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Datasheet for the decision of 22 August 2019

Case Number: T 1129/16 - 3.3.04

Application Number: 04782579.9

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Language of the proceedings: EN

Title of invention:
Delivery of therapeutic compounds to the brain and other tissues

Patent Proprietor:
BioMarin Pharmaceutical Inc.

Opponents:
Dörries, H. Ulrich/df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB

Headword:
Intrathecal delivery/BIOMARIN

Relevant legal provisions:
EPC Art. 56, 83

Keyword:
Main request - meets requirements of EPC (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1129/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 22 August 2019

Appellant: (Patent Proprietor)	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondents: (Opponents)	Dörries, H. Ulrich/df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Fünf Höfe Theatinerstrasse 16 80333 Munich (DE)
Representative:	Dörries, Hans Ulrich df-mp Fünf Höfe Theatinerstrasse 16 80333 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 30 March 2016 revoking European patent No. 1673104 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman	G. Alt
Members:	D. Luis Alves
	M. Blasi

Summary of Facts and Submissions

I. The appeal by the patent proprietor (appellant) concerns the decision of the opposition division to revoke European patent No. 1 673 104, entitled "*Delivery of therapeutic compounds to the brain and other tissues*".

II. In the decision under appeal the opposition division held that the claims according to the main request complied with the requirements of Articles 123(2)(3), 84 and 54 EPC but that the subject-matter of claim 1 contravened the requirements of Article 56 EPC. Further, the opposition division held that claim 1 of auxiliary request 1 did not comply with the requirements of Article 84 EPC and that the further auxiliary requests 2 to 7 were not to be admitted into the proceedings.

III. The reasoning of the opposition division in the decision under appeal as to why the subject-matter of claim 1 of the main request lacked inventive step can be summarised as follows:

The disclosure of document D20 (see section VII below) represented the closest prior art. The problem to be solved was the provision of a method for delivering enzymes to correct enzyme deficiencies in the CNS of patients with lysosomal storage disorders (LSDs).

The treatment of meningeal tissues was an embodiment falling within the scope of claim 1. Such a treatment, by reducing for example swelling caused by lysosomal storage granules present in said tissues, was obvious to the person skilled in the art when starting from the teaching of document D20.

Document D20 addressed the treatment of mucopolysaccharidosis type II (MPS II; Hunter syndrome), being "*a LSD characterised by deposits in the meninges that prevent normal drainage of CSF* [cerebrospinal fluid] *thereby leading to the development of hydrocephalus (see General Reference with regard to Hunter syndrome, page 2, last paragraph)*". In the opposition division's view, the skilled person "*would have had a reasonable expectation of success that intrathecal administration of M6P-IDS* [mannose 6-phosphate iduronate-2-sulfatase] *ameliorates the MPS II symptoms as the CSF is in direct contact with the meninges"*(see point 2.5.4 of the decision). The document reference in the quote above is numbered D58 in the present decision.

IV. With the statement of grounds of appeal, the appellant re-filed the sets of claims of the main request and auxiliary request 1 considered in the decision under appeal and further filed sets of claims of auxiliary requests 2 to 12.

V. The main request contains a single independent claim and 48 dependent claims. The independent claim reads:

"1. A pharmaceutical composition comprising an enzyme that is (a) deficient in a lysosomal storage disease, and (b) comprises or has been engineered to comprise a moiety that allows said enzyme to bind the mannose-6-phosphate (M6P) receptor, for use in the treatment of central nervous system (CNS) manifestations of said lysosomal storage disease by intrathecal administration to a subject mammal in an amount effective to ameliorate the CNS symptoms of said lysosomal storage disease."

VI. The joint opponents (respondents) did not reply to the statement of grounds of appeal or make any other submissions in the appeal proceedings.

VII. The following documents are referred to in this decision:

D1: US 6458574 B1 (1 October 2002)

D2: WO 02/098455 A2 (12 December 2002)

D9: Chavany *et al.*, Molecular Medicine Today, 1998, 4, 158-165.

D10: Stein *et al.*, J. Virol., 1999, 3424-3429.

D20: Daniele *et al.*, Biochimica et Biophysica Acta, 2002, 1588, 203-209.

D21: Aebischer *et al.*, Nature Medicine, 1996, 2, 696-699.

D22: Aebischer *et al.*, Exp Neurol, 1994, 126, 151-158.

D23: Deglon *et al.*, Hum Gen Ther, 1996, 7, 2135-2146.

D25: Bobo *et al.*, Proc. Natl. Acad. Sci., 1994, 91, 2076-2080.

D57f: Misra *et al.*, J. Pharm. Pharmaceut. Sci., 2003, 6(2), 252-273.

D58: Hunter syndrome: Excerpt from the website of The Swedish Information Center on Rare Diseases, University of Gothenburg, http://www.socialstyrelsen.se/rarediseases, published online 20 September 2012.

VIII. The appellant's arguments, insofar as relevant for this decision, may be summarised as follows:

Neither the treatment of brain tissue nor the treatment of the meninges was obvious having regard to the teaching of document D20.

Concerning the treatment of meninges in particular, document D20 had no indication whatsoever (i) of cells of the meninges being affected in MPS II, (ii) that said cells would endocytose and process to an active form the lacking enzyme, (iii) how the cell lines used in document D20 would relate to cells making up the meninges, (iv) that swelling of the meninges would be related to accumulation of glycosaminoglycans and (v) of any link between hydrocephalus in MPS II and meninges.

In respect of the last two points, the opposition division had relied on document D58, which was published, however, later than the filing date of the patent. Without hindsight of the disclosure in the patent, there was no basis for the person skilled in the art to consider that the meninges might be the focus of treatment of MPS II.

The problem to be solved when starting from the teaching of document D20 as the closest prior art was not that of providing a method of delivering enzymes but rather that of providing a method of treatment.

There was no reasonable expectation that the claimed treatment would be successful. With respect to enzyme uptake of brain cells, the cell lines used in document D20 had very different characteristics from those of normal neurons and glial cells, endocytosis *in vitro* was not representative of endocytosis *in vivo*, and endocytosis into a cell was fundamentally different from uptake into the brain. With respect to entry of a substance into the brain it first had to enter the brain parenchyma and then diffuse in the brain. It also had to remain in the CSF long enough to produce effects before being cleared from the CSF.

IX. The appellant requested that the decision of the opposition division be set aside and that the patent be maintained in amended form on the basis of the set of claims of the main request or, alternatively, on the basis of one of the sets of claims of auxiliary requests 1 to 12. The appellant further requested that oral proceedings be held in the event that the main request was not allowable.

Reasons for the Decision

Procedural aspects

1. The appeal is admissible as it complies with the requirements specified in Articles 106 to 108 and the further provisions referred to in Rule 101(1) EPC.

2. Since the respondents did not request oral proceedings and the set of claims of the main request is found to

fulfill the requirements of the EPC, the case can be decided without oral proceedings being held.

Main request - all claims
Inventive step (Article 56 EPC)

Closest prior art

3. In the decision under appeal the disclosure of document D20 was considered to represent the closest prior art. The board sees no reason to depart from this choice.

4. Document D20 concerns the uptake of the enzyme iduronate-2-sulfatase by neuronal and glial cells in the context of treatment of the lysosomal storage disease mucopolysaccharidosis type II (MPS II). It shows that, in cell lines derived from neurons and glial cells, the enzyme comprising a mannose-6-phosphate (M6P) moiety was endocytosed and correctly processed in the lysosomes. The authors conclude that "*In view of the considerable problem of the blood-brain barrier, a potential therapeutic approach could be based on the intrathecal treatment of the recently obtained MPS II mouse model*" (see last sentence of the "Discussion").

Thus, document D20 does not disclose the treatment of a lysosomal storage disease and, consequently, nor the intrathecal administration of the M6P-coupled enzyme. Furthermore, document D20 mentions neither which tissues are affected nor which symptoms can be observed in patients suffering from MPS II.

Problem to be solved

5. Thus, the difference between the subject-matter of claim 1 and the closest prior art as disclosed in document D20 is that the claimed subject-matter relates to the actual treatment of CNS manifestations of a lysosomal storage disease, by intrathecal administration of the enzyme-containing composition.

6. Based on the experimental results in a canine model of mucopolysaccharidosis I (MPS I), disclosed in examples 5 and 6 of the application, the effect of these differences is that the enzyme reaches the cells of the CNS such that lysosomal storage granules are reduced, both in the meninges and in the brain tissues, and that symptoms can be ameliorated.

7. Taking into account these effects achieved by the differences, the objective technical problem may be stated as the provision of a treatment of the CNS manifestations of lysosomal storage diseases.

8. The solution to this problem is the provision of a treatment relying on the intrathecal administration of the M6P form of the enzyme which is lacking in the particular lysosomal storage disease.

Obviousness

9. In accordance with the case law of the boards of appeal, a course of action can be considered obvious to the person skilled in the art not only when the results are clearly predictable but also when there is a reasonable expectation of success.

The latter implies the ability of the person skilled in the art to predict rationally, on the basis of the knowledge existing before the start of a research project, the successful conclusion of said project within acceptable time limits (see also Case Law of the Boards of Appeal of the European Patent Office, 8th edition, 2016, I.D.7.1.).

Whether there is a reasonable expectation of success is thus a matter to be assessed on a case-by-case basis.

10. The appellant pointed to several reasons as to why the person skilled in the art would rather not expect success when aiming at providing a treatment of CNS manifestations of lysosomal storage diseases by the intrathecal delivery of the M6P form of the lacking enzyme.

As submitted by the appellant, starting from the *in vitro* results and the conclusions set out in document D20, there is uncertainty, *inter alia*, as to whether the enzyme will remain in the cerebrospinal fluid (CSF) long enough to produce effects before being cleared from the CSF, whether it will cross from the CSF into the brain tissue, whether it will diffuse through the brain tissue and, finally, whether it will reduce the lysosomal storage granules in the CNS.

Document D57f, which is a review article published in the same year as the priority date of the patent, states that intrathecal delivery did not prove successful due to unfavourable pharmacodynamics and complications inherent to this route of delivery. The limitations on the extent of tissue that could be reached are considered such that only parenchyma adjacent to the site of injection would be reached by

the administered drug (page 265, first column, second paragraph to last full paragraph).

Document D25 too states that diffusion of high molecular weight compounds in the brain is very slow, even when administered by direct injection into the brain tissue. The diffusion from the CSF was too limited (abstract and first paragraph). Said document thus takes a different approach, investigating the possibility of increasing the distribution to the brain tissue based on convection by means of a pressure gradient.

11. The board was not pointed to documents substantiating equally strongly the skilled person's expectation that alleviating the CNS manifestations of a lysosomal storage disease would indeed be achievable by intrathecal delivery of the M6P form of the lacking enzyme.

In this respect, of the documents on file, two broad groups can be distinguished. One group, to which documents D1, D2, D9 and D10 belong, which merely mentions intrathecal delivery but does not demonstrate its successful application. A second group, comprising documents D21 to D23, which concerns gene therapy by implantation of capsules either (i) into the subarachnoid space without providing data on enzyme uptake in the brain/meninges and symptom alleviation (D21 and D23, for delivery of ciliary neurotrophic factor) or (ii) directly into the brain tissue and thus not concerning intrathecal delivery (D22, for dopamine delivery).

12. On weighing the evidence before it, the board comes to the conclusion that the person skilled in the art would

not have been able to predict rationally, on the basis of the existing knowledge as documented by the above-mentioned prior art documents, that ameliorating the CNS manifestations of a lysosomal storage disease would be successfully achieved by intrathecal delivery of the M6P form of the lacking enzyme.

13. In the board's view - which is in contrast to that of the opposition division - this conclusion equally applies to ameliorating symptoms generated by lysosomal storage granules in the meningeal tissues, the embodiment of claim 1 considered as obvious in the decision under appeal (see section III above).

The closest prior art document D20 does not disclose the presence of storage granules in meningeal tissues and their impact in patients having a lysosomal storage disease.

The document relied on by the opposition division in this respect, D58, was published only after the filing date of the patent in suit.

Finally, the board was not pointed to any document in the prior art disclosing the presence of storage granules in meningeal tissues and their impact in patients having a LSD.

The board therefore comes to the conclusion that the person skilled in the art starting from the teaching of document D20 and aiming at providing a treatment for the CNS manifestations of LSDs would not have provided a treatment for meningeal tissues in patients having an LSD.

14. In view of the considerations in points 10 to 13 above, the board concludes that the subject-matter of claim 1 involves an inventive step (Article 56 EPC). The same conclusion applies to the subject-matter of the remainder of the claims, all referring back to claim 1.

Article 83 EPC

15. There are no facts on file that call into question that the application would disclose in a sufficiently clear and complete manner the claimed composition for use in the treatment of CNS manifestations of lysosomal storage disorders by intrathecal delivery of the enzyme that is lacking. In view of the experimental results on file showing the alleviation of symptoms and reduction of lysosomal storage granules in the CNS tissues on the basis of a canine animal model, the board is satisfied that the requirements of Article 83 EPC are met.

Articles 123, 84 and 54 EPC

16. In the decision under appeal the opposition division held that the subject-matter of the claims according to the main request now before the board complied with the requirements of Articles 123(2)(3), 84 and 54 EPC. This finding has not been questioned during the appeal proceedings and the board sees no reason to differ from the conclusion reached by the opposition division in this respect.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of claims 1 to 49 of the main request filed with the statement of grounds of appeal, and a description and any drawings to be adapted thereto.

The Registrar: The Chair:

S. Lichtenvort G. Alt

Decision electronically authenticated