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**Datasheet for the decision
of 29 November 2017**

Case Number: T 1255/11 - 3.3.01

Application Number: 01930965.7

Publication Number: 1292294

IPC: A61K31/215, A61K31/19,
A61K31/205, A61P25/28

Language of the proceedings: EN

Title of invention:

USE OF MEDIUM CHAIN TRIGLYCERIDES FOR THE TREATMENT AND
PREVENTION OF ALZHEIMER'S DISEASE

Patent Proprietor:

Accera, Inc.

Opponent:

Lupton, Frederick

Headword:

Medium chain triglycerides in the treatment of Alzheimer's
disease/ACCERA

Relevant legal provisions:

EPC Art. 123(2), 83, 100(b), 100(c), 111(1)
RPBA Art. 12(4), 13

Keyword:

Amendments - allowable (yes)

Sufficiency of disclosure - (yes)

Remittal to the department of first instance - (yes)

Decisions cited:

Catchword:



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Case Number: T 1255/11 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 29 November 2017

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 29 March 2011
revoking European patent No. 1292294 pursuant to
Article 101(3) (b) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: M. Pregetter
L. Bühler

Summary of Facts and Submissions

- I. European patent No. 1 292 294 is based on European patent application No. 01930965.7, filed as an international application published as WO01/82928.
- II. The patent has 10 claims. The independent claims 1 and 10 read as follows:

"1. Use of an effective amount of medium chain triglyceride for the preparation of a pharmaceutical composition for the treatment or prevention of loss of cognitive function caused by reduced neuronal metabolism in Alzheimer's disease, wherein said treatment or prevention comprises oral administration of a single dose of medium chain triglyceride to a patient such that the blood level of D-beta-hydroxybutyrate in the patient is raised to 1-10mM or patient urinary excretion of D-beta-hydroxybutyrate is in the range 5 mg/dL to 160 mg/dL causing hyperketonemia in the patient resulting in ketone bodies being utilized for energy in the brain in the presence of glucose."

"10. A pharmaceutical composition for use in a method of treatment or prevention of loss of cognitive function caused by reduced neuronal metabolism in Alzheimer's disease, wherein said method of treatment or prevention comprises oral administration of a single dose of medium chain triglyceride to a patient such that the blood level of D-beta-hydroxybutyrate in the patient is raised to 1-10mM or patient urinary excretion of D-beta-hydroxybutyrate is in the range 5 mg/dL to 160 mg/dL causing hyperketonemia in the patient resulting in ketone bodies being utilized for energy in the brain in the presence of glucose."

III. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(11) Reger et al., *Neurobiology of Aging*, 2004, 25, 311-314

(15) Bach et al., *Journal of Lipid Research*, 1996, 37, 708-726

(16) US 2007/0179197

(17) Henderson et al., *Nutrition & Metabolism*, 2009, 6:31

(19) Experimental evidence entitled "A Phase IV, Open-label, Single-dose, Pharmacokinetic Study of MCT administration in Healthy Subjects", filed with the grounds of appeal

(20) Percentage of Civilian, Noninstitutionalized Population with Diagnosed Diabetes, by Age, United States, 1980-2009; printout of <http://www.cdc.gov/diabetes/statistics/prev/national/figbyage.htm>

(21) Experimental evidence entitled "A Phase IV, Open-label, Single-dose, Pharmacokinetic Study of MCT administration in Subjects with Mild to Moderate Alzheimer's Disease (AD)"

(22) *Pharmacotherapy of Alzheimer's disease*, 1998, edited by Serge Gauthier, page 47

(23) Ogawa et al., *J Neurol Sci*, 1996, 139, 78-82

(24) Veneman et al., *Diabetes*, 1994, 43, 1311-1317

(25) Hasselbalch et al., Am J Physiol, 1996, 270, 746-751

(26) US 4,528,197

(27) Rebello et al., BBA Clinical 2015, 3, 123-125

- IV. The appeal lies from the decision of the opposition division to revoke the patent. The opposition division found that the main request - the set of claims as granted - fulfilled the requirements of Article 123(2) EPC but was not sufficiently disclosed. The same applied to the subject-matter of auxiliary requests 1 and 2 (filed on 1 December 2010), which was also not sufficiently disclosed. Auxiliary request 3 (filed during the oral proceedings before the opposition division) was also not sufficiently disclosed and was not admitted into the proceedings.
- V. The patent proprietor lodged an appeal against this decision, and filed, with the statement of grounds of appeal, auxiliary requests 1 to 3. By letter of 28 March 2017, it renumbered auxiliary request 3 from the statement of grounds of appeal as auxiliary request 2 and filed auxiliary requests 3 and 4.
- By letter dated 27 February 2012 the opponent (respondent) filed its reply to the grounds of appeal.
- VI. In a communication pursuant to Article 15(1) RPBA, the board indicated that, if it could establish sufficiency of disclosure, it intended to remit the case for further prosecution to the opposition division.
- VII. Third-party observations were filed on 11 January 2017.

VIII. With letter of 9 November 2017 the respondent withdrew its request for oral proceedings and informed the board that it would not be represented at the oral proceedings. It requested that the board consider its written submissions.

IX. Oral proceedings before the board were held on 29 November 2017 in the absence of the respondent.

X. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Admission of documents (19) to (26)

The filing of documents (19) to (26) had been occasioned by the surprising findings of the opposition division, especially in view of document (15).

Admission of document (27)

The filing of document (27) had been in direct response to the respondent questioning in its reply to the statement of grounds of appeal for the first time that the claimed therapeutic effect could be achieved by administration of medium-chain triglycerides (MTC).

Amendments

The technical features of the independent claims were directly derivable from the application as filed. Oral administration was singled out in claim 2 and described on page 13, line 9. The levels of D-beta-hydroxybutyrate were disclosed on page 14, lines 4 to 6, in direct combination with reference to "dosages" of effective amounts leading to the necessary ketone body concentrations. The induction of hyperketonemia was

explicitly mentioned on page 13, lines 13/14. The introduction of the feature "single dose", which came from page 13, lines 6/7, was thus the only selection necessary in order to arrive at the subject-matter of the independent claims.

Sufficiency of disclosure

Contrary to what was stated in the impugned decision, document (15) did not disclose that the amounts of D-beta-hydroxybutyrate claimed in the independent claims of the patent in suit could not be achieved. Document (15) was a review article. On page 715, right column, second full paragraph, it referred to several studies and summarised their results. It stated that one study had found that a single dose of 45-100 g MCT led to blood ketone levels of 700 $\mu\text{mol/L}$. This statement could not be taken as evidence that blood ketone levels according to claim 1 could not be achieved. There was further information in the same paragraph of document (15) setting out that the level of ketonemia directly correlated with the MCT supply. Document (15) even disclosed studies achieving ketone levels of 1000 $\mu\text{mol/L}$. Consequently, document (15) did not raise serious doubts that the claimed blood D-beta-hydroxybutyrate levels could not be achieved. Furthermore, there was no disclosure in document (15) concerning the urine D-beta-hydroxybutyrate levels. Documents (19) and (21) provided experimental evidence that the claimed levels could be achieved. In addition, document (27) disclosed a ketone peak of 1.7 mM.

The description as filed explained the principles underlying the invention. There was detailed information on the pathogenesis of Alzheimer's disease

and on the metabolism of MCT. It was thus known at the effective date of the patent in suit that loss of cognitive function was associated with impaired glucose metabolism in the brain (document (23)) and that supplemental MCT were readily converted into ketone bodies (document (26)) that could be utilised as energy supply by the cells of the brain (document (25)). Furthermore, it was known that hyperketonemia improved cognitive dysfunction (document (24)). Thus, on the basis of mechanistic metabolic evidence from the prior art cited in the description as filed, it was plausible that administering an effective amount of MCT established hyperketonemia and would enable treatment or prevention of loss of cognitive function caused by reduced neuronal metabolism in patients with Alzheimer's disease. This was supported by the disclosure of document (27).

XI. The respondent's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Admission of documents (19) to (26)

These documents had been filed for the first time at the appeal stage. An appeal was not an opportunity to conduct the case anew. Documents (19) and (21) related to experimental evidence which should have been filed before, since the opponent's arguments concerning sufficiency of disclosure had already been raised in the notice of opposition.

Amendments

The subject-matter of the independent claims contravened the requirements of Article 123(2) EPC,

since the application as filed provided no basis for a combination of administration as a "single dose" and the required blood and urinary ketone levels.

Sufficiency of disclosure

There was no evidence in the patent that demonstrated a link between the particular use or composition claimed, i.e. the single oral administration of a composition comprising MTC, and the technical goal of preventing or treating loss of cognitive function caused by reduced neuronal metabolism in patients with Alzheimer's disease. The skilled person was not taught how to gain the required blood or urinary ketone level such that it provided the therapeutic effect. It was not simply a question of administration of MTC, but a question of administration to secure the claimed technical effect. The specification provided no evidence of a link between the blood or urinary ketone level and the claimed effect. Furthermore, there was no teaching in the patent on how to achieve the claimed results by employing a single dose. In addition, the opposition division had not erred in its assessment of document (15).

The respondent submitted no arguments concerning the appellant's request for remittal of the case to the opposition division for further prosecution.

- XII. The appellant (patent proprietor) requested that the decision under appeal be set aside and that the case be remitted to the opposition division for consideration of the grounds for opposition pursuant to Article 100(a) EPC on the basis of the patent as granted (main request), or, alternatively, on the basis of the first or second auxiliary request filed as the

first and third auxiliary requests with the statement of grounds of appeal, or of the third or fourth auxiliary request filed with letter dated 28 March 2017.

The respondent (opponent) had requested in writing that the appeal be dismissed and European patent No. 1 292 294 be revoked.

XIII. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.
2. The oral proceedings before the board took place in the absence of the respondent who had been duly summoned but chosen not to attend, as announced with letter of 9 November 2017. According to Article 15(3) RPBA, the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying only on its written case. Hence, the board was in a position to announce a decision at the conclusion of the oral proceedings, as provided for by Article 15(6) RPBA.
3. *Admission of documents (19) to (27)*
 - 3.1 *Documents (19) to (26)*

Documents (19) to (26) were filed by the appellant together with its statement of grounds of appeal. Documents (19) and (21) contain comparative data. They are intended to provide evidence that the ketone levels

required by the independent claims of the patent in suit can be achieved. The question of whether the claimed levels were achievable was one of the decisive points of the impugned decision. Documents (20) and (22) are related to information about patient groups and assessment of memory impairment respectively. Documents (23) to (26) are documents cited in the application as filed. They were filed in order to show that the theoretical background described in the application as filed is confirmed in literature. The board considers the filing of these documents to be a legitimate response to the finding of the opposition division that the patent in suit did not provide any information regarding the link between the blood ketone levels and their effect on cognitive impairment in patients with Alzheimer's disease.

Consequently, the filing of these documents is to be seen as a legitimate attempt to strengthen the appellant's argumentative position concerning sufficiency of disclosure.

In view of the above considerations, the board decides to take documents (19) to (26) into account, in accordance with Article 12(1) and (4) RPBA.

3.2 *Document (27)*

In its reply to the statement of grounds of appeal, the respondent had questioned whether the claimed therapeutic effect was due to the administration of MCT. By filing document (27) the appellant intended to provide direct evidence of the link between the administration of MCT and the claimed therapeutic effect.

The board considers the filing of document (27) to be a legitimate response to the argumentation of the respondent in the reply to the statement of grounds of appeal. Document (27) contains straightforward information and does not lead to the consideration of complex issues. It is thus admitted in accordance with Article 13 RPBA.

Main request:

4. *Amendments*

The combination of claims 1 and 2 as filed provides a direct basis for a treatment or prevention of dementia of the Alzheimer's type by oral administration of an effective amount of medium chain triglycerides to a patient in need thereof.

Page 5, lines 15 to 17, of the application as filed states that Alzheimer's disease is associated with decreased neuronal metabolism.

Claim 1 as filed defines the administration of an effective amount of medium chain triglycerides. This is reflected in the description as filed on page 14, lines 1 to 8. D-beta-hydroxybutyrate levels in blood and urine that correspond to such an effective amount are described in this passage in lines 4 to 7. This disclosure defines the concentration of ketone bodies in blood and urine which is necessary to achieve the claimed effect. It is thus a mere definition of the necessary ketone levels and cannot be seen as a selection.

The description as filed indicates that the administration of medium chain triglycerides or fatty

acids results in hyperketonemia, which then results in ketone bodies being utilised for energy in the brain (page 13, lines 13 to 15). This link between high ketone levels and their use as an energy source for brain cells can also be found in the first paragraph of the detailed description of the invention on page 11, lines 5 to 11.

In addition to these features, which are generally disclosed, a further technical feature, the administration as a "single dose", has been added to claim 1. The technical feature "single dose" can be found on page 13, lines 6 to 8. Its introduction constitutes a single selection from two options.

The same amendments have been made for independent claim 10 of the main request.

The board notes that claim 1 is worded as a so-called "Swiss-type claim" and claim 10 is worded in accordance with Article 54(5) EPC 2000. The rewording of claim 1 as filed using these two claim formats does not add subject-matter.

The board thus comes to the conclusion that the subject-matter of the independent claims 1 and 10 of the main request (patent as granted) fulfils the requirements of Article 123(2) EPC.

5. *Sufficiency of disclosure*

5.1 *Treatment of disease*

The application as filed provides information on various background issues that allow for a theoretical understanding of the biochemical processes that are

said to underlie the claimed therapeutic treatment.

The description establishes that Alzheimer's disease is linked to decreased neuronal metabolism (page 5, line 15, to page 7, line 12). One of the documents showing this link is document (23), cited on page 6, line 21, of the description as filed. Document (23) establishes that, while glucose metabolism is suppressed, metabolism of other energy substrates, such as ketone bodies, does not change in Alzheimer's patients ("Discussion" on pages 81/82).

The description of the application as filed goes on to stress the fact that brain cells, especially neurons, are very specialised and can only efficiently metabolise a few substrates, such as glucose and ketone bodies (page 7, line 13, to page 9, line 8).

Thereafter, the metabolism of MTC is discussed. MTC metabolism involves early hydrolysis already in the pre-duodenum and uptake of medium-chain fatty acids (MCFA) into the blood, followed by oxidation in the liver, resulting in freely circulating ketone bodies. Page 10, line 8, of the description as filed refers to document (26). Document (26) states that MCTs are rapidly metabolised in the human body resulting in the generation of ketone bodies (column 1, line 66, to column 2, line 14).

The description as filed links hyperketonemia to increased utilisation of ketone bodies in the brain, an increase in cerebral blood flow and the reduction of cognitive dysfunction (page 13, lines 13 to 18). This passage cites documents (25) and (24). Document (25) provides support for the increased utilisation of ketone bodies as an energy source and the increase in

cerebral blood flow (abstract). Document (24) discusses the effects of hyperketonemia on cognitive dysfunction (abstract).

In sum, the description as filed explains that Alzheimer's disease is linked to a problem of glucose metabolism in the brain and that an alternative energy source for neurons are ketone bodies. It establishes that ketone bodies result from the metabolism of MCT and provides some indications that ketone bodies may improve cognitive dysfunction.

The application as filed thus provides a complete theoretical explanation, backed up by scientific literature, for the treatment of Alzheimer's disease by MCT. In the present case the presence of the claimed effect is plausible in view of this theoretical explanation.

Since the effect has been made plausible by the theoretical background explanations provided in the application as filed, the appellant may provide post-published evidence.

5.2 *Achievability of ketone levels in blood/urine*

It is undisputed that document (15), a review document, discloses that one study found that administration of a single dose of 45-100 g MCT led to blood ketone levels of up to 700 $\mu\text{mol/L}$. The opposition division came to the conclusion that levels above 1000 $\mu\text{mol/L}$, as defined by claim 1 of the main request (i.e. 1-10mM D-beta-hydroxybutyrate), could not be achieved without difficulties. The board cannot endorse this view. Document (15) goes on to disclose that the level of ketonemia is directly correlated with the MCT supply.

Given this information it seems to be reasonable that an increase in the MCT dose would lead to an increase of ketone levels in the blood. There is no evidence to the contrary.

5.3 *Burden to find necessary MCT dose*

In view of the information summarised in document (15) regarding the various blood ketone levels achieved in fed healthy subjects, fasting healthy subjects, patients having untreated diabetes or obese women on a low-energy diet, the effective dose of MCT will indeed have to be determined. However, such a determination is well within the skill of the person skilled in the art. The application as filed provides information of a commercially available product that enables determination of ketone bodies in blood and/or urine by routine measurements (page 15, lines 31/32). Thus, by carrying out routine measurements and by giving consideration to the patient to be treated, a skilled person can find the necessary MCT dose without undue burden.

5.4 *Ketone levels and the claimed effect*

The application as filed does not contain any experimental evidence providing proof of effectiveness for the defined beta-hydroxybutyrate levels. However, the description as filed, on page 13, lines 13 to 16, discloses that the administration of MCT leads to hyperketonemia. In this context "Hasselbalch et al. 1996", which is document (25), is cited. In document (25) hyperketonemia is exemplified by a mean beta-hydroxybutyrate blood concentration of 2.16 mM (abstract), which falls within the range defined in the independent claims of the patent as granted.

Document (24), cited on page 13, lines 16 to 17, as "Veneman et al. 1994", then provides a basis for the link between hyperketonemia and reduced cognitive dysfunction. A link between the claimed ketone levels and the therapeutic effect is thus plausible in view of the literature cited in the application as filed. The respondent has not submitted any arguments questioning this conclusion, which is based on the application as filed and the prior art cited therein.

5.5 The subject-matter of the claims of the patent as granted (main request) is sufficiently disclosed.

5.6 The observations by a third party received on 11 January 2017 in accordance with Article 115 EPC do not contribute any further arguments to the discussion of sufficiency of disclosure and are consequently not taken into account.

6. *Remittal*

The decision under appeal only concerned the grounds of appeal under Articles 100(b) and (c) EPC. Therefore, the patent in suit needs further examination as to the requirements of Article 100(a) in conjunction with Articles 54 and 56 EPC. In these circumstances, and in accordance with the appellant's request, the board finds it appropriate to make use of its power under Article 111(1) EPC and to remit 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 opposition division for further prosecution.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated