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Datasheet for the decision of 3 November 2014

Case Number: T 0226/10 - 3.3.01

Application Number: 96941518.1

Publication Number: 0871440

IPC: A61K31/195, A61K31/16

Language of the proceedings: EN

Title of invention:
TREATMENT OF NEGATIVE AND COGNITIVE SYMPTOMS OF SCHIZOPHRENIA WITH GLYCINE UPTAKE ANTAGONISTS

Patent Proprietor:
Javitt, Daniel, C.

Opponents:
F.Hoffmann-La Roche AG
ABBOTT GmbH & Co. KG
STRAWMAN LIMITED
Amgen Inc.

Headword:
Glycine uptake antagonists/JAVITT

Relevant legal provisions:
EPC Art. 100(a)

Keyword:
Inventive step - reasonable expectation of success (yes)

Decisions cited:

Catchword:

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Case Number: T 0226/10 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 3 November 2014

Appellant: (Patent Proprietor)	Javitt, Daniel, C. 89 Bardonia Road Bardonia, NY 10954 (US)
Representative:	Adam, Holger Kraus & Weisert Patentanwälte PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Respondent 2: (Opponent 2)	ABBOTT GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden (DE)
Representative:	Reitstötter Kinzebach Patentanwälte Im Zollhof 1 67061 Ludwigshafen (DE)
Respondent 3: (Opponent 3)	STRAWMAN LIMITED 34 Lovedon Lane Winchester, Hampshire, SO23 7NU (GB)
Representative:	Potter Clarkson LLP The Belgrave Centre Talbot Street Nottingham, NG1 5GG (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 3 December 2009 revoking European patent No. 0871440 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: C. M. Radke
O. Loizou

Summary of Facts and Submissions

I. European patent No. 0 871 440 relates to the use of a glycine uptake antagonist for the manufacture of a medicament for the treatment of psychosis or schizophrenia.

II. Four oppositions were filed against the grant of this patent. The oppositions were directed against the patent as a whole and were based on grounds under Article 100(a) (alleged lack of novelty and inventive step) and (b) EPC, and, as far as opponent 1 is concerned, on grounds under Article 100(c) EPC.

III. Opponent 1 (F. Hoffmann-La Roche AG) withdrew its opposition by letter dated 13 January 2009.

IV. The patent proprietor appealed the decision of the opposition division, posted on 3 December 2009, revoking its patent.

V. Opponent 4 (Amgen Inc.) withdrew its opposition by letter dated 6 March 2014.

VI. With its letter dated 21 December 2012, respondent 2/ opponent 2, Abbott GmbH & Co. KG, requested registration of the transfer of its opposition to AbbVie Deutschland GmbH & Co. KG. In support of this request, respondent 2 enclosed a copy of the Spin-off and Absorption Agreement and a declaration by John M. Leonard. In its communication dated 5 February 2014, the board expressed its preliminary opinion that a transfer of the opponent status could not take effect without further supporting evidence and invited the respondent 2 to file such evidence. The Board noted that in paragraph I.0.1(i) of the Spin-off and

Absorption Agreement reference was made to "the business, operations and activities (a) related to, arising out of or resulting from the importation, exporting, marketing, distribution, promotion and sale activities conducted by Abbott KG with respect to the products set forth on **Exhibit 0.1-1** (Deed no. 291/2012) – to which reference is hereby made – (the "**AbbVie Products**")...". Said Exhibit 0.1-1 had not been attached to the Spin-off Agreement. The board also remarked that the declaration was signed by Mr. Leonard in his capacity as vice president of Abbott Laboratories (which is not party to said agreement) and did not provide sufficient evidence as to which business assets had been transferred. Finally, according to paragraph 5, section 5.1, of said agreement, the transfer "shall become legally effective" at the point of time of the recording of the spin-off in the commercial register of Abbott GmbH & Co. KG. However, no copy of that part of the commercial register was enclosed.

Respondent 2 did not submit further evidence or put forward counter-arguments; it only stated that it did not share the board's view (see point III of the letter dated 14 October 2014).

VII. In the decision under appeal, the opposition division decided that

- part of the claims did not enjoy the priority claimed,
- the subject-matter of the claims of the main request was not novel in view of documents (D12) and (D20), as glycine as such could be considered as an inhibitor of glycine uptake. The same applied to clozapine, so that the subject-matter of the claims was also not novel in view of

document (D19) when considering the post-published document (D15).

- the claims of auxiliary requests I to III then on file infringed
  - Article 123(2) EPC (auxiliary request I);
  - Articles 123(2) and 84 EPC (auxiliary request II);
  - Article 83 EPC (auxiliary request III); and that
- the subject-matter of the claims of auxiliary request IV then on file was not inventive.

VIII. The documents cited during the opposition procedure include the following:

(D2) E. Toth et al., Research Communications in Psychology, Psychiatry and Behavior, vol. 11 no. 1 (1986), 1-9

(D9) WO-A-93/10 228

(D10) US-A-5 260 324

(D12) D. C. Javitt et al., Am. J. Psychiatry, vol. 151, no. 8 (August 1994), 1234-1236

(D15) D. C. Javitt et al., Molecular Psychiatry, vol. 10 (2005), 276-286

(D16) EP-A-0 432 039

(D19) Römpp Lexikon Chemie, 10th edn., vol 1 A-Cl (1996), Georg Thieme Verlag, Stuttgart/DE, 772

(D20) D. C. D'Souza et al., CNS Drug Reviews, vol. 1 no. 2 (1995), 227-260

IX. The present claims are

- claims 1 to 9 as granted (main request),
- claims 1 to 9 of auxiliary request I,
- claims 1 to 9 of auxiliary request II,
- claims 1 to 9 of auxiliary request III,
- claims 1 to 9 of auxiliary request IV,
- claims 1 to 8 of auxiliary request V and

- claims 1 to 10 of auxiliary request VI,

where the auxiliary requests were filed under cover of a letter dated 7 April 2010.

In the independent claims as set out below, the board indicates (in bold) the features added to each auxiliary request as compared to the main request.

a) The independent claims of the main request (i.e. the claims as granted) read as follows:

"1. Use of a glycine uptake antagonist for the manufacture of a medicament for treating a human patient having a psychosis."

"6. Use of a glycine uptake antagonist for the manufacture of a medicament for treating schizophrenia in a human patient."

b) The independent claims of auxiliary request I read as follows:

"1. Use of a glycine uptake antagonist for the manufacture of a medicament **in the form of a tablet, capsule or oral liquid** for treating a human patient having a psychosis."

"6. Use of a glycine uptake antagonist for the manufacture of a medicament **in the form of a tablet, capsule or oral liquid** for treating schizophrenia in a human patient."

c) The independent claims of auxiliary request II read as follows:

"1. Use of a glycine uptake antagonist for the

manufacture of a medicament **in the form of a tablet, capsule or oral liquid** for treating a human patient having a psychosis, **with the proviso that the glycine uptake antagonist is not glycine."**

"6. Use of a glycine uptake antagonist for the manufacture of a medicament **in the form of a tablet, capsule or oral liquid** for treating schizophrenia in a human patient, **with the proviso that the glycine uptake antagonist is not glycine."**

d) The independent claims of auxiliary request III read as follows:

"1. Use of a glycine uptake antagonist for the manufacture of a medicament **in the form of a tablet, capsule or oral liquid** for treating a human patient having a psychosis, **with the proviso that the glycine uptake antagonist is not clozapine."**

"6. Use of a glycine uptake antagonist for the manufacture of a medicament **in the form of a tablet, capsule or oral liquid** for treating schizophrenia in a human patient, **with the proviso that the glycine uptake antagonist is not clozapine."**

e) The independent claims of auxiliary request IV read as follows:

"1. Use of a glycine uptake antagonist for the manufacture of a medicament **in the form of a tablet, capsule or oral liquid** for treating a

human patient having a psychosis, **with the proviso that the glycine uptake antagonist is not clozapine and is not glycine.**"

"6. Use of a glycine uptake antagonist for the manufacture of a medicament **in the form of a tablet, capsule or oral liquid** for treating schizophrenia in a human patient, **with the proviso that the glycine uptake antagonist is not clozapine and is not glycine.**"

f) The independent claims of auxiliary request V read as follows:

"1. Use of a glycine uptake antagonist for the manufacture of a medicament for treating a human patient having a psychosis, **wherein the antagonist inhibits GLYT1-mediated glycine uptake.**"

"6. Use of a glycine uptake antagonist for the manufacture of a medicament for treating schizophrenia in a human patient, **wherein the antagonist inhibits GLYT1-mediated glycine uptake.**"

g) The independent claims of auxiliary request VI read as follows:

"1. Use of a glycine uptake antagonist for the manufacture of a medicament for treating a human patient having a psychosis, **wherein the glycine uptake antagonist is selected from glycylalkylamides, glycine alkyl esters and sarcosine.**"

"6. Use of a glycine uptake antagonist for the

manufacture of a medicament for treating schizophrenia in a human patient, **wherein the glycine uptake antagonist is selected from glycylalkylamides, glycine alkyl esters and sarcosine.**"

X. The arguments of the appellant as far as relevant for the present decision may be summarised as follows:

The priority is valid for all the claims.

Document (D9) is speculative and not a reliable source of information. The compounds listed in Table 1 are not linked to any physiological effect or a medical use. The combination of the teachings of documents (D9) and (D2) does not render the subject-matter of the present claims obvious, as (D9) deals only with antibodies. Document (D2) is silent on the glycine uptake antagonistic property of glycyldodecylamide. The fact that it reverses PCP-induced hyperactivity does not mean that it is useful for the treatment of psychosis and schizophrenia. Document (D12) is not relevant as it deals with glycine and not with glycine uptake antagonists.

Therefore, the subject-matter of the claims involves an inventive step.

XI. The arguments of the respondents as far as relevant for the present decision may be summarised as follows:

The respondents consider the priority not to be valid for any of the claims.

The subject-matter claimed lacks inventive step in view of any of documents (D9), (D2) or (D12) as the closest prior art.

Document (D2) shows that glycldodecylamide is more effective than glycine in reducing PCP-induced hyperactivity in mice. Therefore, the subject-matter claimed is not inventive in view of document (D2) if combined with the teachings of documents (D12) and (D20).

Document (D9) teaches that schizophrenia is to be treated by blocking the glycine transporter. It shows in Table 1 on page 55 the inhibition of the transport of glycine by several compounds. The use of these compounds, such as sarcosine, for the manufacture of a medicament against schizophrenia was thus obvious.

XII. The parties indicated that they would not be attending the oral proceedings (see appellant's letter dated 13 August 2014, respondent 2's letter of 14 October 2014 and respondent 3's letter of 10 April 2014).

XIII. The appellant (patent proprietor) requested in writing that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 9 as granted (main request) or alternatively on the basis of any one of auxiliary requests I to VI filed with its grounds of appeal of 7 April 2010.

Respondent 2 (opponent 2) requested in writing that the appeal be dismissed. Respondent 3 did not formulate any requests and did not submit any arguments.

XIV. The oral proceedings took place in the absence of the duly summoned summoned parties (see Rule 115(2) EPC,

Article 15 (3) RPBA). At their end, the chairman announced the decision of the board.

Reasons for the Decision

1. The appeal is admissible.

2. Transfer of the opponent status from Abbott GmbH & Co. KG to AbbVie Deutschland GmbH & Co. KG

Respondent 2/opponent 2 neither filed the additional evidence requested to submit in the board's communication, nor submitted any counter-arguments (see point VI above). For the reasons given in said communication, the board maintains its view that the evidence provided does not prove the transfer to AbbVie Deutschland GmbH & Co. KG of business relating to the opposition. Consequently, respondent 2/opponent 2, Abbott GmbH & Co. KG, is considered as the rightful respondent/opponent and its request for registration of a transfer of its opponent status has to be refused. Furthermore, in view of the outcome of this decision the board considers it not necessary to give detailed reasons.

3. In view of the conclusions drawn below on inventive step, there was no need to deal with the other objections or with the extent to which the present claims enjoy the priority claimed.

4. Inventive step

4.1 The claimed invention concerns the use of glycine uptake antagonists for the manufacture of a medicament

for the treatment of psychosis or schizophrenia (see claims 1 and 6 as granted).

The only types of glycine uptake antagonists specifically disclosed in the patent in suit are glycylalkylamides, such as glycyldodecylamide; glycine alkylesters, such as methyl and ethyl esters; and sarcosine (see paragraph [0026] on page 6, and page 10, lines 3 and 18-21; see claims 1 and 6 of auxiliary request VI).

Therefore, these types of glycine uptake antagonists are to be considered most preferred. This implies that they also meet the requirements specified in claims 1 and 6 of auxiliary request V, namely that they inhibit **GLYT1-mediated** glycine uptake.

If the assessment of inventive step shows that it was obvious to use these most preferred glycine uptake antagonists for the given purpose, then the respective use of glycine uptake antagonists in general does not involve an inventive step.

4.2 The closest prior art

4.2.1 The closest state of the art is normally a prior-art document disclosing subject-matter with the same objectives as the claimed invention and having the most relevant technical features in common.

4.2.2 The parties have presented their arguments starting from any of documents (D2), (D9) and (D12) as the closest prior art.

Document (D2) does not relate to the treatment of psychosis or schizophrenia; document (D12) only

discloses the treatment of schizophrenia with glycine, i.e. not with a glycine uptake antagonist.

Document (D9) claims the treatment of schizophrenia by

- **blocking** the binding to the **glycine transporter** by means of an antibody (see claim 88 which is indirectly dependent on claim 44; see also page 28, line 31, to page 29, line 33); or
- **reducing the expression** of the **glycine transporter** by means of an antisense oligonucleotide (see claim 80 which is indirectly dependent on claim 25).

Furthermore, it claims a screening method to identify drugs which interact with, and specifically bind to, a human glycine transporter (see claims 64, 67 and 70; see also page 42, line 14, to page 43, line 23).

It is to be noted that the patent in suit states that **"glycine transport inhibitors"** and **"glycine uptake antagonists"** are synonyms (see paragraph [0016] on page 4).

Therefore, document (D9) concerns the treatment of schizophrenia by means of glycine uptake antagonists. Consequently, document (D9) - rather than (D2) or (D12) - is to be considered as the closest prior art.

4.3 The problem to be solved

Document (D9) does not directly disclose the use of glycylalkylamides, glycine alkylesters or sarcosine for the treatment of schizophrenia.

The problem to be solved in view of document (D9) could thus be considered to be the use of alternative glycine

uptake antagonists for the manufacture of a medicament which is useful for the treatment of psychosis and schizophrenia.

4.4 The solution

4.4.1 Studies # 1 to 3 of the patent in suit show that this problem was indeed solved by the use of glycylalkylamides, glycine alkylesters or sarcosine for the given purpose.

4.4.2 In the description of the technological background, document (D9) states that the "development of selective inhibitors" of neurotransmitters, such as glycine, may "represent a novel therapeutic approach to the treatment of neurological disorders" (see the paragraph bridging pages 1 and 2, in particular its last sentence).

Hence, it was evident to the person skilled in the art that the disclosure of document (D9) was not limited to the antibodies and antisense nucleotides claimed, but that - contrary to the argumentation of the appellant - (D9) teaches that glycine uptake antagonists in general might be useful for the treatment of schizophrenia (see appellant's letter dated 7 April 2010, section 3.1.6 on pages 23-25).

4.4.3 In the framework of the invention claimed in document (D9), the pharmacological specificity of the glycine transporter cloned was determined (see (D9), page 54, lines 24-27, and Table 1 on page 55). In the experiment to that end, the COS-7 cells transfected with the complementary DNA clone encoding the glycine transporter were incubated with [^{3}H]glycine and with several low molecular weight compounds. As shown in

Table 1, glycine ethyl ester, glycine methyl ester and sarcosine displaced 32%, 42% and 100%, respectively, of the tritiated glycine uptake at a concentration of 1 mMol/l. This means that glycine ethyl ester, glycine methyl ester and sarcosine are glycine uptake antagonists.

For this reason and in view of the conclusion drawn under point 4.4.2 above, the board does not share the opinion of the appellant that there is no link in document (D9) between these three compounds and the treatment of schizophrenia (see appellant's letter dated 7 April 2010, section 3.1.6 on pages 23-25).

Hence, it was obvious to the person skilled in the art that these three compounds were likely to be useful for the treatment of schizophrenia once brought into contact with the respective receptor in the central nervous system of the patient to be treated.

For the traditional modes of administration, this means that the drug must pass the blood-brain barrier. Therefore, the person skilled in the art was more likely to consider glycine ethyl ester, glycine methyl ester and sarcosine as useful for the treatment of schizophrenia if he expected these compounds to pass that barrier to a considerable degree.

Document (D2) mentions that "glycine had to be administered in large doses to obtain significant effects since its transport into the brain is very slow. ... Therefore, it was decided to synthesize several glycine derivatives having less polarity and greater lipophilicity than the parent compound, thereby providing more facile penetration of the blood-brain

barrier ... . Short- and long-chain alkyl derivatives of the amino and carboxyl functions of glycine were prepared ..." (see paragraph bridging pages 1 and 2 starting from the third sentence).

The compounds glycine ethyl ester, glycine methyl ester and sarcosine disclosed in document (D9) differ from glycine (H_2N-CH_2-COOH) in that the hydrogen atom of the carboxylic acid group -COOH has been replaced by the less polar methyl or ethyl group, respectively, or that, in the case of sarcosine, one hydrogen atom linked to the nitrogen atom has been replaced by the less polar methyl group. Hence, glycine ethyl ester, glycine methyl ester and sarcosine are methyl or ethyl derivatives, i. e. short-chain alkyl derivatives, of glycine within the meaning of document (D2). Therefore, it was evident to the person skilled in the art that these compounds were less polar and more lipophilic than glycine and would pass the blood-brain barrier more readily than glycine.

Consequently, it was apparent that the compounds glycine ethyl ester, glycine methyl ester and sarcosine disclosed in document (D9) were most likely to be effective in the treatment of schizophrenia.

Hence, the subject-matter of claims 6 and 9 of the main request, of claim 6 of auxiliary request V and of claims 6, 9 and 10 of auxiliary request VI does not involve an inventive step.

4.4.4 The claims of auxiliary requests I to IV additionally require that the medicament be in the form of a tablet, capsule or oral liquid.

This limitation was introduced to establish novelty in the event that the board considered the antibodies claimed in document (D9) to be novelty-destroying (see letter dated 7 April 2010, third paragraph on page 31).

The appellant did not claim that these galenic forms give rise to an unexpected effect. This is in line with the patent in suit which merely states that "Suitable pharmaceutical preparations include tablets, capsules, oral liquids and parenteral injectables" (see page 6, lines 4-5).

These galenic formulations correspond to the routes of administration that document (D9) suggests for the drugs obtained by the claimed screening method (see page 43, line 28, to page 44, line 4: "Once the candidate drug has been shown to be adequately bioavailable following a particular route of administration, for example **orally or by injection** (adequate therapeutic concentrations must be maintained at the site of action for an adequate period to gain the desired therapeutic benefit), and has been shown to be non-toxic and therapeutically effective in appropriate disease models, the drug may be administered to patients by that route of administration determined to make the drug bio-available, in an appropriate **solid or solution formulation**, to gain the desired therapeutic benefit" (emphasis added by the board)).

Reference is also made to

- document (D10) which deals with the treatment of psychotic disorders such as schizophrenia (see the abstract and column 4, lines 37-40) and suggests oral formulations in the form of capsules and tablets (see column 10, lines 49-57) and

- document (D16) which claims an antipsychotic drug and mentions oral formulations "in the form of tablets, capsules, syrup, suspension, etc." (see page 3, lines 50-52).

Hence, it was quite common to select tablets, capsules or oral liquids as galenic forms of drugs effective against psychosis and schizophrenia.

As the appellant pointed out, schizophrenia and psychosis require frequent and long-term administration of medicaments (see the letter dated 7 April 2010, the penultimate paragraph on page 32). As patients consider frequent injections to be undesirable, the person skilled in the art will aim at formulating medicaments for oral administration, e.g. in the form of tablets, capsules or solutions.

Hence, it was obvious for the person skilled in the art to test if the compounds glycine ethyl ester, glycine methyl ester and sarcosine disclosed in document (D9) are orally effective, and, if so, to formulate these compounds as tablets, capsules or oral solutions in order to manufacture a medicament for the treatment of schizophrenia.

Therefore, the subject-matter of claims 6 and 9 of auxiliary requests I, II, III and IV likewise does not involve an inventive step.

5. The board can only decide on a request as a whole. Therefore, neither the main request nor any of the auxiliary requests can be allowed.

Consequently, the appeal of the patent proprietor against the decision revoking the patent is to be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated