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**Datasheet for the decision
of 28 October 2008**

Case Number: T 1309/06 - 3.3.02

Application Number: 01912758.8

Publication Number: 1259230

IPC: A61K 31/00

Language of the proceedings: EN

Title of invention:

Partial fatty acid oxidation inhibitors in the treatment of congestive heart failure

Applicant:

CV THERAPEUTICS, INC.

Opponent:

-

Headword:

Treatment of congestive heart failure/CV THERAPEUTICS, INC.

Relevant legal provisions:

EPC Art. 54, 56, 84, 123(2)

Relevant legal provisions (EPC 1973):

-

Keyword:

"Main request - novelty (yes)"

"Main request and auxiliary request - inventive step - (no):
treatment of congestive heart failure by ranolazine not
specifically disclosed in the prior art, but obvious"

Decisions cited:

-

Catchword:

-



Case Number: T 1309/06 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 28 October 2008

Appellant:

CV THERAPEUTICS, INC.
3172 Porter Drive
Palo Alto
CA 94304 (US)

Representative:

Schnappauf, Georg
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Patent- und Rechtsanwaltskanzlei
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Decision under appeal:

Decision of the Examining Division of the
European Patent Office posted 23 March 2006
refusing European application No. 01912758.8
pursuant to Article 97(1) EPC 1973.

Composition of the Board:

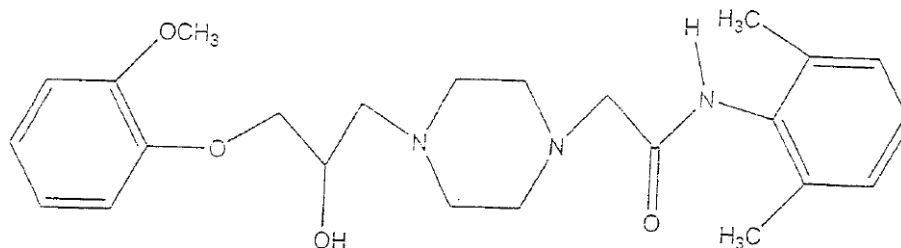
Chairman: U. Oswald
Members: A. Lindner
J.-P. Seitz

Summary of Facts and Submissions

- I. European patent application No. 01 912 758.8 was refused by a decision of the examining division of 22 February 2006 on the basis of Article 97 EPC on the grounds that the main and auxiliary requests were not novel and did not involve an inventive step (Articles 52(1), 54 and 56 EPC).
- II. The documents cited during the proceedings before the examining division and the board of appeal included the following:
- (1) H.N. Sabbah, et al., J Am. Coll. Cardiol. 35(2), Suppl. A, 218A, Feb. 2000
 - (5) WO 00/13687
 - (7) e-mail information regarding the publication date of document (1)
 - (8) A. Aaker, et al., J. Cardiovasc. Pharmacol. 28(3), 353-362, 1996
 - (9) The Merck Manual of Diagnosis and Therapy, 17th edition, Whitehouse Station, N.J., 1682-1693, 1999
 - (14) H.N. Sabbah, et al., Am. J. Physiol. 260, H1379-H1384, 1991
 - (15) M.N. Sack, et al., Circulation 94(11), 2837-2842, 1996
 - (16) U. Thadani, et al., Circulation 90(2), 726-734, 1994
- III. The decision was based on claims 1-13 of the main request, filed with letter of 20 July 2004 and on claims 1-12 of the auxiliary request filed with letter of 10 March 2005.

Independent claim 1 of the main request before the examining division reads as follows:

"1. Use of a compound of Formula I



Formula I

namely (+)-N-(2,6--dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)-propyl]-1-piperazineacetamide, as a racemic mixture or an isomer thereof, or a pharmaceutically acceptable salt or ester thereof, for the preparation of a pharmaceutical composition for treating congestive heart failure in a mammal."

Independent claim 1 of the first auxiliary request before the examining division is identical to claim 1 of the main request except that the term "in a mammal" at the end of the claim was replaced by "in a human".

IV. The arguments in the decision may be summarised as follows:

In connection with the main request, it was held that document (1), which described an animal model showing that ranolazine could improve LV performance in dogs with heart failure, anticipated the subject-matter of claims 1-2, 4-6 and 12 by implicit disclosure, as congestive heart failure and chronic heart failure related to the same disease and as the canine model

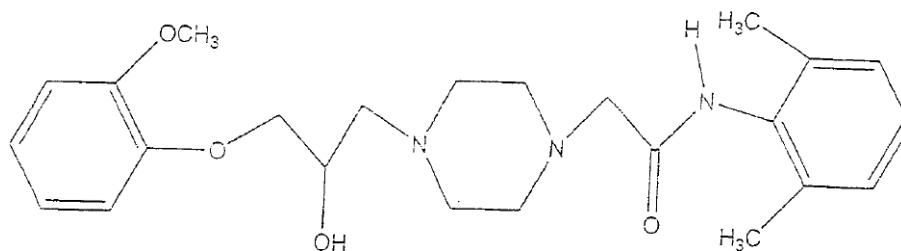
used in document (1) was a valuable model for congestive heart failure. The same reasoning applied *mutatis mutandis* to the subject-matter of claims 1-2 and 4-6 of the auxiliary request.

Moreover, the examining division concluded that the subject-matter as claimed in both the main and the auxiliary requests lacked inventive step with regard to document (1), which had been identified as closest prior art, either alone or in combination with document (5).

V. The appellant (applicant) lodged an appeal against said decision.

VI. Oral proceedings took place on 28 October 2008, at which the appellant filed a new auxiliary request in replacement of the old auxiliary request on file. Claim 1 of the auxiliary request reads as follows:

"1. Use of a compound of Formula I



Formula I

namely (+)-N-(2,6--dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)-propyl]-1-piperazineacetamide, as a racemic mixture or an isomer thereof, or a pharmaceutically acceptable salt or ester thereof,

for the preparation of an orally active sustained release formulation for treating congestive heart failure in a human.

VII. The appellant's submissions can essentially be summarised as follows:

In connection with novelty, it was held that document (1) did not relate to the treatment of congestive heart failure, nor did the improvement of LV function in a dog model with an artificial heart failure condition as disclosed in document (1) anticipate the treatment of congestive heart failure. As regards inventive step, the appellant held that document (1) was not pertinent, as it did not contain any reference to congestive heart failure. Document (1) merely suggested a greater LV mechanical efficiency achieved by the administration of ranolazine in a canine heart failure model but in contrast to the application under appeal did not contain any clinical data. Without this information, the person skilled in the art could not identify the usefulness of ranolazine for the treatment of congestive heart failure.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed with letter of 20 July 2004, or alternatively on the basis of the auxiliary request filed during the oral proceedings held before the board.

Reasons for the decision

1. The appeal is admissible.

2. *Date of publication of document (1):*

According to document (7), document (1) was made publicly available on 4 February 2000. This fact was not contested by the appellant. The board does not have any doubts as to this date of publication either. As a consequence, document (1) belongs to the state of the art according to Article 54(2) EPC.

3. *Main request:*

3.1. *Novelty:*

Document (1) describes experiments wherein the effect of ranolazine on LV performance was tested in a canine model of chronic heart failure, which had been created by intracoronary microembolizations. Document (1), however, does not specifically mention congestive heart failure. It appears that congestive heart failure (CHF) is a special form of heart failure, which is characterised by increased plasma volume and fluid accumulation in the lungs, abdominal organs and peripheral tissues (see document (9), page 1682, first paragraph of the left-hand column). As a consequence the subject-matter as claimed in the main request is novel (Article 54 EPC).

3.2. *Inventive step:*

The application under appeal concerns the use of ranolazine for the preparation of a pharmaceutical composition for treating congestive heart failure in a mammal.

The board came to the conclusion that document (1) represents the closest prior art. As was already mentioned in paragraph 3.1 above, document (1) describes experiments in which the effect of ranolazine on LV performance was tested in a canine model of chronic heart failure which had been created by intracoronary microembolizations. It was found that the administration of ranolazine improves LV performance in dogs suffering from heart failure.

As regards the question how far the results obtained by this canine model can be extrapolated to heart failure in humans, reference is made to document (14), where the animal model used in document (1) is described in detail and where it is said that multiple intracoronary embolizations with microspheres, separated in time, can lead to chronic heart failure in dogs, which manifests many of the sequelae of heart failure including LV hypertrophy and dilatation, increased LV filling pressure and systemic vascular resistance, among other things. Therefore, this model may be well suited for evaluating the efficacy of pharmacological and other therapeutic intervention in connection with heart failure (see page H1383, last paragraph of the right-hand column). As a consequence, the skilled person would consider the results obtained with the canine model as described in document (14) to be representative for chronic heart failure in humans.

It is correct that document (1) does not describe in detail the conditions applied during the microembolizations. However, the skilled person trying to set up a model for studying the efficacy of an

active agent for the treatment of chronic heart failure would select the conditions such that natural chronic heart failure is imitated as closely as possible. Being aware of the disclosure in document (14), he would apply multiple intracoronary embolizations as described therein. In this context, it is noted that the disclosure in document (1) does indeed imply that several intracoronary embolizations were applied in the tests, as the plural form (microembolizations) was used. Reference is made to the paragraph headed "Methods", which reads: "LV dysfunction and failure (LV ejection fraction $27 \pm 2\%$) was produced in 7 dogs by intracoronary microembolizationss" [emphasis by the board].

It follows from this that the skilled person would extrapolate the results obtained from this animal model to chronic heart failure in humans. In the light of these findings, the use of ranolazine for the preparation of a pharmaceutical composition for treating a specific form of heart failure constitutes the problem of the present invention. The problem was solved by using the ranolazine-containing composition for the treatment of congestive heart failure. In view of the examples of the application in suit, in particular examples 8 and 10-11, the board is satisfied that the problem defined above was plausibly solved.

When deciding whether or not the subject-matter of the present main request is obvious, it appears necessary to evaluate the relationship between heart failure or chronic heart failure on the one hand and congestive heart failure on the other hand. In this context, reference is made to the definition proposed by the

appellant in his letter dated 10 March 2005 (see page 4, last paragraph), which indicates that congestive heart failure is a common form of heart failure that results in a patient retaining excessive fluid, often leading to swelling of the legs and ankles and congestion in the lungs. This definition implies that the additional fluid retention observed in patients suffering from congestive heart failure is the only difference between the two diseases; no differences appear to exist, however, as far as the pathological symptoms of the heart itself such as LV dysfunction are concerned. As a consequence, it is obvious for the skilled person also to use the pharmaceutical composition of document (1), which is known to improve LV performance in patients suffering from chronic heart failure, for the treatment of patients suffering from congestive heart failure. As a consequence, the subject-matter as claimed in the main request does not involve an inventive step (Article 56 EPC).

3.3. Further arguments of the appellant in connection with inventive step:

3.3.1. The disclosure of document (8) was contradictory to the teaching of document (1), as it showed on the basis of endurance tests that the chronic administration of ranolazine reduced the work capacity of rats suffering from chronic heart failure. Therefore, ranolazine was not considered to be therapeutically useful in the treatment of chronic heart failure. As the endurance tests of document (8) were much more reliable than the animal model used in document (1), the person skilled in the art from was dissuaded from using ranolazine for the treatment of heart failure.

The summary of document (8) contains indeed the conclusion that the chronic administration of ranolazine may not be useful therapeutically in the treatment of chronic heart failure. However, this conclusion is based on unreliable data and therefore speculative: the authors of document (8) themselves have doubts as to the correct selection of the experimental conditions applied during the endurance tests. Reference is made to page 359, lines 2-16 of the right-hand column, where it is said that the dosage regimen used for the tests probably produced excessive plasma concentrations of the drug and that the results may have been further biased by depriving the animals of food for 12 hours before the exercise. As a consequence, the skilled person, confronted with the contradictory teachings of documents (1) and (8), would dismiss document (8).

- 3.3.2. Document (15) contained the teaching that the chief myocardial energy substrate switched from fatty acids to glucose during the development of heart failure. As a consequence, the skilled person would be dissuaded from using an active agent such as ranolazine, which was known for further shifting the substrate use away from fatty acids to glucose.

The board cannot agree with this reasoning: document (15) contains the teaching that during cardiac development, the chief cardiac energy source switches from glycolysis during the fetal period to fatty acid oxidation after birth and that during the development of heart failure the heart returns to the use of glycolysis as the primary pathway for energy production

(see page 2837, first paragraph of the left-hand column). However, this does not mean that the use of substances such as ranolazine, which further shift the substrate use towards glycolysis, would be contraindicated. On the contrary, a further shift of substrate use towards glycolysis may even be beneficial for the patient suffering from heart failure, as it may lead to the production of more ATP per mole of oxygen and thus to an improved oxygen use (see document (16), page 726, first paragraph after "key words").

Document (1) mentions in the paragraph headed "Background" the hypothesis that switching the substrate use of the heart away from fatty acids towards glucose will ameliorate the hemodynamic abnormalities associated with heart failure. This hypothesis was tested and confirmed by the animal model described above in paragraph 3.2. In view of the above reasoning, this result does not contradict the teaching of document (15), and therefore the skilled person has no reason to doubt the teaching of document (1).

- 3.3.3. The skilled person was dissuaded from applying the teaching of document (1) in the light of document (16), which demonstrated on the basis of a double-blind study that the therapy with ranolazine is not successful with patients suffering from angina pectoris. Again, doubts were expressed in connection with the reliability of the canine model of document (1).

In view of the fact that the teaching of document (16) is limited to the treatment of angina pectoris (see page 726, paragraph headed "Conclusions"), the skilled person would see no contradiction with the content of

document (1), which concerns the treatment of heart failure caused by LV dysfunction.

3.3.4. As a consequence, none of the above documents dissuades the person skilled in the art from applying the teaching of document (1).

4. *First auxiliary request:*

4.1. Amendments of claim 1:

The feature "an orally active sustained release formulation" is based on claim 29 of the application as filed, the feature "for treating congestive heart failure **in a human**" is taken from claim 35 of the original application. The requirements of Article 123(2) EPC are therefore met. Moreover, the above amendments are allowable under Article 84 EPC.

4.2. Inventive step:

The subject-matter of claim 1 is now further limited from the disclosure of document (1), which remains the closest prior art, by the introduction of the galenic form (an orally active sustained release formulation) and by restricting the patient group to humans. As far as the latter feature is concerned, reference is made to paragraph 3.2 above, wherein it is stated that the skilled person would consider the results obtained with the canine model as described in document (14) - and as a consequence those obtained in the tests of document (1) - to be representative for chronic heart failure in humans. This limitation does therefore not make any difference at all in the evaluation of inventive step

according to paragraph 3.2 above. It therefore has to be evaluated whether the introduction of the feature "an orally active sustained release formulation" can establish inventive step over document (1).

The selection of an orally active sustained release formulation does not appear to be accompanied by any non-obvious effects. In this context it is emphasised that the skilled person is aware of the fact that most active agents can be administered by various modes of administration, including injections or oral sustained release formulations as claimed in claim 1 of the auxiliary request. Therefore, the selection of an orally active sustained release formulation *per se* cannot establish inventive step over the parenteral compositions of document (1).

As for the effects obtained by selecting sustained release formulations, reference is made to examples 4 to 10 of the application as filed, which show that the release properties are such that useful plasma levels can be achieved with a bid schedule (see examples 4, 6, 8 and 10) and that there is sufficient safety and tolerability for patients taking such formulations (see example 7). Example 5 shows that peak plasma levels are obtained after 4 to 6 hours. All of these results are typical for sustained release formulations so that no non-obvious effects can be acknowledged. As a consequence, the subject-matter of claim 1 of the auxiliary request does not meet the requirements of Article 56 EPC either.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

M. Schalow

U. Oswald