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Datasheet for the decision of 12 December 2019

Case Number: T 0514/17 - 3.3.01

Application Number: 10763011.3

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Language of the proceedings: EN

Title of invention:
COMPOSITION AND METHOD FOR TREATING COGNITIVE IMPAIRMENTS IN DOWN SYNDROM SUBJECTS

Patent Proprietor:
Centre National de la Recherche Scientifique (C.N.R.S.)

Opponent:
F. Hoffmann-La Roche AG

Relevant legal provisions:
RPBA Art. 12(4), 13
EPC Art. 56

Keyword:

Late-filed facts - submitted with the statement of grounds of appeal
Inventive step - (no)
Late-filed auxiliary requests - justification for late filing (no)

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Case Number: T 0514/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 12 December 2019

Appellant: (Patent Proprietor)	Centre National de la Recherche Scientifique (C.N.R.S.) 3 rue Michel-Ange 75794 Paris Cedex 16 (FR)
Representative:	Lavoix 2, place d'Estienne d'Orves 75441 Paris Cedex 09 (FR)
Respondent: (Opponent)	F. Hoffmann-La Roche AG Grenzacherstrasse 124 4070 Basel (CH)
Representative:	Boult Wade Tennant LLP 5th Floor, Salisbury Square House 8, Salisbury Square London EC4Y 8AP (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 21 December 2016 revoking European patent No. 2470176 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chair	M. Blasi
Members:	R. Hauss
	J. Molina de Alba

Summary of Facts and Submissions

I. European patent No. 2 470 176 (the patent in suit) was granted with a set of 16 claims.

II. The patent in suit was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter did not involve an inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art and extended beyond the content of the application as filed.

III. The documents cited in the course of the opposition proceedings included the following:

D2: JPET 316(3), 1335-1345 (2006)

D6: Nature Neuroscience 10(4), 411-413 (April 2007) & supplementary online data: pp. 2 to 28

D7: Neuroscience Letters 433, 22-27 (2008)

D9: WO 01/38331 A1

D13: Pharmaceutical Research, 21(2), 201-230 (2004)

D14: AAPS PharmSci Tech, 10(1), 166-171 (March 2009)

D15: McKim, Strub: Dimethyl Sulfoxide USP, PhEur in Approved Pharmaceutical Products and Medical Devices, six pages, reprinted from Pharmaceutical Technology, May 2008

D16: Eur J Pharmacology 187, 201-207 (1990)

D17: Advances in Pharmacology 72, 1-36 (2015)

D23: Declaration of Prof. H. Möhler (filed with the opponent's letter of 22 September 2016)

D24: Schematic of $GABA_A$ receptor modulators accompanying D23

D28: JPET 298(3), 986-995 (2001)

IV. The decision under appeal is the decision of the opposition division revoking the patent, announced on 25 November 2016 and posted on 21 December 2016.

V. According to the decision under appeal, the subject-matter of claims 1 and 7 of the patent proprietor's main request met the requirement of sufficiency of disclosure but did not involve an inventive step.

- Starting from the technical teaching of prior-art documents D6 and/or D7, the objective technical problem to be solved was the provision of an alternative compound to enhance cognition in Down syndrome patients without the adverse effects of the known therapies of D6, i.e. without anxiogenic or convulsant side effects.

- Claims 1 and 7 of the main request proposed a compound having inverse agonist functional selectivity for $GABA_A$ receptors containing the α5 subunit, this compound being either the triazolophthalazine compound α5IA (see paragraph [0077] of the patent in suit) or an alternative compound - both identified in the claims by their chemical structures - or a salt thereof.

- However, in view of the teaching of document D6 combined with, *inter alia*, that of document D2 relating to compound α5IA, that solution would have been obvious to the person skilled in the art.

The subject-matter of the claims of auxiliary requests I and II, relating to compositions containing the inverse agonist and a specific surfactant and solvent, also lacked an inventive step.

VI. The patent proprietor (appellant) filed an appeal against that decision, basing its submissions in the statement setting out the grounds of appeal on the

claims of the main request and auxiliary requests I and II as considered in the decision under appeal.

With the statement setting out the grounds of appeal, the appellant submitted the following documents:

D30: Declaration and CV of Dr Fernandez (20 April 2017)

D31: Declaration and CV of Prof. Nutt (19 April 2017)

and documents DX1, DX2, DX3 and DX4 referenced in D30.

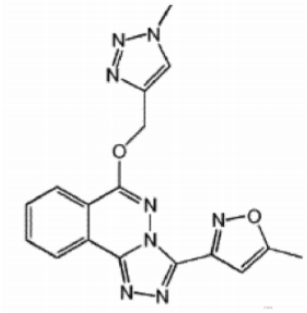
VII. With a letter dated 27 March 2019, the appellant submitted two amended sets of claims entitled "main request" and "auxiliary request I".

VIII. Complying with the requests of the parties, the board issued a summons to attend oral proceedings, accompanied by a preliminary opinion pursuant to Article 15(1) RPBA.

IX. With a letter dated 3 October 2019, the appellant filed a corrected set of claims of its main request.

X. Claim 1 of the **main request** reads as follows:

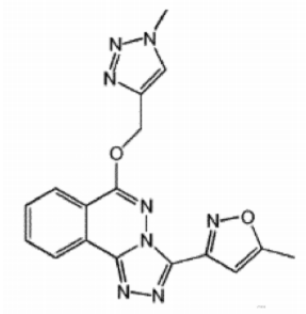
1. A compound having inverse agonist functional selectivity for GABAA [sic] *receptors containing the α5 subunit for use as a medicament for treating or lessening the severity of cognitive impairments in subjects suffering from Down syndrome, wherein the compound has the following structure:*



or pharmaceutically acceptable salt thereof.

Claim 1 of **auxiliary request I** reads as follows:

1. A pharmaceutical composition for treating or lessening the severity of cognitive impairments in subjects suffering from Down syndrome comprising an effective amount of a compound having inverse agonist functional selectivity for $GABA_A$ receptors containing the α5 subunit, in combination with a surfactant polyethoxylated castor oil as excipient and dimethyl sulfoxide as solvent, wherein the compound has the following structure:



or pharmaceutically acceptable salt thereof.

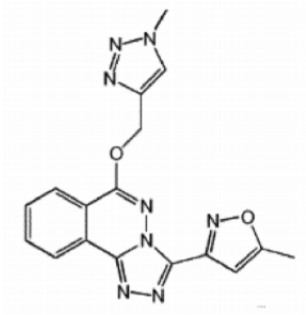
The structure depicted in these claims is that of the compound called "α5IA" or "α5-IA" in the patent in suit (Figure 1a) and document D2 (page 1336, column 2, second paragraph and Figure 1), its chemical name being 3-(5-Methylisoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-4-yl)methyl-oxy]-1,2,4-triazolo-[3,4-α]phthalazine.

XI. Oral proceedings before the board were held on 12 December 2019.

During the oral proceedings, the appellant withdrew the then pending auxiliary request II (see point VI above) and filed two amended sets of claims as auxiliary requests II and III.

XII. Claim 1 of **auxiliary request II** reads as follows (the differences in comparison with claim 1 of auxiliary request I are underlined):

1. A pharmaceutical composition for use in a method for treating or lessening the severity of cognitive impairments in subjects suffering from Down syndrome comprising an effective amount of a compound having inverse agonist functional selectivity for $GABA_A$ receptors containing the α5 subunit, in combination with a surfactant polyethoxylated castor oil as excipient and dimethyl sulfoxide as co-solvent with water, wherein the compound has the following structure:

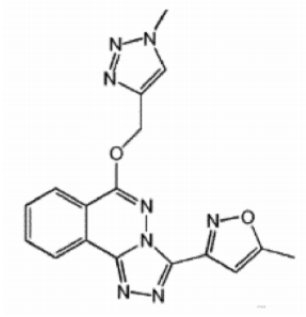


or pharmaceutically acceptable salt thereof, wherein the composition is a parenteral preparation.

Claim 1 of **auxiliary request III** reads as follows (the differences in comparison with claim 1 of auxiliary request I are underlined):

1. A pharmaceutical composition for use in a method for treating or lessening the severity of cognitive impairments in subjects suffering from Down syndrome comprising an effective amount of a compound having inverse agonist functional selectivity for $GABA_A$ receptors containing the α5 subunit, in combination with a surfactant polyethoxylated castor oil as excipient and

dimethyl sulfoxide as co-solvent with water, wherein the compound has the following structure:



or pharmaceutically acceptable salt thereof, wherein the composition is a parenteral preparation, whrein [sic] *the polyethoxylated castor oil represents between 10 and 20% and wherein dimethyl sulfoxide represents between 5 and 15%.*

XIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of:

- the claims of the main request, filed with the letter dated 3 October 2019,

or, in the alternative;

- the claims of auxiliary request I, filed with the letter dated 27 March 2019,

or, in the further alternative;

- the claims of auxiliary requests II or III, both filed at the oral proceedings before the board on 12 December 2019.

XIV. The respondent requested that the appeal be dismissed.

Within the purview of this request, the respondent furthermore requested that documents D30, D31, DX1, DX2, DX3 and DX4 be held inadmissible.

XV. The appellant's arguments may be summarised as follows.

Admittance of evidence

The declarations D30 (with supplementary documents DX1 to DX4) and D31 had been presented with the appellant's statement setting out the grounds of appeal, i.e. at the earliest possible occasion in the appeal proceedings. This was in reaction to certain points in the opposition division's inventive-step reasoning in the decision under appeal which in the appellant's view relied on an over-simplification. The issues concerned had first been brought up with documents D23 and D24, filed by the respondent only two months before the oral proceedings with the opposition division. This had not left sufficient time for the appellant to produce counter-declarations in time for the oral proceedings.

Inventive step - main request

The subject-matter of claim 1 differed from the disclosure of document D6 in the use of a different compound to treat cognitive impairments in Down syndrome.

Starting from the technical teaching of document D6, the objective technical problem (as set out by the appellant in the oral proceedings before the board) could be defined as identifying promising therapeutic candidate compounds to fight against intellectual disability in subjects suffering from Down syndrome, by experimentation in an animal model of Down syndrome, with restoration of memory deficit and improvement in memory performance of the Down syndrome test model evaluated in an object recognition assay.

This problem was solved by the subject-matter of claim 1, as corroborated by example 2 and Figure 12A of the patent in suit which used cognitively impaired

Ts65Dn mice as the animal model of Down syndrome. The data presented in Figure 12A showed that both TsD65Dn mice treated with compound α5IA and euploid (wild-type) mice treated with α5IA had above-normal object recognition performance as compared to wild-type mice receiving a placebo (see the patent in suit, paragraphs [0217] and [0085]).

The pharmacologically active compounds disclosed in document D6 did not attain such superior results (see also the patent in suit, paragraph [0087]).

Compound α5IA of claim 1 differed from the pharmacologically active compounds disclosed in document D6, both structurally and in its activity in relation to $GABA_A$ receptors. Hence, the person skilled in the art would not have expected it to show the same or even improved therapeutic efficacy. This view was supported by the declarations D30 and D31. Document D2, which related to compound α5IA, was silent regarding cognitive impairments in Down syndrome. Hence, the claimed subject-matter was not obvious having regard to the state of the art.

Inventive step - auxiliary request I

Claim 1 of auxiliary request I solved the further technical problem of providing a composition comprising compound α5IA with better solubility and without unwanted side effects. The scope of claim 1 was not unduly broad since three mandatory components were mentioned, and the term "solvent" implied that the composition was a liquid. The combined presence of a surfactant polyethoxylated castor oil as an excipient and dimethyl sulfoxide as a solvent in formulations of compound α5IA resulted in improved properties of the formulations. This was shown in example 4 of the patent in suit, which reported better solubilisation, a

smaller crystal size of the active agent and improved safety, reflected in a lower mortality of test animals. The documents of the prior art would not have prompted the person skilled in the art to employ these excipients to solve this technical problem.

Admittance of auxiliary requests II and III

These requests were filed in a legitimate attempt to address the objections raised against auxiliary request I. The amendments made restricted the claimed scope and did not raise new issues.

XVI. The respondent's arguments may be summarised as follows.

Admittance of evidence

The appellant had presented the two declarations D30 and D31 and supplementary documents DX1 to DX4 to further explain the differences between $GABA_A$ receptor antagonists and $GABA_A$ receptor inverse agonists. This issue had first been addressed by the respondent in the notice of opposition, and it was highly relevant to the appellant's arguments presented to the opposition division. The appellant's evidence should, therefore, have been submitted during the opposition proceedings. Moreover, the six new documents were not more relevant to the key issues of the case than the documents already on file.

Inventive step - main request

The animal study according to example 2 of the patent in suit had not been powered to detect whether the difference observed between placebo-treated and α5IA-treated euploid mice was real. Hence, the results of the object recognition test in example 2 of the patent in suit (paragraph [0217] and Figure 12A) did

not conclusively show a significant improvement in the cognition of Ts65Dn mice (the animal model of Down syndrome used in example 2) beyond a mere restoration of the cognitive deficit relative to euploid (wild-type) mice.

In any case, it could not simply be assumed that such an improvement, if it were attained, could be extrapolated across the entire scope of claim 1, which related to the treatment of humans rather than being restricted to a particular mouse model being studied in a specific assay covering only one aspect of cognitive impairment.

This assumption was furthermore disproved in the patent itself. According to the data of example 8 presumably presented in Figure 10, the memory performance of α5IA-treated Ts65Dn mice in the Morris water maze test was not elevated beyond a restoration of the deficit relative to untreated euploid mice.

As far as the state of the art was concerned, the data as presented in Figures 1d and 2b of D6 did not rule out the possibility that a restoration of object recognition memory of Ts65Dn mice to the level observed in treated wild-type mice might also be attained with the compounds of D6.

In any case, if a benefit in the novel object recognition test going beyond the mere restoration of a cognitive deficit could indeed be attained with compound α5IA, this would not have been considered surprising by a person skilled in the art. The efficacy of compound α5IA was based on its interaction with the $GABA_A$ receptor which resulted in a relief of the $GABA_A$-mediated inhibitory chloride current. This mechanism would occur in wild-type mice as well as in Ts65Dn mice. The Ts65Dn mice merely started from a higher level of inhibition. Thus, it would not have

been surprising that both wild-type and Ts65Dn mice should reach the same level of improved cognition when treated with compound α5IA.

In reality, since the appellant had failed to submit side-by-side comparative data relative to the closest prior art D6, there was no evidence of any improvement provided by the claimed medical use in comparison with the treatment disclosed in D6, except for the absence of (pro-)convulsant and anxiogenic side effects.

Starting from the technical teaching of document D6, the objective technical problem to be solved was therefore the provision of an alternative compound to treat cognitive impairment in subjects having Down syndrome without pro-convulsant or anxiogenic side effects.

According to document D6, $GABA_A$ receptor antagonists had successfully been tested in Ts65Dn mice as a means to reduce the excessive GABA-mediated inhibition in the hippocampus presumed to be the cause of their cognitive deficit. The antagonists of D6 were known as negative modulators of the $GABA_A$ receptor chloride current, and they were also known to have undesirable pro-convulsant and anxiogenic side effects. These undesirable properties of picrotoxin, bilobalide and pentylenetetrazole were mentioned in document D6. Thus, the person skilled in the art would have been prompted to look for alternative negative modulators of the $GABA_A$ receptor chloride current not having these side effects. Document D2 disclosed that compound α5IA met both criteria. The subject-matter of claim 1 was therefore obvious in light of the teaching of D6 combined with that of D2.

Inventive step - auxiliary request I

The presence of the mandatory surfactant and solvent mentioned in claim 1 had no interrelationship with the aspect of treating cognitive impairment in Down syndrome patients with compound α5IA. Thus the partial technical problem of providing favourable formulation properties must be considered in isolation. Example 4 did not render the alleged benefits credible across the entire scope claimed. Without evidence of any specific technical effect achieved by the presence of polyethoxylated castor oil and dimethyl sulfoxide (DMSO), their inclusion in the formulation must be regarded as an arbitrary variation. This variation was obvious since these agents were conventional additives known to be suitable for pharmaceutical compositions (see documents D13 to D16, especially D14: abstract).

Admittance of auxiliary requests II and III

The appellant presented auxiliary requests II and III to address an issue of scope. The opposition division had rejected former auxiliary requests I and II because of that same issue. The amended auxiliary requests should therefore have been presented at the outset of the appeal proceedings rather than in the afternoon of the day of the oral proceedings before the board. Moreover, the claims had been amended by adding features from the description combined with features from dependent claims. This amounted to the appellant presenting a fresh case.

Reasons for the Decision

1. Admissibility of the appeal

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

2. Admittance of evidence

2.1 Documents D30, D31 and DX1 to DX4 were filed for the first time with the statement setting out the grounds of appeal, in compliance with Article 12(1) and (2) RPBA, to provide additional explanations and background information.

2.2 The board saw no compelling reason in this case for holding documents D30, D31 and DX1 to DX4 inadmissible pursuant to Article 12(4) RPBA. In particular, the board was not convinced that the appellant should have filed these documents in the proceedings before the opposition division.

3. Inventive step - main request

Patent in suit

3.1 The patent in suit (see paragraphs [0001] and [0002]) seeks to provide a medicament for treating or reducing the severity of cognitive impairments in subjects suffering from Down syndrome.

3.2 While it had previously been suggested that the use of $GABA_A$ receptor antagonists might be of therapeutic benefit in this respect, it was also known that many $GABA_A$ receptor antagonists tended to cause seizures in animal models as well as in humans (see the patent

in suit, paragraph [0008] citing document D6, and paragraphs [0009], [0014] and [0074]).

3.3 Thus, there existed a need for a non-seizure-inducing therapeutic treatment of cognitive impairments, such as impairment in memory, learning capacity or both, in subjects suffering from Down syndrome (see the patent in suit, paragraph [0016]).

3.4 It had been reported that a certain category of $GABA_A$ receptor inverse agonists with affinity to the benzodiazepine binding site, in particular compound α5IA, had cognitive enhancement properties without (pro-)convulsant or anxiogenic side effects (see the patent in suit, paragraphs [0075] to [0078] citing, *inter alia*, document D2).

3.5 The treatment envisaged in claim 1 of the main request uses compound α5IA or one of its pharmaceutically acceptable salts as the pharmacologically active agent.

Starting point in the prior art

3.6 It was common ground that document D6 was a suitable starting point in the prior art for the assessment of inventive step.

3.7 Document D6 relates to pharmacotherapy for cognitive impairment, studied in a mouse model ("Ts65Dn") of Down syndrome.

The authors of D6 assessed whether a non-epileptic dose of the $GABA_A$ receptor antagonist picrotoxin (PTX) could improve object recognition memory of Ts65Dn mice. They also evaluated the efficacy of bilobalide (BB) and pentylenetetrazole (PTZ), two further $GABA_A$ receptor antagonists, in a novel object recognition test and in a modified spontaneous alternation task (see D6: page 411, bottom of column 1; page 411, column 2,

lines 10 to 13 and lines 29 to 32; supplementary page 26, lines 8 to 10).

D6 reports that chronic systemic treatment with noncompetitive $GABA_A$ receptor antagonists ameliorated cognitive deficits in Ts65Dn mice for a period of months extending beyond the window of drug treatment. Drug-mediated improvements in Ts65Dn learning and memory were accompanied by rescue of impaired long-term potentiation. According to D6, these results suggest that GABAergic over-inhibition contributes to intellectual disabilities associated with Down syndrome and that $GABA_A$ receptor antagonists may have clinical utility for this disorder (see D6: title, abstract, page 411 and paragraph bridging pages 412 and 413).

3.8 D6 also mentions that picrotoxin and pentylenetetrazole have pro-convulsant properties, which may limit their therapeutic value, and that $GABA_A$ antagonists were known to have an anxiogenic potential in humans and rodents (see D6: supplementary pages 21, 26 and 27).

3.9 Thus, document D6 relates to the same therapeutic indication as claim 1 of the main request. D6 does not mention compound α5IA or inverse agonists with affinity to the benzodiazepine binding site of the $GABA_A$ receptor.

Technical background

3.10 Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) $GABA_A$ receptors and (2) $GABA_B$ receptors (see D9: page 1, lines 10 to 14).

3.11 As set out in the patent in suit (paragraph [0071]) and in document D23 (passage bridging pages 1 and 2), $GABA_A$ receptors are ligand-gated ion channel receptors

located on nerve cells throughout the central nervous system (CNS). They have a hetero-pentameric structure with five subunits arranged around a chloride-ion-selective channel pore. There are different types of subunits (α1-6, β1-3, γ1-3, δ, ε, θ, π and ρ1-3). The majority of $GABA_A$ receptor subtypes are composed of two α subunits, two β subunits and one γ subunit.

3.12 The receptors have two extracellular binding sites for their natural ligand GABA, which mediates the receptor activity regulating the chloride current. GABA-induced chloride influx into postsynaptic neurons hyperpolarises the neurons, leading to inhibition of synaptic transmission. Thus, the chloride current mediated by $GABA_A$ receptors is the primary inhibitory current in the CNS (D23: page 4, third paragraph).

3.13 $GABA_A$ receptors possess a number of additional binding sites within the overall receptor structure (allosteric binding sites) through which different drugs can modulate the GABA-mediated chloride current (patent in suit: paragraph [0072]; D9: page 2, lines 13 to 14; D23: page 2, second paragraph). The modulatory activity may be positive, neutral or negative as a result of the stabilisation of different conformations of the receptor.

3.14 A well-known allosteric binding site is the benzodiazepine (BZ) binding site. Based on their modulatory effects on GABA-induced $GABA_A$ receptor activation, BZ site ligands may be agonists (positive allosteric modulators), inverse agonists (negative allosteric modulators) or antagonists (patent in suit: paragraph [0072]). BZ site agonists exert their effect by increasing the frequency of channel opening in the presence of GABA, resulting in increased chloride flux and decreased neuronal excitability. Conversely, BZ

site inverse agonists decrease the frequency of channel opening and thus increase neuronal excitability. BZ site antagonists have no effect of their own on GABAergic activity but inhibit the respective effects of BZ site agonists or inverse agonists by competition (see the patent in suit: paragraph [0073]; D23: page 3, second to fifth paragraphs; D2: page 1336, column 1, lines 37 to 47).

3.15 Compound α5IA has inverse agonist efficacy at the BZ site of $GABA_A$ receptors containing the α5 subunit. Thus, it has the effect of decreasing the chloride flux and hence increases neuronal excitability.

3.16 The antagonist compounds PTX, BB and PTZ mentioned in document D6 are not BZ site ligands and do not have the same modulatory effect as BZ site antagonists. Rather, they are ion channel binding site antagonists that bind to specific sites within the $GABA_A$ receptor ion channel pore and act as inhibitors of the GABA-induced channel current. Thus, these compounds have the effect of increasing synaptic excitatory activity (see D6: page 411, column 2, lines 10 to 13; supplementary page 2, point (c) and page 3, first paragraph; and supplementary page 26, lines 9 to 10; D23: page 4, first and last paragraphs).

Technical problem and solution

3.17 The subject-matter of claim 1 differs from the disclosure of document D6 in that the pharmaceutically active compound is α5IA or a salt of it (see point 3.9 above).

3.18 It was not in dispute that compound α5IA may have therapeutic utility for the desired medical indication without showing (pro-)convulsant or anxiogenic side-effects (see also example 2 and Figure 12A, example 8

and Figure 10, and paragraph [0190] of the patent in suit).

3.19 The appellant based its reasoning in favour of an inventive step on a further technical effect, namely the superior cognition-enhancing efficacy of α5IA resulting in above-normal cognitive performance (see also the patent in suit, paragraphs [0085] to [0087]).

In support of this argument, the appellant relied on the results reported for Ts65Dn mice and wild-type mice in the novel object recognition test according to example 2 and Figure 12A of the patent in suit, in comparison with certain test results reported in document D6 (see D6: page 412, Figures 1d and 2b).

Example 2 of the patent (see paragraph [0217] and Figure 12A) reports that both Ts65Dn mice and wild-type mice when treated with compound α5IA showed above-normal object recognition performance as compared to wild-type mice treated with placebo. According to a declaration by the author of D6 (see D30: page 3), the data presented in D6 do not support any statistically significant effect of PTX, BB or PTZ on wild-type mice.

3.20 The respondent argued, *inter alia*, that this alleged technical effect could not be taken into consideration, because it had not been rendered credible by a suitable side-by-side comparative test that it was attained with compound α5IA but not with the compounds mentioned in D6, nor that it was attained across the entire scope claimed.

3.21 The board concurs with the respondent's view. It has indeed not been rendered credible that the alleged technical effect of above-normal cognitive performance is attained by compound α5IA across the scope claimed

in comparison with the compounds disclosed in the starting point in the prior art, document D6.

3.22 While the patent in suit, in the examples, describes studies carried out with the Ts65Dn mouse model, it does not include comparative tests providing a direct comparison of the performance of compound α5IA with that of the compounds of D6 under identical test conditions.

3.23 Nor can the results obtained with compound α5IA according to example 2 and Figure 12A of the patent be compared directly to the results obtained with compounds PTX, BB and PTZ according to Figures 1d and 2b of D6 because the set-up of the animal studies was different. In particular, the novel object recognition task was carried out according to different protocols.

3.23.1 According to the patent in suit (see paragraphs [0213] and [0214]), 30 minutes after i.p. injection of the drug or placebo (single administration), mice were allowed to explore two identical objects for ten minutes. After a ten-minute retention interval spent in their home cage, mice were presented with one familiar and one novel object and allowed to explore for ten more minutes to test short-term recognition memory. Object exploration was defined as the orientation of the nose to the object at a distance of less than 6 cm.

3.23.2 According to document D6 (see supplementary pages 5 and 6), mice were exposed to two different objects during a 15-minute training session (known as the "complex" protocol), and a 15-minute testing session was conducted 24 hours after training, in which one object was replaced with a new item, to evaluate long-term memory (D6: supplementary page 11, lines 11 to 15). Exploration was any investigative behaviour (head orientation, sniffing occurring within 1 cm or

deliberate contact). Recognition testing was repeated weekly over several weeks while the mice received daily doses of drug or placebo (see D6: page 411, column 2).

3.24 In conclusion, no direct comparative data are available by which it can be verified that the effect of above-normal object recognition performance observed in mice is specific to compound α5IA (the feature distinguishing the claimed subject-matter from the disclosure of D6).

3.25 Moreover, the appellant based its argument on data obtained with mice (in a specific assay covering only one aspect of cognitive performance), whereas the scope of claim 1, by specifying "subjects suffering from Down syndrome", implicitly relates to the treatment of human subjects. The data in the patent obtained with the mouse model (examples 2 and 8, Figures 12A and 10) render it credible that the tested compound may have a therapeutic benefit in treating or lessening the severity of cognitive impairments in subjects suffering from Down syndrome. However, it would be speculative to conclude on the mere basis of example 2, with regard to the magnitude of the effect, that α5IA treatment will attain above-normal cognitive performance in human subjects - irrespective of the question whether the aim of therapy should not be the restoration of the cognitive deficit (according to claim 1, the purpose of the treatment is to address cognitive impairments) rather than above-normal performance.

3.26 For these reasons, the alleged technical effect of superior efficacy of compound α5IA resulting in above-normal cognitive performance of the treated subjects has not been rendered credible in comparison with the compounds of D6 and in relation to the subjects addressed in claim 1.

3.27 Indeed, the definition of claim 1 does not reflect in its technical features most of the criteria mentioned in the technical problem as formulated by the appellant. This would require carrying out an object recognition assay in an animal model of Down syndrome, with restoration of memory deficit and improvement in memory performance of the Down syndrome test model (see point XV on page 7 above).

Claim 1 does not mention any specific assay or animal model, nor the criterion of above-normal performance (improvement). As already mentioned, it is also implicit that the "subjects suffering from Down syndrome" according to claim 1 are human subjects.

These criteria cannot, therefore, enter into the formulation of the objective technical problem.

3.28 In view of these considerations, the objective technical problem to be solved starting from the technical teaching of document D6 is the provision of a compound for treating cognitive impairments in subjects having Down syndrome with an acceptable safety profile (or, as suggested by the respondent, without pro-convulsant or anxiogenic side effects).

3.29 It was common ground (see point 3.18 above) that this technical problem is solved by the subject-matter defined in claim 1.

Obviousness of the solution

3.30 Document D6 explains that Ts65Dn mice, like patients with Down syndrome, show deficits in tasks requiring explicit learning and memory (D6: page 411, column 1, first paragraph; supplementary page 11).

The authors of D6 reference earlier work carried out to characterise the Ts65Dn mice and note that excessive

GABA-mediated inhibition in these mice impairs the induction of long-term potentiation. Assuming that triplicated genes found in Ts65Dn mice shift the optimal balance of excitation and inhibition in the dentate gyrus and perhaps other brain regions to a state in which excessive inhibition obscures otherwise normal learning and memory, the authors of D6 theorise that reducing the inhibitory load in the Ts65Dn brain with $GABA_A$ receptor antagonists might rescue defective cognition (D6: page 411, column 1).

In the studies described in D6, Ts65Dn mice were accordingly treated with $GABA_A$ receptor antagonists (PTX, BB and PTZ) as a means of reducing the inhibitory chloride current.

The $GABA_A$ antagonists were indeed found to be capable of reversing the cognitive deficit of Ts65Dn mice, as measured at the behavioural level using the novel object recognition task (D6: Figures 1 and 2). The improvements were accompanied by rescue of impaired long-term potentiation (Figure 3), according to D6, the most prominent synaptic correlate of learning and memory in the hippocampus (D6: page 412, column 2, second paragraph).

The authors of D6 conclude that these results point to over-inhibition, in at least some brain regions, as a mechanism that reduces cognitive performance in a mouse model of Down syndrome (D6: paragraph bridging pages 412 and 413).

They also mention the anxiogenic potential of $GABA_A$ antagonists and point out the drawbacks of PTX and PTZ, which were known to exhibit pro-convulsant properties (D6: supplementary pages 21, 26 and 27).

3.31 Starting from the teaching of document D6 and faced with the objective technical problem (see point 3.28 above), the person skilled in the art would thus have had an incentive to look for further compounds capable of reducing the inhibitory chloride current mediated by $GABA_A$ receptors, while not exhibiting undesirable side effects such as anxiogenic or (pro-)convulsant activity.

3.32 Document D2 relates to compound α5IA, described as a BZ-site inverse agonist selective for α5-subunit-containing $GABA_A$ receptors. In contrast to BZ site agonists, inverse agonists were known to reduce the inhibitory chloride current (see point 3.14 above). This is also explicitly mentioned in D2 (page 1336, column 1, lines 37 ff). Compound α5IA is described as a negative modulator of $GABA_A$ subtypes having an α5 subunit (D2: page 1339, Figures 2 and 3A, Table 2). Based upon its preferential hippocampal location, it was hypothesised that a compound with inverse agonism selective for α5-containing $GABA_A$ receptors might enhance hippocampally mediated cognitive function (D2: page 1336, paragraph bridging columns 1 and 2).

D2 teaches that, although known nonselective BZ-site inverse agonists enhance cognition in nonhuman species, they are unsuitable for clinical use because of their anxiogenic, (pro-)convulsant or kindling effects. The authors of D2 surmise that different subunits of the $GABA_A$ receptors play a role with regard to these effects - accordingly, "(...) a compound possessing inverse agonism at the $GABA_A$ subtype responsible for the cognition-enhancing effects but devoid of efficacy at those subtypes associated with the anxiogenic and convulsant/proconvulsant properties would be of clinical utility" (D2: page 1336, column 1).

The finding of D2 is that α5IA is such a compound. According to D2, *in vitro* data suggesting that α5IA may enhance cognition without having (pro-)convulsant or anxiogenic effects were confirmed in *in vivo* models using wild-type rats and mice. D2 demonstrates the ability of α5IA to enhance the cognitive performance of rats in a Morris water maze assay (a hippocampus-dependent cognitive test) at doses that did not bring about pro-convulsant or anxiogenic effects (D2: Figures 5, 7 and 8). Moreover, α5IA did not impair motor performance (see D2: abstract and page 1336, column 2, first paragraph).

Based on these data, the authors of D2 conclude that compounds such as α5IA, having inverse agonist selectivity for the α5 subtype of $GABA_A$ receptors, may prove useful for the treatment of disorders with an associated cognitive dysfunction (see D2: abstract and page 1344, column 2, last paragraph).

3.33 The appellant maintained that the skilled person would not have taken document D2 into account. However, if they had, they would not have expected compound α5IA to be of therapeutic benefit against cognitive deficits associated with Down syndrome, much less to produce an effect going beyond the mere reversal of the cognitive deficit. In this context, the appellant presented several arguments.

(a) It was disputed that document D6 provided a general theory to the effect that pharmacological interventions reducing $GABA_A$-mediated inhibition may be an effective therapeutic strategy. This analysis of the document resulted from hindsight.

(b) Moreover, not even the compounds tested according to D6 had the same mechanism and site of action, as was known from document D28 (page 990, column 1;

page 992, column 2, second full paragraph;
page 993, column 2, first and second paragraphs).

(c) The person skilled in the art would not have regarded compounds having BZ site inverse agonist functional selectivity for $GABA_A$ receptors containing the α5 subunit as equivalent to the ion channel binding site antagonists discussed in document D6 since these agents produced different effects in the brain (see also the patent in suit, paragraph [0071], stating that each $GABA_A$ receptor subtype has a distinct pattern of expression within the mammalian brain).

For example, as shown in D6, PTX and PTZ reversed cognitive deficits in Ts65Dn mice but showed no effect in wild-type mice; whereas α5IA, according to D2, had pro-cognitive effects in wild-type mice and rats.

According to the declarations D30 and D31, ion-channel-binding $GABA_A$ antagonists such as PTX and PTZ would have been expected to produce different effects on $GABA_A$ receptor function and receptor occupation across the brain relative to BZ-site α5 inverse agonists (such as α5IA). PTX or PTZ acted on a broader population of $GABA_A$ receptor subtypes located in all areas of the brain, while the action of α5IA would be restricted to those receptors containing α5 subunits, which were mostly found in the hippocampus. Because of the difference in distribution, the two types of agent would have been expected to mobilise different parts of the brain and to produce overlapping but different physiological and behavioural effects. By activating all the $GABA_A$ receptor subtypes, PTX or PTZ would have a profound effect across all the brain. On the other hand, enhancements in activity

in one region could be cancelled out by enhancements in another region so there was no net effect.

D2 was published before D6, yet D6 did not mention compound α5IA as a possible equivalent to PTX and PTZ.

(d) Document D2 did not relate to Down syndrome, and the studies described in D2 did not use the Ts65Dn mouse model but wild-type rats and mice. Neither the presence of a pro-cognitive effect nor the absence of undesired side effects had been demonstrated in a model of Down syndrome in the prior art.

(e) The assay used in D2 ("Morris water maze" relating to spatial memory) was different from the assay of D6 ("novel object recognition task" relating to non-spatial memory), see the patent in suit, paragraphs [0191] to [0192].

3.34 These arguments are not convincing for the following reasons (the board's reasoning in this section 3.34 essentially takes up the respondent's counter-arguments to the appellant's points (a) to (e), as far as deemed relevant by the board, and the reasoning in point 7.4.3 of the decision under appeal).

(a) In view of the statements in D6 summarised above (see point 3.30), it is readily apparent that the authors of D6 were interested in testing $GABA_A$ receptor antagonists to reduce the inhibitory load, i.e. in their function as $GABA_A$ receptor modulators having negative efficacy.

(b) Document D28 reports on a study which investigated the mechanism and site of action of PTZ. The authors of D28 conclude that PTZ and PTX interact

with overlapping but distinct domains of the $GABA_A$ receptor (see D28: abstract). The findings of D28 do not alter the fact that both compounds are negative modulators of the inhibitory chloride current and that this was the activity deemed relevant, according to D6, to their therapeutic utility.

(c) Both D6 and D2 relate to compounds which were believed, due to their activity as negative modulators of the $GABA_A$-induced chloride current, to have pro-cognitive effects. This is the property and mechanism which would have been pertinent, in light of the technical teaching of D6, to the person skilled in the art seeking to solve the objective technical problem.

The authors of documents D30 and D31 submitted by the appellant are specialists in the field of $GABA_A$ receptor research. They can, therefore, not be equated with the person skilled in the art within the meaning of Article 56 EPC, who is rather to be understood as an experienced practitioner with average knowledge and abilities at the relevant date.

The experts were asked to provide an opinion regarding whether the person skilled in the art, at the filing date, would have considered $GABA_A$ antagonists to have the same effects as an α5 $GABA_A$ inverse agonist (such as α5IA) and anticipated that $GABA_A$ receptor antagonists, especially those that function as chloride ionophore blockers, would have the same effect or produce differences in receptor function and receptor occupation across the brain relative to α5IA.

In D30 and D31, the experts explained that, overall, these classes of compounds have different binding and activity profiles. This was already known and not in dispute in these appeal proceedings (see points 3.14 to 3.16 above).

Furthermore, since it remains unspecific regarding effects, the question put to the experts for comment is too general and therefore not relevant to the present objective technical problem. D6 explains (page 411, column 1; see also points 3.7 and 3.30 above) that the cognitive deficit in Ts65Dn mice results from excessive $GABA_A$ receptor-mediated inhibition in the region of the dentate gyrus/hippocampus. The $GABA_A$ antagonists PTX and PTZ can remedy this defect because they inhibit the excessive $GABA_A$ receptor current. Hence, the issue pertinent to inventive step is whether the skilled person would have thought that compound α5IA was capable of producing the same effect, i.e. the inhibition of the excessive $GABA_A$ receptor current in the dentate gyrus. The expert declarations do not really address this more specific issue.

Document D2 teaches the potential utility of α5IA for treating disorders associated with a cognitive deficit and characterises α5IA as a selective negative modulator of α5 $GABA_A$ receptors, i.e. as a compound capable of reducing the $GABA_A$-induced inhibitory chloride current in the hippocampus and a cognition enhancer. The person skilled in the art would have been encouraged by this explicit teaching to consult document D2 and consider compound α5IA.

The statement in D31 that "enhancements in activity in one region could be cancelled out by

enhancements in another region so there was no net effect" is not supported by any reference showing that this would have been part of the common general knowledge of the skilled person. Nor is it put into a theoretical context providing a conclusive argument for a technical prejudice and an inventive step. Hence, the board is not in a position to derive any further conclusions from the statement.

Since the animal studies according to D6 and D2 did not employ the same assays (D6: novel object recognition and spontaneous alternation task; D2: Morris water maze tested in rats - as also pointed out by the appellant, see point 3.33.(e) above), no conclusion can be drawn from the reported results regarding the comparative effects of the respective drugs in wild-type mice.

Contrary to the appellant's argument, the absence of any mention of α5IA in D6 is not proof that the person skilled in the art would not have considered α5IA as an equivalent therapeutic agent. D6 is concerned with studies of ion channel binding site $GABA_A$ antagonists (PTX, BB, PTZ). There is no reason why this document should discuss compound α5IA, which belongs to a different class of $GABA_A$ modulators binding at the BZ site.

(d) Document D2 does not explicitly mention Down syndrome and does not use the TsD65Dn mouse model. However, the general interest of D2 is to treat disorders associated with a cognitive deficit. The experiments of D2 were carried out with wild-type mice or rats, and the teaching of D2 is not particular to Alzheimer's disease (mentioned only once in the very last sentence of D2) any more than to Down syndrome.

It was well established that positive $GABA_A$ modulators impaired learning and memory processes and that negative modulators were pro-cognitive (see D7: page 25, column 2, second paragraph). This was also taught in D6 and D2. Based on this mechanism of action, the skilled person would have had no particular reason to assume that the desired pro-cognitive benefit would not be attained in Ts65Dn mice.

In addition to describing compound α5IA as a selective negative modulator of α5 $GABA_A$ receptors and as a cognition enhancer, D2 also discloses that α5IA had no (pro-)convulsant or anxiogenic activity at the doses required to enhance cognition.

This is expressly acknowledged in the patent in suit (paragraphs [0076] to [0078]) and the corresponding passage of the application as filed (paragraphs [0082] to [0084]), where D2 is cited as [ref 9].

The appellant did not provide substantiated reasons why the person skilled in the art should have expected that the pro-cognitive effects and the lack of side effects observed according to D2 would not occur in Ts65Dn mice. In particular, it was not shown that a technical prejudice existed against α5IA in this regard.

In contrast, prior-art document D9 (paragraph bridging pages 17 and 18 and page 2, line 13 to page 3, line 15) already describes other inverse agonists having functional selectivity for α5 $GABA_A$ receptors for use in enhancing cognition in conditions with an associated cognitive disorder, including Down syndrome.

Thus, there is no specific reason for the assumption that the skilled person consulting D2 would have been discouraged or deterred from considering compound α5IA for Ts65Dn mice or subjects suffering from Down syndrome.

(e) The authors of D2 performed an *in vivo* study in wild-type rats using a Morris water maze task as a hippocampus-dependent cognitive test (see D2: page 1341, column 2 and page 1336, column 2, first paragraph).

The appellant pointed out that this assay relates to spatial memory while the novel object recognition assay used according to D6 relates to non-spatial memory.

However, claim 1 of the main request does not contain any technical feature restricting the desired therapeutic benefit to improved object recognition or non-spatial aspects of learning and memory.

Both assays are recognised approaches to the study of aspects of cognitive performance, and improved performance in either assay is attributed, in the teaching of the prior art (in particular D6 and D2), to inhibition of the GABA-evoked current (see also the decision under appeal, point 7.4.3).

Document D7 (which during the proceedings before the opposition was considered as an alternative starting point for the assessment of inventive step) acknowledges the relevance of the findings of D6 to the treatment of cognitive deficits in the human Down syndrome population. On this basis, the study which is the subject of D7 was "designed to replicate the effect of the non-competitive $GABA_A$ antagonist PTZ on another experimental paradigm in

which Ts mice show defective learning: the Morris water maze" (see D7: page 23, column 1, lines 4 to 16).

Both assays were indeed used in the examples of the patent in suit to assess the cognitive abilities of Ts65Dn mice and wild-type mice (novel object recognition: example 2/Figure 12A; Morris water maze: example 8/Figure 10).

Thus, the appellant's argument that the experimental results reported in D2, due to the use of a different assay, would have been considered irrelevant to the solution of the technical problem must fail.

3.35 For these reasons, the person skilled in the art would have consulted document D2 and would also have derived from its teaching the suitability of compound α5IA for solving the objective technical problem.

3.36 As a consequence, the subject-matter of claim 1 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

4. Inventive step - auxiliary request I

4.1 Claim 1 of auxiliary request 1 relates to a composition rather than a compound but, like claim 1 of the main request, it is drafted as a purpose-related product claim in the format provided for in Article 54(5) EPC.

Starting point in the prior art

4.2 It was common ground that document D6 (see point 3.7 above) was also an appropriate starting point for the assessment of inventive step with regard to this claim.

4.3 D6 does not disclose formulations of compound α5IA. The cited prior-art documents which disclose compound α5IA, such as document D2, do not disclose it in association with polyethoxylated castor oil or DMSO.

Technical problem and solution

4.4 According to the appellant (see point XV above), the additional mandatory components mentioned in claim 1 of auxiliary request 1 (a surfactant polyethoxylated castor oil as an excipient and DMSO as a solvent) convey certain advantageous properties to the claimed composition, namely better solubilisation and smaller crystal size of the active agent and improved safety.

4.5 It was not in dispute that there is no interrelation between these alleged technical effects and the therapeutic indication as such.

As a consequence, two partial objective technical problems apply.

(i) The first technical problem is to provide a compound for treating cognitive impairments in subjects having Down syndrome with an acceptable safety profile (see point 3.28 above).

(ii) The second technical problem, as proposed by the appellant, is to provide a pharmaceutical composition comprising compound α5IA with better solubility and without unwanted side effects.

4.6 However, the board comes to the conclusion that this formulation of the second technical problem is not appropriate, since it has not been established that the alleged technical effects will credibly be attained across the entire scope claimed (see points 4.7 to 4.11 below).

4.7 The appellant based its argument in favour of inventive step on the observations reported in example 4 of the patent in suit (see paragraphs [0222] and [0223]).

4.8 Yet these observations relate to only two specific compositions, containing either α5IA/free base or α5IA/HCl salt, both formulated in the same vehicle (DMSO/Cremophor EL®/water - 10:15:75). Cremophor EL® is PEG-35 castor oil, i.e. a specific embodiment of polyethoxylated castor oil. The compositions were administered to the test animals intra-peritoneally.

Still according to example 4, the two compositions conforming to claim 1 were compared to one specific formulation of α5IA/free base in a different vehicle (PEG-300/NaCl 9% - 7:3).

This comparative composition was more viscous, with a larger crystal size of the active compound, and it was found to impair motor skills and result in a death rate/placebo mortality of 10% of injected mice, whereas these unfavourable effects were not observed with the two compositions according to claim 1.

4.9 As pointed out by the respondent, the results reported in example 4 are not persuasive, for the following reasons.

4.9.1 The description of the comparative test does not mention how many test animals were used, in how many animals the adverse events occurred and whether the results reported with regard to adverse events (impaired motor skills and placebo mortality) have statistical significance.

Also, it is not made clear in paragraph [0223] of the patent whether the "death rate" of 10% reported for the comparative composition was observed for the formulation containing α5IA (as suggested by the

passage on page 32, lines 16 to 21) or for the placebo vehicle (page 32, table, line 39 specifying "placebo mortality"). In the latter case, the adverse effect would have been unrelated to compound α5IA.

As a consequence, the relevance of the reported test results cannot be established on the basis of the available information.

4.9.2 The samples tested are not sufficiently representative of the scope claimed, nor of the scope outside claim 1.

(a) The information provided in example 4 does not permit the conclusion to be drawn that any physical (crystal size, solubilisation) or pharmacological properties observed for the specific sample formulations containing DMSO and Cremophor EL® can be extrapolated to all compositions and modes of administration within the scope of claim 1.

The definition of claim 1 employs the term "comprising" and does not provide quantitative limitations. Also, the term "solvent" does not necessarily imply that DMSO must be the main component of the composition. Thus, claim 1 encompasses compositions of α5IA or any salt of it, in combination with a large scope of possible concentrations and ratios of polyethoxylated castor oil and DMSO, in the presence or absence of further excipients or solvents, and formulated for any route of administration. Dependent claim 3, for instance, specifically mentions not only suspensions but also liquid solutions (in which, by definition, crystal size would not play a role) and gel capsules. The sample formulations and route of administration tested in example 4 are not representative of that full scope.

(b) Moreover, only one specific comparative composition was tested. The results obtained cannot necessarily be extrapolated to other compositions of α5IA not falling within the definition of claim 1 and conceived for any mode of administration.

Example 4 does not explain how the "comparative" vehicle was chosen, or why it should be representative of all or most other plausible vehicles outside the scope of claim 1.

According to paragraph [0126] of the patent in suit, a vehicle "based on" 70% PEG-300 and 30% water was known (the literature references [12] and [13] mentioned in this context refer to documents which are not part of these appeal proceedings). However, it is not certain if this vehicle is identical to (PEG-300/NaCl 9% - 7:3) used according to example 4 of the patent.

By contrast, the vehicle used for compound α5IA according to prior-art document D2 (also cited in the patent in suit as reference [9], see paragraph [0077]), was completely different (0.5% methyl cellulose, see D2: page 1338, column 1, bottom paragraph). D2 does not report increased mortality of test animals.

4.10 The respondent's arguments which cast doubt on the probative value of example 4 are not mere speculation. They address, specifically and plausibly, the evident shortcomings of example 4, namely the experimental set-up with a very limited spread of samples and the lack of information regarding the statistical significance of the reported data. Contrary to the appellant's view, it was thus not incumbent on the respondent to provide further experimental data in support of its objections. Rather, it was for the

appellant to substantiate its own presumption that the alleged technical effects were attainable across the entire scope claimed.

4.11 In view of the considerations under point 4.9, the appellant has not rendered it credible that the claimed compositions, across the entire scope claimed, have specific properties (in particular regarding crystal size, solubilisation and adverse effects) which set them apart from other pharmaceutically acceptable compositions containing compound α5IA or a salt of it.

4.12 As a consequence, the second partial technical problem has to be reformulated. Starting from the teaching of document D6, the appropriate objective technical problem is thus:

(i) to provide a compound for treating cognitive impairments in subjects having Down syndrome with an acceptable safety profile;

(ii) and to formulate a pharmaceutical composition of this active compound.

4.13 Technical problem (ii) is solved by providing a composition of α5IA containing DMSO and surfactant polyethoxylated castor oil.

Obviousness of the solution

4.14 As far as technical problem (i) relating to compound α5IA and its presumed therapeutic activity is concerned, the board's assessment and negative conclusion on inventive step are presented in section 3 above. The following remarks under points 4.15 to 4.17 address the (separate) technical problem (ii).

4.15 DMSO and polyethoxylated castor oil were well known as a solvent and a surfactant (solubilising excipients)

for pharmaceutical formulations (see D13: Table II; D15). They were also known to be used in combination (see DMSO/ethanol/polyethoxylated castor oil disclosed in D14: Abstract; 5% DMSO/5% Cremophor® EL /water in D16: page 202, point 2.3, general teaching of the combination DMSO / polyethoxylated castor oil in D15: Table II).

4.16 Combining compound α5IA with a conventional pharmaceutical solubilising system to provide a pharmaceutical composition of α5IA would not have required inventive skill.

4.17 Contrary to the appellant's view, it is not crucial that the prior-art disclosures of the excipient/solvent combination do not specifically mention its suitability for compound α5IA. The appellant has brought forward no reason why the person skilled in the art should have been prejudiced against considering a DMSO/poly-ethoxylated castor oil system.

4.18 For these reasons, the subject-matter of claim 1 of auxiliary request I does not involve an inventive step within the meaning of Article 56 EPC.

5. Admittance of auxiliary requests II and III

5.1 The independent claims of auxiliary requests II and III (see point XII above) restrict the pharmaceutical compositions to parenteral preparations and add water as an additional mandatory component. Claim 1 of auxiliary request III furthermore indicates concentration ranges for the mandatory surfactant and co-solvent which include the concentrations used in example 4 of the patent in suit.

5.2 These amendments seek to address the objection that the alleged technical effects - improved solubilisation of compound α5IA and improved safety of the compositions - would not be attained across the entire scope claimed.

5.3 The board rejecting auxiliary request I because of this objection (see section 4 above) cannot be regarded as a surprising procedural development that would have justified the filing of additional claim requests. Former auxiliary request I was rejected in the proceedings before the opposition division for the very same reason (see the decision under appeal, Reasons 11.2), and the objection was taken up again in the respondent's reply to the statement setting out the grounds of appeal (see the respondent's letter dated 18 September 2017, page 23, lines 29 to 35). The issue was therefore not new and the appellant must have been aware of the possibility that the board might agree with the respondent's objection.

5.4 Auxiliary requests II and III attempting to address this objection should therefore have been filed at an earlier stage rather than at the very advanced stage of oral proceedings before the board.

5.5 Furthermore, the amendments made in the claims of auxiliary requests II and III introduced features taken from the description, and the respondent could not reasonably have been expected to deal with subject-matter so modified at the oral proceedings.

5.6 For this reason, the board, exercising its discretion pursuant to Article 13(1) and (3) RPBA, decided not to admit auxiliary requests II and III into the proceedings.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

M. Schalow M. Blasi

Decision electronically authenticated