Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 6 November 2023

Case Number: T 2790/17 - 3.3.02

Application Number: 08755799.7

Publication Number: 2154969

IPC: A01N43/62, A61K48/00, A61K38/47, A61K38/48

Language of the proceedings: EN

Title of invention:
TREATMENT OF SYNUCLEINOPATHIES

Patent Proprietor:
The Brigham and Women's Hospital, Inc.

Opponent:
Vossius & Partner
Patentanwälte Rechtsanwälte mbB

Headword:

Relevant legal provisions:
EPC Art. 83

Keyword:
Sufficiency of disclosure - (no)

Decisions cited:
G 0002/21

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2790/17 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 6 November 2023

Appellant: (Opponent)	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Respondent: (Patent Proprietor)	The Brigham and Women's Hospital, Inc. 75 Francis Street Boston, MA 02115 (US)
Representative:	Williams, Gareth Owen Marks & Clerk LLP 62-68 Hills Road Cambridge CB2 1LA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 8 December 2017 concerning maintenance of the European Patent No. 2154969 in amended form.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	B. Burm-Herregodts

Summary of Facts and Submissions

I. The appeal of the opponent (hereinafter appellant) lies from the interlocutory decision of the opposition division according to which European patent 2 154 969 in amended form and the invention to which it relates were found to meet the requirements of the EPC.

According to the contested decision, the set of claims of the auxiliary request (labelled "AR1") submitted on 1 November 2017 *inter alia* met the requirements of sufficiency of disclosure.

II. The following documents, *inter alia*, submitted during opposition proceedings, were referred to by the parties in appeal proceedings:

D17: Cullen *et al.*, Ann. Neurol. 2011; 69:940-953.
D23: Rocha *et al.*, Neurobiology of Disease, 82 (2015), 495-503.

III. In a communication pursuant to Article 15(1) RPBA, sent in preparation for oral proceedings, the board *inter alia* expressed the preliminary view that on the basis of the information in the patent itself, the invention defined in claim 1 of the main request (the set of claims found by the opposition division to meet the requirements of the EPC) was not sufficiently disclosed. Whether post-published documents D17 and D23 could be relied upon for evidence of the alleged effect was the subject-matter of then pending Enlarged Board of Appeal proceedings in case G 2/21. Since the outcome of G 2/21 appeared decisive to the issue of sufficiency of disclosure in the present case, the board cancelled

the oral proceedings scheduled for 15 March 2022 pending the issuance of a decision in case G 2/21.

IV. Subsequent to the issuance of the decision in case G 2/21, the board issued a further summons to oral proceedings, scheduled for 16 November 2023.

V. By minuted phone conversation dated 21 September 2023, the representative of the patent proprietor (hereinafter respondent) stated that it would not attend oral proceedings scheduled for 16 November 2023.

VI. With letter dated 11 October 2023, the appellant stated that it would not attend the scheduled oral proceedings.

VII. Since both parties stated that they would not attend, the scheduled oral proceedings were cancelled.

VIII. Requests relevant to the present decision

The appellant requested that the contested decision be set aside and that the patent be revoked in its entirety.

The respondent requested dismissal of the appeal, implying maintenance of the patent in amended form on the basis of the auxiliary request found by the opposition division to meet the requirements of the EPC (present main request).

IX. For the text of independent claim 1 of the main request, reference is made to the reasons for the decision, below.

X. For the relevant party submissions, reference is made to the reasons for the decision, below.

Reasons for the Decision

Sole Main request

1. Claim interpretation

The interpretation of claim 1 is relevant for the assessment of sufficiency of disclosure, set out below.

Independent claim 1 of the main request, a Swiss-type second medical use claim, reads as follows:

"*1. Use of one of:*
an acid-beta-glucocerebrosidase (GBA) polypeptide or a polynucleotide encoding an acid-beta-glucocerebrosidase (GBA) polypeptide, in the preparation of a medicament for use in a method of treating a subject with a synucleinopathy, but not a clinically diagnosed lysosomal storage disease, wherein the polypeptide or polynucleotide is administered alone, and in an amount effective to reduce a level of α-synuclein in the subject's central or peripheral nervous system, or both."

1.1 The interpretation of the expression "administered alone" in claim 1 was a matter of dispute.

1.2 According to the contested decision, "administered alone" had a clear technical meaning in the context of claim 1. In line with decision T 197/08, it was to be understood as referring to a monotherapy with a GBA polypeptide or polynucleotide as the sole active

ingredient ("mono-therapy"). The term therefore excluded additional substances active in the claimed therapy, but did not exclude the presence of further compounds such as preservatives, co-solvents, and other excipients.

1.3 This view was shared by the respondent, and the board agrees. Hence, in line with the respondent's view (e.g. reply to the statement of grounds of appeal, points 5.1, 5.3 and 5.4), co-administration of GBA or a polynucleotide encoding GBA with GBA-activating polypeptides such as prosaposin (patent, paragraphs [0011], [0015], [0046]; example 5) is distinct from a monotherapy, and is consequently excluded from the scope of contested claim 1. No detailed reasoning for this finding is required since although it lies in the respondent's favour, the board's overall decision is in line with the appellant's main request.

2. Sufficiency of disclosure

2.1 Independent claim 1, in summary, is a Swiss-type second medical use claim directed to the **use of a GBA polypeptide or a polynucleotide encoding a GBA polypeptide** in (the manufacture of a medicament for) the therapeutic treatment of a subject with a **synucleinopathy**.

Examples of synucleinopathy conditions are listed in contested claim 3 and include certain types of Alzheimer's and Parkinson disease.

2.2 According to the application as filed (WO 2008/144591 A2), an increased abundance and aberrant processing of α-synuclein (αS) was implicated in the development of several neurodegenerative

disorders including Parkinson disease and others (page 1, 'Background', first 5 lines). The invention was based on the discovery that *inter alia* GBA polypeptides can reduce the intracellular levels of αS, and treat said conditions (application, page 2, 'Summary', first 10 lines).

2.3 As acknowledged in Enlarged Board of Appeal decision G 2/21 (Reasons for the decision, point 74, second paragraph), it is established case law that in a second medical use claim such as contested claim 1, the therapeutic effect, in the present case the treatment of a synucleinopathy with GBA polypeptide, or a polynucleotide encoding a GBA polypeptide, is a functional technical feature of the claim, so that the issue of whether it has been shown that this effect is achieved is a question of sufficiency of disclosure under Article 83 EPC.

2.4 According to the contested decision (point 14.3), example 5 of the application as filed provided sufficient evidence that increasing GBA activity by treatment with GBA or a polynucleotide encoding GBA according to contested claim 1 led to lowered αS levels. Since the association between αS and synucleinopathy was known, it had been adequately demonstrated that the claimed effect could be achieved. Hence, sufficiency of disclosure could be acknowledged.

2.5 With the statement of grounds of appeal the appellant challenged this conclusion. It *inter alia* argued that example 5 on which the respondent relied did not credibly demonstrate a causative relationship between GBA and a decrease in αS levels in the MES23.5 cell lines tested. In view of the absence of any further credible evidence that the effect had been achieved,

the burden of proof lay with the respondent, and had not been discharged. Furthermore, in view of the lack of credible evidence, post-published documents such as D17 and D23 could not be taken into account.

2.6 The board agrees with the appellant's position.

2.6.1 In example 5 (application as filed pages 39-40), MES23.5 cells prepared in example 4 with 0.5 µg αS-encoding SNCA cDNA, an "α-synuclein protein-overexpression system" according to example 4, were transfected with either 1.25, 2.5 or 5 µg of GBA-encoding cDNA, in the absence or presence of 5 µg of prosaposin-encoding cDNA (prosaposin is a GBA-activating polypeptide; e.g. application, page 4, second full paragraph). 24 hours later, the cells were lysed and probed for GBA and α-S protein levels.

2.6.2 The results are depicted in the Western blot of figure 2B. Here, only the left side of the blot ("No Prosaposin Co-transfected") is relevant since, as set out above, the expression "administered alone" in contested claim 1 excludes the co-administration of further active agents such as prosaposin (Figure 2B, right hand side, "Plus-Prosaposin Co-transfected").

2.6.3 The amount of αS in the lysed cells is also depicted in the table of figure 2C, which according to the application as filed (page 40, first full paragraph, final sentence) is a "semi quantitative summary" of the data shown in figure 2B. In this table, the amount of intra-cellular αS is indicated by the grey bars (again, only the entries for "No Prosaposin" are relevant).

2.6.4 Figures 2B and 2C of the application as filed are reproduced below for reference.

Figure 2B:

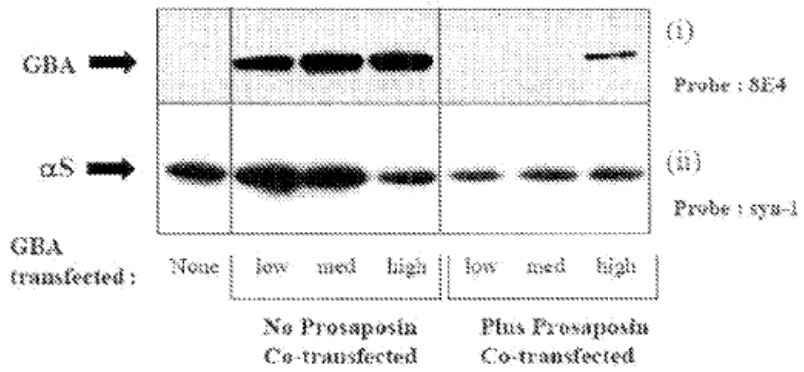
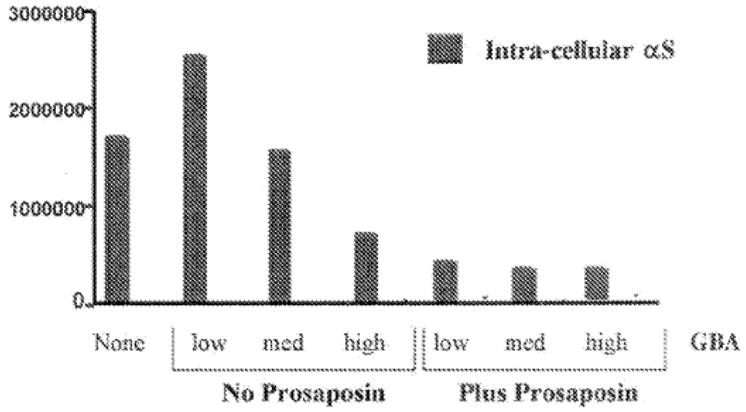


Figure 2C:



2.6.5 As noted by the appellant, the Western Blot of figure 2B indicates, by way of the relative blot intensities, that "low" levels (1.25 µg) of transfected GBA led to an **increase** rather than the desired decrease in levels of αS compared to the αS level of the negative control when no GBA is transfected ("None"). With medium ("med") levels of transfected GBA (2.5 µg), there is no

difference in αS levels (although from the above Western Blot, the board would visually estimate a slight increase in αS levels), while only "high" (5 µg) GBA transfection resulted in an apparent decrease in αS. These observations are also depicted graphically in the semi-quantitative summary shown in figure 2C.

2.6.6 The board agrees with the appellant that the marked increase in the level of αS indicated for the "low" level of GBA in both figure 2B and 2C is the opposite of what would be expected if GBA were to effect a lowering of αS levels.

2.6.7 Although as argued by the respondent, it is correct that certain drugs only exert an effect when a certain threshold is reached, this does not correspond to the present situation. Rather, the data shows that a lower amount of GBA transfection leads to an effect which is diametrically opposed to that which is desired, namely increased αS levels, while a higher amount leads to the desired effect.

2.6.8 It has not been argued by the respondent that such a situation is known in the art, nor is such a phenomenon known to the board. Hence, in the absence of a credible explanation of these observations, a doubt arises as to the scientific validity of the Western blot results shown, and whether any meaningful conclusions may be drawn therefrom. More specifically, since the increase in αS levels for the "low" GBA transfection cannot credibly be attributed to GBA expression, the same must apply to the apparent decrease in αS levels for the "high" GBA transfection. Rather, the explanation for the variation would be expected to lie elsewhere, such as in experimental error or variability, or an inherent

unreliability in the relative blot intensities depicted.

2.6.9 As stated by the appellant, this problem is further exacerbated by the fact that expression of GBA in the "med" and "high" experiments in figure 2B (top row, second and third blots) appears to be the same, i.e. there is no obvious difference in the intensity of the blots depicted. This casts further doubt on the apparent decrease in αS for the "high" experiment. Furthermore, there is no indication that example 5, or indeed the Western Blot characterisation itself, was carried out repeatedly, i.e. more than once, thereby providing more reliable results.

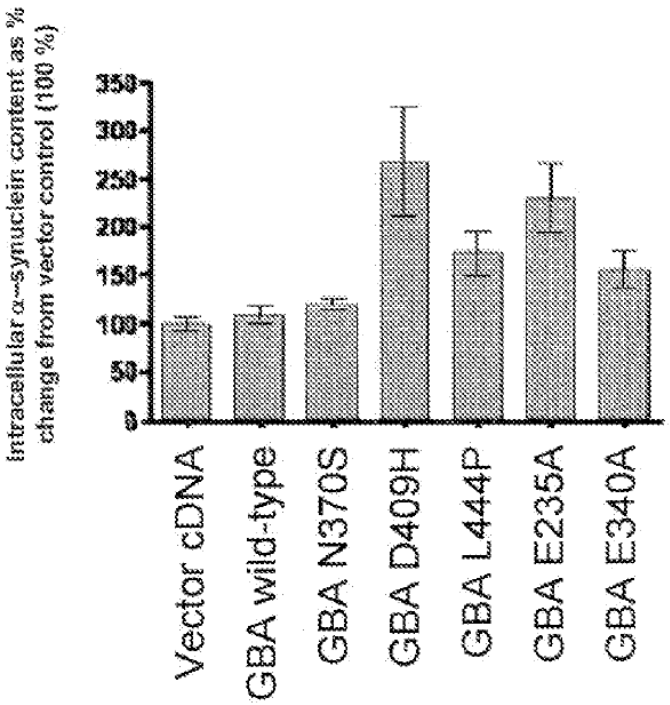
2.6.10 For these reasons the skilled person would not attribute a decrease in αS levels to GBA expression on the basis of the results of example 5 depicted in figure 2B and 2C.

2.7 As submitted by the appellant, this conclusion is further supported by examples 6 and 7 of the application as filed (pages 40-44), which provide counter-evidence to the allegation that a cause-effect relationship exists between GBA expression and a lowering of αS levels.

2.7.1 Example 6 concerns a "*first-in-kind, **sensitive** and **precise** ELISA system to **quantitatively** determine α-synuclein concentrations in transfected MES23.5 cells*" (emphasis added by the board).

This system, in comparison to Western blot methods, is said to have "improved sensitivity, optimized specificity and dynamic range (patent, paragraph [0145]), and is used to measure αS levels in example 7.

2.7.2 Example 7 concerns the use of the ELISA read-out system of example 6 to examine the effects of over-expression of mutant GBA proteins on αS levels in the same MES23.5 cells used in example 5 (application as filed, page 42). These cells were transfected with 0.5 µg αS-encoding SNCA cDNA and 5 µg GBA-encoding cDNA, either using wild-type GBA or various GBA mutants. αS expression was analysed by ELISA after 24 hours. The results are depicted in figure 4:



2.7.3 This figure shows that there is at best no difference between the negative control (left bar, "Vector cDNA") and the experiment for wild-type GBA (second bar from the left). This result is reported in the application as filed (page 43, lines 4-10):

"... when comparing the changes in α-synuclein steady-state to known quantities or recombinant α-synuclein protein that was loaded in parallel, it was recorded

that the co-expression (5 µg, 10 cm dish) of wild-type GBA (but not prosaposin) with αS under these conditions ***did not significantly change αS levels*** *(109.7 +/- 9.88% of vector cDNA control levels).* ***This is in contrast to the result observed in Example 5 above***". (emphasis added by the board)

2.7.4 Hence, according to the conclusions of example 7, stated in the application as filed as being a more reliable method than that of example 5, the expression of GBA does not significantly change αS levels.

2.7.5 Consequently, the functional technical effect mentioned in claim 1 is not credibly demonstrated on the basis of the data provided in the application as filed.

2.8 The respondents arguments to the contrary failed to convince the board, as set out in the following.

2.8.1 First, in relation to example 5 of the application as filed, the respondent argued that the apparently similar GBA expression level for the "med" and "high" experiments (figure 2B, top row) could not simply be compared with each other because the blots represented "semi-quantitative results".

The board notes however that if this argument were to be accepted, then the same could equally apply to a comparison of αS levels for the "med" and "high" experiments (figure 2B, bottom row) such that for the same reason, it could not be concluded that αS levels were lowered for the "high" experiment compared to the "med" experiment.

2.8.2 Second, the respondent also submitted that the panel "no prosaposin transfected" in figure 2B should be

compared with the panel "plus prosaposin transfected" in which large reductions in αS levels are demonstrated. The latter showed that a reduction in αS levels was due to activated GBA.

The board does not see the relevance of this argument. The co-transfection of GBA plus prosaposin (i.e. GBA *activated* by prosaposin) does not fall within the scope of contested claim 1. Consequently, whether or not a specific effect is convincingly demonstrated in figure 2B for the co-therapy is irrelevant to the question of whether the same effect can be achieved with GBA, administered alone.

2.8.3 Third, the respondent dismissed example 7 of the application as filed on the basis that it was concerned with whether over-expression of mutant GBA leads to accumulation of αS levels, and not whether over-expression of wild-type GBA can reduce αS levels. Although wild-type GBA was tested (figure 4, supra), the data present therefor was not comparable to that of example 5. Specifically, not only was no "balancing" DNA used in example 7 (example 5 employs 5.0 µg "Empty vector" to balance up to a total of 10.5 µg cDNA; see application, page 39, example 5, while example 7 employs none), but in contrast to example 5 (figure 2B, top row), there was no confirmation in example 7 that GBA was actually expressed by the cells.

The board notes that although example 7 concerns the effect of mutant GBA on αS levels, it also includes an experiment with wild-type DNA (figure 4, left hand result). Furthermore, the argument that the lack of balancing DNA in example 7 explains the discrepancy in the results compared to example 5 cannot be accepted. Specifically, as noted by the appellant, no apparent

technical reason nor explanation was provided as to why the absence of empty vector in example 7 could lead to a failure to successfully transfect cells with wild-type GBA, or that said absence would have any effect on the expression level of transfected GBA. In example 7 it is merely stated that the observed discrepancy (with example 5) **can** reflect differences in the total DNA transfected thereby leading to changes in the DNA:Lipofectamine® 2000 ratio (example 7, page 43, second paragraph), without any mechanistic explanation. This is confirmed by the fact that, according to the application as filed (example 4, page 38), Lipofectamine® 2000 is used to avoid the problem of MES23.5 cell clones gradually loosing αS expression after passaging for 2-months or more. There is no indication that it is relevant to GBA expression in the transfected cells of example 7.

2.8.4 Fourth, the respondent argued that the burden of proof remained with the appellant to demonstrate that the invention is insufficiently disclosed. The respondent acknowledged that the disclosure must be considered at the filing date (i.e. on the basis of the application documents as filed), and that the application must at least make it plausible that the problem addressed by the invention is indeed solved. However, the respondent argued that this standard was met because example 5 credibly taught that the administration of GBA alone was sufficient to reduce αS levels in a cell model (reply to the statement of grounds of appeal, page 15, point 6.23).

As set out above, the board does not agree that example 5 of the application as filed credibly teaches that the alleged effect is achieved. Hence, the effect is not considered credible on the basis of the application as

filed, and the burden of proof rests with the respondent.

2.8.5 Fifth, insofar as the respondent relied upon post-published evidence D17 and/or D23 in support of the alleged technical effect (e.g. reply to the statement of grounds of appeal, 6.9, 6.12, 6.21, 6.22 and 6.23), the board notes that according to Enlarged Board of Appeal decision G 2/21, reasons 77:

"*...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.*"

As set out above, even though experimental data is provided in the application as filed, it is not credible on the basis of this data that the claimed therapeutic effect is achieved. Hence, in the present case, post-published evidence D17 and D23 cannot be taken into account.

2.9 It follows from the foregoing that the invention defined in claim 1 of the main request is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, as required by Article 83 EPC.

3. The sole main request is consequently not allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar: The Chairman:

M. Schalow M. O. Müller

Decision electronically authenticated