to 5 have an increased storage stability compared to solutions having a higher pH. The solutions at pH 6 degrade indeed earlier when the storage temperature and/or the AMG 416 concentration increase. A long term storage stability at 5°C for solutions having a pH in the presently claimed range (pH between 3.0 and 3.6) is furthermore experimentally substantiated by the data in D37. The Board observes that the results provided in D37 (submitted after filing of the present patent) do merely confirm the teaching of the patent and may thus be taken into account in the assessment of inventive step in line with G 2/21. These results are considered to indicate an improved storage stability within the claimed pH range.

3.2.5 Regarding the alleged effect linked to the use of HCl salt, paragraph [0063] of the patent provides a mechanistic explanation in support thereof upon intravenous administration.

3.3 Objective technical problem

Accordingly, starting from the examples 1-2 of D6 or the embodiment on page 10 of D1a, the objective technical problem resides in the provision of a ready-

to-use formulation of AMG 416 having high storage stability and being well tolerated when administered intravenously.

3.4 Non-Obviousness

3.4.1 As stated above (see 3.2.5), paragraph [0063] of the patent explains the rationale behind the advantage (tolerability upon iv administration) linked to the choice of an HCl salt. However, this forms part of common general knowledge of a formulation chemist, so that this effect would be expected. The choice of a strong acid such as HCl to achieve said effect cannot therefore provide inventiveness.

3.4.2 Regarding the preparation of an aqueous solution having a pH of 2.0 to 5.0 with the aim of providing a ready-to-use formulation having high storage stability, the Board considers that the situation is the same as in T 2342/19 concerning the parent application. The conclusions reached in said earlier case (see r. 3.4) apply *mutatis mutandis* in the present case as follows.

The idea of providing an aqueous solution of an active ingredient may appear obvious to the skilled person willing to provide a ready-to-use solution *per se*.

However, in the present case, the active ingredient is a peptide and the formulation of peptides in aqueous solution is known to possibly be challenging due to stability issues (see for example D40, page 105 last full paragraph, last sentence, and page 101, table 1) The closest prior art D6 or D1a do further not provide any particular hint towards an aqueous solution of AMG 416. As already discussed above, no unambiguous information is provided regarding the actual

composition of the liquid formulations administered according to said documents. In the present case, the skilled person willing to solve the problem posed would thus not have found in D6 or D1a any particular motivation to prepare specifically an aqueous solution of AMG 416, let alone with the presently claimed pH, with the expectation of obtaining a storage stable and thus ready-to-use composition.

Furthermore, none of the remaining cited documents suggests an aqueous formulation of AMG 416 having a pH between 2.0 and 5.0 to solve the problem posed.

3.4.3 According to the appellant, the optimization of the pH of a formulation forms part of the common approach in the development of pharmaceutical solutions in particular in the field of peptides, known to have pH-dependent stability issues. The appellant considered therefore that the skilled person would have arrived at the present pH range by carrying out routine pH stability studies.

This argument is not convincing. There is no indication in the prior art that would have particularly motivated the skilled person to formulate AMG 416 as an aqueous solution. On the contrary, issue with the formulation of peptides in solution were highlighted (see D10, S5, left column, 2nd paragraph and S22 right column, 2nd paragraph). Performing pH stability studies would thus not have been obvious, in particular as the pH does not appear to be the only parameter influencing degradation reactions and hence storage stability (see for example D10, S5, left column, 2nd paragraph and D31, page 20 2nd paragraph).

3.5 As a result, the Board considers that the subject-matter of granted claim 1 involves an inventive step. The same reasoning applies *mutatis mutandis* to granted claims 2-15. The ground of opposition under Article 100(a) in combination with Article 56 EPC does therefore not prejudice the maintenance of the patent.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos E. Duval

Decision electronically authenticated