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Datasheet for the decision of 11 November 2021

Case Number: T 1821/18 - 3.3.04

Application Number: 10794938.0

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Language of the proceedings: EN

Title of invention:
Monoclonal antibodies against the RGM A protein for use in the treatment of retinal nerve fiber layer degeneration

Patent Proprietor:
AbbVie Deutschland GmbH & Co KG

Opponent:
Mitsubishi Tanabe Pharma Corporation

Headword:
RGM A binding proteins for treatment of retinal nerve fiber layer degeneration/ABBVIE

Relevant legal provisions:
EPC Art. 100(a), 100(b), 54(2), 56
RPBA Art. 12(4)

Keyword:

Grounds for opposition - insufficiency of disclosure (no)
Late-filed facts - request could have been filed in first instance proceedings (yes)
Novelty - second (or further) medical use
Inventive step - reasonable expectation of success (no)

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Case Number: T 1821/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 11 November 2021

Appellant: (Opponent)	Mitsubishi Tanabe Pharma Corporation 3-2-10, Dosho-machi, Chuo-ku, Osaka-shi Osaka 541-8505 (JP)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Patent Proprietor)	AbbVie Deutschland GmbH & Co KG Max-Planck-Ring 2a 65205 Wiesbaden (DE)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 17 May 2018 rejecting the opposition filed against European patent No. 2510001 pursuant to Article 101(2) EPC**

Composition of the Board:

Chair	R. Morawetz
Members:	A. Schmitt
	R. Romandini

Summary of Facts and Submissions

I. The appeal lodged by the sole opponent (appellant) lies from the opposition division's decision to reject the opposition filed against European patent No. 2 510 001 (patent). The patent proprietor is the respondent.

Claim 1 of the patent as granted reads as follows:

"1. A binding protein for human Repulsive Guidance Molecule A (RGM A) for use in the treatment of retinal nerve fiber layer (RNFL) degeneration."

II. The patent, entitled "*Monoclonal antibodies against the RGM A protein for use in the treatment of retinal nerve fiber layer degeneration*", was granted on European patent application No. 10 794 938.0, which had been filed as an international application published as WO 2011/070045 (application).

III. The opposition proceedings were based on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) in Article 100(a) EPC and on the ground in Article 100(b) EPC.

IV. In the notice of opposition, the appellant had argued on the ground in Article 100(b) EPC that the patent did not make the claimed therapeutic effect credible because it did not provide any experimental evidence that an anti-RGM A antibody had an effect on RNFL degeneration and that Example 13 of the patent was unsuitable to show such an effect.

V. On 14 February 2018, one month before the oral proceedings in opposition, the respondent introduced

document D15 and submitted arguments to the effect that an anti-RGM A antibody binding to the C-terminus of RGM A only had a neuroregenerative effect while treatment of RNFL degeneration required both neuroprotective and neuroregenerative effects.

VI. During the oral proceedings in opposition, the appellant argued on the ground in Article 100(b) EPC that in view of the respondent's latest submissions, claim 1 encompassed subject-matter, namely anti-RGM A antibodies binding to the C-terminus of RGM A, that did not have the therapeutic effect recited in the claim and that the invention defined in the claim was therefore not sufficiently disclosed in the patent (see points 2.5 and 2.6 of the decision under appeal).

VII. In the decision under appeal, the opposition division considered that none of the respondent's arguments on sufficiency of disclosure submitted during the opposition proceedings was convincing. Example 13 of the patent demonstrated that an RGM A binding protein had both neuroprotective and neuroregenerative effects on RNFL degeneration and therefore provided experimental evidence in support of the claimed therapeutic treatment. Moreover, a medical use claim only encompassed the agents which exhibited the therapeutic effect recited in the claim.

VIII. With the statement of grounds of appeal, the appellant submitted four documents, including D20, D21 and D22, and provided, *inter alia*, arguments to the effect that the subject-matter of claim 1 as granted was not novel and lacked an inventive step and that the invention as defined in claim 1 as granted was not sufficiently disclosed in the patent, *inter alia,* because the skilled person was not able to provide proteins binding

to human RGM A which achieved the desired treatment effect without undue burden; the patent did not support the "broad class" of RGM A binding proteins as claimed; neither a neuroprotective nor a prophylactic treatment as defined in dependent claim 2 was sufficiently disclosed in the patent; and the internal designations "5F9" and "8D1" used in dependent claim 17 were unclear to the extent that it resulted in a lack of sufficiency of disclosure.

IX. In reply, the respondent, submitted, *inter alia*, 11 auxiliary requests and arguments in favour of novelty, inventive step and sufficiency of disclosure of the claims as granted. Moreover, it submitted that the appellant had raised in the statement of grounds of appeal a series of new lines of attack on sufficiency of disclosure which had not been presented during opposition proceedings and should thus not be admitted into the appeal proceedings.

X. Both parties made a further submission on, *inter alia*, sufficiency of disclosure of the invention as defined in the granted claims.

XI. The board summoned the parties to oral proceedings, as they had requested, and issued a communication pursuant to Article 15(1) RPBA setting out its preliminary opinion that it was, *inter alia*, inclined not to admit into the appeal proceedings any of the new lines of attack on sufficiency of disclosure raised in the appellant's statement of grounds of appeal.

XII. In response to the board's communication, the appellant submitted, *inter alia*, arguments on admittance of documents D20 and D21.

XIII. The oral proceedings were held as scheduled. At the end of the oral proceedings, the Chair announced the board's decision.

XIV. The following documents are referred to in this decision.

D1 Mueller et al., Phil. Trans. R. Soc. B, 361, 2006, 1513-1529

D4 Tassew et al., Mol. Cell. Neurosci., 37, 2008, 761-769

D5 WO 2009/106356 A1

D13 Schnichels et al., Gene Expression Patterns, 8, 2007, 1-11

D14 Gheith et al., Clinical Ophthalmology, 2, 2008, 15-19

D15 Koeberle et al., Neuroscience, 169, 2010, 495-504

D18 Hata et al., J. Cell. Biol., 173, 2006, 47-58

D19 Leaver et al., Gene Therapy, 13, 2006, 1328-1341

D20 Bertrand et al., Neurobiology of Disease, 25, 2007, 65-72

D21 Rao and Epstein, Biodrugs, 21(3), 2007, 167-177

D22 Sequence information on N- and C- terminus of RGM

XV. The appellant's arguments relevant to the decision are summarised below.

Admittance of lines of attack on sufficiency of disclosure (Article 12(4) RPBA 2007)

It had been argued before the opposition division that the claimed invention was not sufficiently disclosed in the patent over the whole claimed scope, as evident from the teaching in document D15. This document, introduced by the respondent one month before the oral proceedings in opposition, taught that antibodies binding to the C-terminal domain of RGM A did not achieve the claimed neuroprotective effect. Consequently, no new line of attack had been raised on this on appeal.

Furthermore, the objections to various treatment options listed in dependent claim 2 were likewise a direct response to arguments provided by the respondent shortly before the oral proceedings in opposition. The attack on the "prophylactic treatment" embodiment listed in dependent claim 2 was merely a more detailed part of an argument that had been raised previously.

There had not been sufficient time to raise these objections in writing during the opposition proceedings, but they had been presented during the oral proceedings before the opposition division. Consequently, they should be admitted into the appeal proceedings.

The appellant did not provide any arguments on admittance of the line of attack that the patent did not provide support for the "broad class" of RGM A

binding proteins or the line of attack on the antibody denominations in dependent claim 17.

Main request (patent as granted)

Sufficiency of disclosure (Article 100(b) EPC)

The opposition division's rejection of the argument that the invention as defined in claim 1 as granted was not sufficiently disclosed in the patent across the claimed scope was based on the wrong legal framework and an incorrect assessment of facts. First, the section of the Guidelines of Examination in the European Patent Office cited in the decision under appeal (G-VI.7.2) related to novelty of non-medical uses and not sufficiency of disclosure and was therefore not relevant. Moreover, antibodies binding to the C-terminal part of RGM A were encompassed in the claimed scope but did not have a neuroprotective effect, as evident from document D15 and the respondent's submission during the opposition proceedings. Thus, the claimed invention was not sufficiently disclosed across its entire claimed scope.

Furthermore, the optical nerve injury animal model used in Example 13 of the patent was not suitable for assessing treatment of RNFL degeneration since it was not clear whether this animal model even suffered from RNFL degeneration. Moreover, the data of Example 13b of the patent did not support a statistically significant therapeutic effect of the RGM A antibody "5F9" on the RNFL because, as evident from Figure 17 of the patent, the two agents used as treatment controls (a PBS buffer and a p21 antibody) displayed statistically significant differences in their effects on retinal nerve fibre

bundles. The observed effects of the RGM A antibody "5F9" could therefore not be trusted.

The data of Example 13b did not support a therapeutic effect of the RGM A antibody "5F9" for the additional reason that the number of nerve fibre bundles was not directly related to the survival of retinal ganglion cells. Since it was determined only five weeks after the treatment, the observed increased density of the nerve fibre bundles could also result from neuroregeneration of retinal ganglion cells which had not died after optic nerve crush, i.e. from an increase in the number of sprouting neurons as measured in Example 13c.

Furthermore, the imaging method used to evaluate the experiments of Example 13 was prone to errors since it depended on the selected imaging window, i.e. a random snapshot, which did not allow drawing any statistically relevant conclusions.

Consequently, the patent did not provide any evidence that a binding protein for human RGM A could be used in the treatment of RNFL degeneration and therefore did not sufficiently disclose the invention as defined in the claims of the patent as granted.

Novelty (Article 100(a) EPC and Article 54 EPC)

Document D5 aimed at showing that anti-RGM A antibodies were suitable for regenerating neuronal cells (see last paragraph of page 24) and disclosed that anti-human RGM A antibodies were able to induce long-distance regeneration of nerve fibres in an *in vivo* rat model of optic nerve injury (see page 3, lines 24 to 27; page 20, lines 15 to 22; Example 11; Figures 12A, 12B,

14A, 14B). This animal model was, according to document D5, suitable for testing "*various substances that stimulate*[d] *regeneration of the optic nerve fibers and reduce*[d] *the massive cell death of retinal ganglion cells*" (see page 108, lines 25 to 27).

Indeed, the optic nerve consisted of axons sprouting from retinal ganglion cells. These axons were injured in the optic nerve crush model closely behind the entry point into the eye. Therefore, any treatment effects detectable in these injured axons were a necessary and direct consequence of what happened to the retinal ganglion cells themselves. It was therefore not relevant that in document D5 only the optic nerve regeneration distal to the crush site had been analysed because this anyhow reflected RNFL regeneration.

This was also evident from the fact that document D5 identified a list of neurodegenerative diseases, including glaucoma, which could be treated with RGM A antibodies (see page 15, lines 19 to 27). In these diseases, in particular glaucoma, RNFL degeneration could occur (see paragraphs [0005] and [0010] of the patent). Document D5 also pointed to numerous studies which had shown that antibodies to RGM A induced long-distance regeneration of injured nerve fibres (see page 2, lines 9 to 11 and lines 19 to 23). Document D5 thus disclosed that antibodies to RGM A treated glaucoma in a long-distance manner.

Consequently, the subject-matter of claim 1 lacked novelty over the disclosure in document D5.

Admittance of lines of attack on inventive step (Article 12(4) RPBA 2007)

The appellant did not provide any arguments on admittance of the lines of attack on inventive step using the problem-solution approach starting from documents D1 or D18 as the closest prior art.

Admittance of documents D20, D21 and D22 (Article 12(4) RPBA 2007)

Documents D20 and D21 were submitted in view of the opposition division's decision to uphold the patent. They should be admitted because they were *prima facie* relevant. They disclosed compounds which resulted in both neuroregeneration and neuroprotection in retinal ganglion cells and thus showed that a neuroprotective effect was not a surprising property. These documents were therefore suitable as starting points for the assessment of inventive step.

The appellant did not provide any arguments on admittance of document D22.

Inventive step (Article 100(a) EPC and Article 56 EPC)

Document D5 as the starting point

Documents D5 related to a similar use as recited in claim 1 and required minimal structural and functional alterations. It was therefore a better starting point for the assessment of inventive step than document D19.

Document D5 disclosed that human RGM A antibodies were able to treat neuronal cell regeneration. The difference to the claimed subject-matter was that

document D5 did not explicitly mention the treatment of retinal neuronal cell degeneration, i.e. a treatment inside the eye. Since there was no improvement associated with this difference, the objective technical problem was the provision of an alternative treatment option for a human RGM A binding protein.

The treatment of retinal neuronal cells with the RGM A antibody of document D5 was obvious to the skilled person in view of the teaching in document D5 alone.

Document D5 showed that systemic treatment with a human RGM A antibody caused regeneration of long-distance optical nerve fibres in an optic nerve crush animal model (see Example 11). These nerve fibres were the axons of retinal ganglion cells that also formed the RNFL. The skilled person would hence necessarily understand that treatment with this antibody inevitably also increased regeneration and survival of retinal ganglion cells. Moreover, document D5 disclosed that glaucoma, a disease characterised by RNFL degeneration, could be treated with human RGM A antibodies (see page 15, line 28).

The skilled person therefore reasonably expected from the teaching of document D5 alone that treatment with an anti-RGM A antibody would also regenerate retinal neural cells and the RNFL.

This conclusion was confirmed by the teaching of document D19 that showed that in an optic nerve crush animal model, injection of an active compound led to regrowth of the damaged axon across the crush site into the distal optic nerve (see page 1332, paragraph bridging the left- and right-hand columns) and increased the number of retinal ganglion cells and

nerve fibres in the retina (see Figure 2). In view of this teaching, the skilled person would expect that an RGM A antibody known from document D5 to cause regrowth of the damaged axon across the crush site would also increase the number of retinal ganglion cells in the retina.

The disclosure in any of documents D4, D13 and D14 also confirmed that the skilled person would have reasonably expected that RNFL degeneration could be treated with an RGM A antibody. Document D4 disclosed that RGM A was expressed in retinal ganglion cell axons and was involved in intraretinal outgrowth (see page 766, left-hand column, last two lines). Document D13 disclosed that RGM A was highly expressed in the retinas of glaucoma-affected mice (see abstract), and document D14 confirmed that the main cause of the clinical symptoms of glaucoma was the loss of retinal ganglion cells (see page 15, first paragraph).

Document D14 as the starting point

Claim 1 was also not inventive in view of the disclosure of document D14 combined with the teaching in document D5. Document D14 disclosed the treatment of glaucoma, an optic neuropathy characterised by progressive loss of retinal ganglion cells, by reducing intraocular pressure. The difference between the teaching in document D14 and the claimed subject-matter was the use of a different therapeutic agent; the objective technical problem was thus the provision of an alternative treatment for RNFL degeneration. The skilled person looking for an alternative treatment had a clear pointer in document D14 to directly treat the loss of retinal ganglion cells (see first sentence of document D14's abstract) and would therefore turn to a

document that provided an alternative treatment for glaucoma, preferentially by a compound that directly affected neuronal cells. As argued in the problem-solution approach starting from document D5 as the closest prior art, document D5 disclosed both the treatment of glaucoma with an RGM antibody as well as the beneficial effects of an RGM A antibody on neuronal cells and therefore suggested an RGM A antibody as an alternative therapeutic agent for use in the treatment disclosed in document D14.

Document D19 as the starting point

If document D19, which disclosed the treatment of RNFL degeneration by intravitreal injection of, *inter alia*, a viral construct expressing CNTF, was selected as the starting point for the assessment of inventive step, the difference of the claimed subject-matter to the teaching in document D19 was also an alternative agent for use in the treatment of RNFL degeneration.

The skilled person knew from document D5 that treatment with a human RGM A antibody led to axon regeneration outside the eye in the same optic nerve crush animal model used in document D19. Furthermore, the skilled person knew from document D19 that the same agent which led to axon regeneration outside the eye (CNTF) also increased survival of retinal ganglion cells inside the eye.

In view of this teaching, the skilled person would reasonably expect that the RGM A antibody analysed in document D5 also had both effects, i.e. could also, in addition to its regenerative effect on axons outside the eye, regenerate retinal ganglion cells within the eye and could therefore be used as an alternative agent

for the treatment of RNFL degeneration. This was further confirmed by the teaching in document D5 that the RGM A antibody could treat glaucoma, a disease associated with RNFL degeneration.

Consequently, the claimed subject-matter was obvious to the skilled person and did not involve an inventive step.

XVI. The respondents' arguments relevant to the decision are summarised below.

Admittance of lines of attack on sufficiency of disclosure (Article 12(4) RPBA 2007)

The lines of attack raised by the appellant on sufficiency of disclosure in relation to the provision of human RGM A binding proteins having the claimed therapeutic effect, the broad class of RGM A proteins encompassed by the claim, the therapeutic options in dependent claim 2 and the antibodies defined in dependent claim 17 should not be admitted into the appeal proceedings. These objections had not been raised during the opposition proceedings, and the appellant neither provided any justification nor had any reasons for raising them only at the appeal stage.

Main request (patent as granted)

Sufficiency of disclosure (Article 100(b) EPC)

It was established case law of the boards of appeal that the purpose of a second medical use claim was an explicit feature of the claim that had a limiting effect. The subject-matter of claim 1 therefore did not extend to the use of molecules that did not work and,

thus, the claim was sufficiently disclosed as regards this aspect of the appellant's objection. Moreover, the possible existence of molecules which might not be useful for the claimed purpose had no bearing on the ability of the skilled person to carry out the claimed invention based on the patent's disclosure.

The patent provided sufficient information and experimental data for the skilled person to carry out the invention as defined in claim 1 of the patent without undue burden. Example 13 and Figure 17 reported the effect of the monoclonal RGM A antibody "5F9" on both nerve fibre density and the number of sprouting neurons in retinae in an optic nerve crush model. Example 13 therefore provided evidence for both neuroprotection and neuroregeneration in the retinae by the RGM A antibody. These effects were supported by two control agents, neither of which had these effects when compared to the RGM A antibody, and no evidence to the contrary had been provided by the appellant. The skilled person was not required to investigate the reasons for the diverging results observed for the two control agents. The invention defined in the granted claims was therefore sufficiently disclosed in the patent.

Novelty (Article 100(a) EPC and Article 54 EPC)

Document D5 did not disclose the use of an anti-RGM A antibody for the treatment of RNFL degeneration. In document D5's Example 11 and the patent's Example 13, the effects of an RGM A antibody on two different phenomena of the optic nerve crush model were analysed. Document D5 described the degeneration of axons at the optic nerve crush site outside the eye and their regeneration distal to the crush site following

treatment with an RGM A antibody. In Example 13 of the patent, RNFL degeneration within the eye and the antibody's effect on nerve fibre bundles and axons in the retina were assessed.

The disclosure of the RGM A antibody's effect on axonal outgrowth outside the eye and distal to the crush site in document D5 did not implicitly also disclose what happened within the eye. Without examination of the retina, the skilled person could not know whether treatment with the antibody had any effect on RNFL regeneration. The subject-matter of claim 1 hence related to a therapeutic effect different from those described in document D5 and consequently was novel over the disclosure in document D5.

Admittance of lines of attack on inventive step (Article 12(4) RPBA 2007)

The new lines of attack on inventive step based on documents D1 or D18 as the closest prior art should not be admitted into the appeal proceedings because the appellant did not provide any reasons why it could not raise these arguments in the proceedings before the opposition division.

Admittance of documents D20, D21 and D22 (Article 12(4) RPBA 2007)

Documents D20, D21 and D22 should not be admitted into the appeal proceedings because they introduced new aspects that were not a development of an existing case, and no reasonable justification had been provided why these documents could not have been introduced during the proceedings before the opposition division.

Inventive step (Article 100(a) EPC and Article 56 EPC)

Documents D14 and D19 were more suitable as the starting point for the assessment of inventive step of the subject-matter of claim 1 than document D5 proposed by the appellant because they were concerned with the same purpose as the claimed subject-matter, i.e. the treatment of RNFL degeneration. Document D5, in contrast, only proposed an anti-RGM A binding protein for the treatment of various neurological disorders based on its ability to stimulate regeneration of axons outside the eye.

Document D19 as the starting point

Document D19 disclosed that treatment of retinal ganglion cell death in an optic nerve crush animal model by intravitreal injection of CNTF- or BDNF-expressing viral constructs increased the number of surviving retinal ganglion cells (see page 1329, right-hand column, last paragraph; Figure 2).

The claimed subject-matter differed from the teaching of document D19 in that an RGM A binding protein was used in the treatment of RNFL degeneration. The objective technical problem was the provision of an alternative agent for the treatment of RNFL degeneration; the solution proposed in claim 1 of the patent was the use of an RGM A binding protein.

In document D19, the effects of known neurotrophic agents after optical nerve crush were analysed after intravitreal injection. Document D19 was thus concerned with assessing a route of administration for known agents and provided no motivation to use alternative agents.

Furthermore, document D19 disclosed that the protection of retinal ganglion cells following optic nerve crush and the regrowth of axons proximal to the crush site were separate effects which did not necessarily both occur when using a neurotrophic agent. This was evident from the fact that only CNTF-expressing constructs led to a regrowth of axons across the crush site, whereas the number of surviving retinal ganglion cells was increased by both the CNTF- and BDNF-expressing viral construct.

Consequently, the effects of an agent inside and outside the eye had to be examined separately, irrespective of the fact that the optic nerve was made of axons of the retinal ganglion cells. The fact that the axons outside the eye were myelinated whereas the fibres in the RNFL were not further demonstrated that the environment inside the eye was different from the one outside the eye.

The skilled person thus had no reasonable expectation that an RGM A antibody, for which document D5 only reported effects on regeneration and remyelination of axons at the optic nerve crush site outside the eye, would also have an effect within the retina and could be used to treat RNFL degeneration.

Consequently, even if the skilled person combined the teachings of document D19 and D5, they would not have arrived at the claimed subject-matter.

Document D14 as the starting point

Document D14 could also be used as the starting point for the assessment of inventive step. Document D14

disclosed the treatment of glaucoma with a compound that reduced intraocular pressure. Starting from document D14 as the closest prior art, the objective technical problem was the provision of an alternative agent for the treatment of RNFL degeneration, and the solution proposed in claim 1 as granted was the use of an RGM A binding protein. Document D14 did not motivate the skilled person to consider agents for the treatment of glaucoma which did not reduce intraocular pressure. Moreover, even if considering document D5, the skilled person would not have arrived at the claimed subject-matter for the same reasons indicated when starting from document D19 as the closest prior art and combining its teachings with that of document D5.

Document D5 as the starting point

If document D5 was used as the closest prior art, the objective technical problem was the provision of a new medical use for human RGM A binding proteins. The solution provided in claim 1 was the treatment of RNFL degeneration.

The solution provided in claim 1 was not obvious to the skilled person considering the disclosure in document D5 alone or in conjunction with any of documents D19, D4, D13 and D14. Document D5 demonstrated the effects of RGM A binding proteins on regeneration and remyelination of optic nerves, i.e. neuronal axons outside the eye. No conclusions could be drawn from the teaching of document D5 on RNFL regeneration within the eye.

This was also evident from document D19, which separately assessed the effects of other agents on

neuronal axons outside the eye and retinal ganglion cells within the eye in an optic nerve crush model.

Document D4 related to the investigation of the role of RGM A in the development of the retina. It did not disclose RGM A expression in the mature eye and was therefore not relevant for the claimed subject-matter. Document D13 reported on the gene expression of RGM A and neogenin in the eyes of glaucoma model mice which was dependent, *inter alia*, on the mouse strain and the age of the mice (see sections 1.2.1 and 1.2.2 on pages 7 to 8). No information was presented on RNFL degeneration or how the information presented could relate to the treatment of glaucoma. Document D14 reported on the treatment of glaucoma with agents that reduced intraocular pressure and thus would not have been considered by the skilled person seeking a new therapeutic target for human RGM A binding proteins.

Consequently, the claimed subject-matter involved an inventive step.

XVII. The parties requests relevant for the decision were as follows.

The appellant requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the appeal be dismissed and that the patent be maintained as granted (main request).

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is admissible.

Admittance of lines of attack on sufficiency of disclosure (Article 12(4) RPBA 2007)

2. In the statement of grounds of appeal, the appellant submitted several new lines of attack on sufficiency of disclosure of the invention as defined in claims 1, 2 and 17 of the patent as granted (see section VIII.).

3. However, none of the lines of attack referred to in point 2. above were raised during the proceedings before the opposition division (see sections IV. and VI.).

4. The primary purpose of the appeal proceedings is to judicially review the impugned decision (see G 10/93, OJ EPO 1995, 172, point 4. of the Reasons; G 9/91, OJ EPO 1993, 408, point 18. of the Reasons, and now explicitly confirmed in Article 12(2) RPBA 2020). Appeal proceedings under the EPC are not a continuation of the proceedings before the opposition division.

5. The appellant's statement of grounds of appeal was filed on 27 September 2018, i.e. before the date of the entry into force (1 January 2020) of the revised version of the Rules of Procedure of the Boards of Appeal (RPBA 2020), and the respondent's reply to it was filed in due time. Consequently, under Article 25(2) RPBA 2020, Article 12(4) of the Rules of Procedure of the Boards of Appeal in the version valid until 1 January 2020, i.e. Article 12(4) RPBA 2007, continues to apply.

6. Under Article 12(4) RPBA 2007, the board has the power to hold inadmissible facts, evidence or requests which could have been presented or were not admitted in the proceedings before the opposition division, even if they were presented with the statement of grounds of appeal or the reply, relate to the case under appeal and comply with Article 12(2) RPBA 2007. Admittance of the appellant's submissions (see point 2. above) hinges on, *inter alia*, whether the appellant could and should have made these submissions earlier under the circumstances (see also Case Law of the Boards of Appeal of the European Patent Office, 9th edn., 2019, ("CLBA"), section V.A.4.11.1).

7. The appellant's new submissions on sufficiency of disclosure are directed to the invention as defined in claims 1, 2 and 17 of the patent *as granted*. For this reason alone, they could and should have been submitted during the opposition proceedings.

8. According to the appellant, it had argued before the opposition division that the disclosure in document D15 made evident that antibodies which bound to the C-terminal domain of repulsive guidance molecule A (RGM A) were ineffective and that therefore the claimed invention was not sufficiently disclosed in the patent over the whole claimed scope. Hence, no new line of attack had been raised in this context. Indeed, a line of attack based on document D15 was submitted during the oral proceedings in opposition (see section VI.) and is considered on appeal (see points 15. to 29. below).

9. The line of attack raised in the statement of grounds of appeal is, however, different from the one submitted

during the oral proceedings in opposition, where the appellant argued that in view of the teaching in document D15, the granted claim encompasses ineffective antibodies (non-working embodiments). In the statement of grounds of appeal, the line of attack was that the skilled person could not provide effective antibodies without undue burden because document D15 showed that not all RGM A antibodies could be used for the recited treatment. This line of attack was not raised before the opposition division but evidently could have been since the claimed subject-matter is unchanged (see point 7. above).

10. The appellant also brought forward that the objections to the different therapeutic options in dependent claim 2 were a direct response to submissions made late by the respondent in the opposition proceedings and that the appellant did not have sufficient time to respond to this new development of the case during the opposition proceedings. Moreover, the attack on the "prophylactic treatment" embodiment listed in dependent claim 2 was merely a more detailed part of an argument that had been raised previously.

11. However, the relevant submissions were made by the respondent at the date fixed by the opposition division pursuant to Rule 116(1) EPC, and the appellant addressed these submissions at the oral proceedings before the opposition division. Furthermore, it had not requested that document D15 or any of the submissions based on document D15 not be admitted into the opposition proceedings.

12. It is moreover not evident from the minutes of the oral proceedings before the opposition division that the appellant requested more time to respond to the

respondent's submissions or a postponement of the oral proceedings before the opposition division in view of the respondent's submissions. The board is therefore not persuaded by the appellant's arguments that these lines of attack could not have been brought forward during the opposition proceedings.

13. Furthermore, the board is also not persuaded that the attack on the "prophylactic treatment" recited in claim 2 as granted was only a more detailed part of the appellant's argument that the patent, and in particular Example 13, did not credibly disclose that an RGM A antibody could treat retinal nerve fibre layer (RNFL) degeneration. This is so because the assessment of enablement of a prophylactic treatment, i.e. the prevention of RNFL degeneration, is different from and goes beyond the consideration on the enablement of the therapeutic treatment of RNFL degeneration. This is a new and independent attack that was not brought forward during the opposition proceedings despite the fact that a prophylactic treatment formed part of the subject-matter of claim 2 as granted.

14. In view of the above facts and considerations, the board decided to hold inadmissible the lines of attack at issue under Article 12(4) RPBA 2007.

Main request (patent as granted)

Sufficiency of disclosure (Article 100(b) EPC)

15. Claim 1 of the main request is a so-called second medical use claim, i.e. a purpose-limited product claim. The requirements of sufficiency of disclosure of a second medical use claim are complied with (1) if the patent discloses that the claimed product is suitable

for the claimed therapeutic application, unless this is already known to the skilled person at the priority date, and (2) if, at the effective date of the patent, the skilled person was able to obtain the claimed product, here a binding protein of human RGM A, without undue burden (see also CLBA, II.C.7.2.).

16. In a first line of argument, the appellant considered, with reference to post-published document D15, that binding proteins of human RGM A were encompassed within the scope of the claim, which could not achieve the claimed therapeutic effect, and that the opposition division, in refuting this argument with reference to section G-VI.7.2 of the EPO's 2017 Guidelines for Examination, had relied on the wrong legal framework.

17. Section G-VI.7.2 of the EPO's 2017 Guidelines is concerned with claim interpretation. It indicates that a claim to the use of a known compound for a purpose based on a technical effect is interpreted as including this technical effect as a functional technical feature. Since claim construction is the same regardless whether novelty or sufficiency of disclosure is at stake, this section of the Guidelines is also relevant for the assessment of sufficiency of disclosure.

18. It is indeed established case law of the boards of appeal that when a therapeutic application is claimed in the form of a second medical use claim, attaining the therapeutic effect recited in the claim is a functional technical feature of the claim (see CLBA, section II.C.7.2 and decision T 609/02 cited there). Binding proteins for human RGM A that do not achieve treatment of RNFL degeneration are therefore not encompassed by the claim and the appellant's argument

that the claimed subject-matter comprised products which did not achieve the therapeutic effect recited in the claim cannot succeed. Accordingly, the decision under appeal was correct on this point.

19. A lack of sufficiency of disclosure arises if the skilled person could not provide the claimed product without undue burden (see condition (2) in point 15. above), i.e. could not provide those binding proteins for human RGM A which indeed achieved the recited therapeutic effect without undue burden. However, this is a different line of attack which does not form part of the appeal proceedings (see also points 8. to 9. above).

20. The board is also not persuaded by the appellant's second line of attack that Example 13 did not credibly disclose that a therapeutic treatment of RNFL degeneration could be achieved with a binding protein for RGM A because of the animal model used in this example.

21. The patent discloses that in the optic nerve crush model used in Example 13 of the patent, "*massive cell death of retinal ganglion cells*" takes place (see paragraph [0294] of the patent). This is also confirmed in document D5 (lines 25 to 27 on page 108). It was therefore credible to the skilled person that RNFL degeneration occurs in this animal model. Moreover, in Example 13 of the patent, adult retinae from the eyes of rats with optic nerve crush were explanted, and the effects of the RGM A antibody on the retinal ganglion cells compared to control agents were assessed. It was shown that the treatment increased the density of nerve fibre bundles and the number of sprouting of retinal neurons in the degenerating RNFL (see also point 22.

below). In view of this disclosure, the board is not persuaded by the appellant's arguments that the treatment of RNFL degeneration could not be assessed with the optical nerve injury animal model.

22. As to the interpretation of Example 13b of the patent, the board notes that a significantly higher density of nerve fibre bundles (see Example 13b; Figure 17) and a significantly higher number of sprouting intraretinal neurons (see Example 13c; Figure 18) were observed in retinae of animals systemically treated with the RGM A antibody "5F9" compared to control treatments. The higher density of nerve fibre bundles was interpreted in the patent as a neuroprotective effect of the antibody on the RNFL, whereas the higher number of sprouting intraretinal neurons was interpreted as a neuroregenerative effect.

23. The appellant considered that the increased density of the nerve fibre bundles observed in Example 13b could likewise result from neuroregeneration rather than neuroprotection or might be an artefact of the imaging method. No evidence was submitted in support of these arguments.

24. In accordance with the case law of the boards of appeal, a successful objection of lack of sufficiency of disclosure presupposes that alleged serious doubts are substantiated by verifiable facts (see CLBA, II.C.5.3., II.C.7.1.4 and II.C.9.).

25. In the case at hand, the interpretation of the results of Example 13b put forward in the patent constitutes a credible explanation for the observed effects (see point 22. above).

26. Consequently, in the absence of any evidence that this interpretation was wrong and the appellant's suggested interpretation was right, the appellant's alleged "serious doubts" remain unsubstantiated and fail to go beyond speculation.

27. The appellant also argued that since the two control treatments performed in Example 13b of the patent (PBS buffer and control antibody p21) differed in their respective effects on the retinal ganglion cells, Example 13b could not support a statistically relevant effect of the RGM A antibody.

28. The board, however, considers it irrelevant that the two control treatments differed in their effects on the retinal ganglion cells relative to each other because the treatment with the RGM A antibody had statistically significant effects compared to both controls (see Figure 17). The divergent effects of the "treatment" with a buffer and a control antibody could have various explanations and do not therefore constitute, in isolation, sufficient reason to doubt the results shown for the RGM A antibody treatment compared to both control treatments.

29. Therefore, considering the evidence before it, the board is not persuaded by the appellant's arguments why the invention claimed in claim 1 and its dependent claims 2 to 17 was not sufficiently disclosed in the patent and could not be carried out by the skilled person without undue burden.

30. The ground for opposition in Article 100(b) EPC hence does not prejudice the maintenance of the patent as granted.

Novelty (Article 100(a) EPC and Article 54 EPC)

31. Claim 1 is directed to a compound for the treatment of RNFL degeneration (see section I. above). To destroy novelty, document D5 must disclose the claimed subject-matter. This can be by way of explicit or implicit disclosure. Implicit disclosure relates solely to matter not explicitly mentioned in the cited art but necessarily implied by the explicit disclosure.

32. Document D5 discloses that local and systemic administration of anti-human RGM A antibodies induces regeneration of damaged optic nerve axons in an animal model of optic nerve injury distal to the nerve crush site (see Example 11; pages 108 to 111). This was analysed by preparing the optic nerves and assessing the regenerating fibres by fluorescence microscope imaging (see Figures 11, 12 and 14). However, in document D5, neither the retina nor the RNFL was analysed. Therefore, document D5 does not explicitly disclose that the RNFL is regenerated by treatment with the RGM A antibody in the optic nerve crush model.

33. The board is also not persuaded by the appellant's arguments that document D5 implicitly disclosed the claimed subject-matter. Document D5 discloses that the optic nerve crush animal model could be used to test for substances that reduced "*the massive cell death of retinal ganglion cells*" (see lines 25 to 27 on page 108). However, the teaching that tests could be performed is not a disclosure of the results of such hypothetical tests. In document D5, only the effects of an RGM A antibody on damaged optic nerve fibres outside the eye, distal to the crush site, were investigated; not its possible effect on survival and sprouting of retinal ganglion cells and the RNFL.

34. The appellant also argued that the regrowth of crushed myelinated axons across the crush site outside the eye observed in Example 11 of document D11 was a necessary and direct consequence of an effect of the RGM A antibody on the retinal ganglion cells and the RNFL because the optic nerve fibres were composed of axons of retinal ganglion cells, which also formed the RNFL inside the eye. However, it is common general knowledge that the cellular environment for the unmyelinated nerve fibres within the eye and the myelinated axons outside the eye is different and that multiple different cellular signalling events take place in each cell. The prevention of cell death of retinal ganglion cells and the regeneration of unmyelinated fibres within the RNFL by the RGM A antibody observed in Example 13 of the patent is therefore not necessarily caused by the same cellular signals that stimulate the regrowth of myelinated axons across the crush site observed in Example 11 of document D5.

35. The appellant also referred to the fact that it was known in the prior art that RGM A antibodies induced long-distance regeneration of injured nerve fibres (see the background information disclosed in document D5: page 2, lines 9 to 11, 14 to 23 and 28 to 29; page 3, lines 24 to 27; Figure 12A and 12B of document D5) and that document D5 also disclosed that neurodegenerative diseases, including, *inter alia*, glaucoma, could be treated with an RGM A antibody, a treatment, which also had to rely on long-distance neuroregeneration (see page 15, lines 19ff). However, from the disclosure that treatment with an RGM A antibody induces axonal regrowth *distal* to the site of a nerve injury, even if it is "long distance", it is not immediately apparent to the skilled person that this treatment would also

have an effect on neuronal survival and sprouting within the eye *proximal* to the site of the injury since the intracellular signalling events responsible for these different effects are not necessarily the same.

36. Consequently, the board is not persuaded that document D5 implicitly discloses the treatment of RNFL degeneration with an RGM A binding molecule and therefore holds that the opposition division was correct in finding that the subject-matter of claim 1 is novel over the disclosure of document D5 (Article 100(a) EPC and Article 54 EPC). The dependent claims 2 to 17 are *a fortiori* also novel over document D5.

Admittance of lines of attack on inventive step (Article 12(4) RPBA 2007)

37. In the statement of grounds of appeal, the appellant argued for the first time that documents D1 or D18 could also serve as the closest prior art for the assessment of inventive step of claim 1 as granted. Admittance of these new lines of attack is governed by Article 12(4) RPBA 2007 (see also point 6. above).

38. No reasons were provided why this line of attack was only presented in the appeal proceedings. Documents D1 and D18 had been in the opposition proceedings. Furthermore, the new attacks on inventive step starting from documents D1 or D18 as the closest prior art are directed to claim 1 as granted. These lines of attack therefore could and should have been raised in the proceedings before the opposition division.

39. Consequently, the board decided to hold the new lines of attack starting from documents D1 or D18 as the

closest prior art inadmissible
(Article 12(4) RPBA 2007).

Admittance of documents D20, D21 and D22
(Article 12(4) RPBA 2007)

40. The appellant argued that documents D20 and D21 were introduced as new closest prior art documents in view of the opposition division's decision to uphold the patent and because they were *prima facie* relevant.

41. However, appeal proceedings are not a continuation of the proceedings before the opposition division (see point 4. above). Therefore, neither the fact that the opposition division upheld the patent as granted nor an alleged *prima facie* relevance can serve as justification for submitting, on appeal, additional prior art documents and new lines of attack on inventive step based upon them.

42. Moreover, since the claims at issue are unamended, the submission of documents D20 and D21 and the inventive step attacks based on these documents do not constitute a response to an amendment of the respondent's case. Consequently, the appellant could and should have submitted documents D20 and D21 in the proceedings before the opposition division.

43. Document D22 was submitted by the appellant to indicate which amino acids of RGM A are part of its N-terminus and its C-terminus. This was, however, not disputed by the respondent. The filing of document D22 therefore does not constitute a response to an amendment of the respondent's case and, thus, also this document could and should have submitted in the proceedings before the opposition division.

44. The board therefore decided to hold documents D20, D21 and D22 and the submissions based on these documents inadmissible (Article 12(4) RPBA 2007).

Inventive step (Article 100(a) EPC and Article 56 EPC)

Closest prior art and objective technical problem

45. In the decision under appeal, the opposition division considered that document D14 was the most suitable "closest prior art" because it related to the same purpose as the claimed subject-matter, namely the treatment of glaucoma and RNFL degeneration. Document D5 was considered as an alternative "closest prior art".

46. On appeal, the appellant maintained that documents D5, D14 or D19 qualified as the "closest prior art". Document D19 discloses that CNTF and BDNF expression upon intravitreal injection of an adenoviral vector construct promotes retinal ganglion cell survival in the retina in an optic nerve crush animal model (page 1329, right-hand column, last paragraph; Figure 2) and thus, similar to the teaching of document D14, discloses the treatment of RNFL degeneration with a different therapeutic agent.

47. The parties agreed that when inventive step was assessed using either document D14 or D19 as the starting point, the objective technical problem was the provision of an alternative agent for the treatment of RNFL degeneration. Furthermore, when inventive step was assessed using the disclosure in document D5 as the starting point, the objective technical problem was the provision of the treatment of an alternative clinical

condition with an RGM A binding protein. The board sees no reason to differ from this assessment.

Obviousness

48. The problem-solution approach arguments presented by the appellant either start from the disclosure in document D5 or combine the teaching in documents D19 or D14 with that of document D5. Irrespective of the document selected as the starting point for the assessment of inventive step and the formulation of the objective technical problem (see point 47. above), obviousness of the claimed subject-matter hinges on whether the skilled person would have reasonably expected from the teaching in document D5 that RNFL degeneration could be treated with an RGM A binding protein.

49. The teaching in document D5 is summarised in point 32. above. In document D5, the retinae of the model animals were not examined, and thus document D5 contains no teaching on RNFL degeneration or treatment. The RNFL, the innermost layer of the retina, is formed by the axons of retinal ganglion cells which, outside the eye, form the optic nerve fibres. However, in contrast to the optic nerve outside the eye, within the eye, i.e. in the RNFL, the axons of the retinal ganglion cells are not myelinated. The environment of the axons in the RNFL and the optic nerve is therefore different. Furthermore, the regeneration of the myelinated optic nerve fibres after injury outside the eye at the site of the injury and the regeneration of the RNFL within the eye are entirely separate events. Consequently, the board holds that the skilled person would not consider that any effect seen outside the eye will necessarily occur also inside the eye.

50. The board finds support for this view in document D19, where it is assessed, in two separate independent experiments, whether expression of a neurotrophic factor in the eye of an optic nerve crush animal model has an effect on (1) regrowth of the damaged axon at the crush site and (2) the number of retinal ganglion cells and nerve fibres within the retina (see page 1329, right-hand column, last paragraph to page 1332, right-hand column, first line; Figures 2 and 3). Indeed, document D19 discloses that the effects of a therapeutic agent within and outside the eye are not necessarily correlated. This is evident from the fact that one of the neurotrophic agents (BDNF) that shows an effect inside the eye (Figure 2) has no effect on the axonal growth distal to the crush site (Figure 3), i.e. on the same phenomenon analysed in Experiment 11 of document D5.

51. Thus, the appellant's arguments that the regenerative effect of the RGM A antibody on axonal outgrowth distal to the crush site could be extrapolated to an effect on the RNFL inside the eye simply because the respective nerve fibres were derived from the same retinal ganglion cells does not persuade the board.

52. In document D5, the retinae of the model animals were not examined. Thus, document D5 contains no teaching on RNFL degeneration or treatment. The skilled person therefore could not reasonably expect from the experimental section of document D5 that an RGM A antibody would have an effect on RNFL degeneration.

53. This assessment is not changed by the fact that document D5 also refers to glaucoma as one of several neurodegenerative diseases that could possibly be

treated with an RGM A antibody (see document D5, page 15, line 28). This passage of document D5 refers to a long list of neurodegenerative disease not specifically associated with RNFL degeneration and therefore does not suggest the treatment of RNFL degeneration.

54. The appellant also referred to documents D4, D13 and D14. However, document D4 only discloses RGM A expression during the development of the retina but not in the mature eye. The board therefore cannot see how the disclosure in document D4 could be relevant for the treatment of RNFL degeneration by an RGM A binding protein. Document D13 discloses that RGM A is expressed in the eyes of glaucoma-affected mice. This, however, is dependent on mouse age and strain (see sections 1.2.1 and 1.2.2 on pages 7 to 8). Moreover, no conclusions are drawn on the possible relevance of RGM A expression for RNFL degeneration or treatment of glaucoma. Document D14 is not concerned with RGM A at all but discloses the treatment of glaucoma with agents that reduce intraocular pressure. The disclosure in documents D13 and D14 therefore does not affect the conclusion of the board that the reference to glaucoma in a long list of various neurodegenerative diseases in document D5 does not disclose or suggest the treatment of RNFL degeneration with an RGM A antibody.

55. Consequently, the teaching of document D5 does not allow the skilled person to draw any conclusions on the effects of an RGM A antibody within the retina. Hence, it was neither obvious to the skilled person from the teaching of document D5 that RNFL degeneration could be treated with a human RGM A binding protein nor that a binding protein of human RGM A could be an alternative

therapeutic agent for the treatment of RNFL degeneration.

56. In view of the above considerations, the board holds that the claimed subject-matter was not obvious to the skilled person starting from the disclosure in document D5 as the "closest prior art", alone or combined with the teaching in any of documents D4, D13, D14 and D19. Nor was it obvious when starting from the disclosure in document D19 or D14 as the "closest prior art" combined with the teaching of document D5.

57. Therefore, the board concludes that the subject-matter of claim 1 and its dependent claims 2 to 17 involves an inventive step (Article 100(a) EPC and Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

I. Aperribay R. Morawetz

Decision electronically authenticated