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Datasheet for the decision of 12 March 2021

Case Number: T 2218/16 - 3.3.08

Application Number: 08836776.8

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IPC: C12N15/864, A61K48/00

Language of the proceedings: EN

Title of invention:
Widespread gene delivery to motor neurons using peripheral injection of AAV vectors

Patent Proprietor:
Genethon
Centre National de la Recherche Scientifique

Opponent:
Bezzubova, Olga

Headword:
Gene therapy of motor neuron disorders/BEZZUBOVA

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)
EPC R. 80
RPBA 2020 Art. 13(2)

Keyword:
Admission of the main request - (yes)
Admission of late filed arguments - (no)
Requirements of the EPC met - (yes)

Decisions cited:
G 0002/88, G 0006/88, G 0003/14, T 0836/01, T 0406/06, T 0433/14

Catchword:
Sufficiency of disclosure - burden of proof, Novelty - new clinical situation

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Case Number: T 2218/16 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 12 March 2021

Appellant: (Opponent)	Bezzubova, Olga Jones Day Intellectual Property Prinzregentenstrasse 11 80538 Munich (DE)
Representative:	Bezzubova, Olga Jones Day Rechtsanwälte, Attorneys-at-Law, Patentanwälte Prinzregentenstrasse 11 80538 München (DE)
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Representative:	Sekhri, Redha Cabinet Becker & Associés 25, rue Louis le Grand 75002 Paris (FR)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 August 2016 concerning maintenance of the European Patent No. 2212424 in amended form.**

Composition of the Board:

Chairman	B. Stolz
Members:	M. Montrone
	A. Bacchin

Summary of Facts and Submissions

I. The appeal lies against the decision of an opposition division to maintain the European patent No. 2 212 424 in amended form. The patent was filed under the PCT and published as international patent application WO 2009/043936 (hereinafter the "patent application").

II. The opposition division held that the main request filed during oral proceedings met the requirements of the EPC.

III. With its statement of grounds of appeal, the opponent (hereinafter "appellant") submitted objections under Rule 80, Articles 84, 123(2),(3), 87, 54, 56 and 83 EPC against the subject-matter of the main request as maintained by the opposition division, and filed documents D16 and D17.

IV. In reply, the patent proprietors (hereinafter "respondents") submitted the main request on the basis of which the patent was maintained, seven auxiliary requests, and documents D18 to D20. Auxiliary requests 1 to 6 corresponded to the respective sets of claims submitted during the first instance proceedings, while auxiliary request 7 was new to the proceedings.

V. In reply, the appellant submitted further arguments and document D21.

VI. In a communication pursuant to Article 15(1) RPBA, the parties were informed of the board's provisional, non-binding opinion.

VII. In reply, the respondents filed a main request and two auxiliary requests. The main request and auxiliary request 1 were new to the proceedings, while auxiliary request 2 corresponded to auxiliary request 6 filed in reply to the appellant's statement of grounds of appeal.

VIII. In a further reply, the respondents submitted additional arguments.

IX. Oral proceedings before the board were held on 12 March 2021 by video conference as requested by the parties. In the oral proceedings the respondents submitted a main request which was identical to auxiliary request 2 submitted with a letter dated 21 January 2021.

X. Claim 1 of the main request reads:

"1. An AAV vector comprising a therapeutic gene for use in a method for treating a motor neuron disorder in a subject, wherein said AAV vector is administered by by intraperitoneal (i.p.), intramuscular (i.m.) or intravenous (i.v.) injection, preferably intravenous injection, to said subject, said administration causing infection of spinal cord motor neurons and expression of the gene in spinal cord motor neurons, wherein said AAV vector is:
- a double-stranded self-complementary AAV9 vector, or
- a pseudotyped AAV vector comprising a double-stranded self-complementary AAV genome derived from an AAV serotype different from the AAV9 serotype and a capsid derived from an AAV9 capsid; and
wherein the therapeutic gene is operably linked to a promoter specific or functional in motor neurons".

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

D1: WO 2009/013290 (published on 29 January 2009);

D2: EP 07301263.5 (Prio-document of D1, published as EP 2019143 on 28 January 2009);

D3: US 2007/0196338 (published on 23 August 2007);

D4: Fu H. *et al.*, Molecular Therapy, 2003, Vol. 8(6), 911-917;

D5: Inagaki K. *et al.*, Molecular Therapy, 2006, Vol. 14(1), 45-53;

D6: Cearley C.N. and Wolfe J.H., Molecular Therapy, 2006, Vol. 13(3), 528-536;

D7: Gao G. *et al.*, Journal of Virology, 2004, Vol. 78(12), 6381-6388;

D8: WO 03/055983 (published July 10, 2003);

D9: Kaspar B.K. *et al.*, Science, 2003, Vol. 301, 839-842;

D16: Lefebvre S. *et al.*, Nature Genetics, 1997, Vol. 16, 265-269;

D17: Zincarelli C. *et al.*, Molecular Therapy, 2008, Vol.16(6), 1073-1080;

XII. The appellant's submissions, insofar as relevant to the present decision, may be summarised as follows:

Main request

Admission into the proceedings of the main request, new lines of argumentation under added subject-matter and lack of clarity, and a new document

The amendments in claim 1 did not address any of the grounds of opposition, in particular lack of novelty over document D2. Furthermore, the feature "*wherein the therapeutic gene is operably linked to a promoter specific or functional in motor neurons*" (hereinafter the "promoter feature") introduced additional issues under added subject-matter and lacked clarity. Thus, the amendments were not occasioned by a ground of opposition and did not result in a request that was clearly allowable, contrary to the requirements of Rule 80 EPC.

Objections under added subject-matter were raised for the first time during the oral proceedings against the subject-matter of claims 4 and 5 which were both dependent on claim 1. The combination of the therapeutic genes and diseases referred to in claims 4 and 5 with a method of treating a spinal cord motor neuron-associated disorder according to claim 1 had no basis in the application as filed. Although these objections were submitted late in the appeal proceedings, they were relevant, and hence, should be admitted.

Furthermore, a new objection under lack of clarity was raised against the subject-matter of claim 5 in conjunction with claim 1. Also this objection should be admitted into the proceedings, despite it's late submission, since it was relevant.

A scAAV9-based treatment of spinal muscular atrophy (SMA) was achievable only by directly transfecting motor neurons. The disease-causing gene named survival of motor neuron (SMN) encoded an intracellular protein that could not be supplemented from extracellular sources. This was common general knowledge at the relevant date of the patent in suit. Since the board asked for evidence of this fact, document D16 should be admitted into the proceedings.

Added subject-matter

Several features of claim 1 had no basis in the patent application.

The "promoter feature" in claim 1 was allegedly based on page 13, lines 9 and 10 of the patent application. However, the term "*the promoter*" in this passage was "*a most preferred embodiment*", and indicated that this term referred to the promoter in previous lines 1 to 7 which comprised further elements, for example, leader and PTD sequences. Thus, the second and the third paragraph on page 13 of the patent application were not independent from each other. Nor was a basis for the "promoter feature" in claim 1 derivable from page 12, lines 3 to 5 of the patent application which disclosed that the preferred promoters "*shall be functional in nervous cells, particularly in human cells, more preferably in motor neurons*". This passage was, however, silent on a "*specific*" promoter for motor neurons. The leader and PTD sequences mentioned on page 13, line 6 of the patent application were closely linked to the promoter. This was derivable from page 12, lines 18 to 29 of the patent application which disclosed, as a preferred embodiment, that the nucleic acid comprised a "*leader sequence allowing secretion of*

the encoded protein", or that the "*transgene is fused with PTD sequences [...] in order to cause or improve secretion of the therapeutic protein from the transduced cells and re-uptake by neighbour ones*". The omission of these two promoter elements in claim 1 resulted in an intermediate generalisation. The patent application was silent on any specific promoter for spinal cord motor neurons too, which was however, encompassed by the claimed subject-matter. Furthermore, neither the disclosure on page 4, lines 1 to 7, nor claim 3 as filed mentioned a promoter. Thus, there was no disclosure for the combination of spinal cord motor neurons and promoters in the application as filed, not even an implicit one.

Further features in claim 1 objected to were:

"*a double-stranded self-complementary AAV9 vector*" (hereinafter the "scAAV9 vector" feature);

"*a pseudotyped AAV vector comprising a double-stranded self-complementary AAV genome derived from an AAV serotype different from the AAV9 serotype and a capsid derived from an AAV9 capsid*" (hereinafter the "pseudotyped scAAV9 vector" feature). It implied that the vectors were characterised by an AAV9-derived capsid, while their genomes were derived from any other AAV serotype. The patent application, however, was silent on such vectors, including any definition for the term "*pseudotyped AAV vector*". While page 11, lines 1 to 10 of the patent application mentioned a pseudotyped scAAV9 vector, it contained an AAV2-derived genome. All pseudotyped AAV vectors disclosed in the patent application contained an AAV2-derived genome (see page 17, lines 23 to 25). Such pseudotyped vectors were likewise known from the prior art (see document

D7). Furthermore, although claim 9 as filed mentioned a "*scAAV9 which may be pseudotyped*", this meant according to the common understanding of the term in the art, that the vector contained an AAV9-derived genome, while the capsid was derived from any other AAV serotype;

"*administered by by intraperitoneal (i.p.), intramuscular (i.m.) or intravenous (i.v.) injection*" (hereinafter the "administration" feature);

"*treating a motor neuron disorder*" (hereinafter the "treatment" feature);

"*causing infection of spinal cord motor neurons and expression of the gene in spinal cord motor neurons*" (hereinafter the "result-to-be-achieved" feature);

Lastly, an objection was raised against the specific combination of the features cited in claim 1 as constituting an impermissible selection of features derived from several lists of substantial length, which were, moreover, taken out of context (hereinafter the "combination" feature). Claims 3 and 9 as filed, for example, were silent on spinal cord motor neurons.

Clarity and support

The subject-matter of claim 1 lacked clarity for two reasons.
Firstly, the definition of the "promoter feature" as being "*specific*" for motor neurons in claim 1 was more limited than the "*tissue-specific*" promoters cited in dependent claim 6. The former allowed gene expression in a single cell-type, the latter in any tissue-type, even in unrelated tissues, such as liver. Since the

definition of promoters in dependent claim 6 was broader than in claim 1, a contradiction existed which rendered the claimed subject-matter unclear. A lack of clarity objection could be raised against amended claim 1 (see G 3/14, published in OJ 2015, 102), since (i) a feature was introduced from the description ("*spinal cord*"), while (ii) another one was deleted ("*glial cells*") from claim 1 as granted.
Secondly, claim 1 required that the "promoter feature" was "*specific or functional in motor neurons*", while it likewise required that the vector infected and expressed the therapeutic gene in "*spinal cord motor neurons*", i.e. within a subset of motor neurons only. In other words, claim 1 defined a promoter as being "*specific*" in motor neurons, while it referred to different motor neuron cell-types. This lacked clarity.

Sufficiency of disclosure

The term "motor neuron disorder" in claim 1 did not define the disorders encompassed by it. Claim 5 being dependent on claim 1 mentioned a list of disorders which should at least be encompassed by these disorders. However, some of these were unrelated to motor neuron disorders, for example, cancer and sleeping disorders. More disorders unrelated to motor neurons were disclosed in paragraphs [0044] and [0045] of the patent, including, autism. Moreover, the underlying cause of most of these disorders was unknown, including agents required for their treatment. According to the established case law in the context of second medical use claims, attaining a therapeutic effect was a functional feature of the claim. The information provided in the patent taking common general knowledge of the skilled person into account, had therefore to disclose the suitability of AVV9

vectors for the claimed therapeutic applications, at least in a plausible manner. Aside the disorders, the patent did not disclose the suitability of the claimed AVV9 vectors when administered intraperitoneally (i.p.), or intra muscularly (i.m.). Further, the patent was silent on using any other viral genome than that of AVV2 for attaining a therapeutic effect, although claim 1 encompassed all AVV genome-subtypes. Thus, based on the information disclosed in the patent, the skilled person was unable to perform the claimed invention across the whole breadth claimed, in particular without undue burden. Although no evidence was submitted demonstrating that AVV9 vectors were not suitable for the therapeutic applications claimed, objections under insufficiency could nevertheless be raised in the present case, since the patent neither disclosed a mechanism by which the AAV9 vectors achieved a therapeutic effect, nor a causal link between spinal cord motor neurons and the diseases cited in claim 5. In this situation the suitability of AVV9 vectors for the treatment of certain diseases, such as SMA, could not be generalised to all diseases covered by claim 1. This shifted the burden of proof to the respondents (see T 2571/12 and T 609/02).

Priority

The right of priority of the patent in suit was invalid, since the condition of Article 87 EPC was not met that the earlier application was the first application in respect of the same invention as the one to which the patent application related. Document D2 was filed by the same inventors more than twelve month prior to the present patent application, and disclosed the claimed invention. Document D2, therefore, was the

first application within the meaning of Article 87(1) and (4) EPC.

Novelty

Documents D1 and D2 were both prior art documents under Article 54(3) EPC and disclosed in essence the same subject-matter. In the following, references were only made to document D2.
It is uncontested that document D2 disclosed the same scAAV9 vector, therapeutic genes, disorders to be treated, and the same mode of administration as referred to in claim 1. The treatment of motor neuron disorders was disclosed on page 1, first paragraph, page 6, lines 17 to 19 or page 12, lines 15 to 23, which included the expression of therapeutic proteins in nervous tissue. Specific motor neuron diseases mentioned were SMA, amyotrophic lateral sclerosis (ALS), or Kennedy's disease (see page 12, lines 22 and 23). The treatment disclosed in document D2 was not restricted to the secretion of therapeutic proteins into the cerebrospinal fluid (CSF). The document disclosed a transgene expression *inter alia* in "*upper motor neurons*" (see page 15, lines 22 to 24, page 16, lines 2, 26 to 30, Figures 3E and 4C), and in brain cells having a "*neuron-like*" and "*glial-like*" phenotype (see page 17, lines 9 and 10). While the cell bodies of upper motor neurons were located in the cortex, their axons reached into the spinal cord, i.e. they were spinal cord motor neurons.
Even if document D2 did not explicitly disclose the subject-matter claimed, it was implicitly disclosed. This was so because an AAV9 vector-based gene therapy of the motor neuron disorder SMA was impossible without directly transfecting motor neurons, since the disease-causing SMN was an intranuclear protein that interacted

with RNA-binding proteins (see document D16, abstract). Defective intracellular proteins could not be supplemented by a secretion into the CSF, because motor neurons were unable to take them up. It worked by an AAV9 vector-based direct delivery of the wild-type gene into the motor neurons only.

The "result-to-be-achieved" feature in claim 1 ("*said administration causing infection of spinal cord motor neurons and expression of the gene in spinal cord motor neurons*") was not a technical feature. According to the case law, the remaining features in the claim had to achieve the desired result (see T 809/12). Even if it was a technical feature, it did not open a new clinical situation, since as set out above, document D2 disclosed the same vector for treating the same disorders. The mechanism of directly transfecting motor neurons by scAAV9 vectors (instead of infecting epithelial cells and secreting the therapeutic protein into the CSF as mentioned in document D2), merely explained the mechanism how the therapeutic effect was achieved. Since document D2 disclosed the treatment of SMA by scAAV9 vectors, which necessarily required a transfection of motor neurons, the treatment was inherently disclosed. As an aside, claim 1 was not limited to the treatment of a new patient subgroup. It was established case law, that a new technical effect alone, i.e. without establishing a new clinical situation, was not sufficient to establish novelty (see T 433/14 and T 406/06).

Document D2 further disclosed several promoters for expressing therapeutic genes (see e.g. paragraph [0030], claim 9), including ubiquitous ones, such as the CMV promoter, which was likewise disclosed in the patent and referred to in claim 6.

Document D3 disclosed AAV vectors, including an individualised AAV9, and their therapeutic applications (see paragraphs [0005], [0008] and [0010], claims 2, 10, 38 and 46). These vectors were pseudotyped and double-stranded (see paragraphs [0047], [0048]). They were administered *inter alia* by i.v. and i.m. injections to deliver genes to different organs, including brain and motor neurons. The treatment of ALS and SMA was mentioned (see paragraphs [0118], [0120], [0124], and [0170]). Promoters were used for expressing the transgenes (see paragraphs [0131] to [0133]). Thus, the subject-matter of claim 1 lacked novelty over document D3.

Inventive step

Document D4 represented the closest prior art. It disclosed a study using scAAV2 vectors in combination with mannitol for developing methods that delivered transgenes into the central nervous system (CNS) for obtaining a widespread AAV-mediated transgene expression (see abstract and page 912, column 1, fourth paragraph). The treatment of CNS disorders was mentioned as a potential application of double-stranded self-complementary AAV2 (scAAV2) vectors (see page 916, column 1, second paragraph). The addition of mannitol disrupted the blood brain barrier (BBB) so that a subsequent i.v. injection of scAAV2 containing a green fluorescent protein (GFP) gene transfected various cells in the brain and the spinal cord, including neurons, and glial cells. Without mannitol, no scAAV2-based GFP expression was found in the brain (see page 912, column 1, last paragraph to column 2, third paragraph, page 915, column 1, first paragraph, Figure 2).

The subject-matter of claim 1 differed from document D4 in that a different AAV serotype was used.
The technical problem was the provision of an AAV vector without mannitol for the treatment of motor neuron disorders.

This problem was not solved by the subject-matter of claim 1 across the whole breadth of the claim. Furthermore the selection of scAAV9 for an efficient targeting of the CNS was obvious, since the AAV2 vector had drawbacks (see document D5, page 1, last paragraph).

The skilled person starting from document D4 was faced with the problem of finding a vector that crossed the BBB. Document D5 disclosed a study wherein pseudotyped AAV8 and AAV9 vectors were compared in transferring genes *in vivo* to various organs, including the brain (see page 4, last paragraph). The transfection of brain by AAV9 vectors was stated to be superior compared to AAV8, robust and highly efficient following an i.v. infection. The BBB separated the brain from the vascular system. The finding of vector copies and marker gene products in brain tissue and cells necessarily implied that AAV9 crossed this barrier (see page 4, third paragraph and Table 3). A different reading of document D5 did not make sense. A further pointer in document D5 that AAV9 crossed the BBB was derivable from the statement that the transfection of various tissues after an i.v. injection required an efficient "*crossing of capillary endothelial cell barriers*" (see page 5, last paragraph to page 6, first paragraph, and Table 3). The disclosure in document D5 that AAV9 crossed the BBB and infected brain cells with a higher efficiency than AAV8 was a pointer for the

skilled person to use this vector instead of AAV2 in the treatment of CNS disorders.

In this context, the disclosure of a low AAV9 vector copy number in the brain compared to other tissues was irrelevant, since efficiency was not a requirement of claim 1. Furthermore, although document D5 mentioned that the expression of the transgene was impaired in the brain, the skilled person was not disencouraged to use this vector, since the document suggested as solution the use of suitable ubiquitous or tissue-specific promoters (see page 6, second paragraph).

Therefore, the skilled person starting from document D4 in search for an alternative AAV vector for the transfection of cells in the spinal cord would have selected with a reasonable expectation of success AAV9 in light of document D5 disclosing its robustness and superior infectivity of brain cells. A reasonable expectation for its suitability in treating motor neuron disorders was further derivable from AAV9's known ability to transfect neurons, and its broad distribution within the CNS (see document D6, page 529, column 2, last paragraph, page 531, column 2, second paragraph, page 532, column 1, second paragraph to page 534, column 2, first paragraph). Document D6 was cited in document D5 too (see page 2, second full paragraph). The non-mentioning of motor neurons in document D5 was irrelevant for the assessment of inventive step. The skilled person could reasonably expect that AAV9 vectors infected motor neurons, since the viral capsid proteins determined this property (see document D6).

Furthermore, the i.m. or i.p. administration cited in claim 1 of the AAV9 vectors were not associated with an improvement over the use of the AAV2 vector in document

D4. It was known that i.m. or i.p. injected AAV vectors were efficiently delivered to motor neurons by a retrograde transport without the need to cross the BBB (see documents D8 and D9).

XIII. The respondents' submissions, insofar as relevant to the present decision, may be summarised as follows:

Main request

Admission into the proceedings of the main request, new lines of argumentation under added subject-matter and lack of clarity, and a new document

The present main request corresponded to auxiliary request 6 already submitted during the first instance proceedings. This request was not assessed by the opposition division because the patent was maintained on the basis of the then main request in the respondents favour. The present main request was convergent with the claims as granted. Furthermore, the amendments were introduced to overcome objections under lack of novelty and inventive step raised by the appellant already in their notice of opposition. Further, present claim 1 of the main request corresponded to claim 3 as granted, except that two features were added ("*spinal cord*" and the "*promoter*"), while one was deleted ("*glial cells*"). The added features had a proper basis in the patent application, and did not result in new issues, in particular not in a lack of clarity.

The new objections under added subject-matter and lack of clarity were raised by the appellant for the first time at the oral proceedings. They were too late, caught the respondents by surprise, and would have

required a significant amount of time to be addressed. They should not be admitted into the proceedings.

Document D16 was only submitted with the appellant's statement of grounds of appeal. No reasons were apparent why this document was not submitted during the first instance proceedings.

Added subject-matter - claim 1

The "scAAV9 vector" feature in claim 1 had a basis in claim 3 as filed combined with claim 6 as filed.

The "pseudotyped scAAV9 vector" feature in claim 1 had a basis in claim 3 as filed combined with claim 9 as filed. The patent application provided a definition for the term pseudotyped vector on page 11, lines 1 to 5. The skilled person reading the application as a whole would have necessarily derived from the term "*scAAV9 which may be pseudotyped*" in claim 9 as filed that it directly and unambiguously referred to an AAV vector with a capsid protein from the AAV9 serotype, and a genome from any AAV serotype, except AAV9. Any other construction was contrary to the teaching of the patent application as a whole.

The "administration" feature in claim 1 had a basis in the combination of claims 3 and 5 as filed.

The "treatment" feature in claim 1 was mentioned in claim 3 as filed.

The "result-to-be-achieved" feature in claim 1 had a basis in claim 3 as filed combined with page 4, lines 1 to 7 of the patent application.

The "promoter" feature in claim 1 had a basis on page 13, lines 9 and 10, in combination with page 12, lines 3 to 5 of the patent application. The disclosure of the second and third paragraphs on page 13 was independent from each other. It was directly and unambiguously derivable from the patent application as a whole that the leader sequence and the PTD sequence mentioned in line 6 of page 13 were not linked to the promoter feature in claim 1. Claim 1 required that the AAV9 vectors infected spinal cord motor neurons and expressed therapeutic genes in these cells, i.e. not a secretion of proteins from motor neurons, as implied by the terms leader sequence and PTD sequence.

The "combination" of the features in claim 1 had essentially a basis in claim 3 as filed in combination with features from claims being dependent thereon. The mentioning of features in a claim indicated their preferred use. Also the description of the patent application indicated that the used features were preferred. It was established case law that the combination of preferred features in a claim did not add subject-matter (see Case Law of the Boards of Appeal of the EPO, 9th edition 2019, hereinafter "Case Law", II.E.1.6.1).

Clarity and support

Claim 6 was not open for an objection under lack of clarity since it corresponded to claim 9 as granted. There was no contradiction between the terms "*specific*" and "*tissue-specific*" in claims 1 and 6. The skilled person construed the subject-matter of both claims in a sensible manner. Since claim 1 was directed to the treatment of motor neuron disorders, the skilled person would not have construed "*tissue-specific*" in claim 6

to relate to any tissue-specific promoter, but only to those being specific for motor neurons. There was likewise no contradiction between a "*specific*" promoter for *"motor-neurons*" and "*spinal cord motor neuron*" in claim 1, since a spinal cord motor neuron was a motor neuron, and the term "*specific*" indicated only that the promoter was specific for motor neurons, irrespective of their location.

Sufficiency of disclosure

The patent provided the skilled person with all the information necessary for performing the claimed therapeutic treatment over the whole scope claimed. The teaching in the patent was not in contradiction with the common general knowledge. On the contrary it provided a complete set of experimental data in animal models that demonstrated as a proof of principle the suitability of scAAV9 vectors in transfecting motor neurons after i.v. administration for the claimed therapeutic applications (see Example 6). Moreover, since Example 6 demonstrated the successful delivery and expression of a reporter gene in spinal cord motor neurons, the same was to be expected for any therapeutic gene. Although Example 6 was silent on i.p. and i.m. injected scAAV9 vectors, it was plausible that scAAV9 vectors administered in this manner likewise efficiently delivered a transgene to spinal cord motor neurons. The peritoneum and muscles were highly vascularised. Since AAV9 vectors crossed the BBB, they necessarily entered the blood vessels in these two tissues too, and reached the motor neurons as if they had been i.v. injected. It was uncontested that the use of scAAV9 vectors successfully treated SMA as a motor neuron disease. There was further no evidence submitted by the appellant casting doubts on the suitability of

scAAV9 vectors for the other claimed therapeutic applications, let alone verifiable facts. The burden of proof was on the appellant, and in the absence of such evidence, the claimed invention was sufficiently disclosed in the patent application.

Novelty

Documents D1/D2 did not directly and unambiguously disclose the subject-matter of claim 1, in particular, not the infection of spinal cord motor neurons by AAV9 vectors. Document D2 disclosed the infection of epithelial cells only, i.e. of blood vessel cells in the brain, or the spinal cord (see page 2, lines 18 to 21, 25 to 29, page 15, lines 22 to 24, page 16, line 2, page 16, lines 26 and 27). Although document D2 mentioned on page 16, lines 27 to 30 transfected fibers in the corticospinal tract of the motor cortex, the identity of these fibers was unclear, since no direct and unambiguous conclusion was derivable from the term "*likely*" in the context of "*upper motor neurons*". Moreover, these fibers were located in the brain, i.e. the motor cortex, and not in the spinal cord. A conclusion about the identity of the transfected cell-types in the brain was likewise not derivable from cells having a "*neuron-like*" and "*glial-like phenotype*" (see page 17, lines 9 and 10 of document D2). Moreover, these cells were not located in the spinal cord, but in the brain. Document D2 further disclosed a different subset of promoters to express therapeutic genes, since they were not specific for motor neurons (see page 10, lines 17 to 19).

The scAAV9 vector-based therapy in document D2 relied thus on a different mechanism of action, namely the transfection of cells that secreted therapeutic

products into the CSF to attain indirectly a therapeutic effect on disease-causing cells. In other words, document D2 disclosed a therapeutic concept different from that of claim 1.

The "result-to-be-achieved" feature in claim 1 was a functional feature (see G 2/88, published in OJ 1990, 93, G 6/88, published in OJ 1990, 114), that amounted to a new therapeutic effect, because spinal cord motor neurons, i.e. the disease-causing cells, were directly transfected by AAV9 vectors and expressed a therapeutic gene. This resulted in a new clinical situation in the treatment of patients, for example, by circumventing an existing resistance to anti-apoptotic molecules secreted into the CSF, by enabling gene editing, by transfecting receptor genes to introduce into spinal cord motor neurons new ligand sensibilities, or by a direct repression of a disease-causing gene expression, mediated e.g. by inhibitory RNA. These therapeutic effects were not obtained by the secretion of products into the CSF. Therefore, the claimed therapeutic concept was complementary, but not identical to that reported in document D2. The mechanism of action underlying the "result-to-be-achieved" feature limited the scope of claim 1. The identity between the disorders and the therapeutic agent in document D2 and in claim 1 was thus not detrimental to the novelty of the claimed subject-matter (see T 836/01, T 1229/03, T 1642/06, T 1955/09 and T 2251/14).

Document D2 did also not inherently disclose the mechanism of action underlying the "result-to-be-achieved" feature, since this feature was not made available to the public.

Document D3 was not detrimental to the claimed subject-matter. It required multiple selections of non preferred features derived from long lists to arrive at the subject-matter of claim 1.

Inventive step

Document D4 represented the closest prior art for the subject-matter of claim 1. It disclosed an AAV vector of a different serotype and used mannitol to circumvent the BBB for the delivery of transgenes into various tissues including brain. Document D4 was silent on transfected motor neurons, let alone motor neurons in the spinal cord. The claimed subject-matter differed from document D4 in the use of an scAAV9 vector for transfecting spinal cord motor neurons. This allowed the provision of means to deliver peripherally administered therapeutic genes by a non-invasive method for treating motor neuron disorders without a need for mannitol.

The subject-matter of claim 1 solved this problem in a non obvious manner since none of documents D5 to D7 taught or suggested that peripherally administered scAAV9 vector infected spinal cord motor neurons.

Document D5 disclosed a study that compared the suitability of pseudotyped AAV8 and AAV9 vectors for delivering a reporter gene to various tissues after peripheral administration. The document did not mention the spinal cord, let alone transfected spinal cord motor neurons, or any other specific transfected brain cell. It was even doubtful that document D5 disclosed the successful crossing of the BBB by the AAV9 vector and, hence, the transfection of neuronal cells in the brain. This was so because document D5 used whole

tissue extracts for analysing vector transfection into the genome (see page 8, third paragraph). Since epithelial cells around blood vessels were strongly transfected by AAV9 (see document D2 above), extracts from the whole brain necessarily comprised such cells located before the BBB. A further indicator for this assumption was that brain was not mentioned in the summary part of document D5 (see title and abstract). As an aside, the AAV9 copy number in the brain genome as an indicator for its delivery was very low compared to liver, muscle or heart tissues (see Tables 2B and 3). Furthermore, the AAV9-mediated gene expression in the brain was impaired (see page 5, last paragraph, page 6, second paragraph).

Document D6 disclosed a direct intracranial injection of pseudotyped AAV vectors, including AAV9 into the brain. It did not mention any peripheral administration of AAV vectors, the transfection of motor neurons, let alone of spinal cord motor neurons. Thus, document D6 contained no hint for the skilled person to arrive at the claimed invention.

Document D7 did not assess AAV9 delivery to brain tissue, let alone to spinal cord motor neurons after peripheral administration. The transfection of various tissue samples including brain was assessed *in vitro* only, not *in vivo*. There was not even an incentive for the skilled person to turn to document D7 when starting from document D4.

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

XV. The respondents requested that the appeal be dismissed, or alternatively that the decision under appeal be set

aside and that the patent be maintained on basis of the main request submitted at the oral proceedings on 12 March 2021. Further the respondents requested that documents D16 and D17 not be admitted into the appeal proceedings.

Reasons for the Decision

Admission into the proceedings of the main request

1. The appellant objected to the admission of the main request into the appeal proceedings under Rule 80 EPC. The amendments in claim 1 were not occasioned by a ground of opposition, added subject-matter and lacked clarity. Accordingly, the main request should not be admitted since it was clearly not allowable.

2. The board is not convinced by the appellant's arguments. The present main request was filed as auxiliary request 6 already during the first instance proceedings, and submitted as auxiliary request 6 at the earliest possible opportunity in appeal proceedings, namely in reply to the appellant's statement of grounds of appeal. Since this set of claims is on file since the written phase of the opposition proceedings, the criterion for its admittance is not "clear allowability", but it suffices that it represents a genuine attempt to address a ground of opposition raised in the present proceedings.

3. The appellant raised objections under lack of novelty and insufficiency of disclosure against *inter alia* claims 1 and 2 as granted (see e.g. notice of opposition, points 6.1 and 8.2).

4. The contested amendments in claims 1 and 2 directly address these objections. The question of whether or not the amendments overcome the objections in substance - as contested by the appellant too - properly pertains to the merits of the request. Since this has to be assessed under the respective ground of opposition, it is of no relevance for the issue of Rule 80 EPC.

5. The main request complies with Rule 80 EPC, and is admissible.

Admission into the proceedings of various new lines of argumentation under added subject-matter and lack of clarity, and of a document

6. The appellant raised during the oral proceedings for the first time new lines of argument under added subject-matter against claim 1 combined with claims 4 or 5, and under lack of clarity against claim 1 combined with claim 4.

6.1 According to Article 13(2) RPBA 2020, any amendment to a party's appeal case made after the expiry of a period specified by the Board in a communication under Rule 100, paragraph 2, EPC or, where such a communication is not issued, after notification of the summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

6.2 The appellant has not submitted that exceptional circumstances prevented the submission of these new lines of argument at an earlier stage of the proceedings. As a cogent reason, solely the relevance of the arguments was brought forward.

6.3 However, relevance of an argument alone is no cogent reason for admitting new lines of attack at such a late stage of the proceedings. In particular, not in the present case, since as set out above, the main request has been on file since the first instance proceedings. Therefore, the board decided to disregard all new lines of argument (Article 13(2) RPBA 2020).

7. Document D16 was filed by the appellant with its statement of grounds of appeal. The respondents requested not to admit it into the appeal proceedings.

8. The board, pursuant to Article 25(2) RPBA 2020 in conjunction with Article 12(4) RPBA 2007, has a discretion not to admit facts, evidence or requests into the appeal proceedings, which could have been presented or were not admitted in the first instance proceedings.

8.1 During the oral proceedings in the context of novelty, the parties were asked by the board whether or not the treatment of spinal muscular atrophy (SMA) by gene therapeutic means was possible without directly transfecting motor neurons with an adeno-associated virus 9 (AAV9) vector. In reply, the appellant referred to document D16 as evidence of common general knowledge in support of their case.

8.2 In these circumstances, since the reference to document D16 became relevant in reaction to a specific question of the board during the oral proceedings, the board exercised its discretion to admit document D16 into the proceedings.

9. Since the appellant did not refer to document D17 during the oral proceedings, there was no need to decide on its admission into the proceedings.

Added subject-matter - claim 1

10. The appellant submitted several lines of argument under added subject-matter against various features of claim 1. These features are:

- "*a double-stranded self-complementary AAV9 vector*" (hereinafter the "scAAV9 vector" feature),

- "*a pseudotyped AAV vector comprising a double-stranded self-complementary AAV genome derived from an AAV serotype different from the AAV9 serotype and a capsid derived from an AAV9 capsid*" (hereinafter the "pseudotyped scAAV9 vector" feature),

- "*administered by by intraperitoneal (i.p.), intramuscular (i.m.) or intravenous (i.v.) injection*" (hereinafter the "administration" feature),

- "*treating a motor neuron disorder*" (hereinafter the "treatment" feature),

- "*causing infection of spinal cord motor neurons and expression of the gene in spinal cord motor neurons*" (hereinafter the "result-to-be-achieved" feature),

- "*wherein the gene of interest is operably linked to a promoter specific or functional in motor neurons*"

in claim 1 (hereinafter the "promoter" feature), and lastly,

- the combination of features in claim 1 was derived from an impermissible selection of features derived from several lists of substantial length, and of features taken out of context (hereinafter the "combination" feature).

11. In order to determine whether the subject-matter of a claim extends beyond the content of the patent application, it has to be examined whether that claim comprises technical information which a skilled person would not have clearly and unambiguously, using common general knowledge and seen objectively and relative to the date of filing, derived from the application as a whole. This includes subject-matter which is implicitly disclosed (see Case Law, II.E.1.3.1, and II.E.1.3.3).

12. The appellant submitted that the amendments in claim 1 were derived from different lists, that features were taken out of their context, and combined in a new manner.

13. The case law has established that a selection of features taken from separate embodiments normally violates Article 123(2) EPC. The premise is that the patent application is not a reservoir from which features could be artificially combined to create a new embodiment (see Case Law, II.E.1.6.1). However, for that assessment further circumstances need to be taken into account, such as pointers to that selection or combination in the description or the claims, for instance whether the contested features have been mentioned in the patent application as "preferred".

14. The "scAAV9 vector" feature in claim 1:
Claim 3 as filed is directed at the use of an AAV vector comprising a therapeutic gene for the manufacture of a medicament for treating a motor neuron disorder in a subject, and further specifies that the AAV vector is "a *double-stranded self-complementary AAV vector*" (i.e. a "scAAV vector"). Claim 6 as filed which depends on claim 3 as filed mentions that the AAV vector is "*most preferably AAV9*". Hence, both claims in conjunction directly and unambiguously disclose the "scAAV9 vector" of claim 1.

15. The "pseudotyped scAAV9 vector" feature in claim 1:
Claim 1 characterises a pseudotyped scAAV9 vector as an "*AAV genome derived from an AAV serotype different from the AAV9 serotype and a capsid derived from an AAV9 capsid*". In other words, the claimed pseudotyped scAAV9 vectors are chimeric, because they contain genomes from any AAV serotype, except AAV9, while the capsid is necessarily of the AAV9 serotype.

15.1 The appellant submitted that the patent application did not provide a basis for this feature, since it was silent on a general definition of pseudotyped AAV9 vectors, while disclosing instead a specific pseudotyped AAV2/9 vector only, i.e. a vector with an AAV2-derived genome and an AAV9-derived capsid protein (see page 11, lines 1 to 10, page 17, line 23). Furthermore, it was contested between the parties what the skilled person understood by the term pseudotyped scAAV9 vector. The appellant was of the view that the serotype number indicated that the vector contained the genome of this serotype, while the respondents took the view that it indicated the capsid protein.

15.2 Claim 9 as filed is dependent on claim 3 as filed and specifies that "*the AAV vector is a scAAV9 which may be pseudotyped*". Thus, both claims in conjunction disclose a "*pseudotyped scAAV9 vector*". How is this term construed by the skilled person? Does it relate to a chimeric vector that comprises an AAV9-derived capsid protein and a genome from any other other AAV serotype, except AAV9 as required in claim 1, or does it relate to a chimeric vector with an AAV9-derived genome and a capsid protein from any other AAV serotype, except AAV9?

15.3 The patent application states in this context on page 11, lines 1 to 11: "*In another particular embodiment, the AAV vector is a pseudotyped AAV vector, i.e. comprises sequences or components originating from at least two distinct AAV serotypes. In a particular embodiment, the pseudotyped AAV vector comprises an AAV genome derived from one AAV serotype (for example AAV2), and a capsid derived at least in part from a distinct AAV serotype. Specific examples of such pseudotyped AAV vectors include, without limitation, vectors comprising an AAV2-derived genome in an AAV4-derived capsid ; or vectors comprising an AAV2-derived genome in an AAV6-derived capsid ; or vectors comprising an AAV2-derived genome in an AAV8-derived capsid; or vectors comprising an AAV2-derived genome in an AAV9-derived capsid;*" (emphasis added).

15.4 This passage in the patent application discloses a generic definition for a pseudotyped AAV vector. The first two sentences specify that the only requirement for a pseudotyped vector is that the genome and the capsid have to be derived from different AAV serotypes. A serotype is identified by its serotype number, this was uncontested. The passage further mentions examples

of pseudotyped vectors, which all contain an AAV2-derived genome and capsids from other AAV serotypes including AAV9. Further examples are disclosed on page 17, lines 23 to 25 of the patent application which mentions "*AAV2/1 and AAV2/9 vectors*". Based on the disclosure on page 11, lines 1 to 11 (see above) these two vectors can only be construed to contain an AAV2-derived genome and either an AAV1, or an AAV9-derived capsid. Thus, the patent application discloses as an example of a pseudotyped AAV9 vector solely one with an AAV9-derived capsid, but none with an AAV9-derived genome.

15.5 It was uncontested that the capsid protein of a specific AAV serotype determines the tropism of the virus, i.e. its ability to infect a specific cell-type, but not another cell-type.

15.6 The working examples of the patent application disclose that of the two scAAV vector subtypes tested (scAAV1 and scAAV9), solely scAAV9 vectors can cross the blood brain barrier (BBB) after peripheral administration (see Examples 1 and 2). Since the crossing of the BBB requires the infection of blood vessel epithelial cells, the AAV9-derived capsid protein must be responsible for this property (see above).

15.7 Thus, in the board's view, the skilled person taking common general knowledge into account would have derived from the patent application as a whole that the pseudotyped scAAV9 vector of claim 9 as filed necessarily relates to a vector with an AAV9-derived capsid. This follows from the fact that firstly, pseudotyped scAAV9 vectors with an AAV9-derived genome are neither disclosed in the patent application, nor would such a vector be consistent with the disclosure

on page 11, lines 1 to 11, and page 17, lines 23 to 25. Secondly, the patent application discloses that ssAAV9 and scAAV9 vectors only (i.e. vectors comprising an AAV9 capsid) cross the BBB and infect motor neurons (see Examples 1 to 6), a function necessarily determined by the capsid (see above). In view thereof, the skilled person would construe the pseudotyped scAAV9 vector feature of claim 9 to necessarily contain an AAV9-derived capsid. Since the feature in claim 9 is silent on a second serotype number, and in a pseudotyped AAV vector the other component (i.e. here the genome) must be derived from another serotype (see page 11, line 4), the genome must be derived from all AAV serotypes, except AAV9. Therefore, the patent application directly and unambiguously discloses the "pseudotyped scAAV9 vector" feature of claim 1.

16. The "administration" feature of claim 1 is directly and unambiguously disclosed in the combination of the subject-matter of claim 3 and claim 5 as filed being dependent thereon. Claim 5 as filed literally mentions the administration routes referred to in claim 1.

17. The "treatment" feature of claim 1 is mentioned in claim 3 as filed.

18. The "result-to-be-achieved" feature of claim 1 is disclosed in claim 3 as filed in conjunction with page 4, lines 6 and 7 of the patent application, which discloses an AAV vector-based infection and gene expression in "*spinal cord*" motor neurons.

19. The appellant submitted that the "promoter" feature of claim 1 was an intermediate generalisation of page 13, lines 5 to 10 of the patent application, which disclosed that the promoter was linked to additional

elements, including "*leader sequence and a PTD sequence*", which were both lacking in the claim. This passage on page 13 reads as follows:

"*In a further particular embodiment, the nucleic acid comprises, operably linker, a promoter, a leader sequence and a PTD sequence, to allow expression and secretion of the encoded protein.*

In a most preferred embodiment, the promoter is specific or functional in motor neurons, i.e., allows (preferential) expression of the transgene in said cells" (emphasis added).

19.1 When the two paragraphs on page 13 of the patent application are read in conjunction, the independence of the second paragraph (forming the literal basis for the promoter feature in claim 1) from the first paragraph is not clear, because the first paragraph refers likewise to a promoter. As set out above, amendments can be made within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge from the patent application as a whole.

19.2 Page 11, lines 24 to 31 of the patent application relates to AAV vectors too and reads: "*As discussed above, the AAV-derived genome comprises a nucleic acid encoding a therapeutic protein. Typically, the nucleic acid also comprises regulatory sequences allowing expression and, preferably, secretion of the encoded protein, such as e.g., a promoter, enhancer, polyadenylation signal, internal ribosome entry sites (IRES), sequences encoding protein transduction domains (PTD), and the like. In this regard, the nucleic acid most preferably comprises a promoter region, operably*

linked to the coding sequence, to cause or improve expression of the therapeutic protein in infected cells" (emphasis added). Furthermore, page 12, lines 3 to 5 of the patent application states: "*Most preferred promoters for use in the present invention shall be functional in nervous cells, particularly in human cells, more preferably in motor neurons*" (emphasis added). Also claim 12 as filed refers to vectors citing a promoter element only.

19.3 The "*leader sequence and a PTD sequence*" are responsible for the secretion of a gene encoded product from the cell. Since secretion is only a preferred embodiment of the regulatory sequences allowing gene expression (see above), the "promoter" feature is not inextricably linked to the "*leader sequence and a PTD sequence*", and the promoter is, hence, an independent vector element.

19.4 Thus, the board cannot agree with the appellant and the "promoter" feature is directly and unambiguously derivable from the patent application as a whole.

20. Lastly, for the reasons set out above, the "combination" of features in claim 1 is not derived from an impermissible selection of features from different lists of considerable length, or from features taken out of their context. On the contrary, these features are primarily derived from claim 3 as filed and from claims being dependent thereon. This points to them as being preferred. Also the description of the patent application mentions them as preferred. Thus, in line with the case law (see above), the patent application directly and unambiguously discloses the combination of the features of claim 1.

21. The main request therefore complies with the requirements of Article 123(2) EPC.

Clarity and support

22. The appellant raised two lines of argument under lack of clarity. The first was directed against the terms motor neuron "*specific*" promoter in claim 1, and "*tissue-specific*" promoter in dependent claim 6. A cell-specific promoter was more limited than a tissue-specific promoter. Consequently, dependent claim 6 had a broader scope than independent claim 1, which rendered the claimed subject-matter unclear. The second objection was raised against the terms "*expression of the gene in spinal cord motor neurons*" and "*promoter specific [...] in motor neurons*" in claim 1. Spinal cord motor neurons formed a subset of motor neurons only, i.e. the cell-types referred to in claim 1 were different. Since the term "*specific*" in the context of a promoter referred to different motor neuron cell types, claim 1 lacked clarity. In line with the case law it was allowable to raise a lack of clarity objection against amended claim 1 (see G 3/14, published in OJ 2015, 102), because, compared to the corresponding claim 3 as granted, claim 1 was amended by (i) adding a feature from the description ("*spinal cord*"), and by (ii) deleting a feature ("*glial cells*").

23. The respondents contested that it was allowable to raise an objection of lack of clarity against claim 1, since Article 84 EPC was not a ground of opposition.

24. The board does not agree with the respondents. According to decision G 3/14 (OJ 2015, 102, catchword), the claims of a patent may be examined for compliance with the requirements of Article 84 EPC only when, and

then only to the extent that, the amendment introduces non-compliance with Article 84 EPC. In other words, any amendment in a claim irrespective of its origin that introduces a lack of clarity which did not previously exist in the granted claims can be examined under Article 84 EPC (see G 3/14, Reasons point 3(b)). Since current claim 1 has been amended after grant, these amendments to claim 1 have to comply with Article 84 EPC.

25. The first issue to be assessed is whether an inconsistency or contradiction exists between promoters "*specific*" in motor neurons and "*tissue-specific*" promoters as mentioned in claims 1 and 6, respectively.

26. According to the case law, claims must be free of contradiction in order to be clear. Furthermore, the skilled person, when considering a claim, should rule out interpretations which are illogical or which do not make technical sense. In this context, the patent must be construed by a mind willing to understand, not a mind desirous of misunderstanding. The description may be taken into account too for interpreting the claims (see Case Law, II.A.3.1., II.A.6.1., II.A.6.3.).

27. Claim 1 relates to a method of treating motor neuron diseases, which requires the infection of spinal cord motor neurons, i.e. of motor neurons located in the spinal cord, and the expression of therapeutic genes therein. The appellant argued that the term "*tissue-specific*" promoter in claim 6 would be construed to encompass any tissue-specific promoter, for example, liver-specific ones. The board does not agree, since the skilled person would rule out any non-sensible meaning in the interpretation of the subject-matter of claims 1 and 6. As regards promoters, the patent reads

in paragraph [0030], lines 30 to 36: "*Such a promoter may be ubiquitous, tissue-specific, strong, weak, regulated, chimeric, etc., to allow efficient and suitable production of the protein in the infected tissue. [...]. Most preferred promoters for use in the present invention shall be functional in nervous cells*". Thus, tissue-specificity in the context of claim 6 in conjunction with claim 1 is to be construed as neuronal-tissue specific. Furthermore, claim 6 is not broader or contradictory to claim 1, since the latter is not limited to motor neuron "*specific*" promoters, but includes all "*functional*" promoters in these cells too ("*specific or functional*"). The term functional promoter is even broader than the term tissue-specific promoter of claim 6, since it's activity is not limited to neuronal cells.

28. As regards the second line of argument, the term "*spinal cord motor neurons*" in claim 1 indicates that these cells are located in the spinal cord and not, for example, in the cortex. Spinal cord motor neurons, however, irrespective of their location are motor neurons. Thus, there is no contradiction between the cell-types cited in claim 1, since a motor neuron-specific promoter indicates that it is specifically functional in motor neurons, irrespective of their location in the body.

29. Thus, the subject-matter of claims 1 and 6 is clearly defined, and hence, the main request complies with Article 84 EPC.

Sufficiency of disclosure

30. According to Article 83 EPC the European patent application shall disclose the invention in a manner

sufficiently clear and complete for it to be carried out by a person skilled in the art over the whole breadth of the claim.

31. The appellant submitted that the patent did not disclose the suitability of scAAV9 vectors for all therapeutic applications referred to in claim 5. It was uncontested that scAAV9 vectors were available in the art at the relevant date, including their suitability for the treatment of some motor neuron disorders, such as SMA, as demonstrated in the patent. However, other disorders cited in claim 5 were neither related to disorders characterised by a motor neuron origin, for example cancer and sleeping disorders, nor was the underlying cause known for the majority of motor neuron disorders, including agents to be used for their therapy. The appellant argued that the patent did not disclose evidence that the scAAV9 vector was suitable for all of the therapeutic applications claimed, although the burden of proof was on the respondents.

32. According to the established case law the provision of evidence in the patent application for a claimed effect is not a prerequisite for patentability, if, based on the data in the patent application/patent, or from common general knowledge, it is plausible that a product (here scAAV9) is suitable for the claimed therapeutic applications (see Case Law, II.C.7.2.).

32.1 Furthermore, a successful objection of lack of sufficiency of disclosure presupposes that there are serious doubts, substantiated by verifiable facts that the skilled person is not able to carry out the invention as claimed without undue burden. In order to establish insufficiency of disclosure in *inter partes* proceedings, the burden of proof as a general rule is

upon an opponent to establish, on the balance of probabilities, that a skilled person reading the patent, and using common general knowledge, would be unable to carry out the invention. This is so because in principle a presumption exists that a patent relates to an invention which is sufficiently disclosed.

32.2 The burden of proof can be reversed, however, in limited circumstances, depending on the strength of such a presumption in view of the information provided in the patent. When the patent does not contain detailed information of how to put the invention into practice, and hence, a weak presumption exists only that the invention is sufficiently disclosed, the opponent can discharge its burden by plausibly arguing that common general knowledge would not enable the skilled person to put this feature into practice. It is then up to the patent proprietor to prove the contrary, i.e. that the skilled person's common general knowledge would enable him to carry out the invention. The weight of arguments and evidence required to rebut this presumption depends on its strength. A strong presumption requires more substantial arguments and evidence than a weak one (see Case Law, II.C.9.).

33. Accordingly, the issue arises which party carries the burden of proof in the present case.

34. The appellant, who in *inter partes* proceedings at least initially carries the burden of proof, has not submitted any evidence in support of their arguments that the use of the scAAV9 vector according to claim 1 is not suitable for any of the therapeutic applications cited in claim 5. According to the case law this would be sufficient if, based on the information disclosed in the patent, only a weak presumption exists for the

scAAV9 vector's suitability for the claimed therapeutic applications. The board also does not disregard that the subject-matter claimed in claims 1 and 5 is broad. Nevertheless this is not *per se* a sufficient reason for discharging the actual burden on proving insufficiency.

35. It is uncontested that the patent provides sufficient information about the general availability of the scAAV9 vector, including its production. The working examples in the patent further demonstrate that an i.v., i.m., or i.p. administered scAAV9 vector in mice and cats delivers and expresses a reporter gene in spinal cord motor neurons (see Examples 3, 4 and 6). Although Example 3 only mentions that "*cells with a motor neuron-like phenotype*" show green fluorescent protein (GFP) expression in the spinal cord after an i.m. and i.p. injection of scAAV9 (see paragraph [0059], lines 28 to 30), the designation of these cells as spinal cord motor neurons is considered plausible in view of a double staining test in Example 6 that unambiguously demonstrates that the cells transfected in the spinal cord after an i.v. administration of scAAV9 are indeed motor neurons (see paragraph [0063], lines 37 to 41). Since the scAAV9-mediated delivery and expression of a reporter gene and of a therapeutic gene to spinal cord motor neurons are based on the same mechanisms, the board is satisfied that the patent discloses a concept which is generally suitable for the delivery of therapeutic genes to spinal cord motor neurons, and hence, the suitability of scAAV9 vectors for the claimed therapeutic applications. Example 6 of the patent further confirms this suitability by an *in vivo* experiment in an animal model for SMA, a specific motor neuron-associated disorder.

36. Since the patent discloses that peripherally administered scAAV9 vectors qualify as universal vehicles for transfecting spinal cord motor neurons with therapeutic genes, the board is convinced that the information provided in the patent puts the skilled person in a position to carry out the invention across the whole breadth of the claim.

37. Consequently, the board considers that the overall technical teaching provided in the patent - far from being a mere statement - amounts to a strong presumption of suitability, so that in the present situation the appellant carries the burden of proof. Moreover, since the appellant's submissions on insufficiency are not supported by evidence, i.e. verifiable facts, the burden of proof is not shifted to the respondents. Thus, in the absence of any evidence to the contrary, the board decides that the main request complies with Article 83 EPC.

Priority

38. The appellant submitted that the right of priority of the patent in suit was invalid, since the condition of Article 87 EPC was not met that the earlier application was the first application in respect of the same invention as the one to which the patent application relates. According to the appellant, document D2 was the first application for the claimed invention, which however was filed more than twelve months prior to the present patent application.

39. Since the validity of the priority right of the patent in suit has no effect on the status of documents D1 and D2 as being prior art under Article 54(3) EPC, the

board considered the issue of priority to be irrelevant in the present case, and left it unanswered.

Novelty

40. In a first line of argument, the appellant submitted that the subject-matter of claim 1 lacked novelty over documents D1 and D2. Since, as the appellant further submitted, the disclosure of both documents is "*very similar, if not identical*", in the following reference will be made to relevant passages in document D2 only.

40.1 Document D2 discloses the same scAAV9 vector, therapeutic genes, motor neuron disorders to be treated (e.g. SMA, amyotrophic lateral sclerosis (ALS), or Kennedy's disease), including the same mode of administration as referred to in claim 1 (see for example page 1, first paragraph; page 6, lines 1 to 3, 17 to 19; page 12, lines 3 to 10 and 15 to 23). Document D2 further discloses ubiquitous promoters, like CMV (see page 9, lines 17, 27 and 28), which as shown in the patent, are functional in motor neurons too. The board is therefore not convinced by the respondents' argument, that document D2 discloses a promoter subset that is different from the "*functional*" promoters cited in claim 1.

40.2 It was contested between the parties whether or not document D2 discloses motor neurons transfected by the scAAV9 vector. Example 4 on page 16 of document D2 discloses GFP expression in various brain cells, including neuronal cells in the "*enthorhinal cortex*", after i.p. and i.m. injections of scAAV9. Document D2 states in the last paragraph on page 16: "*GFP expression was further detected in blood vessels throughout the brain and the spinal cord. Unexpectedly,*

a strong GFP expression was also found in fibres of the corticospinal tract that cross at the cervical spinal cord level (Fig. 3E and 4C). Transduction of these fibres likely results from infection of upper motor neurons whose somas are located in the motor cortex and that also appeared GFP-immunopositive" (emphasis added).

40.3 The board agrees with the opposition division that the passage in document D2 indicated above does not directly and unambiguously disclose that motor neurons are transfected, since the term "*likely*" implies a probability only that the transfected cells are indeed motor neurons. According to established case law, subject-matter is directly and unambiguously derivable from a prior art document only, if it is "beyond doubt - not merely probable" (see Case Law, I.C.4.1).

40.4 The appellant further submitted that it was irrelevant whether or not document D2 disclosed transfected motor neurons, since the feature "*causing infection of spinal cord motor neurons and expression of the gene in spinal cord motor neurons*" (i.e. the "result-to-be-achieved" feature) in claim 1 was not a technical feature, but a mere *desideratum*. Infection of spinal cord motor neurons had to be achieved by the remaining features of the claim, all of which were disclosed in document D2. Therefore document D2 inherently disclosed the "result-to-be-achieved" feature. This case resembled the situations discussed in decisions T 433/14 (reasons 18 and 19) and T 406/06 (reasons 12.3) which both denied novelty of a second medical use claim, because a new technical effect alone did not result in a new clinical situation.

40.5 The board disagrees. Claim 1 is directed to an scAAV9 vector or a pseudotyped scAAV9 vector both comprising a therapeutic gene for use in a method for treating a motor neuron disorder. The claim *inter alia* specifies that the administration of these vectors cause *"infection of spinal cord motor neurons and expression of the gene in spinal cord motor neurons*". Accordingly, the claimed use of the scAAV9 vectors is defined by a functional feature that indicates the desired result to be achieved, namely the transfection of spinal cord motor neurons as a necessary prerequisite to achieve a therapeutic effect. According to the case law, functional features are technical features of the claim (see Case Law, II.A.3.4., II.C.7.2.). As set out above, document D2 does not disclose the transfection of motor neurons. Thus, the "result-to-be-achieved" feature in claim 1 relates to a **new technical effect**.

40.6 The scAAV9 vector-based therapeutic effect in treating motor neuron disorders as described in document D2 results from the transfection of cerebrospinal fluid (CSF) secreting cells, such as epithelial cells of the plexus choroids, and/or the ependyma, and/or a meningeal membrane (see e.g. page 2, lines 17 to 29). From there the vector-encoded therapeutic product is secreted into the CSF, where it acts from the external, i.e. indirectly, on disease-causing cells. Thus, document D2 teaches an **indirect** therapeutic effect on motor neurons. This is different from the technical effect relied upon in claim 1, i.e. the **direct** transfection of motor neurons.

40.7 The claimed direct transfection of motor neurons allows, for example, the treatment of disorders where the motor neurons are resistant to externally added therapeutic compounds, for example compounds secreted

into the CSF as disclosed in document D2. This in the board's opinion, allows for the treatment of a new subgroup of patients, namely of a patient group that can no longer be treated by the extracellular approach disclosed in document D2, and hence, identifies a **new clinical situation** (see T 836/01, reasons 8).

40.8 The appellant further argued that the treatment of SMA required that the gene coding for the survival of motor neuron protein (SMN) was located in the cell nucleus of motor neurons and hence, could not be supplemented extracellularly to these cells but required their direct transfection (see document D16, abstract). Since document D2 disclosed the treatment of SMA by using SMN as a therapeutic gene, the document inherently disclosed the transfection of motor neurons, since otherwise document D2 contained a non-enabling disclosure.

40.9 According to established case law, attaining a new technical effect (here: the direct transfection of motor neurons) is a functional technical feature of a claim that refers to a new use of a known substance. If that technical feature has not been previously made available to the public, then the claimed invention is novel, even though the technical effect may have inherently taken place in the course of carrying out what has previously been made available to the public (see G 2/88 and G 6/88, OJ EPO 1993, 93 and 114; Reasons point 9).

40.10 As set out above, document D2 is silent on directly transfecting motor neurons, and relates to the transfection of other target cells that, after secretion of a therapeutic product, have an indirect effect on cells involved in the development of

particular diseases, *inter alia*, SMA. The respondents did not dispute that a scAAV9-based therapy that did not directly transfect motor neurons was not suitable for treating SMA. In these circumstances document D2 provides a non-enabling disclosure for the treatment of SMA. Since for the reasons outlined above, the new mechanism of action creates a new clinical situation, the board concludes that the situation in the present case differs from that underlying the decisions T 433/14 and T 406/06.

40.11 In light of the considerations above, the board concludes that the subject-matter of claim 1 is novel over the disclosure of documents D1 and D2.

41. In a second line of argument, the appellant submitted that the subject-matter of claim 1 lacked novelty over document D3. In particular, the appellant argued that this document disclosed an AAV9 vector in individualised form, including pseudotyped and double-stranded versions thereof, for use in therapeutic applications that included motor neuron disorders, such as ALS and SMA (see paragraphs [0005], [0008], [0010], [0047], [0048], and [0124], claims 2, 10, 38 and 46). The AAV vectors were administered in document D3 by various routes including i.v. and i.m. to deliver therapeutic proteins and nucleic acids (see paragraphs [0118], [0120], and [0170]). Promoters for regulating gene expression were mentioned too (see paragraphs [0131] to [0133]).

41.1 The board disagrees. According to the case law regarding selection inventions in the field of chemistry, if two classes of starting substances were required to prepare end products, and examples of individual entities in each class were given in two

lists of some length, the substance resulting from the reaction of a specific pair from the two lists could be regarded for patent purposes as a selection and, hence, as new (see Case Law, I.C.6.2.1.b)). In analogy thereto, a selection of AAV vectors derived from two or more lists of individualised vectors of some length, which achieve a particular therapeutic effect, can be regarded as new.

41.2 Document D3 discloses long lists of AAV vector subtypes (see paragraph [0032]), AAV vector forms (see paragraph [0050]), disorders to be treated (see paragraph [0137]), and various modes of administration (see paragraph [0170]), without pointing to the combination of features referred to in claim 1.

41.3 Although paragraph [0124] of document D3 mentions the use of "*the virus vector of this invention*" for the treatment of "*disorders involving motor neurons*", such as ALS and SMA, by administering it to "*muscle tissue*", inter alia by i.m., from which it can "*migrate into neurons*", the paragraph is silent on AAV9 vectors, in particular scAAV9 or pseudotyped AAV9. However, to arrive at the subject-matter of claim 1, a selection from two different lists containing the specific AAV9 vector subtype (see paragraph [0032]), and a "*hybrid*" (i.e. pseudotyped) or "*duplexed*" (i.e. double-stranded self-complimentary (sc)) form (see paragraph [0050]) must be carried out, in the absence of any pointer in document D3 to do so. Moreover, paragraph [0124] of document D3 is silent on any transfection of motor neurons.

41.4 In light of the considerations above, the board concludes that the subject-matter of claim 1 is novel

over document D3 too. Accordingly, the main request meets the requirements of Article 54 EPC.

Inventive step

Closest prior art and technical problem

42. It was common ground between the parties that document D4 represented the closest prior art for the subject-matter of claim 1, and the board sees no reason to disagree.

43. Document D4 discloses a study using scAAV2 vectors in combination with mannitol to develop a method for delivering transgenes into the central nervous system (CNS) to obtain a wide dispersion of AAV-mediated transgene expression (see abstract, and page 912, column 1, fourth paragraph). The document mentions that mannitol disrupts the BBB for a short period of time, which allows a subsequently i.v. injected scAAV2 vector with a GFP reporter gene regulated by a CMV promoter to cross the BBB and to express GFP in brain cells, including "*various neurons, some glial cells and cells of the choroid plexus*". The cells are located *inter alia* in the spinal cord, wherein "*More cells were seen to express GFP in the areas with cerebral-spinal fluid contact, i.e., the cells surrounding the ventricle system. Only sporadic cells, in cerebral cortex and spinal cord, expressed GFP*" (see page 912, column 2, third paragraph, page 915, column 1, first paragraph, Figures 2 and 3). The treatment of CNS disorders is mentioned as a potential application of scAAV2 (see page 916, column 1, second paragraph). Document D4 is silent on motor neurons and associated diseases, including any scAAV2-transfected motor neurons.

44. The subject-matter of claim 1 differs from document D4 in that a scAAV9 vector is used instead of scAAV2 which does not require a prior treatment of patients with mannitol to deliver the vector into the CNS. Further, the use of scAAV9 vectors allows the infection and expression of therapeutic transgenes in motor neurons, and the treatment of motor neuron disorders.

45. In view of the effects associated with these distinguishing features the technical problem is defined as the provision of an improved AAV vector for use in the treatment of specific CNS disorders, in particular those associated with motor neurons.

46. The appellant submitted that this problem was not solved across the whole breadth of the claim.

47. However, since claim 1 is directed to a second medical use and achieving an infection of spinal cord motor neurons is a technical feature of the claim, in line with the established case law, the issue of whether the invention can be preformed across the whole breadth of the claim has to be assessed under sufficiency of disclosure. This issue has already been decided in the respondents' favour for the reasons set out above.

Obviousness

48. It remains to be assessed whether or not the skilled person, starting from the scAAV2 vector for use in treating CNS disorders as disclosed in document D4, and faced with the technical problem identified above, would have arrived at scAAV9 vectors for use in treating motor neuron disorders in an obvious manner.

49. The appellant argued that the selection of a scAAV9 vector for efficiently targeting the CNS was obvious for the skilled person in light of the teaching of document D5. This document disclosed the scAAV2 vector's drawbacks, and mentioned the advantages of scAAV9 vectors, for example, their robustness and ability to infect brain tissue after peripheral administration. Although document D5 was silent on transfected motor neurons, the skilled person had a reasonable expectation of success that scAAV9 vectors transfected these cells, due to their ability to infect neuronal cells, and their wide distribution within the CNS (see documents D6 and D7).

50. The board disagrees. Document D5 discloses a study that compares the suitability of pseudotyped AAV8 and AAV9 vectors as means for an *in vivo* gene transfer, since AAV2 vectors are "*suboptimal in many instances*" (see page 45, last paragraph and page 46, fourth paragraph). In view of scAAV2's known drawbacks, the board agrees with the appellant that the skilled person would have turned to document D5 to look for alternative vectors in the treatment of CNS disorders.

50.1 Although document D5 mentions that i.v. administered pseudotyped AAV8 and AAV9 vectors infect *inter alia* brain tissue with a "*considerable efficiency*", the expression of transgenes is indicated as "*poor*" or "*impaired*" (see page 5, second and fourth paragraph, page 6, second paragraph, Figure 4, Table 3). However, document D5 is silent on the CNS cell-types infected by AAV9, including their location, because whole tissue extracts are analysed (see page 8, third paragraph).

50.2 Document D5 further states on page 6, second paragraph that "*As we have demonstrated here, rAAV vector*

infection does not necessarily result in transduction even if substantial rAAV vector genomes are processed into ds circular monomers. In the present study, we found that many nonhepatic tissues other than the heart, pancreas, and skeletal muscle did not express a sufficient level of transgene products despite the presence of a substantial amount of ds circular monomer genomes. A reasonable explanation for this inconsistency is that the promoters we used were not active in these tissues. However, a rAAV2 vector carrying exactly the same AAV2-CMV-lacZ vector genome sequence as was used for producing our pseudotyped AAV8- or 9-CMV-lacZ vectors, when injected into murine kidney by intraparenchymal injection, expressed β-galactosidase in renal tubular cells around the injection site |25|. This suggests that the vector entry pathway into cells could determine vector genome activity. Although the mechanism underlying the impaired transgene expression from ds circular rAAV genomes has yet to be elucidated, a possibility exists that changing the promoter from that of CMV or EFlα to another ubiquitous or tissue-specific promoter might solve this issue" (emphasis added).

51. In the board's opinion, the skilled person could derive from this passage in document D5 that a promoter change may improve the transgene expression in various non-hepatic tissues, including the brain. However, this may not be sufficient, since other technical obstacles may occur. Since gene expression is necessarily required for the therapeutic use of pseudotyped AAV9 vectors, document D5 provides the skilled person with no more than a speculation how this fundamental problem might be solved (see page 6, second paragraph). Aside the technical problems associated with the use of AAV9 vectors in transfecting brain cells, document D5 does

neither disclose which cells in the brain have been infected by AVV9, nor provide any suggestions. Consequently, document D5 provides no pointer or motivation to the skilled person to use AAV9 vectors for treating motor neuron disorders. In such a situation, the question of whether or not the skilled person had a reasonable expectation of success, as likewise argued by the appellant, is irrelevant, and can be left unanswered.

52. The subject-matter of claim 1 is not obvious in light of the combined teaching of documents D4 and D5.

53. The appellant in a further line of argument submitted that the use of i.m. or i.p. administered scAAV9 vectors in the treatment of motor neuron disorders provided no improvement over the AAV2 vectors disclosed in document D4. This was so because it was known that AAV2 vectors administered in this manner were efficiently delivered to motor neurons by retrograde transport without the need to cross the BBB (see documents D8 and D9). A further substantiation was not submitted by the appellant.

54. The board sees no reason to arrive at a conclusion different from that outlined above, since document D4 is silent on AAV vectors that have been administered via the i.m. or the i.p. route. Consequently, the i.m. or i.p. embodiments of claim 1 are distinguished from document D4 not only by the use of the AAV9 vector, but also by this mode of administration. An i.p. or i.m. administration of the AAV9 vector is also not known from document D5. Accordingly, the reasons provided above equally apply for these two other embodiments of claim 1.

55. The main request therefore complies with the requirements of Article 56 EPC.

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 on the basis of claims 1 to 7 of the main request submitted at the oral proceedings on 12 March 2021 and a description to be adapted thereto.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated