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Datasheet for the decision of 5 October 2007

Case Number: T 0385/07 - 3.3.04

Application Number: 02770106.9

Publication Number: 1435991

IPC: A61K 38/15

Language of the proceedings: EN

Title of invention:
Use of aplidine for the treatment of pancreatic cancer

Applicant:
PHARMA MAR, S.A.

Opponent:
-

Headword:
Aplidine/PHARMA MAR

Relevant legal provisions:
EPC Art. 84, 123(2), 54, 56

Keyword:
"Main request: clarity (yes)"
"Added subject-matter (no)"
"Novelty (yes)"
"Inventive step (yes)"
"Remittal (yes)"

Decisions cited:
G 0005/83, T 0241/95, T 0158/96, T 0919/99

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0385/07 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 5 October 2007

Appellant: PHARMA MAR, S.A.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 24 October 2006 refusing European application No. 02770106.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chair: U. Kinkeldey
Members: R. Gramaglia
R. Moufang

Summary of Facts and Submissions

I. The appellant (applicant) lodged an appeal against the decision of the examining division refusing European patent application No. 02 770 106.9 (published as WO 03/033013) with the title "Use of aplidine for the treatment of pancreatic cancer" on the grounds of lack of novelty and lack of inventive step.

II. The decision was based on claims 1 to 6 filed on 7 September 2006, claim 1 reading as follows:

"1. The use of aplidine in the preparation of a medicament for a method of treating a mammal affected by pancreatic cancer to prevent the risk of developing tumours, to promote tumour regression, to stop tumour growth and/or to prevent metastasis which comprises administering to the affected individual a therapeutically effective amount of aplidine, or a pharmaceutical composition thereof."

III. The following documents are cited in the present decision:

D1 WO-A-01/35974;

D2 WO-A-91/04985;

D3 Raymond E. et al., Proceedings of the American Association for Cancer Research, Vol. 41, Abstract No. 3886 (March 2000);

D4 Faircloth G. et al., Proceedings of the American Association for Cancer Research, Vol. 39, Abstract No. 1551 (March 1998);

D5 Faircloth G. et al., Proceedings of the American Association for Cancer Research, Vol. 40, Abstract No. 2612 (March 1999).

IV. The examining division held that the subject-matter of claim 1 lacked novelty in view of document D1 because this document explicitly mentioned in Example 17 (page 39) and in Example 18 (page 43) "pancreatic cancer as one of the different types of cancers treatable with aplidine". The examining division also held that the present application did not disclose any in vivo results in humans (only human cell lines in mice had been tested) so that the present application had not really developed the subject-matter further compared to the teaching of document D1.

V. As for the inventive step, the examining division considered that the skilled person starting from document D1 as the closest prior art and wishing to find an alternative treatment for pancreatic cancer, would use aplidine with a reasonable expectation of success. This is because the general effectiveness of aplidine was known from document D1, which explicitly mentioned pancreatic cancer, and from documents D2 to D5, wherein the effectiveness of aplidine against various types of cancers was proven.

VI. The appellant (applicant) lodged an appeal against this decision. The Statement of Grounds of Appeal included new claims 1 to 6, of which claim 1 read as follows:

"1. The use of aplidine in the preparation of a medicament for the treatment of a mammal affected by pancreatic cancer to prevent the risk of developing tumours, to promote tumour regression, to stop tumour growth and/or to prevent metastasis."

VII. The appellant's arguments in writing, insofar as they are relevant to the present decision, may be summarized as follows:

Novelty

– Document D1 merely disclosed in Examples 17 and 18 that some patients with pancreatic cancer had been enrolled in the phase I clinical trials of aplidine but no data were given which would allow the reader of document D1 to deduce whether or not pancreatic cancer was treatable with aplidine.

– In both phase I trials described in Examples 17 and 18, the cancer patients were divided into groups, with each group being given a different dosage level of aplidine. There was no disclosure of which dosage levels were given to the subjects with pancreatic cancer.

– According to decision T 158/96 of 28 October 1998, the information in a citation that a medicament was undergoing a clinical phase evaluation for a specific therapeutic application was not prejudicial to the novelty of a claim directed to the same therapeutic application of the same medicament if the content of said citation did not

allow any conclusion to be drawn with regard to the actual existence of a therapeutic effect underlying the claimed medical use.

Inventive step

– Document D1 failed to teach that aplidine actually exhibited a therapeutic activity in patients suffering from pancreatic tumours.

– The skilled person would not be in a position to predict whether or not a drug shown to be effective in the treatment of one type of cancer would also be effective against a different type of cancer, especially the difficult-to-treat pancreatic cancer, characterised by its strong resistance to chemotherapy.

VIII. The appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 6 filed on 6 February 2007.

Reasons for the Decision

Article 84 EPC

1. Present claim 1 no longer comprises the reference to a "method of treating" and the reference to the "pharmaceutical composition" to be administered in said method, which have been objected under Article 84 EPC by the examining division (see paragraph I of the decision under appeal). Therefore, present claim 1 and

dependent claims satisfy the requirements of Article 84 EPC.

Article 123(2) EPC

2. New claim 1 is based on claim 1 as filed with the feature "to prevent the risk of developing tumours, to promote tumour regression, to stop tumour growth and/or to prevent metastasis" having a basis on page 10, lines 18 to 20 of the published WO application. Claims 2 to 6 are based on method claims 2 to 6 as filed, reformulated as use claims. Therefore, present claims 1-6 do not infringe Article 123(2) EPC.

Novelty

3. Claim 1 is drafted in the form of a second/further medical use of aplidine for making a medicament for the treatment of a mammal affected by pancreatic cancer. The relevant issue under the law currently in force is whether or not this use relates to a novel medical use in the sense of decision G 5/83 (OJ EPO 1985, 064).

Document D1

4. This document relates to aplidine and its use in the treatment of cancers. The experimental data given in D1 relate to in vitro experiments with MOLT-4 leukemia cells (see Example 1 on page 16) or gastric tumour cells MRI-H254 and prostate PC-3 tumour cells (see Table 1 of Example 2 on page 17), or to phase I clinical trials. Example 17 describes a phase I trial involving 30 patients given a 1-hour weekly infusion of aplidine. Of the 30 enrolled patients, one had

pancreatic cancer. Example 18 describes a phase I trial involving 43 patients given a 24-hour biweekly infusion of aplidine. Of the 43 enrolled patients, four had pancreatic cancer. In both trials, patients were divided into groups, with each group being given a different dosage level of aplidine ranging from 133 to 3600 mcg/m^2/wk in Example 17, and from 200 to 7000 mcg/m^2/2wks in Example 18.

5. Both trials described in Examples 17 and 18 report limited results concerning pharmacokinetic data and potential dose-limiting toxicities. There is no disclosure of which dosage levels were given to the patients with pancreatic cancer, let alone that these dosages might have been therapeutic dosages.

6. As for the therapeutic activity of aplidine, Example 17 (see under the heading "Hints of activity") reports clinical improvements in one patient with gastric adenocarcinoma and in two patients with kidney carcinoma, whereas Example 18 (see under the heading "Conclusions") states that "antitumour activity has also been noted in patients with NHL and renal carcinoma" (NHL is an acronym for non-Hodgkin lymphoma).

7. Insofar as pancreatic cancer is concerned, the board concludes that document D1 lacks any anticipation of a preliminary positive or negative therapeutic outcome of the trials, as the skilled person is not taught by document D1 whether or not aplidine actually exhibits any therapeutic activity in patients suffering from pancreatic tumours. Nor can any information about the effectiveness of aplidine against pancreatic cancer be derived from the in vitro experiments, since these

involved MOLT-4 leukemia cells, MRI-H254 gastric tumour cells and PC-3 prostate tumour cells (see point 4 supra) rather than pancreatic tumour cells. Consequently, the board does not adhere to the view expressed by the examining division (see paragraph IV supra) that Examples 17 and 18 of document D1 explicitly teach that "pancreatic cancer was one of the different types of cancers treatable with aplidine".

8. In the absence of any data in document D1 demonstrating a therapeutic effect of aplidine against pancreatic cancer, in the board's judgement, the use of claim 1 is not anticipated by the disclosure of this document.

9. The above conclusion is in keeping with the rationale of decision T 158/96 (supra; see point 3.4.1 of the Reasons), according to which the information in a citation that a medicament was undergoing a clinical phase evaluation for a specific therapeutic application was not prejudicial to the novelty of a claim directed to the same therapeutic application of the same medicament if the content of said citation did not allow any conclusion to be drawn with regard to the actual existence of a therapeutic effect or any pharmacological effect which directly and unambiguously underlay the claimed therapeutic application.

10. The examining division also held that the present application did not disclose any in vivo results in humans, so that the present application had not really developed the subject-matter further compared to the teaching of document D1.

11. Failure by a patent application to provide a "new element" vis-à-vis the teaching of a prior art document may indeed lead to a lack of novelty of a claimed medical use (see e.g. decision T 919/99 of 7 April 2003, points 7 and 22 to 24 of the Reasons). However, the board does not adhere to the examining division's view that the present application has not really developed the subject-matter further compared to the teaching of document D1. This is because while document D1 deals with in vitro experiments involving cancer cells other than pancreatic tumour cells, the present application in fact reports in vivo experiments investigating on the anti-tumour effect of aplidine against 2 human pancreatic carcinomas, NP9 and NP18, implanted in mice, which experiments thus illustrate the antitumour effect of aplidine on both primary tumours and metastases of human pancreatic carcinomas implanted in mice (tumours in the animals of the control group invaded the spleen and the peritoneum (see page 17, first paragraph of the published WO application)).

12. Furthermore, it is true that the present application relates to in vivo results in mice, not humans, however, it is an accepted principle of the case law that, for the purpose of patent protection of a medical application of a substance, a pharmacological effect or any other effect such as an effect observed on animal models is considered to provide sufficient evidence of a therapeutic application if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application (see e.g. T 241/95, OJ EPO 2001, 103). Based upon the said principle and on the passage on page 5, second paragraph of the published WO application, it can be

accepted in the present case that, in the absence of any data on human patients, the in vivo experiment are sufficiently predictive of the in vivo anti-tumour activity in humans.

Inventive step

13. The examining division also appears to have rejected the application on the basis that the skilled person had a reasonable expectation of success in using aplidine in the treatment of pancreatic cancer in view of the disclosure in document D1 taken in combination with any of the disclosures in documents D2 to D5. The examining division considered that the closest prior art document D1 showed a general effectiveness of aplidine against numerous cancer types, among which pancreatic cancer was explicitly mentioned.

14. However, the board firstly notes that of the 30 cancer patients of the trial of Example 17 of document D1 (suffering from at least 10 different cancers), only one patient with gastric adenocarcinoma and two patients with kidney carcinoma obtained clinical improvements, whereas of the 43 cancer patients of the trial of Example 18 (suffering from at least 20 different cancers), only those with non-Hodgkin lymphoma and renal carcinoma could benefit of some antitumour activity (see point 6 supra). Therefore, the board would not speak of "general effectiveness of aplidine against numerous cancer types" taught by document D1.

15. But more importantly, document D1 fails to teach that aplidine actually exhibits a therapeutic activity in

patients suffering from pancreatic tumours (see point 7 supra). Nor can any information about the effectiveness of aplidine against pancreatic cancer be derived from any of documents D2 to D5, dealing with patients not suffering from pancreatic cancer or describing in vitro/in vivo experiments involving tumour cells other than pancreatic tumour cells.

16. In the light of the (non-pancreatic) results of documents D1 to D5, the question arises whether or not the anti-tumour activity of a drug against a certain cancer type is predictive of its anti-tumour activity in another cancer type. To answer this question, it should be noted that different types of cancer affecting different organs, such as those listed on page 43 of document D1, have each a different aetiology, a different underlying spectrum of molecular alterations (e.g. mutation in an onco-suppressor, translocation, etc), and a different way of growing and producing metastases. Due to their unique characteristics, different types of cancer (but even patients having the "same" tumour) are treated differently and no compound ("the magic bullet") has been found so far to treat cancers of all types. In view of the above, a skilled person would not be in a position to predict whether or not a drug shown to be effective in the treatment of one type of cancer would also be effective against a different type of cancer.

17. Accordingly, the skilled person would normally not have a reasonable expectation of success in switching type of cancer, while keeping using the same drug.

18. This is even more true when switching to the difficult-to-treat and aggressive pancreatic cancer, characterised by its strong resistance to chemotherapy, early metastasis formation and very poor prognosis (see page 1, last paragraph to page 3, second paragraph of the published WO application).

19. In conclusion, the subject-matter of claim 1 and dependent claims 2 to 6 satisfies the requirements of Article 56 EPC.

Impact of Article 54(5) EPC 2000

20. Although the subject-matter of the claims complies with the requirements of the EPC as currently in force, the board does not consider it appropriate to remit the case to the examining division with the order to grant the patent on the basis of these claims. It has to be taken into account that the EPC 2000 will enter into force on 13 December 2007 and that, according to Article 1 No. 3 of the Decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act revising the EPC of 29 November 2000, the new Article 54(5) of the EPC 2000 shall apply to European patent applications pending at the time of its entry into force, in so far as a decision on the grant of the patent has not yet been taken.

21. Since it is highly unlikely in the present case that a grant decision will be taken before 13 December 2007 (it appears that the description still has to be adapted) and since Article 54(5) EPC 2000 allows a claim format different from the so-called Swiss-type

claim format endorsed by the Enlarged Board of Appeal in its decision G 5/83, the appellant might consider to amend its claims in view of the forthcoming change of substantive law. The board therefore remits the case to the department of first instance for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance for further prosecution.

The Registrar: Chair:

P. Cremona U. M. Kinkeldey