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Datasheet for the decision of 12 April 2018

Case Number: T 2145/13 - 3.3.04

Application Number: 03779091.2

Publication Number: 1556083

IPC: A61K39/395, G01N33/53

Language of the proceedings: EN

Title of invention:
Methods for treating post-surgical pain by administering an antibody against nerve growth factor and compositions containing the same

Patent Proprietor:
Rinat Neuroscience Corp.

Opponents:
Regeneron Pharmaceuticals, Inc.
Sanofi (opposition withdrawn)

Headword:
RINAT/Treatment of post-surgical pain

Relevant legal provisions:
EPC Art. 54
RPBA Art. 13(1)

Keyword:
Novelty - main request (no)

Decisions cited:

Catchword:

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Beschwerdekammern

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Case Number: T 2145/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 12 April 2018

Appellant: (Opponent 1)	Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591-6707 (US)
Representative:	Hayes, Emily Anne Luxford Mewburn Ellis LLP City Tower 40 Basinghall Street London EC2V 5DE (GB)
Respondent: (Patent Proprietor)	Rinat Neuroscience Corp. 230 East Grand Avenue South San Francisco, CA 94080 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)

Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 23 September 2013 concerning maintenance of the European Patent No. 1556083 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	A. Chakravarty
	L. Bühler

Summary of Facts and Submissions

I. In an interlocutory decision, the opposition division decided that European patent No. 1 556 083, entitled "*Methods for treating post-surgical pain by administering an antibody against nerve growth factor and compositions containing the same*", in amended form, met the requirements of the EPC (Article 101(3)(a) EPC).

II. The patent had been opposed by two parties, opponent 1 and opponent 2 on the grounds of Article 100(a), (b) and (c) EPC. Opponent 2 withdrew their opposition in the course of the proceedings before the opposition division.

III. An appeal was filed against the opposition division's decision by opponent 1 (appellant). The patent proprietor is respondent to the appeal.

IV. With the statement of grounds of appeal, the appellant filed a declaration of Professor Brennan.

V. With the reply to the appellant's statement of grounds of appeal, the respondent re-submitted the set of claims considered allowable by the opposition division as a main request and sets of claims of auxiliary requests 1 to 3.

VI. Two third parties filed observations according to Article 115 EPC.

VII. The board issued a summons to oral proceedings and subsequently, a communication pursuant to Article 15(1) RPBA in which it informed the parties of its view that a review of the opposition division's

construction of the term "*post-surgical pain*" would be an important element in the appeal and at the scheduled oral proceedings and that, in its preliminary opinion, no substantiation had been provided for auxiliary requests 1 to 3. It was therefore inclined to regard these requests as not being validly filed and becoming effective only at the date on which they are substantiated.

VIII. The respondent replied to the board's communication and concurrently filed document A30.

IX. Oral proceedings before the board were held on 12 April 2018. At the oral proceedings the respondent withdrew all pending auxiliary requests and filed a new first auxiliary request. At the end of the oral proceedings the chairwoman announced the decision of the board.

X. Claim 1 of the main request reads as follows:

"1. An anti-NGF antibody for use in the treatment of post-surgical pain".

Claim 1 of auxiliary request 1 reads:

"1. An anti-NGF antibody for use in the treatment of post-surgical pain, wherein the anti-NGF antibody is for use in suppressing or ameliorating resting pain."

XI. The following documents are mentioned in this decision:

A1 - Woolf C. et al., Neuroscience, 1994, 62(2), 327-331.

A2 - Leem J. et al., Society for Neuroscience Abstract Archive, 2000, 2000-2005; Presentation Number 633.1, Neuroscience 2000 Abstract.

A3 - Ramer S. and Bisby, M., European Journal of Neuroscience, 1999, 11, 837-846.

A17 - Zhou X.-F. et al., European Journal of Neuroscience, 2000, 12, 100-105.

A19 - Ro L.-S. et al., Pain, 1999, 79, 265-274.

A20 - Brennan T. et al., Pain, 1996, 64, 493-501.

A21 - Li L. et al., Experimental Neurology, 2002, 175, 23-24.

A22 - Bennett G. and Xie, Y.-K., Pain, 1988, 33, 87-107.

A23 - Brennan T. et al., Anesthesiology, 1997, 87, 1517-1528.

A25 - Declaration of Dr David Shelton.

A26 - Declaration of Prof. Timothy Brennan.

A30 - Kawamata M. et al., Anesthesiology, 2002, 97, 550-559.

XII. The arguments of the appellant presented in writing and during the oral proceedings before the board are summarised as follows:

Main request - Claim 1

Construction of the expression "post-surgical pain"

The expression "post-surgical pain" used in the claims was defined in paragraph [0065] of the patent. Both parties and the opposition division had accepted that this definition of the term "post-surgical pain" was correct. The definition was very broad and included pain arising from an external trauma, such as a cut, puncture, incision, tear, or wound into the tissue of an individual, as was confirmed by Professor Brennan in his declaration. Therefore, "post-surgical pain", as defined in the patent, was not limited to pain arising as a result of an incision, i.e. "incisional pain".

In its decision, the opposition division wrongly read limitations into the term that did not exist. In particular, on the basis of the disclosure of document A23 they considered that "post-surgical pain" was "*usually greatest immediately after surgery, severe for several days and then gradually decreases*" (see paragraph 5.4.2 of the decision under appeal).
This was a misinterpretation of the disclosure of document A23 which made it clear, by the use of the words "*not necessarily*", that there were circumstances in which surgical incisions themselves may cause inflammation or nerve injury. For example, in the case of major surgery (e.g. organ transplantation), traumatic injury, inflammation and/or nerve injury was almost certainly present on top of any incisional pain.

Thus, neuropathic pain could be a component of "post-surgical pain".

Although paragraph [0012] of the patent mentioned "*obvious differences*" between "post-surgical" and inflammatory, visceral and neuropathic pain, it was not clear what these differences were or how they could be used to distinguish the various types of pain. In fact, these different types of pain did not represent discrete categories and there was some overlap between the various types of pain, given that "post-surgical pain" had both inflammatory and neuropathic components.

The label "post-surgical" did not distinguish neuropathic pain from other types of pain arising from a surgical procedure. This view was supported by Professor Brennan in his declaration, where he stated that "*post-surgical pain, neuropathic pain and inflammatory pain in the acute setting are difficult to distinguish*" (see paragraph 7 of A26).

Novelty - Article 54 EPC

Documents A2, A3, A17 and A19 all disclosed studies done on rats in which surgical procedures were carried out that included the severance or ligation of spinal nerves. As a result, the rats experienced pain at the site of the incision but also remote from this, due to the nerve injury. Although these documents concerned studies aimed at neuropathic pain, this did not mean that the neuropathic pain experienced by the rats was not "post-surgical". Each of the above cited documents disclosed that the "post-surgical pain" experienced by

the rats was alleviated by treatment with anti-NGF antibodies. The cited documents each anticipated the subject-matter of claims 1, 3, 10 and 11 of the main request.

Admissibility of auxiliary request 1 - Article 13(1) RPBA

The request should not be admitted into the appeal proceedings because it gave rise to new issues that were not straightforward to deal with at the oral proceedings and because it was filed so late in the appeal proceedings as to preclude the formulation of a proper response. Finally, the amendments made did not overcome the problem of lack of novelty.

The claim request was derived from auxiliary request 2 filed with the statement of grounds of appeal. This request, as pointed out in the board's communication, had not been substantiated. The substantiation provided in the respondent's letter dated 20 March 2018 related to the topic of inventive step but did not explain how the amendments overcame the lack of novelty of the main request. Thus, the request should be considered as filed during the oral proceedings before the board. The objection of lack of novelty of the main request had been raised in the statement of grounds of appeal and the respondent had therefore had ample opportunity to submit claim requests that took it into account.

The deletion of "*and/or mechanically induced pain*" from the claim meant that the prior art had to be re-analysed for its disclosure of the treatment of "*resting pain*" which had not been the focus previously, since the respondent's case on inventive step set out

in the statement of grounds of appeal revolved around the treatment of mechanically induced pain.

Furthermore, the amendments did not overcome the issue of lack of novelty. Correct reading showed that the claimed subject-matter was not limited to the treatment of only post-surgical resting pain. Instead, the claim merely described the type of antibody to be used in treating all types of post-surgical pain. Even if the claim were construed as being limited to treatment of only resting pain, this was not novel in the light of the disclosure in document A19 of the use of an anti-NGF antibody to treat thermally induced pain, a sub-category of resting pain.

The respondent's (and the opposition division's) assertion that the sham operated rats mentioned in documents A21 and A22 provided evidence that post-surgical pain experienced proximal to the site of incision was not treated by administration of an anti-NGF antibody, was misleading. In fact, the sham operated rats mentioned in these documents had not received any anti-NGF antibody at all. Thus, the observations made on these rats were irrelevant to the skilled person's knowledge on the efficacy of the treatment of pain by anti-NGF antibody administration.

XIII. The arguments of the respondent made in writing and at oral proceedings before the board are summarised as follows:

Main request - Claim 1

Construction of the expression "post-surgical pain"

The term "post-surgical pain" used in the claims was correctly defined in paragraph [0065] of the patent and this definition was in keeping with the way the term was used in the art at the relevant date of the patent. The cited paragraph made it clear that "post-surgical pain" included thermal sensitivity, mechanical sensitivity and/or resting pain.

Certain spatial and temporal characteristics were known in the art to be typical of post-surgical pain. For instance, document A30 (page 550, right column, lines 4 to 10) disclosed that the term "*took into account the known facts regarding the temporal and spatial nature of post-surgical pain - both primary and secondary - in humans. In particular, it was known that the primary pain was restricted to the site of injury, whereas the secondary hyperalgesia was also observed in undamaged skin adjacent to the injured area*". The use of the term "*adjacent*" showed that the skilled person would not have considered pain at locations very distant from the site of surgery as included in the term post-surgical pain, and also explained why an express restriction to the injured tissue in the definition of post-surgical pain would not have been appropriate. The patent had therefore been written to be fully consistent with this understanding of "post-surgical pain".

Another document representative of the skilled person's understanding of "post-surgical pain" at the relevant date was document A23. It confirmed that "*in postoperative patients, pain is usually the greatest immediately after surgery, is severe for several days later, and then gradually decreases. Surgical incisions do not necessarily cause chronic pain like inflammation or nerve injury. The duration of mechanical hyperalgesia in this study is similar to the period of mechanical sensitivity and evoked pain from coughing observed postoperatively in humans*" (see page 1525, right column).

Thus, at the relevant date of the patent, the skilled person was able to and did distinguish between "post-surgical pain" and neuropathic pain and, as set out in paragraph [0012] of the patent, they would not have considered that "post-surgical pain" included neuropathic pain. Indeed, the pain model used in the patent mimicked post-surgical but not neuropathic pain (see paragraph [0165]). By contrast, the skilled person seeking to investigate the use of an agent for treating inflammatory pain would have chosen a model suitable for this purpose, such as the CFA model disclosed in document A1. Similarly, when seeking to investigate the utility of an agent for treating neuropathic pain, the skilled person would have chosen an appropriate model, such as those described in documents A2, A3, A17 and A19.

In summary, pain following surgery had various components which the skilled person would have distinguished. For example, the pain experienced as a result of cutting or severing a (major) nerve would have been classified as neuropathic, whereas the pain experienced as a result of a surgical incision, while

complex mechanistically (see paragraphs [0011] and [0012] of the patent) was known in the art as post-surgical pain.

Novelty - Article 54 EPC

Each of documents A2, A3, A17 and A19, cited by the respondent as disclosing the treatment of post-surgical pain by administration of an anti-NGF antibody, in fact disclosed the treatment of neuropathic pain by administration of an anti-NGF antibody. None of the cited documents contained any evidence that pain falling within the skilled person's understanding of the term post-surgical pain could be treated (i.e. suppressed or ameliorated) by administration of an anti-NGF antibody.

Even if post-surgical pain were construed to include neuropathic pain caused by surgery or trauma, which was disputed, none of the cited documents disclosed the successful treatment of such pain by administration of an anti-NGF antibody. Instead, these documents reported that pain remote from the incision site was ameliorated. As noted by the opposition division, parallel “sham” surgery disclosed in documents A21 and A22 did not result in pain that was treated by anti-NGF antibodies at locations distant from the site of surgery (see paragraph 5.4.4 of the decision under appeal).

In summary, the documents A2, A3, A17 and A19, cited by the respondent as anticipating the claimed invention did not disclose the measurement of the pain resulting from the surgical trauma that was necessary to selectively dissect the respective nervous structures. What was measured was neuropathic pain, which is a

result of the nervous system reacting to the respective interruption of neuronal circuits. The character, time course and indeed the site of the neuropathic pain were entirely separate from any post-surgical pain the animals may have experienced as well.

XIV. The parties' requests were as follows:

The appellant (opponent) requested that the decision under appeal be set aside and that European patent No. 1 556 083 be revoked.

The respondent (patent proprietor) requested that the appeal be dismissed (main request), or, alternatively, that the patent be maintained on the basis of the claims of the first auxiliary requests filed during the oral proceedings before the board.

Reasons for the Decision

Admission of third party observations and of document A30 into the proceedings - Article 13(1) RPBA

1. The issue of admission of the third party observations need not be decided on, since neither of the parties relied on them in their submissions and the board has not relied on them in reaching its decision.

2. The appellant did not object to the admission of document A30 into the proceedings. The board decided to admit the document.

Main request - Claim 1

Novelty - Article 54 EPC

3. The claim is for an anti-NGF antibody for use in the treatment of post-surgical pain.

4. Documents A2, A3, A17 and A19 all disclose studies involving the administration of an anti-NGF antibody to rats which have undergone a surgical procedure in which the spinal chord or spinal nerves are severed (see documents A2, A17 - see page 101, left column), constricted (CCI) or ligated (SNL) (document A3 - see page 838, left column, document A19 - see page 266, right column). In each case, pain experienced by the rats was ameliorated by the administration of the anti-NGF antibody.

5. The above assessment of the prior art was common ground between the parties. There was however disagreement about whether the pain treated by anti-NGF antibody administration, was "post-surgical" within the meaning of term as used in the patent.

6. The appellant was of the view that any pain, including neuropathic pain, that was a result of a surgical procedure should be regarded as "post-surgical" pain. By contrast, the respondent took the view that each of the above mentioned documents related to the treatment of neuropathic pain, which was known in the art as being a distinct and different category of pain, distinguished from post-surgical pain, *inter alia*, by site and duration (time-course) and indeed measured using a different experimental model.

7. In deciding on the novelty of the claimed subject-matter, the question to be answered is therefore whether nor not the term "post-surgical pain" encompasses neuropathic pain caused by surgery.

8. Terms used in patent documents should be given their normal meaning (cf. Case Law of the Boards of Appeal of the European Patent Office, 8th edition, II.A.6.3.3). The normal meaning of the terms "post-surgical" and "pain" are "after surgery" and "pain of any type", respectively. Adopting this interpretation would mean that neuropathic pain caused by surgery must be encompassed by the expression "post-surgical pain".

9. The respondent argued that the expression "post-surgical pain" had a particular meaning in the art which excluded neuropathic pain, even if it was caused by surgery. The skilled person distinguished between on the one hand, post-surgical, post-incisional or post traumatic pain and on the other hand, types of pain such as neuropathic pain and inflammatory pain. This was reflected in the use of specific models when testing agents for the treatment of the different types of pain. The examples in the patent used the Brennan model of incisional pain disclosed in document A20 rather than the model of inflammatory pain disclosed in document A1 or the model of neuropathic pain used in documents A2, A3, A17 and A19.

10. Both parties submitted expert declarations on the construction of the term "post-surgical pain". The appellant submitted document A26, a declaration of Professor Brennan (an author of, *inter alia,* document A20), while the respondent submitted document A25, a declaration of Dr Shelton (one of the inventors of the patent in suit). While agreeing that "post-surgical

pain" referred to pain arising or resulting from an external trauma such as a cut, puncture, incision, tear, or wound into tissue of an individual, the experts disagreed on whether neuropathic pain resulting from a surgical procedure fell within the meaning of the term (cf. document A25, page 2, penultimate paragraph and document A26, paragraphs 7 and 8). This disagreement reflects that found in the parties' respective arguments.

11. In the board's view, the documents cited by the respondent disclose that the skilled person, at the effective date of the patent, was able to and did distinguish between pain caused by different mechanisms, such as inflammatory (cf. document A1), neuropathic (cf. paragraph [0010] of the patent). There is however no absolute definition of the term "post-surgical pain" in any of these documents that would lead the skilled reader to ascribe the term a meaning different to that set out in point 8. above. In other words, it is established that the skilled person knew about different types of pain and about the corresponding experimental animal models for these. This does not mean, however, that it is established that the skilled person would have understood that each of these types of pain could not be considered as pain arising as a result of surgery.

12. It is established case law of the boards that "*the description and drawings are used to interpret the claims and identify the subject-matter, in particular in order to judge whether it is novel and not obvious*" (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition, II.A.6.3.1).

13. The patent defines "post-surgical pain" at paragraph [0011] and more extensively at paragraph [0065]. This latter paragraph reads as follows: ["post-surgical pain" is] "*pain arising or resulting from an external trauma such as a cut, puncture, incision, tear, or wound into tissue of an individual (including that that arises from all surgical procedures, whether invasive or non-invasive). As used herein, "post-surgical pain" does not include pain that occurs without an external physical trauma. In some embodiments, post-surgical pain is internal or external pain, and the wound, cut, trauma, tear or incision may occur accidentally (as with a traumatic wound) or deliberately (as with a surgical incision). As used herein, "pain" includes nociception and the sensation of pain, and pain can be assessed objectively and subjectively, using pain scores and other methods well-known in the art. Post-surgical pain, as used herein, includes allodynia (i.e., increased response to a normally non-noxious stimulus) and hyperalgesia (i.e., increased response to a normally noxious or unpleasant stimulus), which can in turn, be thermal or mechanical (tactile) in nature. In some embodiments, the pain is characterized by thermal sensitivity, mechanical sensitivity and/or resting pain. In some embodiments, the post-surgical pain comprises mechanically-induced pain or resting pain. In other embodiments, the post-surgical pain comprises resting pain. The pain can be primary or secondary pain, as is well-known in the art*".

14. The board notes that the above cited definition of "post-surgical pain" refers to pain in general arising from surgery and does not exclude any type of pain, in particular, it does not exclude neuropathic pain. Furthermore, there is no passage in the patent that excludes neuropathic pain caused by surgery from the

intended meaning of "post-surgical pain". Indeed, it is explained that the term is understood to include pain resulting from accidental trauma, which could cause both tissue damage and nerve damage. Moreover, it is made clear that both primary (pain local to the site of injury) and secondary pain (pain at a site outside of the area of injury) are included in the meaning of the term. The board notes that neuropathic pain is often secondary pain (cf. document A3, page 838, "*Behavioural testing*").

15. Considering the *prima facie* meaning of the expression "post-surgical pain" and taking into account its definition in the description, the board can only conclude that said expression, as used in the patent, includes neuropathic pain caused by surgery or trauma.

16. As discussed above, it was not disputed by the respondent that documents A2, A3, A17 and A19 all disclose an anti-NGF antibody for use in treating neuropathic pain resulting from surgery or trauma. The respondent did argue that, even if post-surgical pain were construed to include neuropathic pain caused by surgery or trauma, none of the cited documents disclosed the successful treatment of such pain by administration of an anti-NGF antibody. Instead, these documents reported that pain, remote from the surgical incision site, was ameliorated.

17. In the board's view this argument is essentially the same as the initial argument that "post-surgical pain" would not have been understood by the skilled person to include neuropathic pain caused by surgery, except that it concedes that incisional pain relatively local to the site of injury may have a neuropathic aspect. However, this is not the construction of the term

"post-surgical pain" arrived at by the board and hence this argument must fail for the reasons set out in point 15., above.

18. Thus the subject-matter of claim 1 lacks novelty with respect to the disclosure in documents A2, A3, A17 and A19.

19. The board therefore holds that the appellant's appeal is allowable.

Admission of auxiliary request 1 into the proceedings - Article 13(1) RPBA)

20. The filing of the claims of auxiliary request 1 by the respondent during the oral proceedings represents an amendment to their case. The admission of this request is therefore at the board's discretion (cf. Article 13(1) RPBA).

21. The claim request was presented at the oral proceedings and thus at a very late stage in the appeal proceedings. The respondent argued that the amendments were done specifically to address the board's finding under Article 54 EPC announced at the oral proceedings and were intended to qualify the type of treatment. They were also straightforward, being the amalgamation of subject-matter claims 1 and 2 of the granted patent. The appellant should have been prepared to deal with the claim request since its subject-matter had been present in the claims since the grant of the patent and raised no new issues.

22. However, the board notes that the objection under Article 54 EPC that led to the finding of lack of novelty was already raised by the appellant in the

statement of grounds of appeal. The respondent was thus aware of that objection when filing the reply to said statement of grounds of appeal. That the board might agree with the appellant on the construction of the phrase "post-surgical pain" therefore cannot be considered as having been unforeseeable. Furthermore, no new objection was raised *ex officio* by the board and no new line of argument was raised by the appellant during the oral proceedings (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition IV.E.4.4.12). Therefore, in the present case, the board cannot conclude that an unexpected development of the case occurred that could justify the late filing of auxiliary request 1.

23. Moreover, the amendments made raise issues of claim construction and inventive step, which have not been previously addressed in the appeal proceedings (see point XII., above). The admission of the claim request would therefore have added complexity to the case and would have led to a discussion of certain topics for the first time at the oral proceedings before the board.

24. In view of the above considerations, the board has not admitted auxiliary requests 1 into the proceedings (Article 13(1) RPBA).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated