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Datasheet for the decision of 21 January 2025

Case Number: T 0867/23 - 3.3.07

Application Number: 13805597.5

Publication Number: 2925324

IPC: A61K31/495, A61P25/18

Language of the proceedings: EN

Title of invention:
TRANS-4-{2-[4-(2,3-DICHLOROPHENYL)-PIPERAZIN-1-YL]-ETHYL}-N,N-DIMETHYLCARBAMOYL-CYCLOHEXYLAMINE FOR TREATING PRIMARY NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Patent Proprietor:
Richter Gedeon Nyrt.

Opponents:
Wittkopp, Alexander
Krka, d.d., Novo mesto

Headword:
Cariprazine for treating primary negative symptoms of schizophrenia / RICHTER GEDEON NYRT.

Relevant legal provisions:
EPC Art. 100(a), 100(b), 100(c), 54(2), 56

Keyword:

Sufficiency of disclosure - proof of the claimed therapeutic effect - post-published evidence - (yes)
Novelty - (yes)
Inventive step - reasonable expectation of success (no)
Amendments - added subject-matter (no)

Decisions cited:

G 0002/21, G 0002/08, T 0779/18, T 0254/93, T 0979/23, T 0609/02

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Case Number: T 0867/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 21 January 2025

Appellant: (Opponent 1)	Wittkopp, Alexander Jungfernstieg 38 20354 Hamburg (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Appellant: (Opponent 2)	Krka, d.d., Novo mesto Smarjeska cesta 6 8000 Novo mesto (SI)
Representative:	Hoefer & Partner Patentanwälte mbB Pilgersheimer Straße 20 81543 München (DE)
Respondent: (Patent Proprietor)	Richter Gedeon Nyrt. Gyömröi út 19-21. 1103 Budapest (HU)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 9 March 2023 rejecting the opposition filed against European patent No. 2925324 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	Y. Podbielski

Summary of Facts and Submissions

I. The appeals were filed by both opponents against the decision of the opposition division to reject the oppositions filed against the patent.

II. Claim 1 as granted related to:

"Trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine and/or pharmaceutically acceptable salts and/or hydrates and/or solvates and/or polymorphs thereof for use in treating primary negative symptoms of schizophrenia."

In the following, the compound trans-4-{2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine is referred to by its international non proprietary name cariprazine.

III. The following documents are relevant to the present decision:

D1: WO 2008/142462 A1
D3: Buchanan, R.W., "Persistent Negative Symptoms in Schizophrenia: An Overview" Schizophrenia Bulletin, 2007, 33(4):1013-1022
D5: Peralta, V. et al., "Differentiating Primary From Secondary Negative Symptoms in Schizophrenia: A Study of Neuroleptic-Naive Patients Before and After Treatment" Am. J. Psychiatry, 2000, 157(9):1461-1466
D6: Alphs, L. et al., "Asenapine in the Treatment of Negative Symptoms of Schizophrenia: Clinical Trial Design and Rationale" Psychopharmacology Bulletin, 2007, 40(2):41-53

D7: Danion, J.-M. et al., "Improvement of Schizophrenic Patients With Primary Negative Symptoms Treated With Amisulpride" Am. J. Psychiatry, 1999, 156(4):610-616
D8: Murphy, B. P. et al., "Efficacy of amisulpride in treating primary negative symptoms in first-episode psychosis: a pilot study" Hum. Psychopharmacology Clin. Exp., 2006, 21:511-517
D9: Lindenmayer, J.-P. et al., "A Randomized Controlled Trial of Olanzapine Versus Haloperidol in the Treatment of Primary Negative Symptoms and Neurocognitive Deficits in Schizophrenia" J. Clin. Psychiatry, 2007, 68(3):368-379
D10: Murphy, Brendan P. et al., "Pharmacological treatment of primary negative symptoms in schizophrenia: A systematic review" Schizophrenia Research, 2006, 88:5-25
D12: Möller H.-J., European Psychiatry, 2007, 22:380-386
D13: Nemeth et al., The Lancet, 2017, 389:1103-1113
D16: WO 2010/126527 A1
D17: Carpenter et al. , "Treatment Of Negative Symptoms", Schizophrenia Bulletin, 1985, 11(3):440-452
D22: Internet publication (http://news.frx.com/press-release/rd-news/forest-laboratories-incandgedeon-richter plc-announce-results-two-positive-p), Forest Laboratories, Inc., dated February 28,2012, captured by "The Wayback machine" October 27, 2012, retrieved: September 15, 2022
D24: Mosolov S. N. et al., Front. Psychiatry 2022, 12:766692, 1-12
A28: American Psychiatric Association, "Diagnostic and Statistical Manual of Mental Disorders", Fourth Edition, 1994, page 277
A29: J. Bobes et al. (J. Clin. Psychiatry 2010, 71(3): 280-286

IV. The opposition division decided as follows:

(a) The change of the conjunction "and" to "and/or" in claim 1 did not introduce added subject-matter.

(b) The criteria of sufficiency of disclosure were met, because the claimed therapeutic effect, namely the treatment of primary negative symptoms of schizophrenia, could be identified and was enabled, and the claimed compounds were accessible.

(c) The claimed subject-matter was novel over D1, D16 and D22.

(d) Starting from any of D6 to D10, the technical problem was to provide an alternative treatment of primary negative symptoms of schizophrenia. The claimed solution involved an inventive step.

V. In reply to the appeals by both opponent 1 (appellant 1) and opponent 2 (appellant 2), the patent proprietor (respondent) defended their case on the basis of the patent as granted.

VI. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

VII. By letter dated 9 December 2024, the respondent submitted an auxiliary request.

VIII. Oral proceedings were held before the Board.

IX. The parties' requests were the following:

(a) Both appellant 1 and appellant 2 request that the decision under appeal be set aside and that the patent be revoked in its entirety.

(b) The respondent requests that the appeals be dismissed, or, alternatively, that the patent be maintained on the basis of the auxiliary request filed on 9 December 2024.

X. The arguments of the appellants may be summarised as follows:

(a) Added subject-matter

Claim 1 as filed recited cariprazine and salts and hydrates and solvates and polymorphs thereof. The replacement of the term "and" with the term "and/or" in the main request introduced added subject-matter.

(b) Sufficiency of disclosure

Claim 1 of the main request pertained to the use of the known antipsychotic cariprazine in the treatment of primary negative symptoms of schizophrenia. The application as filed, i.e. the post-hoc analysis of the clinical study comparing the general ITT population with the S4S6 subgroup, did not make the claimed therapeutic effect on primary negative symptoms plausible, i.e. neither for cariprazine HCl nor for other forms. In addition, the application did not teach how a patient suffering from primary negative symptoms could be identified and thus how to put the claimed therapy into practice.

(c) Novelty

D1, D16 and D22 described the use of cariprazine in the treatment of (negative symptoms of) schizophrenia. Primary negative symptoms were ambiguously defined and not distinguishable from other symptoms of schizophrenia, and the groups of patients were identical. Primary negative symptoms were furthermore inherently and necessarily treated in the known cariprazine treatment. Hence the criteria of novelty were not met.

(d) Inventive step

Starting from the use of cariprazine in the treatment of negative symptoms of schizophrenia known from D1, D16 or D22, the distinguishing feature was the selection of primary negative symptoms of schizophrenia. However, the patent did not show the effect of cariprazine specifically on primary negative symptoms of schizophrenia, such that no problem was solved. Furthermore, considering the clinical relevance of primary negative symptoms, and knowing about cariprazine’s efficacy in the treatment of negative symptoms in general, it was obvious to test cariprazine for efficacy in the treatment of primary negative symptoms. The skilled person would have taken cariprazine with a reasonable expectation of success for a medical use in connection with the treatment of schizophrenia and the negative symptoms thereof. The criteria of inventive step were thus not met.

XI. The respondent's arguments may be summarised as follows:

(a) When considered in context, the expressions "and" and "and/or" in original claims 1 and 2 of the application were construed in the same way. Hence the main request did not introduce added subject-matter.

(b) There was prior art on file showing that the treatment of primary negative symptoms of schizophrenia was a recognized medical indication. Furthermore, the data in the patent plausibly showed that cariprazine was effective for the treatment of primary negative symptoms, which was confirmed by the subsequent clinical trial of D13. Hence the criteria of sufficiency of disclosure were met.

(c) There was no indication or hint in the prior art that cariprazine might be useful against primary negative symptoms. As a result, the claimed subject matter was novel over the prior art.

(d) With respect to inventive step, starting from any of D1, D16, D22 or D6-D10, the relevant question was whether the skilled person would have used cariprazine for the treatment of primary negative symptoms with a reasonable expectation of success, which was not the case. Thus, the claimed subject matter also involved an inventive step.

Reasons for the Decision

1. The present decision is taken on the basis of the patent as granted (main request). Claim 1 of the main

request relates to cariprazine "and/or pharmaceutically acceptable salts and/or hydrates and/or solvates and/or polymorphs thereof for use in treating primary negative symptoms of schizophrenia."

2. Added subject-matter, Article 100(c) EPC

Claim 1 of the application as filed pertained to cariprazine "and pharmaceutically acceptable salts and hydrates and solvates and polymorphs thereof for use in treating primary negative symptoms of schizophrenia".

In contrast, in claim 1 of the main request, the word "and" has been replaced with "and/or", i.e. claim 1 relates to cariprazine "and/or pharmaceutically acceptable salts and/or hydrates and/or solvates and/or polymorphs thereof" for the same therapeutic use.

The Board concurs with the respondent that the word "and" in claim 1 as filed would not be read by the skilled person as meaning that a mixture or combination of all of the listed items is required. Such an unrealistic interpretation is not supported by the description. The conjunction "and" in claim 1 must therefore be interpreted, and can be construed in light of claim 2 as filed, which relates to cariprazine "for use according to claim 1, in the form of [cariprazine] hydrochloride and/or hydrates and/or solvates and/or polymorphs thereof". Considering the dependency of claim 2 on claim 1, the conjunction "and" in claim 1 can only be read as "and/or", i.e. as a reference to each of the recited cariprazine forms individually or their (sub)-combinations.

Accordingly, the main request does not contain added subject-matter.

3. Sufficiency of disclosure, Article 100(b) EPC

3.1 Claim 1 is worded as a purpose-limited product claim in accordance with Article 54(5) EPC. The treatment of "primary negative symptoms of schizophrenia" is a functional feature of claim 1.

3.2 The parties debate whether the claimed therapeutic indication can be identified.

Sufficiency of disclosure must be assessed taking into account the disclosure of the patent as a whole, supplemented with the common general knowledge of the skilled person.

The patent provides general background information on the claimed therapeutic indication and distinguishes, within the cardinal symptoms of schizophrenia, between positive symptoms, negative symptoms and cognitive dysfunction. Among the negative symptoms, the patent further differentiates primary from secondary negative symptoms. According to paragraphs [0002]-[0005] of the patent:
- the negative symptoms of schizophrenia reflect the absence or diminution of normal behaviours and functions, and include problems with motivation, social withdrawal, diminished affective responsiveness, speech, and movement;
- among the negative symptoms, primary negative symptoms refer to the symptoms that are intrinsic to schizophrenia, while secondary negative symptoms can be consequent upon several factors including medication side effects (such as extrapyramidal side effects), depression, or positive symptoms.

This concept of primary negative symptoms of schizophrenia is not only explained in the patent, but is also part of the common general knowledge of the skilled person, as reflected by the review article D24 (see the Introduction). The same concept is also shown in D17 (see the abstract; page 440, middle column, to page 441, right column), D3 (see "Terminology", page 1014), D6 (see the paragraph bridging pages 42 and 43; figure 1), or D12 (see §2). While D17 mentions some caveats regarding the term "negative symptoms", these issues are resolved in D17 by making the same distinction between primary and secondary negative symptoms as in the patent (see page 441, paragraphs bridging the left and middle columns, and the middle and right column).

The Board does not share the view of appellant 2 that the patent redefines the meaning of the expression "primary negative symptoms of schizophrenia". The paragraphs [0027] or [0035] contain no such redefinition, but only explain the Positive and Negative Syndrome Scale (PANSS) for measuring schizophrenia symptoms and describe the inclusion criteria based on this PANSS in the clinical trial of the example.

The appellants suggest that there are divergent uses of the expression "primary negative symptoms of schizophrenia" in the prior art. However, the cited passage of D3 (regarding a "substantial terminological conundrum in the area of negative symptoms", see page 1014, left column), D17 (see page 441, column 2, first paragraph), or D6 (regarding the absence of severity threshold, see page 46) do not establish that there are divergent definitions of the expression "primary negative symptoms". At any rate, to the extent that

there would be uncertainty as to the boundaries of the class of symptoms referred to by the expression "primary negative symptoms of schizophrenia" of claim 1, the appellants do not show how this alleged uncertainty would prevent the skilled person from carrying out the invention.

As explained in paragraph [0010] and [0011] of the patent, primary negative symptoms cannot be assessed as such. To evaluate the effect of a medicinal product on primary negative symptoms, secondary negative symptoms, which are mainly caused by positive symptoms, extrapyramidal side effects and depression, must be excluded as much as possible. However, this does not mean that the identification of a patient in need of a therapy of primary negative symptoms is impossible or not sufficiently disclosed. This would contradict the fact that the treatment of primary negative symptoms is an indication generally accepted in the state of the art, as shown by the literature on primary negative symptoms and their practical relevance (see D10, D12, D24), and the fact that other active ingredients are studied for efficacy against primary negative symptoms (see D6-D10). In particular, the Board sees no support for appellant 1's argument that the identification of the patient would require at the same time stopping all medical treatment (to avoid extrapyramidal side effects) and reducing depression (to rule out secondary negative symptoms caused thereby). The above documents show that primary negative symptoms are a recognized problem in the field of schizophrenia, and also that they can be diagnosed, despite the possible difficulties mentioned in D6 (see page 46) or possible duration to establish a diagnosis (see the flow chart of Figure 1 of D17). Lastly, for the reasons given below (see 3.3.1), the Board considers that the patent

provides a reasonable approach for differentiating the effects of cariprazine on primary negative symptoms from those on other symptoms.

3.3 The parties further debate whether the application as filed makes the claimed therapeutic effect plausible, and whether post-published evidence may be taken into account.

The relevant question is whether cariprazine is demonstrated to have the claimed therapeutic effect on primary negative symptoms of schizophrenia. This question of fact must firstly be answered based on the evidence contained in the application as filed.

3.3.1 The application as filed reports the results of a post-hoc study on clinical data in a double blind, placebo- and risperidone-controlled, fixed-dose trial. The post-hoc study compares the efficacy of cariprazine in a general ITT (intent to treat) population, and in a subpopulation with predominant negative symptoms corresponding to the subgroups of patients in State 4 and State 6. These S4 and S6 groups of patients are defined according to PANSS scores on page 9 of the application as filed and exhibit severe negative symptoms and low to moderate positive symptoms, i.e. this subpopulation comprises patients with predominantly negative symptoms. In this respect, contrary to the appellants' view, the patent does not simply teach to compare cariprazine and risperidone, but aims explicitly at the comparison of the ITT and S4+S6 groups (see paragraph [0013]).

Figures 2-4 show that cariprazine at different dosages leads to a stronger decrease in PANSS negative factor scores (defined on page 7 of the application as filed)

for the S4+S6 groups, compared with the general ITT population. The same effect is not observed with risperidone (see Figure 1).

It is not contested that the impact of the S4+S6 subgroup selection on PANSS scores cannot directly show an effect on primary negative symptoms. In order to infer an effect on primary negative symptoms from this post-hoc study, i.e. to show that the apparent effect on negative symptoms is proof of an effect on primary negative symptoms, and to exclude secondary negative symptoms as a reason for the effect, the application as filed makes the following reasoning (see pages 3-4, corresponding to paragraphs [0010]-[0017] of the patent):
- since negative symptoms are dominant in the S4+S6 groups, and positive symptoms are presented less prominently, it can be presumed that negative symptoms secondary to positive symptoms are less determinant than primary negative symptoms;
- to rule out extrapyramidal symptoms (EPS) as cause for the negative symptoms, a further subgroup of patients without EPS within the S4+S6 group was selected. The efficacy of cariprazine is not influenced (see Figure 5);
- the fact that patients in the S4+S6 group would have low to moderate depressive symptoms (i.e. ≤4 for PANSS depression item G6) would also exclude depression as a cause for secondary negative symptoms.

3.3.2 In the Board's view, the data in the patent comparing the general population with the sub-population with predominantly negative symptoms, together with the above explanations and data, suggest that cariprazine has a therapeutic effect on primary negative symptoms of schizophrenia.

The appellants criticise the data in the patent on account that no appropriate exclusion of depression, positive symptoms, EPS and further secondary negative symptoms was carried out, especially since both the ITT population and the S4+S6 subpopulation include only patients that have a score ≥ 4 on at least 2 of 4 PANSS positive symptoms (in contrast to the study in D13).

The Board does not consider these counter-arguments convincing. It must firstly be borne in mind that the claimed therapeutic indication is a mental illness which presents particular challenges as to diagnosis and quantification. The evidence presented in support of therapeutic activity must be evaluated taking into account the nature of this illness, and cannot be required to reach an unrealistic level of proof. It can for instance not be expected that the schizophrenia patients of the study display no positive symptoms and no depression at all. In this respect, the appellants' argument that the study mentioned in the patent includes patients with a score ≥ 4 on at least 2 PANSS positive symptoms, whereas the study in D13 excludes those patients (see page 1105, left column, middle of 2nd paragraph) cannot modify the Board's conclusion, because the fact that the study of D13 is conducted with stricter criteria does not in itself demonstrate that the study of the patent is deficient.

Thus, under the present circumstances, the Board considers it reasonable to assign the different outcome for the general ITT population and for the S4+S6 subgroup to their different selection criteria, namely the selection of patients with a comparatively higher ratio of negative vs positive symptoms in the PANSS

scale, and in turn, following the above explanations and data, to an efficacy on primary negative symptoms.

3.4 The respondents further submitted the following criticisms:
- the study and its *post-hoc* evaluation lack relevant information ensuring that the ITT and S4S6 groups may be meaningfully compared, especially regarding depression and EPS;
- the study is limited to patients having schizophrenia with acute exacerbation, which is characterised by particular "psychotic phasic primary negative symptoms" not occurring at other stages of the disease (according to D3, page 1014, column 2, paragraph 1);
and
- the duration of the study was insufficient.

The Board is of the opinion that the appellants' observations regarding the aspects of the study that could be improved may at most suggest that the study could have been conducted differenly, but do not necessarily raise in themselves serious doubts about the effectiveness of cariprazine in treating primary negative symptoms of schizophrenia. Nevertheless, it is for the purposes of the present decision not necessary to decide if these further criticisms are justified or if the evidence in the application as filed is still sufficiently convincing on its own, i.e. whether this evidence alone allows the Board to conclude that the claimed therapeutic use is sufficiently disclosed. This is because, in any case, the Board considers that this initial evidence is sufficient to take the post-published evidence D13 into account to back-up or support the initial evidence, and further that the evidence taken together makes the claimed effect credible. The reasons are the following:

3.4.1 The Enlarged Board of Appeal in decision G 2/21 did not extend the scope of the referred questions beyond the issues for assessing inventive step to the assessment of sufficiency of disclosure (see points 8-11 of the reasons). Nevertheless, the Enlarged Board of Appeal cited several Board of Appeal decisions addressing the issue of reliance on post-published evidence for a purported technical effect in the context of sufficiency of disclosure, and in particular in the case of second medical use claims (see points 73-76), from which the Enlarged Board concluded the following (see point 77):

"The reasoned findings of the boards of appeal in the decisions referred to above make clear that the scope of reliance on post-published evidence is much narrower under sufficiency of disclosure (Article 83 EPC) compared to the situation under inventive step (Article 56 EPC). In order to meet the requirement that the disclosure of the invention be sufficiently clear and complete for it to be carried out by the person skilled in the art, the proof of a claimed therapeutic effect has to be provided in the application as filed, in particular if, in the absence of experimental data in the application as filed, it would not be credible to the skilled person that the therapeutic effect is achieved. A lack in this respect cannot be remedied by post-published evidence."

In the Board's view, this statement, taken in its context, does not set a new standard for reliance on post-published evidence in the context of sufficiency of disclosure, i.e. a standard which would depart from the previously cited case law it summarises (as noted in T 979/23, see point 13 of the reasons). Following

G 2/21, a reliance on post-published evidence is not ruled out generally in the context of sufficiency of disclosure for second medical use claims. The reliance on post-published evidence can also not be limited to situations where it serves no useful purpose, i.e. it is not limited to cases where the effect is already convincingly proven in the application to such a point that the use of post-published evidence as a superfluous confirmation of the already proven effect would be of no relevance. In other words, the scope of reliance on post-published evidence is not zero.

3.4.2 In the present case, the Board considers that the application as filed contains experimental data reflecting an effect on primary negative symptoms of schizophrenia, and thus discloses the suitability of cariprazine for the claimed therapeutic indication (see T 609/02, point 9 of the reasons). In these circumstances, the post-published evidence D13 may be taken into account to backup the findings in the application as filed and to refute the appellants' criticisms.

The post-published evidence D13 reports the results of a randomised, double-blind phase 3b trial on patients with predominantly negative symptoms and comparing the effects of fixed-dose cariprazine and risperidone. The inclusion criteria in this study exclude patients even with moderate positive symptoms (see page 1105, left column, middle of 2nd paragraph), which addresses the appellants' corresponding criticism of the study in the application as filed. The criteria of D13 also exclude depression and EPS, and ensure comparability with respect to these symptoms as well as positive symptoms (see table 2: PANSS-FSPS, PANSS factor score for positive symptoms; Calgary Depression Scale for

Schizophrenia scoring (CDSS), a measure for depression; SAS (Simpson-Angus Scale), a measure for the occurrence of EPS). The outcome shows a stronger reduction in negative symptoms with cariprazine than with risperidone, but no significant difference between these arms with respect to the change of positive symptoms, depression and EPS (see Figure 2; Table 2). The duration of the study of D13 also addresses the appellants' concern regarding the data in the application as filed. The appellants argued that the post-published evidence D13 should not be taken into account following G 2/21, but otherwise did not raise any objection as to the study design of D13.

Thus, D13 confirms the findings of the patent, and shows improvements in negative symptoms while excluding indirect effects related to positive, depressive, or EPS symptoms as causal factor. Accordingly, D13 supports the conclusion that cariprazine is effective on primary negative symptoms and refutes the appellants' objection that the improvement could relate to secondary negative symptoms.

3.5 Lastly, appellant 2 submits that no proof of activity had been provided for cariprazine forms other than the tested HCl salt. However, the appellants have not provided any substantial reason why the effect observed for the HCl salt could not be extrapolated to other cariprazine forms. This objection is accordingly not convincing.

3.6 Accordingly, the criteria of sufficiency of disclosure are met.

4. Novelty

The appellants raised objections of lack of novelty over D1, D16 and D22.

D1 discloses cariprazine for use in the treatment of schizophrenia including negative symptoms of schizophrenia (see claims 15 and 36, and page 4, last paragraph), and describes a prospective clinical study to be conducted, without reporting any results (see example 1).

Likewise, D16 mentions the treatment of negative symptoms of schizophrenia with cariprazine or a salt thereof (see claim 30 in combination with claim 15 or 16).

Lastly, D22 reports positive phase III trials on cariprazine for the treatment of schizophrenia (see title).

According to the appellants, the use of cariprazine in the treatment of (negative symptoms of) schizophrenia shown in D1, D16 and D22 anticipates the claimed subject-matter, firstly because the patent does not enable treatments beyond those of the prior art. The Board does not share this view. Firstly, the treatment of primary negative symptoms is enabled for the reasons given above (see 3.3). And secondly, the alleged lack of enablement would in any case not justify that, for the purposes of novelty, the explicit functional limitation of claim 1 to primary negative symptoms be ignored. Likewise, the term "primary negative symptoms of schizophrenia" is well known in the technical field (see 3.2 above), and its alleged ambiguity does not justify that it be disregarded for the assessment of novelty.

The appellants also submit that 22% of the patients treated for negative symptoms suffer from primary negative symptoms (see A29, page 280, "Results", "One or more negative symptoms were present in 57.6% of patients, with primary negative symptoms in 12.9% of subjects"). According to the appellants, the group of patients having primary negative symptoms is not distinguishable from the group of patients having (negative symptoms of) schizophrenia, because primary negative symptoms are intrinsic to schizophrenia and are present from the outset of the disease and throughout the course thereof, as shown in D12 and D5. D1 (see claim 36 together with a selection from the definition of "treatment" on pages 15-16) would disclose the use of cariprazine to delay the onset of negative symptoms of schizophrenia, which would imply a treatment of primary negative symptoms.

It can be left undecided whether primary negative symptoms are intrinsic in all or only part of schizophrenia patients. The Board notes that D12 shows a scenario (see fig. 1 on page 382) wherein primary negative symptoms appear at the onset of the disease, but this scenario is only presented for a specific group of patients and is not indicated to be generally valid (see page 382, last paragraph on the right).

In any case, even if it were accepted that (part of) the patients treated in the prior art inherently also exhibit primary negative symptoms, this would not make available to the public that cariprazine is effective in treating these symptoms. For the reasons set out above (see 3.2), primary negative symptoms are distinguishable from secondary negative symptoms. The claimed therapeutic indication is thus different from that of the prior art (contrary to the situation in

T 779/18, cited by the appellants, see point 4.1 of the reasons) and does not represent a mere explanation of the known effect on negative symptoms (contrary to the situation in T 254/93). Irrespective of any definition for the terms "schizophrenia", "negative symptoms" or "treatment" provided in D1 (see pages 14-16), any possible disclosure in D1 of the use of cariprazine in the treatment of (negative symptoms of) schizophrenia does not amount to a disclosure of the effectiveness of cariprazine against each and every symptom subsumed by these terms. Appellant 2's attempt to equate the onset conceptually mentioned in D1 (see then definition on page 16, lines 1-2) with the "mainly primary" negative symptoms rated during a first psychotic episode of D5 (see the abstract), or to equate the "enduring negative symptoms" mentioned in a reference cited in D1 (see D1, page 14, third paragraph, referring to A28; D28, page 277, end of second paragraph) to "deficit symptoms" and in turn to "primary negative symptoms" on the basis of D3 (see page 1014, right column, lines 8-15), can for this reason already not lead to a conclusion of lack of novelty.

Considering the above conclusion that primary negative symptoms are distinguishable from the secondary negative symptoms, the argument of the appellants that the new group of subjects cannot be distinguished from the former is moot, because claim 1 does not relate to the treatment of the same disease as the prior art. While a novel group of subjects treated may establish novelty for the use of the same compound in the treatment of the same illness (see e.g. G 2/08, point 5.10.7; Case Law of the Boards of Appeal, 10th edition, 2022, I.C.7.2.4.b)), a new group of subjects distinguished from the former is not a necessary condition if the illness is different in the first

place. In the absence of a teaching that cariprazine is effective in treating precisely the primary negative symptoms, the criteria of novelty are met.

5. Inventive step

5.1 In a first line of reasoning, the appellants start from the use of cariprazine in the treatment of negative symptoms of schizophrenia, as described D1 or D16. A further objection starts from D22. The disclosure of D22 does however not go beyond that of D1 and D16, in the sense that it is not concerned with the treatment of negative symptoms but more generally of schizophrenia (see 4. above).

The claimed subject-matter differs in that it pertains to the treatment of primary negative symptoms of schizophrenia. As explained above for novelty, this specific therapeutic indication differs from those of the prior art (see 4.).

The argument of the appellants that the effect on primary negative symptoms is not shown to be achieved is refuted in the context of sufficiency of disclosure (see 3.3 above).

The technical problem may accordingly be formulated, as in the appealed decision, as the provision of a further use of cariprazine.

The appellants firstly see a suggestion of the efficacy of cariprazine in the prior art for the same arguments as presented for novelty. Furthermore, according to the appellants, D7-D10 show the need to determine whether known antipsychotic agents might be used in an early state treatment, i.e. mainly primary negative symptoms,

or rather in later stages. Primary negative symptoms were particularly focused on (see D10, abstract; D12, abstract and §3). The clinical trial of the patent would thus be an obvious step to take in the further development of cariprazine as an antipsychotic for the treatment of negative symptoms of schizophrenia, and its results could not render the claimed subject-matter inventive.

However, for the following reasons, the Board does not consider that the skilled person could have had a reasonable expectation that cariprazine would be effective in treating primary negative symptoms of schizophrenia. The argument of the appellants that the skilled person had a motivation to test and identify which symptoms of schizophrenia could be treated by cariprazine, or in other words the interest in exploring this area, does not establish a reasonable expectation of effectiveness on primary negative symptoms. On the contrary, the prior art gave no reason to the skilled person to predict rationally the ability of cariprazine to treat primary negative symptoms. D12 (see page 385, last paragraph) emphasises that the lack of reliably effective therapy for these symptoms represented a major *unmet* need, and D10 confirms this difficulty and only mentions one active ingredient (namely amisulpride) as effective against primary negative symptoms (page 17, bottom right; page 19, §5). In addition, the expectation of success depends on the complexity of the technical problem to be solved (see the Case Law of the Boards of Appeal, 10th edition, 2022 I.D.7.1). Here, the demonstration of effectiveness on primary negative symptoms is anything but a routine evaluation, and does not simply consists in a post-hoc statistical analysis of existing clinical data relating to negative symptoms, but requires an elaborate study

design and additional data to rule out secondary negative symptoms caused by positive symptoms, extrapyramidal symptoms or depression (see 3.3.1 and 3.4.2 above).

5.2 Appellant 2 raised alternative objections starting from D6-D10. These alternative starting points explore the use of different active ingredients in the treatment of primary negative symptoms of schizophrenia. In particular, D10 reviews the effects of several atypical antipsychotics on negative symptoms, and especially primary negative symptoms, in schizophrenia (see §3.1). Among these atypical antipsychotics, amisulpride is reported to have a consistent though modest effect on primary negative symptoms (see §3.1.1). As to risperidone, D10 expresses the view that firm conclusions cannot be made with regard to primary negative symptoms (see §3.1.3.3). For zotepine, a pronounced improvement in primary negative symptoms is said to have been found, but no statistical difference compared with placebo (see §3.1.5).

Starting from any of D6-D10, the technical problem is the provision of an alternative treatment of primary negative symptoms of schizophrenia.

In the Board's view, the selection of D6-D10 as a starting point does not change the fact that the prior art did not allow the skilled person to have any reasonable expectation of success that cariprazine would be effective in treating primary negative symptoms of schizophrenia (see 5.1 above). Contrary to appellant 2's position, it cannot be concluded from D10 that atypical antipsychotics are generally promising candidates for the treatment of primary negative symptoms in schizophrenia, considering that only one of

them (namely amisulpride) is deemed advisable for first-line treatment for patients with primary negative symptoms (see page 19). Any disclosure that cariprazine would qualify as an atypical antipsychotic would accordingly offer no hint as to its use against primary negative symptoms.

5.3 In conclusion, the requirements of inventive step are met.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated