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Datasheet for the decision of 21 April 2016

Case Number: T 1872/14 - 3.3.01

Application Number: 08100474.9

Publication Number: 1920764

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Language of the proceedings: EN

Title of invention:
Fluprostenol isopropyl ester for use in the treatment of glaucoma and ocular hypertension

Patent Proprietor:
Alcon Research, Ltd.

Opponents:
Actavis Group Ptc Ehf
RAFARM S.A.
Generics [UK] Limited
Pohlman, Sandra M.
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STADA Arzneimittel AG
LAMDA PHARMACEUTICALS S.A.

Headword:
Travoprost/ALCON

Relevant legal provisions:
EPC Art. 84, 101(3), 100(c), 123(2), 123(3), 87(1), 89, 100(b), 54(2), 54(3), 54(5), 56
EPC 1973 Art. 102(3), 54(4)
RPBA Art. 12(2), 12(4)

Keyword:
Undisclosed disclaimer, allowable in the light of G 1/03, G 2/10, G 3/14
Main Request: Inventive step (no) - obvious alternative suggested in closest prior art
Auxiliary request 1: Inventive step (yes) - unexpected improvement credible within claimed scope

Decisions cited:
G 0003/14, G 0002/10, G 0001/03, G 0002/98, G 0001/93, G 0005/83, T 0181/82, T 0197/86, T 0967/97, T 0942/98, T 0451/99, T 0507/99, T 0609/02, T 0777/08, T 1364/08, T 1570/09, T 1850/10, T 1222/11, T 1760/11

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Case Number: T 1872/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 21 April 2016

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Representative:	Roukounas, Dimitrios Dietlindenstraße 18 80802 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 9 September 2014 concerning maintenance of the European Patent No. 1920764 in amended form.**

Composition of the Board:

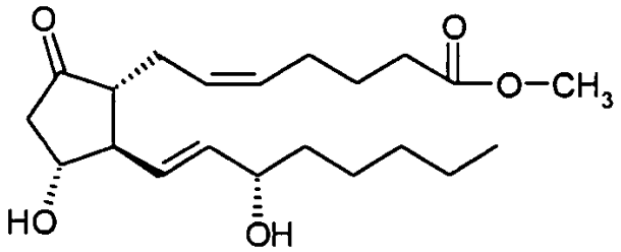
Chairman	A. Lindner
Members:	L. Seymour
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 920 764 was filed as patent application No. 08 100 474.9 (document (34)). It is a divisional application of the parent application No. 04 077 870.6, which in turn is a divisional application of the root application No. 94 305 752.1 (document (35)), filed on 3 August 1994 and claiming priority of 3 August 1993 from the US patent application No. 08/101,598 (document (36)).

II. Independent claim 1 of the patent in suit as granted reads as follows (emphasis added):

"1. A topical ophthalmic composition for use in the treatment of glaucoma and ocular hypertension comprising a therapeutically effective amount of fluprostenol isopropyl ester, **with the proviso that** the composition does not include the following composition: compound (F) 0.0001 wt%, fluprostenol isopropyl ester 0.001 wt%, benzalkonium chloride 0.01 wt%, dextran 70 0.1 wt%, disodium edetate 0.05 wt%, potassium chloride 0.12 wt%, sodium chloride 0.77 wt%, hydroxypropyl methyl cellulose 0.3 wt%, HCl and/or NaOH to adjust pH, and purified water q.s. to 100%, wherein compound (F) has the following formula:



"

Independent claim 6 reads as follows (emphasis added; the definition of the excluded composition is identical

to that of claim 1 and has been omitted for reasons of conciseness):

"Use of fluprostenol isopropyl ester for the manufacture of a medicament for topical application for the treatment of glaucoma and ocular hypertension, **with the proviso that** the medicament does not include the following composition: ..."

III. In addition to those appearing in above point I, the following documents, cited during the opposition/appeal proceedings, are referred to below:

(1) EP-A-0 603 800

(1a) US 07/993,586

(3) EP-A-0 364 417

(4) D F Woodward et al., J. Lipid Mediators, 1993, 6(1/03), 545 - 553

(10) G S Ang et al., Brit. J. Ophthalmol., 2008, 92, 1129 - 1133

(11) Y Nomura et al., Clin. Ophthalmol., 2010, 4, 643 - 647

(13) The Merck Index, 11th Edition, 1989, item 4121

(14) C Liljebris et al., Bioorg. Med. Chem. Lett., 1993, 3(2), 241 - 244

(15) L Z Bito, Exp. Eye Res., 1984, 38, 181 - 194

(18) A Alm, J Villusen, in Ocular Effects of

Prostaglandins and Other Eicosanoids,
1989 Alan R Liss, Inc., 447 - 458

(20) K S Crawford, P L Kaufman, Invest. Ophth. Vis. Sci., 1991, 32(3), 510 - 519

(23) J Stjernschantz, B Resul, Drugs Fut., 1992, 17(8), 691 – 704

(27) B Resul et al., J. Med. Chem., 1993, 36(2), 243 - 248

(30) L Z Bito et al., J. Lipid Mediators, 1993, 6(1/03), 535 - 543

(31) N Pfeiffer, Klin. Monatsbl. Augenh., 1993, 203, 1 - 9

(37) Supplement to WHO Chronicle, 1975, 29(3), 1, 12

(42) D Binder et al., Prostaglandins, 1974, 6(1), 87 - 90

(46) WO 90/02553

(54) Travatan, Summary of Product Characteristics, Annex 1, European Medicines Agency, 1 - 24

(58) M R Hellberg et al., J. Ocul. Pharmacol. Th., 2001, 17(5), 421 - 432

(59) E O MacKay et al., Vet. Ophthalmol., 2012, 15, Supplement 1, 31 - 35

(60) M Karmel, Eyenet, August 2012, 27 - 29

(66) Experimental report, Project Pharmaceutics GmbH, dated 17 December 2013, submitted by appellant opponent 4 with letter dated 28 March 2014

(67) US-A-5 631 287

(70) Declaration of David H. Sherman, Ph.D., dated 23 May 2013, submitted by appellant opponent 4 with letter dated 28 March 2014

(71) L Z Bito et al., in Ocular Effects of Prostaglandins and Other Eicosanoids, 1989 Alan R Liss, Inc., 349 - 368

(73) WO 93/00329

(74) L Z Bito, Ophthalmol. Clin. North Am., 1989, 2(1), 65 - 76

(111) Statement, Project Pharmaceutics GmbH, dated 5 June 2014, submitted by appellant opponent 4 with letter dated 10 June 2014

(112) G H C Bodenhausen, Guide to the application of the Paris Convention for the Protection of Industrial Property", WIPO Publication, reprinted 2007, pages 1 - 60

(117) J Shin et al., J. Ocul. Pharmacol. Th., 2014, 30 (10), 803 - 809

(118) S Mizoue et al., Clin. Ophthalmol., 2014, 8, 347 - 354

IV. The appeals lie from the interlocutory decision of the opposition division maintaining the patent in amended

form based on auxiliary request 4, previously filed as auxiliary request 2B with letter of 25 April 2014.

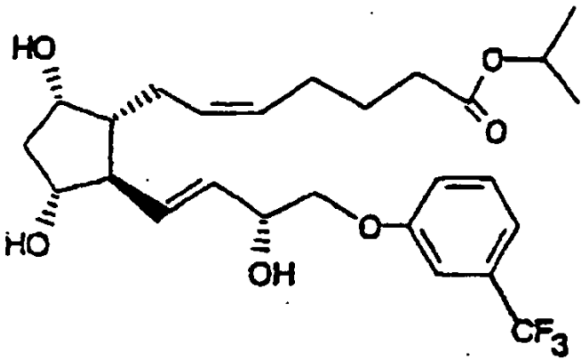
The higher ranking requests were rejected: the main request and auxiliary requests 1 and 2, previously filed with letter of 25 April 2014 as main request A, main request B and auxiliary request 1A, respectively, were considered to contain added matter, pursuant to Article 100(c) EPC, owing to the introduction of an unallowable disclaimer. Auxiliary request 3, previously filed with letter of 25 April 2014 as auxiliary request 2A, was not admitted, since the addition of new dependent claims was found to contravene Rule 80 EPC.

V. The patentee, and opponents 1 and 3 to 6 each lodged an appeal against this decision.

VI. With its reply dated 8 June 2015 to the appellant opponents' statements of grounds of appeal, the appellant patentee *inter alia* filed an auxiliary request 17, previously filed as main request B' with letter of 25 April 2014, and an auxiliary request 18, previously filed as auxiliary request 1A' with letter of 25 April 2014.

Auxiliary request 17 consisted of claims 1 and 2, corresponding to claims 1 and 6 as granted, respectively (cf. above point II), with the insertion of the following passage at the end of each claim:

"and wherein fluprostenol isopropyl ester has the following formula:



"

Auxiliary request 18 differed from auxiliary request 17 in the insertion of an additional feature relating to dosage ranges, such that the portion of the claims preceding the provisos read as follows (emphasis added):

"1. A topical ophthalmic composition for use in the treatment of glaucoma and ocular hypertension comprising a therapeutically effective amount of fluprostenol isopropyl ester, **wherein the dosage range for topical administration of fluprostenol isopropyl ester is between 0.05 and 10 micrograms per eye**, ...

2. Use of fluprostenol isopropyl ester for the manufacture of a medicament for topical application **of a dose of fluprostenol isopropyl ester between 0.05 and 10 micrograms per eye** for the treatment of glaucoma and ocular hypertension, ..."

VII. Oral proceedings were held before the board from 19 to 21 April 2016.

During the course of the oral proceedings, the appellant patentee renumbered its auxiliary requests 17 and 18 filed with letter of 8 June 2015 (cf. above point VI) as its main request and auxiliary request 1,

respectively. All other claim requests on file were withdrawn.

VIII. The appellant opponents' arguments, insofar as they are relevant to the present decision, may be summarised as follows:

It was argued that the appellant patentee's main request and auxiliary request 1 should not be admitted into the appeal proceedings, since these requests had first been filed during the opposition procedure, but had not been pursued with the appellant patentee's statement of grounds of appeal.

With respect to the main request, the appellant opponents raised a number of objections under Article 84 EPC: The disclaimer in the claims recited the unclear feature "HCl and/or NaOH to adjust pH". Since the pH to which the composition should be adjusted was not specified, this feature led to ambiguity regarding the exact values intended. Although this feature had been present in the claims as granted, it nevertheless gave rise to an inadmissible disclaimer in view of the requirement laid down in point II.4 of the Headnote of decision G 1/03. Moreover, it was submitted, with reference to decision T 1570/09, that the presence in a single request of a purpose-limited product claim and a Swiss-type claim led to further lack of clarity. Finally, it was unclear whether the formula introduced, defining "fluprostenol isopropyl ester" (FIE) as designating the (+)-enantiomer, referred only to said term in the disclaimer, or also to the preceding occurrences thereof.

This last amendment further gave rise to an objection under Article 123(3) EPC. With particular reference to

documents (13), (37) and (42), it was argued that, in the claims as granted, the term FIE was to be read as encompassing the racemate. In contrast, through the amendment now introduced into the claims of the main request, the disclaimer had been restricted to a composition of the (+)-enantiomer. However, the same was not true of the portion of claim 1 defined in positive terms. In view of the "comprising" language used therein, the composition defined was open to the presence of any further components, and the presence of a racemate was therefore not excluded. Since the disclaimer had been shrunk, but not the remaining part of the claim, this amendment led to an extension of the claimed scope. An additional objection was raised based on the premise that the term FIE in the claims as granted exclusively designated the racemate, whereas the compositions according to the claims now also encompassed the (+)-enantiomer.

Regarding their objections pursuant to Article 100(c) EPC, the appellant opponents endorsed the approach in the decision under appeal, based on the reasoning in decision T 1222/11 (points 6 and 12). As the undisclosed disclaimer had the purpose of restoring novelty over document (1), it was first necessary, in view of the criteria developed in G 1/03, to determine whether this document was prior art under Article 54(2) or 54(3) EPC. As had correctly been established in the decision under appeal, the appellant patentee's earlier-filed priority document (1a) related to the same invention as the present priority document (36). Consequently, the latter was not the first application within the meaning of Article 87(1) EPC, and the priority claim for the combination of features defined in positive terms in the main request was not valid, at least to the extent that it related to the subject-

matter of Example E of documents (1a) and (1). Document (1) therefore constituted prior art pursuant to Article 54(2) EPC. Since it was not an accidental anticipation, the introduction of the disclaimer in the present claims, directed to said Example E, was not allowable in view of the criteria set out in decision G 1/03, and resulted in added matter, contrary to Article 100(c) EPC.

This analysis in the decision under appeal could not be faulted. As stated in the cited decision T 1222/11, with reference to decision G 1/03, "the introduction during the prosecution of a European patent application of an allowable disclaimer does not change the identity of the invention within the meaning of Article 87(1) EPC". It followed that the correct starting point for assessing the validity of the priority claim must indeed be based on the subject-matter claimed prior to the introduction of the disclaimer. The appellant patentee's position based on decision G 2/98 made the assumption that there was a priority right to claim, which was not the case here, since document (36) could not be acknowledged to represent the first application.

It was not possible to repair an invalid priority claim by disclaiming subject-matter disclosed in a first application. This would jeopardise the legal purpose of Article 87(1) EPC in preventing chained priorities. Allowing the patentee to rectify its mistakes in this manner would result in an effective extension of priority claim beyond the priority year, contrary to Article 87 EPC and the Paris Convention. The desire for legal certainty for third parties should outweigh any interest of the patentee to overcome potential problems arising through self-collision. After all, the appellant patentee would have been aware of his own

prior art and could therefore have anticipated and circumvented such issues prior to filing.

Contrary to the appellant patentee's submissions, the Headnote II.1 of decision G 1/03 did indeed provide an exhaustive list of all situations in which an undisclosed disclaimer could be allowed, and this did not include "Article 87 disclaimers". Moreover, even if said list were to be seen as non-exhaustive, there could be no justification for extending it to include disclaimers that would be contrary to provisions of both the EPC and the Paris Convention.

In any case, the disclaimer in question was not allowable, since it failed to fulfil the requirement of decision G 1/03 that it should restore novelty over document (1). Contrary to the assertions of the appellant patentee, the disclosure of document (1) with respect to FIE was not limited to the specific disclaimed example. In particular, the sentence on page 6, lines 26 to 27, of document (1) provided a clear link establishing FIE as a representative, preferred compound of formula (I) in the context of the more general disclosure, including its combination with compounds of formula (II). Moreover, in order to reach the conclusion on page 2, lines 34 to 39, and on page 5, lines 40 to 43, the respective individual compounds exemplified, including FIE, must also have been tested. This therefore amounted to a disclosure of the use of FIE in the monotherapy of glaucoma and ocular hypertension. In addition, from page 5, lines 38, 39, 44 and 45, it could be calculated that the dosages foreseen for the component of formula (II) encompassed negligible amounts, such that the component of formula (I), including FIE, would then effectively be present as the sole active ingredient.

On the other hand, if the disclosure of document (1) with respect to FIE was to be seen as limited to Example E, the disclaimer would also not be allowable: In this example, the pH of the composition was not specified. From the description of document (1), it was evident that the pH range to be applied in all examples, including composition E, must be between 4.5 and 8.0. The absence of said limitation in the present disclaimer meant that it removed more than was necessary, in violation of Article 100(c) EPC.

In addition, it was submitted that, in accordance with the patent in suit, the only pH that had specifically been disclosed in connection with FIE was the pH range of 7.3 to 7.4 in Formulation 4, and this was therefore the range applicable to the disclaimer. In contrast, as had previously been explained, a broader range of "between 4.5 to 8.0" was disclosed for the compositions of document (1). These upper and lower limits were therefore to be considered as novelty destroying for the subject-matter now claimed.

Regarding Article 100(b) EPC, the appellant opponents submitted that the invention was insufficiently disclosed as it could not be carried out over the entire claimed scope. The second medical use claims at issue were not limited to a particular type of glaucoma. An entire medical indication falling under this generic term, namely, normal tension glaucoma (NTG), was not treatable with the claimed composition. In particular, according to document (10), FIE (travoprost) did not lower intraocular pressure (IOP) by more than the required 30% in the majority of treated patients, and it could also not be predicted which patients, if any, would benefit from such a

treatment, as was also confirmed in document (60). Furthermore, it was disclosed in document (11) that a reduction of IOP alone would not be sufficient for the management of NTG. The cited passages from documents (117) and (118) could not help, since they merely disclosed IOP lowering ability, which, according to the appellant patentee's own statements, could not be equated with treatment of glaucoma.

Similarly, the patent in suit relied solely on IOP data in order to support its claim to treating glaucoma and ocular hypertension. If both IOP lowering activity and tolerability were to be seen as being important for clinical use, as argued by the appellant patentee, then both should have been tested simultaneously on the same animals. Moreover, the tests had been performed on monkeys rather than humans, and the monkeys were not diseased. Therefore, contrary to the principles set out in decision T 609/02, insufficient evidence had been provided in the patent in suit that FIE was suitable for the intended use.

Finally, the patent in suit failed to disclose how the skilled person could formulate FIE according to the claimed invention. An independent laboratory had investigated whether compositions could be prepared, in accordance with formulation 4 of the patent in suit and comprising the concentrations of FIE of Example 5. The corresponding results reported in documents (66) and (111) demonstrated that the solubility of FIE in the vehicle tested could only reach a maximum concentration of approximately 40 µg/mL, which was well short of the target of 100 µg/mL FIE required to achieve the dose of 1.0 µg per eye used in Example 5, and yet further removed from the upper limit of the most preferred concentration range, which was ten times higher. Such

formulations would contain large amounts of precipitated compound, and could hardly be viewed as being suitable for administration to the eye. In addition, the experiments performed revealed that even the formulations that could be manufactured in suitable form suffered from significant problems with stability. The patent in suit failed to provide adequate guidance as to how to overcome these failures. Paragraph [0020] offered a long list of potential co-solvents and a broad range of concentrations thereof; no guidance was given as to how the specific selections should be made within this very general disclosure, in order to achieve higher concentrations of FIE in a formulation suitable for delivery to the eye. Subsequent patents of the appellant patentee, such as document (67), confirmed that a research programme would be required in order to arrive at a solution to said problems.

The appellant patentee's criticism with respect to the tests of document (66) was not justified. It was true that benzalkonium chloride, present in Formulation 4 of the patent in suit, had been omitted in the formulations of document (66), but only so as to avoid potential problems with eye irritation. No evidence had been provided that, in the small amounts present in Formulation 4, this additive would act as a surfactant.

It was further argued that, even if sufficiency of disclosure could be acknowledged at the filing date of the patent in suit, the same would not be true for the priority date, since the only specific disclosure in the patent in suit of a composition comprising FIE was Formulation 4, and this was not present in the priority document (36). In the absence of this guidance, the skilled person would not be in a position to put into practice the claimed invention.

The appellant opponents maintained their objection of lack of novelty of the subject-matter of the main request with respect to document (1), based on the previous submissions that the disclaimer introduced did not restore novelty over this document.

Turning to the issue of inventive step, the appellant opponents submitted that document (4) should be considered to represent at least an equally suitable candidate for closest prior art as document (3). Like the patent in suit, both documents concerned ophthalmic compositions for reducing IOP. The compounds tested in document (4), including fluprostenol, were designated as being potent ocular hypotensives. This effect had been well-established at the priority date of the patent in suit as the gold standard for establishing suitability in the treatment of glaucoma and ocular hypertension, as was confirmed by documents such as documents (71), (73) and (74). Therefore, document (4), like document (3), was clearly concerned with identifying prostaglandins useful for this clinical use. After all, the authors of document (4) were not a university laboratory focused on determining mechanisms of action, but a global pharmaceutical company interested in developing therapeutics. The side effect of hyperemia was a secondary consideration that might be relevant in assessing inventive step, but not in selecting the closest prior art. In terms of structural features, FIE differed from compound 4 of document (3) in the *meta*-CF_3 substitution at the phenyl ring, and from fluprostenol as disclosed in document (4) in isopropyl esterification. Therefore, there was one structural difference in each case. However, the function of esters as prodrugs in this class of compound, as facilitating corneal penetration and

increasing efficacy of delivery to intraocular tissues, had been well known before the priority date from numerous citations, such as document (15). Therefore, since document (4) already disclosed the present therapeutically active core (pharmacophore), this was arguably to be seen as a closer starting point than document (3), but at least equally promising, in contrast to the situation considered in decision T 1760/11. In a case such as the present, it was established case law, as represented, for example, by decision T 967/97, that the problem-solution approach should be performed for both documents before an inventive step could be acknowledged. After all, the problem-solution approach was not to be seen as an end in itself, but merely as a methodological instrument designed to save time. An analysis of inventive step starting from document (4) could not therefore be avoided.

However, even if document (3) were to be considered to be the closest prior art, it was submitted that the subject-matter of the patent in suit would not be based on an inventive step.

In the decision under appeal, the opposition division had formulated the objective technical problem as lying in "the provision of a treatment of glaucoma and ocular hypertension with an efficacious IOP reduction, for which, compared to the closest prior art, hyperemia is decreased". However, the test data provided in the patent could not be relied upon to demonstrate an improvement in hyperemia over the whole scope claimed. Thus, it was clearly evident from Table 3 of the patent in suit that, at a dosage of below 0.1 µg, the hyperemia score for that FIE (compound B) was worse than for the structurally closest prior art compound of

document (3), namely, compound 4 which was designated as compound C in the patent in suit. Such amounts corresponded to suitable therapeutic dosages, as set out in paragraph [0016] of the patent in suit.

Moreover, as had been confirmed in the declaration submitted as document (70), the selection of scores of 2 to 4 to quantify animals experiencing hyperemia was arbitrary. If the scores of 1 were included, the actual differences between compounds B and C were quite modest, for example, at 0.1 µg. As could be seen from the experiments summarized in Table 3 and Figure 1, an inexplicable decrease of side effects with increased dose had frequently been obtained. Given the evident lack of reliability of this data, which was based on a very limited number of animals of a single species, there was no trend which could be reliably extrapolated, and it was not possible to draw any clear conclusions regarding the alleged general superiority of FIE over compound C. This lack of reliability was compounded by the fact that FIE was much more difficult to formulate as a solution than compound C, as had been demonstrated in document (66). The alleged improvement in the side effect profile for FIE compared to compound C at a dose of 1 µg per eye (100 µg/mL) might therefore simply be a result of differences in the amount of dissolved active ingredient.

The problem to be solved was therefore to be defined in a less ambitious manner, namely, as lying in the provision of an alternative treatment of glaucoma and ocular hypertension. The solution proposed was rendered obvious by document (3) itself, since trifluoromethyl substitution at the phenyl ring was a preferred option suggested therein. Based on this teaching, the skilled person would have had a clear expectation that

equivalent efficacy would be achieved by means of this modification. Moreover, the disclosure of document (4) with respect to fluprostenol provided further confirmation that *meta*-CF_3 substitution would deliver a compound with potent IOP lowering effects, particularly in view of the fact that yet better results were to be expected on formation of an ester prodrug, as set out, for example, in document (15). Contrary to the submissions of the appellant patentee, no useful conclusions could be drawn from document (23), since the teaching therein with respect to substitution at the phenyl ring pertained to a different core structure, and the substituents investigated differed from the present either in nature or position.

With respect to auxiliary request 1, the appellant opponents maintained their submissions with respect to the main request, and additionally raised the following objections:

The amendment specifying a dosage range for FIE of "between 0.05 and 10 micrograms per eye" gave rise to objections under Article 84 EPC, since it was unclear how this feature could be seen as limiting with respect to the product administered, and it was meaningless without the specification of further variables such as the time interval of dosing. Moreover, its juxtaposition with the feature "therapeutically effective amount" in claim 1 led to further lack of clarity, and also presented a problem with respect to Article 100(b) EPC, since undue experimentation would be required to reconcile these inconsistent parameters.

The amended claims were also in conflict with the provisions of Articles 100(c) and 123(2) EPC. In the originally filed specification, document (34), this

dosage range had only been disclosed in the context of the Markush formula (IV) and not (+)-FIE. Therefore, in order to arrive at the subject-matter now claimed it would be necessary to select FIE from a list of six preferred compounds appearing in the first complete paragraph on page 7 of document (34), further select the (+)-enantiomer thereof, and combine this with one of three dosage ranges disclosed in the following paragraph. The appropriate dosage would depend on the individual structure of the compound concerned, and these lists could not therefore be combined at will. Examples 5 and 6, and the corresponding figures, could also not provide support for this combination since discrete data points and not ranges had been measured therein. Moreover, there would be no reason to focus on Figure 1, since the dose range as claimed did not relate to the reduction of hyperemia. The singling out of features in the claims therefore led to added matter.

This reasoning applied all the more to the priority document (36), such that the priority claimed must be viewed as being invalid. In particular, FIE was not disclosed therein in the general part of the description, but only in the examples, namely, Examples 1 and 2. At the bottom of page 4 and at the top of page 5, it was mentioned that out of the five compounds tested, only two were "compounds of the present invention"; however, the latter were not identified. Therefore, in order to arrive at the subject-matter now claimed, it would be necessary to extract FIE from a set of features originally disclosed in the context of said specific examples, and combine this with a specific dosage range only disclosed in the context with Markush formula (IV). This would amount to an unallowable intermediate generalisation. Thus, when

applying the same standards that had been argued for assessing the disclosure of document (1) with respect to FIE, it must be concluded that the subject-matter of auxiliary request 1 could not validly claim priority from document (36). It followed that document (1) was prior art under Article 54(2) EPC, and that the undisclosed disclaimer was not allowable in accordance with G 1/03.

The novelty objection previously raised for the main request with respect to document (1) was also maintained, since the preferred dosage range disclosed therein overlapped significantly with that appearing in the claims of auxiliary request 1 and analogous reasoning therefore applied.

On the issue of inventive step, the appellant opponents reiterated the lack of reliability associated with the hyperemia data in the patent in suit. Moreover, no data point had been provided for the lower limit of the range introduced, namely, 0.05 µg per eye. Owing to its proximity to the data point of 0.03 µg, for which no improvement in hyperemia scores had been observed, it was to be assumed that the same would apply. An effect had also not be rendered plausible for the upper limit of the claimed range.

Finally, appellant opponent 5 submitted, with reference to decision T 942/98, that it was not sufficient in the case of a selection invention to only demonstrate an improvement at the direct interface to the prior art. Therefore, in order to rely upon the more ambitious problem as formulated by the appellant patentee, it would have been necessary not only to demonstrate the alleged improvement with respect to the structurally closest compound C, but also with respect to the

remaining relevant compounds disclosed in document (3), such as latanoprost. It could be seen from Figures 1 and 2 of the patent in suit that this 13,14-dihydro derivative was highly effective in lowering IOP and exhibited a lower incidence of hyperemia than FIE. For this reason too, the problem to be solved could not be formulated in the more ambitious manner. Consequently, the assessment of inventive step presented for the main request applied *mutatis mutandis* to auxiliary request 1.

Even if, for the sake of argument, it were to be accepted that the patent in suit demonstrated an improvement in hyperemia for FIE for the full scope claimed, the solution proposed to the more ambitious problem formulated by the appellant patentee would in any case have been obvious starting from compound 4 of document (3). The skilled person would namely have seen from Table III that this compound was almost free of ocular irritating effects, and from Table V that it also exhibited excellent efficacy in reducing IOP. However, the skilled person would also have noted from Table IV that the hyperemia score of compound 4 left room for improvement. In seeking to further develop this compound, the skilled person would have learned from page 11 of document (3) that the introduction of substituents at the ring structure further reduced side effects, including hyperemia. Therefore, the skilled person would turn to the preferred substituents suggested in document (3), such as the trifluoromethyl group listed in claim 6. Thus, document (3) alone provided a clear path to the use of a compound having the structure of FIE as a solution to the problem of reducing the hyperemia side effect. Moreover, the skilled person would again derive further encouragement owing to the ready availability of fluprostenol, and

the fact that it was known from document (4) to be a "potent ocular hypotensive". It was notable that document (4) was published just before the present priority date, and the skilled person would have considered this to be an important addition, shedding light on the possible modifications already disclosed in document (3). The skilled person would therefore have been motivated to combine the disclosures of documents (3) and (4) and establish the side-effect profile of the resulting compound. By analogy with decisions T 777/08 and T 1364/08, an inventive step could not be acknowledged in a situation where the skilled person only needed to determine by routine tests whether a promising candidate had the desired effect. It was therefore submitted that, starting from document (3), alone or in combination with document (4), the skilled person would have arrived at the subject-matter claimed as a solution to the problem posed without inventive effort.

IX. The appellant patentee's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

It was argued that the main request and auxiliary request 1 should be admitted into the proceedings, since they had been filed with the appellant patentee's reply to the appellant opponents' statements of grounds of appeal, in accordance with Article 12(4) RPBA.

Regarding the main request, the appellant patentee contested the objections raised by the appellant opponents under Article 84 EPC. The term "HCl and/or NaOH to adjust pH", appearing in the disclaimer, clearly designated pH values that were compatible with the use as an ophthalmic composition. This matter had

been examined prior to grant, and could not now be reopened, in accordance with decision G 3/14. Similarly, the presence of two second medical use formats in the request was not open to objection under Article 84 EPC, since this issue did not arise from the amendments now introduced. Finally, the limitation of FIE to its (+)-enantiomer was clearly to be read as applying to all occurrences of this term in the claims.

There had been no extension of scope as a result of this last amendment (Article 123(3) EPC). In the claims as granted, the term FIE clearly at least encompassed the (+)-enantiomer. In the main request, said term had now explicitly been specified to have this absolute stereochemistry, and any FIE present would be in the form of this enantiomer. Any narrowing of the disclaimer was therefore mirrored by a limitation in the subject-matter claimed.

In connection with the ground of opposition raised under Article 100(c) EPC, the appellant patentee disagreed with the appellant opponents' submissions. The reasoning in the decision under appeal, based on decision T 1222/11, was flawed. It was illogical to deny the right to priority for subject-matter which was not claimed. This was also in contradiction with decision G 2/98, which confirmed that entitlement to priority was to be assessed on the basis of what was claimed, in other words, in the present case, on the basis of the subject-matter remaining in the claims after the introduction of the disclaimer, in the sense of decision G 2/10. The present disclaimer excluded the novelty-destroying disclosure of documents (1a) and (1). Therefore, document (36), not document (1a), was the first disclosure of the remaining subject-matter. Moreover, said disclaimer met the fundamental

requirement underlying decisions G 1/93, G 1/03 and G 2/10, according to which it should not make a "technical contribution" going beyond the original content of the application, or earlier applications, as filed. It followed that the claims of the main request were entitled to the claimed priority date, and that document (1) constituted prior art under Article 54(3) EPC. The disclaimer was therefore allowable in accordance with decision G 1/03, and its introduction did not contravene Article 100(c) EPC.

Moreover, even were the present priority claim to be viewed as invalid, to the extent that it encompassed the subject-matter of Example E of document (1a), the present case would represent a further situation, in addition to those identified in G 1/03, where an undisclosed disclaimer should be considered to be allowable, since it only served a specific legal purpose, namely, of validating a claim to priority.

The approach proposed in decision T 1222/11 created an unfair situation where an applicant faced with its own prior art would not be able to deal with it by way of a disclaimer, whereas a third party would be permitted to do so, in contradiction with the analysis in decision G 1/03 according to which "the legislator did not want to make a distinction between the cases of third party collision and self-collision". The "first application" requirement of Article 87(1) EPC, as set out in document (112), was "designed to avoid a chain of successive claims of priority for the same subject". Contrary to the submissions of the appellant opponents, this purpose would not be frustrated by the introduction of a disclaimer in situations of self-collision, provided that the subject-matter disclosed in the earlier application was properly excluded.

On the question of the scope of the disclaimer, the appellant patentee argued that this had appropriately been drafted to be identical to Example E of document (1), and could therefore neither be considered to be too narrow, nor too broad. In particular, said example related to a very specific embodiment comprising functionally related features. Expanding this disclosure to encompass a composition comprising FIE in any amount, combined with with any derivative of formula (II), and any excipients would be an impermissible intermediate generalisation. All the other examples of document (1) disclosed different structures of formula (I), and several used different esters. Therefore, contrary to the submissions of the appellant opponents, there was no implied disclosure of a preference for FIE within the general context of the description, and certainly not of monotherapy with this agent. The passages of document (1) cited by the appellant opponents merely amounted to broad statements of what had already been known in the art, namely, that particular classes of prostaglandins were capable of lowering IOP. This could not be equated with a direct and unambiguous disclosure attributable to any specific compound of formula (I) or (II).

The appellant patentee further submitted that the objections under Article 100(b) EPC were unfounded since the skilled person would have no difficulty in putting the invention into practice over the whole scope claimed. In particular, it could not be accepted that FIE was ineffective in the treatment of NTG. Indeed, documents (10) and (11) demonstrated that FIE produced a statistically significant reduction in IOP for NTG patients. The skilled person would not have seen a 30% reduction in IOP as a requirement for

treatment of NTG, as had been confirmed in document (60). As with all medical treatments, a certain percentage of non-responders or difficult-to-treat sub-populations could not detract from the fact that FIE had a significant role to play in the treatment of NTG, as further supported by documents (117) and (118).

Moreover, the patent in suit contained comprehensive experimental data rendering the claimed use of FIE plausible. In particular, Example 6 demonstrated IOP reduction in lasered cynomolgus monkeys, and Example 5 reduced incidence of conjunctival hyperemia in guinea pigs. Contrary to the assertions of the appellant opponents, these were valid models: In Example 6, the monkeys tested had been subjected to laser trabeculoplasty to induce ocular hypertension, so they could not be classified as being "healthy". Furthermore, there was nothing unusual in performing tests in different animal species depending on the effect to be demonstrated, as was confirmed in document (3). Therefore, in the present case, both essential aspects in relation to clinical utility had plausibly been demonstrated in the sense of decision T 609/02, namely, the pharmacological effect in combination with the lack of unacceptable side effects. Moreover, document (54) confirmed the existence of a commercial product comprising FIE, approved for the indications claimed.

Finally, the FIE formulations for topical application were sufficiently disclosed in the patent in suit. The authors of document (66) had had no difficulty in formulating FIE at the same concentration as used in Formulation 4 of the patent in suit, namely, 0.003 wt%, which translated to 30 µg/mL or 0.3 µg in a 10 µL drop. In the ophthalmic vehicle used in document (66), the

benzalkonium chloride excipient of present Formulation 4 had been omitted, even though this quaternary ammonium salt would clearly have an impact on solubility. The teaching of the patent in suit had not been faithfully followed in this respect. Moreover, the appellant opponents were incorrect to suggest that the skilled person would limit himself to the use of Formulation 4 for guidance with respect to FIE compositions. Indeed, further examples were provided in the patent in suit of compositions with higher concentrations of prostaglandin. These contained the excipient polysorbate 80, which was listed in paragraph [0020] as being one of several co-solvents useful in increasing the water solubility of prostaglandins. Furthermore, the skilled person would be aware of other means for adjusting dose without needing to alter concentration, such as variation drop size or number, and the possibility of administering FIE as a suspension was not excluded. With respect to the issue of stability, the appellant patentee submitted that document (66) did not in fact prove instability, since no degradation products had been detected, and certainly not on the time-scale required for therapeutic use. The reference to subsequent patents, such as document (67), was also not relevant: this related to research aimed at providing improved FIE formulations, and did not prove that the skilled person could not make suitable formulations based on the teaching of the patent.

The priority document (36) also provided corresponding clear guidance on means of formulating suitable formulations, on page 7 and in Example 3.

On the question of novelty, the appellant patentee submitted that the same reasoning applied as that advanced with respect to the scope of the disclaimer.

Turning to the issue of inventive step, the appellant patentee contested the position taken by the appellant opponents regarding the purpose or effect of the invention as being merely to identify a new prostaglandin derivative capable of lowering IOP. The critical issue that had been preventing the application of prostaglandins as useful drugs was their unacceptable side effect profile, in particular, ocular irritation and conjunctival hyperemia. This had been recognised not only in the patent in suit, but also in a whole series of further documents published in the period leading up to the present priority date, including document (3). At the priority date, IOP lowering ability would have been seen as a necessary but not sufficient requirement for the successful clinical treatment of glaucoma and ocular hypertension. In document (3), it had been demonstrated for the first time that it was in fact possible, using modified $PGF_{2\alpha}$ derivatives, to achieve a suitable therapeutic window, in which the ability to lower IOP was retained without unacceptable side effects. Based on the primary consideration of "purpose or effect", as set out in decision T 1760/11, this was therefore to be seen as a realistic starting point for the skilled person seeking further or improved clinically useful $PGF_{2\alpha}$ derivatives. In contrast, document (4) was directed to an investigation of the receptors involved in the ocular hypotensive activity of prostaglandins, and said nothing at all about the issue of side effects. In terms of structural similarity, compound 4 of document (3) and fluprostenol of document (4) were on an equal footing, since both exhibited a single

structural modification with respect to FIE. The question of whether these modifications were obvious was a matter to be assessed after the selection of closest prior art and after the technical problem has been formulated; otherwise an element of hindsight would inevitably be introduced. Consequently, document (4) was not to be considered as an "equally valid" or "feasible" starting point. As identified in the patent in suit, the appropriate closest prior art for an objective assessment of inventive step was document (3).

The appellant patentee defined the problem to be solved, starting from document (3) as closest prior art, as lying in the provision of a treatment of glaucoma and ocular hypertension with an efficacious IOP reduction, and reduced incidence of conjunctival hyperemia. The proposed solution as defined in the main request related to the use of FIE as active ingredient, which differed from compound 4 of document (3), designated as compound C in the patent in suit, in the *meta*-CF_3 substituent at the 16-phenoxy group. Examples 5 and 6 of the patent in suit demonstrated that this subject-matter successfully solved the problem posed.

Contrary to the allegations of the appellant opponents, the comparative data provided rendered it credible that the effects relied upon were present over the full scope claimed. In the graph of Figure 1, which represented the incidence of hyperemia as a function of dose, a clear separation could be seen between the curves for FIE and compound C. The skilled would interpret the results observed at a dose of 0.03 µg in the light of the results seen at higher doses. The reduced incidence of hyperemia was an intrinsic property of FIE. The failure to detect this at such low

doses was a function of the limitations of biological model employed. The skilled person would not be particularly interested in what was happening at the extremities of the dose-response curves. The combined results of Examples 5 and 6 of the patent in suit demonstrated that, at relevant therapeutic doses, FIE delivered a reduction in IOP that was comparable to compound C, whilst causing less hyperemia. It had been confirmed in decision T 1850/10 that the data had to be assessed "as a whole" in order to establish whether the problem posed had been credibly solved across the full scope of the claim.

The further criticism raised by the appellant opponents with respect to the reliability of the data was also unfounded. It was not arbitrary to select a score of 2 as a cut-off value, since this was indicative of conjunctival hyperemia, which was the side effect of interest, as stated in paragraph [0062] of the patent in suit. In any case, even if scores of 1 were included, the data still showed an overall advantage for FIE compared to compound C. With *in vivo* models, such as the present, the increase in biologic effect with increasing drug dose was frequently not monotonic. There was therefore nothing unusual about the small variations of the hyperemia incidence scores as a function of dose observed in Table 3 and Figure 1 of the patent in suit. There was also no reason to doubt that reliable conclusions could be drawn based on the experimental model employed, which involved twenty-four observations on six guinea pigs. Finally, as explained previously in the discussions on sufficiency of disclosure, document (66) was deficient and failed to prove the assertions made by the appellant opponents. In the absence of counter-evidence to contradict the

findings of Example 5, there would be no reason to doubt the plausibility of the effect demonstrated.

Moreover, even were it to be accepted that the problem of reducing propensity to cause hyperemia was not solved across the full scope claimed, this subject-matter would nevertheless be inventive, since the prior art provided no indication that *meta*-CF_3 substitution would result in a compound with comparable efficacy in IOP reduction to compound C. Document (3) itself did not provide any data for this type of substitution, so its effect in this respect could not be predicted. Table IV pointed to different structural modifications, and the only example of phenyl substitution disclosed was with a *para*-OMe group, which led to a decrease in IOP-lowering activity. Similarly, document (4) presented only modest results for IOP reduction with fluprostenol, and would therefore dissuade the skilled person from looking to *meta*-CF_3 substitution in the compounds of document (3). Citations, such as document (15), confirmed that esterification would be expected to increase potency, but not efficacy. The skilled person would further be discouraged by document (23). Therein, the effect of substituents at the phenyl ring in $PGF_{2\alpha}$ analogues had been examined by means of the miotic effect in cats, as an indicator for IOP lowering in primates and man. Substitution with *meta*-OMe was found to markedly reduce activity, and *para*-CF_3 substitution rendered the molecule practically inactive. Based on electronic considerations, *meta*-CF_3 substitution would be expected to be similarly detrimental to activity. Consequently, starting from document (3), FIE would not have been an obvious choice for the skilled person seeking compounds with equally efficacious IOP reducing properties.

The additional objections raised by the appellant opponents with respect to auxiliary request 1 were clearly without merit.

The amendment specifying a dose range of "between 0.05 and 10 micrograms per eye" provided a limitation relating to the therapeutic use, defining the dose at each instance of administration. Example 6 of the patent in suit demonstrated IOP lowering activity at a dose of 0.3 µg, and documents (58) and (59) confirmed this effect at other claimed doses, including the lower end and beyond. There was also no inconsistency with the feature "therapeutically effective amount" since the latter related to the amount of FIE in the composition administered. The amended claims were therefore clear and sufficiently disclosed.

The requirements of Articles 100(c) and 123(2) EPC were also fulfilled. Basis for the amendments was to be found on page 7 of the description as originally filed, and of the identical descriptions of the earlier applications as originally filed. There had only been a single selection, namely, of (+)-FIE, designated as compound B; the dose had merely been limited to the most preferred range. Said combination was fully supported by the data in Examples 5 and 6. In particular, a separation of curves could be seen in Figure 1 for the full range of doses now claimed. Furthermore, basis was also present on page 6, lines 19 to 20 of the priority application (36). Contrary to the assertions of the appellant opponents, the skilled person would have no difficulty identifying (+)-FIE as a compound of the invention, from Table 1 in combination with the remaining description. Therefore these claims are entitled to the claimed priority date.

On the issue of novelty with respect to document (1), the appellant patentee referred to its previous submissions with respect to the main request.

With respect to inventive step, the appellant patentee submitted that, in view of the limitation to the specific dose range of "between 0.05 and 10 micrograms per eye", it was certainly legitimate to rely on the more ambitious problem previously formulated. The interpolation between data points in Figure 1 was scientifically justifiable, and it was reasonable to assume that the separation of curves for FIE and compound C (compound 4 of document (3)) started at a value of 0.03 µg, and this was still observable at the upper limit of 10 µg.

Document (3) did not provide any guidance on how to reduce hyperemia. In particular, there was no pointer to *meta*-CF_3 substitution of the structurally closest prior art compound 4, as a solution to the problem posed. The only disclosure in document (3) of the effect of substitution at the phenyl ring related to a different substituent (OMe) at a different position (*para*) on the propensity to cause a different side effect (ocular irritation). With reference to the data in Tables III and IV of document (3), the appellant patentee emphasised that ocular irritation and hyperemia were distinct and separable side effects, which could not always simultaneously be addressed by the same structural modification.

The analysis of appellant opponent 5 starting from latanoprost was not in accordance with established case law of the boards of appeal, which stipulated that the structurally closest compound was to be used for

comparison. In any case, an inventive step would also have to be acknowledged starting from latanoprost: In the patent in suit, superior IOP reduction had been demonstrated for FIE (Figure 2), coupled with low hyperemia incidence (Figure 1). Both results could not have been expected. In particular, latanoprost but not FIE belonged to the sub-group designated as being most preferred in document (3), and unacceptable levels of hyperemia would have been expected to result from this structural modification, in view of the poor results obtained for compound 4 in Table IV of document (3).

Finally, the absence of direction in document (3) was not remedied by any other cited prior art. The appellant opponents' focus on document (4) was guided by hindsight. This document made no mention of side effects and could not therefore provide any useful information in this respect.

X. The parties as of right (opponents 2 and 7) did not take an active part in the appeal proceedings.

XI. The appellant patentee requested that the decision under appeal be set aside and that the patent be maintained on the basis of

- the main request filed as auxiliary request 17 with letter of 8 June 2015 (previously filed as main request B' on 25 April 2014),

or, alternatively, on the basis of

- auxiliary request 1 filed as auxiliary request 18 with letter of 8 June 2015 (previously filed as auxiliary request 1A' on 25 April 2014).

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

XII. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. *Admission of the appellant patentee's main request and auxiliary request 1 into the proceedings*

The requests in question were first filed during opposition proceedings with letter of 25 April 2014 as main request B' and an auxiliary request 1A'. They were not considered in the decision under appeal since a higher ranking request was found to be allowable (cf. above point IV). In its statement of grounds of appeal, the appellant patentee presented arguments as to why the opposition division's decision to refuse the higher ranking requests was incorrect, in accordance with Article 12(2) RPBA. It therefore stands to reason that, at this stage of the appeal proceedings, the appellant patentee only refiled the requests that were relevant to its appeal, and this cannot be considered to amount to a tacit abandonment of lower ranking requests. The subsequent filing of said requests as auxiliary requests 17 and 18, with the appellant patentee's reply to appellant opponents' statements of grounds of appeal, was aimed at addressing specific issues raised (cf. letter of 8 June 2015, paragraphs 14, 69 and 79), and is therefore to be regarded as a legitimate and timely response in accordance with the provisions of Article 12(2) RPBA.

Consequently, the Board saw no reason to hold these requests inadmissible in the exercise of its discretion pursuant to Article 12(4) RPBA.

Main request filed as auxiliary request 17 with letter of 8 June 2015

3. *Main request, Article 84 EPC*

3.1 According to Enlarged Board of Appeal decision G 3/14 (see OJ EPO 2015, A102, Order), "In considering whether, for the purposes of Article 101(3) EPC, a patent as amended meets the requirements of the EPC, the claims of the 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."

3.2 In the present case, claims 1 and 2 of the main request differ from claims 1 and 6 as granted, respectively, in the addition of a definition for the term "fluprostenol isopropyl ester" (FIE) by means of the structural formula depicted in Table 2 of the description, having a specific absolute stereochemistry (see above points II and VI). From the position of the inserted passage at the end of the respective claims, rather than in immediate proximity to one or other of the occurrences of said term, the skilled reader would clearly understand, in the absence of any indication to the contrary, that this constituted a definition that was generally applicable to each occurrence of said term within the context of the claims. Certainly, the board cannot recognise anything in the syntax employed that would indicate to the skilled reader that said definition was only intended to apply to the disclaimer.

3.3 A further objection was raised with respect to the term "HCl and/or NaOH to adjust pH" appearing in the disclaimer. However, this feature was already present in the disclaimer of the claims as granted, and the alleged lack of compliance cannot therefore be said to have been introduced as a result of the post-grant amendment specifying the absolute stereochemistry of FIE (cf. above point 3.2). In accordance with decision G 3/14 (cf. above point 3.1), said feature is not open to objection under Article 84 EPC.

The board cannot agree with the appellant opponents' argument, according to which the clarity of the disclaimer should nevertheless be evaluated, as an overriding requirement of Enlarged Board of Appeal decision G 1/03 (OJ EPO 2004, 413). In this decision, it is stated, "A claim containing a disclaimer must meet the requirements of clarity and conciseness of Article 84 EPC" (Order, point 2.4; see also Reasons, point 3, penultimate paragraph). However, as set out in decision G 3/14 (cf. Reasons, points 47 and 48), this evaluation is one that is to be performed at the time of introduction of the amendment in question, in other words, pre-grant in the present case. No indication can be found in decision G 3/14 that an amendment by way of a disclaimer should be treated any differently to any other type of amendment, nor can such an exception be derived from decision G 1/03. Indeed, in the referring decisions in that case, the disclaimers had been introduced post-grant, and the corresponding claims were therefore to be examined for compliance with Article 84 EPC, in accordance with the provisions of Article 102(3) EPC 1973, the predecessor of Article 101(3) EPC (cf. T 507/99, OJ EPO 2003, 225, see Facts

and submissions, point II; T 451/99, OJ EPO 2003, 334, see Facts and submissions, points I, II and IV).

3.4 Finally, the appellant opponents raised an objection under Article 84 EPC owing to the presence in one claim set of two different second medical use formats, namely, claim 1 drafted as a purpose-limited product claim as provided for in Article 54(5) EPC, and claim 2 in the Swiss-type format instituted by decision Enlarged Board of Appeal decision G 5/83 (OJ EPO 1985, 64). However, the decision relied on by the appellant opponents in this context, namely, T 1570/09, related to pre-grant proceedings. In contrast, in the present case, these two claim formats were to be found in the claims as granted. Therefore, in accordance with decision G 3/14, this issue cannot form the basis for an objection under Article 84 EPC.

3.5 Consequently, to the extent that clarity may be raised as an issue in these appeal proceedings, the board finds the subject-matter of the main request to comply with Article 84 EPC.

4. *Main request, Article 123(3) EPC*

4.1 The claims as granted comprised two independent claims in second medical use format, namely, claim 1 relating to a topical ophthalmic composition for use in the treatment of glaucoma and ocular hypertension comprising a therapeutically effective amount of FIE, and claim 6 to the corresponding use of FIE in the Swiss-type format (cf. above point II). The claims of the main request differ from these claims in the insertion of a formula defining the structure of FIE, specifying the absolute configurations at the five chiral centres present (cf. above point VI).

4.2 The appellant opponents raised an objection under Article 123(3) EPC based on the argument that the term "fluprostenol isopropyl ester" in the claims as granted would be understood to relate exclusively to the racemate, and would not include the (+)-enantiomer now claimed.

The board cannot agree: It is firstly noted that such a reading would be in direct contradiction to the description of the patent in suit, since FIE is disclosed therein as exhibiting the specific absolute configuration of the (+)-enantiomer, corresponding to the naturally-occurring prostaglandin $PGF_{2\alpha}$ (see paragraph [0060], Table 2, compound B; cf. paragraph [0002], formula (I)). Moreover, on reading the term FIE, the person skilled in the art would understand this to designate the isopropyl ester of the carboxylic acid "fluprostenol", the structure of which was known from standard reference sources such as document (13), as cited in paragraph [0003] of the patent in suit, or document (37). In both these documents, the structure depicted for "fluprostenol" has the absolute configuration of the (+)-enantiomer. However, it is clear from document (37), and in particular from the use of the symbol (±) therein, as well as of the descriptors R^* and S^* designating relative stereochemistry, that the name "fluprostenol" not only encompasses the compound having the absolute configuration depicted, but also the racemic mixture. This is confirmed in document (42), which is cited in document (13) with respect to the preparation of fluprostenol: therein the synthesis of the racemic mixture is disclosed, starting from the racemic aldehyde, and also that of "both optical isomers ... starting with the optically active aldehyde (III) and

its enantiomer"; moreover, specific reference is made to "the enantiomer with the same absolute stereochemistry as the natural prostaglandins" (see page 90, and accompanying scheme on page 89 (formulae III and VII, ICI 81,008) and text on page 88). It is therefore concluded that the skilled person would understand the term "fluprostenol", and by extension "fluprostenol isopropyl ester", as it appears in the claims as granted, to encompass both the racemic mixture and the enantiomer now claimed. Therefore, no extension of claimed scope results from the limitation to the latter.

4.3 The appellant opponents raised the further objection that the introduction of the structural formula defining absolute stereochemistry for FIE had the effect of restricting the disclaimer of claim 1, but not the portion defined in positive terms, owing to the "comprising" language used in the latter. However, the board does not consider this to be a technically sensible reading of the claim. The feature in question is clearly to be understood as defining the FIE molecules present within the composition as being in the specific stereochemical form depicted. Therefore, the presence of the (-)-enantiomer thereof, or even a racemic mixture, as suggested by the appellant opponents, would necessarily be excluded by the skilled reader, since the features depicting absolute stereochemistry of the (+)-enantiomer would otherwise be rendered meaningless.

It is therefore concluded that the restriction of the disclaimer resulting from the amendment to the claims as granted is mirrored by the limitation of the remaining subject-matter of the claim, such that there has been no extension of the protection conferred.

4.4 In view of the above considerations, the subject-matter of the main request is considered to satisfy the conditions of Article 123(3) EPC.

5. *Main request, Article 100(c) EPC*

5.1 Objections were raised by the appellant opponents owing to the fact that document (35), which is the root application as originally filed (cf. above point I), does not disclose the disclaimer now appearing in claims 1 and 2 of the main request. Hence, the question to be addressed in this context is whether the introduction of the undisclosed disclaimer based on document (1) gives rise to subject-matter extending beyond the content of this earlier application as filed, based on the criteria laid down in decision G 1/03 (see Order, point 2). Accordingly, it will have to be examined whether, for the subject-matter now claimed, document (1) qualifies as state of the art under Article 54(3) EPC and Article 54(4) EPC 1973, and whether the disclaimer has been properly drafted to fulfil its purpose of restoring novelty, as set out in points 2.1, item 1, and 2.2 and 2.3 of said Order. It is noted that the issue of conformity with Article 84 EPC, in accordance with point 2.4 of the Order, has already been addressed above in point 3.3.

In addition, as further elaborated in Enlarged Board of Appeal decision G 2/10 (OJ EPO 2012, 376) with reference to decision G 1/03, the subject-matter remaining in the claim after the introduction of the disclaimer should not present the skilled person with technical information which he would not derive directly and unambiguously from the application as filed; the same standard is to be applied when

assessing entitlement to priority (see, in particular, G 2/10, Reasons, point 4.4; points 4.5.1, 4.5.2 and 4.5.4; point 4.6).

5.2 *Scope of disclaimer based on document (1)*

5.2.1 Document (1) is a European patent application filed and published between the present priority and publication dates. The fact that document (1) validly claims an earlier priority date from document (1a) was not disputed by the appellant patentee. Moreover, the same contracting states are designated in document (1) as in the patent in suit. Accordingly, the content of the former must indeed be considered as being comprised in the state of the art for the latter, at least for the purposes of novelty (for status of document (1) under Article 54 EPC, see point 5.4 below, first sentence, and preceding analysis in point 5.3).

5.2.2 Document (1) relates to topical ophthalmic compositions for the treatment of glaucoma and ocular hypertension, comprising combinations of prostaglandins of formula (I) and (II) (cf. claim 1). The representative examples include the composition of Example E, which comprises a compound of formula (I) designated as "Compound 4, isopropyl ester" (page 8, lines 1 to 15), whereby Compound 4, as defined in Table 1 (page 4), is fluprostenol having the same absolute configuration as that specified for FIE in the present claims. In other words, composition E comprises (+)-FIE. In the following, for the sake of conciseness, this compound will simply be referred to as FIE.

In composition E, FIE is present in combination with a specific prostaglandin (compound (F) in present disclaimer), together with a number of specific

excipients and solvents, in defined percentages by weight. This is **the only disclosure of FIE** to be found in document (1).

In the summary of the invention, it is emphasised that "an optimum combination of a compound of formula (I) and a compound of formula (II) will allow a more potent reduction of intraocular pressure without the side-effects produced by treatment with an adequate dose of a single component" (see page 2, lines 52 to 54). The skilled person would recognise from this disclosure that each individual exemplified combination is characteristic, in the sense that the two active compounds are specifically chosen in order to obtain optimum results, and closely linked to the other characteristics of the composition, most notably the concentrations of said components. This is confirmed by the fact that Examples A to J according to document (1) each relate to different individualised combinations in individually adapted concentrations.

Contrary to the appellant opponents' submissions, it cannot be accepted that the composition of Example E is open to generalisation on the basis of further passages of document (1). As explained above, FIE is locked into a specific combination of functionally related features. There is no direct and unambiguous disclosure of this compound as being a representative, preferred compound of formula (I) in the context of the more general disclosure. The appellant opponents sought to establish such a link by reference to the paragraph introducing the examples (cf. page 6, lines 25 to 27). However, the examples are designated therein as "representative pharmaceutical **compositions** of the invention" (emphasis added), and not in terms of their separate components. Moreover, no such link can be

derived from the reference to Table 1 in said paragraph, since this is merely mentioned in the context of providing a key to the numbers used in defining the compounds of formula (I) within the exemplified compositions. In Table 1 itself and in the remaining passages of document (1), fluprostenol is listed amongst the preferred compounds, but not FIE (see page 3, line 31 to page 4, line 55; claims 2 and 3).

Consequently, the board concludes that FIE is only disclosed in document (1) in combination with the particular features of Example E.

5.2.3 Monotherapy with FIE is also not disclosed in document (1).

The paragraph on page 2 cited by the appellant opponents in this respect reads as follows (see lines 34 to 39, emphasis added; note: IOP stands for intraocular pressure):

"It has been unexpectedly discovered that co-administration of an E series prostaglandin and an F series prostaglandin in combination produces a greater reduction of IOP than the same dose of **either type of compound given separately**. In fact, as described in greater detail below, representative mixtures of the prostaglandins of the present invention produce a profound and long lasting IOP decrease. Administration of both types of prostaglandins in combination is apparently necessary to produce the desired IOP lowering effect for glaucoma therapy, while decreasing the likelihood of systemic side effects."

It is noted that the statements in this paragraph are rather general, with an emphasis on the "type of compound". This is is also echoed in the following two paragraphs on page 2 (lines 40 to 54), and the corresponding paragraph on page 5 (lines 40 to 43), in which trends are disclosed with general reference to compounds of formulae (I) and (II). Therefore, it cannot directly and unambiguously be derived therefrom that the reported observations are based on a separate and combined testing of each and every one of the active ingredients appearing in the examples.

The further submission in this respect, which relied on modifying the doses disclosed in Example E by reference to selected ratios and doses appearing elsewhere in different paragraphs on page 5 of the description, clearly falls short of the standards required for a direct and unambiguous disclosure.

5.2.4 From points 5.2.2 and 5.2.3 above, it follows that the relevant disclosure in document (1) with respect to FIE is restricted to the specific composition E and its use in the treatment of the conditions indicated.

In this respect, the appellant opponents additionally argued that, in the absence of a specific range assigned to the pH, the disclaimer was broader than the corresponding disclosure of Example E in document (1). However, in said example, there is also no pH value specified. Therefore, the skilled person would read this parameter in context, as only being limited in so far as the values encompassed should be compatible with the defined composition and use. Contrary to the submission of the appellant opponents, the passage of document (1) on page 5, lines 50, 51, does not support a more specific limitation, since it is merely stated

therein that "the mixtures are **generally** formulated ... at a pH between 4.5 to 8.0" (emphasis added). Moreover, since the use defined in the present claims is the same as that disclosed in document (1), a technically meaningful reading of the disclaimer in context imposes a corresponding functional limitation on the pH of the disclaimed composition. It follows that the subject-matter of Example E in document (1) and of the present disclaimer are identical in scope.

The appellant opponents' further line of argument, according to which the disclaimer was narrower than the corresponding disclosure of Example E in document (1), must also fail. This submission relied on the description of the patent in suit to justify a reading of the disclaimer as being limited to the pH range of 7.3 to 7.4, as disclosed in the only specific composition comprising FIE, namely, Formulation 4. However, in view of the claim construction set out in the previous paragraph, it is evident that no recourse to the description is required in order to understand the disclaimed subject-matter within the context of the claims. Furthermore, it is noted that Formulation 4 differs in several aspects from that disclaimed, and there would therefore be no reason to apply the pH values of the former to the latter.

5.2.5 In view of the above considerations, it is concluded the disclaimer introduced in claims 1 and 2 of the main request (cf. proviso in above point II, combined with the definition of FIE reproduced in point VI) removes that which is necessary to restore novelty over the disclosure of document (1).

5.3 *Entitlement of claimed subject-matter to priority from document (36)*

5.3.1 Document (36) generally discloses compounds of formula (I) and corresponding topical ophthalmic compositions, as well as their use in the treatment of glaucoma and ocular hypertension (see e.g. claims 1 and 9; see also page 1, lines 4 to 7; page 5, lines 12 to 25; page 6, lines 15 to 17, and 23 to 30). With reference to Table 1, it is further disclosed that five specific compounds were tested, "two of which are compounds of the present invention" (page 4, line 26 to page 5, line 3). From a comparison of formula (I) and the structures depicted in Table 1, the two compounds of the invention are readily identifiable, namely, cloprostenol isopropyl ester (compound A) and FIE (compound B), whereby the structure of the latter is identical to that defined in claims 1 and 2 of the main request. Therefore, in order to arrive at the features defined in positive terms in the main request, only a single, allowable selection within the disclosure of document (36) is required, namely, of FIE from a list of two specifically named compounds.

5.3.2 The appellant opponents further argued that document (36) insufficiently disclosed the claimed invention, such that no priority right could be validly claimed. However, the board cannot concur with this line of argumentation for the reasons given below in points 6.2 and 6.3 (in particular, last paragraphs of points 6.2 and 6.3.1; Article 100(b) EPC).

5.3.3 Finally, the introduction of the disclaimer is not considered to lead to a loss of priority in the present case:

As a result of the exclusion of an isolated specific embodiment, the technical information presented to the

skilled person has not been modified, in the sense that the disclaimer does not result in a singling out a novel subgroup in the subject-matter remaining in the claim (cf. G 2/10, Reasons, point 4.5.4, and reference therein to G 1/03, Reasons, point 2.1.3, second paragraph; see also G 2/10, Reasons, point 2.3, third paragraph). Since the identity of the claimed subject-matter has not been changed by said amendment, it does not affect the right to priority (cf. G 1/03, Reasons, point 4).

Moreover, since the disclaimer appropriately delimits the claimed subject-matter with respect to the disclosure of document (1), as set out above in point 5.2, it is considered that document (36) represents the first application, in the sense of Article 87(1) EPC, for the subject-matter remaining in the claims, and priority can be validly claimed therefrom.

5.3.4 It is therefore concluded that the main request is entitled to the priority date claimed from document (36), in accordance with Article 89 EPC.

5.4 *Allowability of claim amendments by way of disclaimer*

A consequence of the finding on priority in above point 5.3 is that document (1) constitutes prior art under Article 54(3) EPC and Article 54(4) EPC 1973.

The present disclaimer serves the purpose of restoring novelty over the relevant disclosure of this document (cf. above point 5.2).

Moreover, applying the same considerations as those set out in the second paragraph of above point 5.3.3, it is

concluded that the skilled person is not presented with new technical information as a result of the introduction of the disclaimer.

Consequently, the claim amendment by way of disclaimer is considered to be allowable, pursuant to Article 100(c) EPC, in agreement with the criteria set out above in point 5.1.

5.5 The present board does not consider that the approach proposed by the appellant opponents for evaluating the allowability of the present disclaimer, based on that adopted in decision T 1222/11, is in accordance with Enlarged Board of Appeal decision G 2/98, G 1/03 and G 2/10 for the following reasons:

The decisive element in the reasoning of the appellant opponents was that the correct point of departure for assessing the entitlement to priority was the subject-matter claimed prior to the introduction of the disclaimer. In support of their position, the appellant opponents relied on decision G 1/03, and in particular the highlighted phrase from the following passage (see Reasons, point 4):

"In order to avoid any inconsistencies, the disclosure as the basis for the right to priority under Article 87(1) EPC and as the basis for amendments in an application under Article 123(2) EPC has to be interpreted in the same way. This means that **a disclaimer**, not providing a technical contribution as outlined above, **which is allowable during the prosecution of a European patent application does not change the identity of the invention within the meaning of Article 87(1) EPC**. Therefore, its introduction is allowable also when drafting and filing the European

patent application without affecting the right to priority from the first application, which does not contain the disclaimer."

The board cannot concur with the appellant opponents' reading of this paragraph:

In the first sentence reproduced above it is reiterated that "the concept of disclosure must be the same for the purposes of Articles ... 87 and 123 EPC" (see Reasons, point 2.2.2, last paragraph; cf. also G 2/10, Reasons, point 4.6). In the second sentence, the phrase "not providing a technical contribution as outlined above" has been neglected in the appellant opponents' analysis. This refers back to previous sections of decision G 1/03, such as points 2.1.3 and 2.2.1, according to which disclaimers excluding state of the art under Article 54(3) EPC or an accidental anticipation, respectively, having no bearing on the technical information in the application, are not in contradiction to Article 123(2) EPC (see also analysis in decision G 2/10, Reasons, point 4.4). In the final sentence of the above paragraph, it is concluded that, by the same token, the introduction of such a disclaimer does not change the identity of the invention and would not affect the right to priority.

Therefore, on a objective reading, said passage cannot be said to advocate that the entitlement to priority is to be evaluated based on the subject-matter claimed prior to the introduction of the disclaimer; rather, the subject-matter actually claimed is to be taken as the starting point and compared with the content of the priority document, in order to establish whether the introduction of the disclaimer changes the identity of what is claimed, in analogy to the criteria set out in

decision G 2/10 (see Reasons, points 4.5.1, 4.5.2 and 4.5.4). This is also consistent with Enlarged Board of Appeal decision G 2/98 (OJ EPO 2001, 413, see Reasons, point 6.2), according to which, "pursuant to Article 84 EPC, the claims of the European patent application define the matter for which protection is sought and, hence, determine the matter for which priority may be claimed".

In the present case, as explained above in point 5.3, regardless of whether document (1) is to be classified as a document under Article 54(2) or 54(3) EPC with respect to a notional claim not containing the disclaimer, the fact remains that, once the novelty destroying subject-matter disclosed in document (1) had been disclaimed, for the remaining claimed subject-matter, the priority date is then valid, and document (1) is prior art in the sense of Article 54(3) EPC. The introduction of such a disclaimer only serves the purpose for which it was intended, and does not represent an arbitrary reshaping of the claims, in keeping with the rationale underlying decision G 1/03 (see Reasons, point 2.6.5, and point 3, second paragraph).

Differing views were presented by the parties as to the fairness of allowing an applicant to disclaim its own prior art. However, the board cannot recognise anything in the reasoning or conclusions of decision G 1/03 from which it could be derived that such a possibility was to be excluded. It is noted that the situations listed in point 2.1 of the Order are not confined to ones of which an applicant could not have been aware at the time of filing. Moreover, in view of the fact that the relevant subject-matter has been disclaimed, the board cannot agree that there has been an extension of

priority right for this subject-matter beyond the prescribed twelve-month time limit. Therefore, the cited purpose of Article 87(1) EPC, with reference to document (112) (see page 36, section (d)), namely, "to avoid a chain of successive claims of priority for the same subject", has not been undermined.

5.6 The board therefore concludes that the disclaimer of claims 1 and 2 of the main request does not result in subject-matter extending beyond the content of the root application as originally filed (document (35)).

6. *Main request, Article 100(b) EPC*

6.1 The request under consideration consists of two independent claims in second medical use format. Specifically, claim 1 relates to a purpose-limited claim to a topical ophthalmic composition for use in the treatment of glaucoma and ocular hypertension comprising a therapeutically effective amount of FIE, and claim 2 to the corresponding use of FIE in the Swiss-type format (cf. above points II and VI).

In order to determine whether the requirement of sufficiency of disclosure is fulfilled in the present case, it must be assessed whether, for the whole scope claimed, the patent in suit, in the light of common general knowledge, discloses sufficient information allowing said products to be obtained, and establishing their suitability for the claimed therapeutic application (see e.g. T 609/02, Reasons, point 9).

6.2 With respect to the preparation of fluprostenol, the patent in suit refers to document (13), and the fact that esterification reactions, required for the conversion thereof to FIE, are well known (see

paragraphs [0003] and [0014]). Methods for formulating suitable compositions and the use thereof in the claimed therapeutic applications are generally disclosed in paragraphs [0016] to [0021], and corresponding formulations are disclosed in Example 9. The results of the tests with FIE disclosed in Example 5 show a low incidence of conjunctival hyperemia in guinea pigs, and in Example 6 IOP reduction in lasered cynomolgus monkeys (see also Figures 1 and 2, respectively). In accordance with the information provided in the patent in suit, with reference to document (3) (cf. patent in suit, paragraphs [0004] to [0006] and [0010], references to "Stjernschantz et al."), these tests reflect two aspects that are central to the treatment of glaucoma and ocular hypertension, namely, the minimisation of side effects whilst maintaining the IOP-lowering effect.

The board therefore concludes that the requirement of sufficiency of disclosure is fulfilled, since the general guidance and examples provided in the patent in suit enable the skilled person to provide FIE and topical ophthalmic compositions thereof, and employ them in the treatment of medical conditions of the type claimed.

The same is true of the priority document (36), since the corresponding relevant disclosure can be found therein in the following passages: page 2, lines 1 to 11; page 6, lines 6 to 9; page 6, line 15 to page 7, line 31; and Examples 1 to 3.

6.3 The appellant opponents' arguments cannot alter this assessment for the following reasons:

6.3.1 In the present case, it was not contested that the skilled person would know how to produce FIE. Rather, it was argued, in particular by appellant opponent 4 with reference to document (66) and (111), that the skilled person would not have been able to formulate FIE at the higher concentrations of, for example, 100 µg/mL, required to achieve the dose of 1.0 µg per eye used in Example 5. However, what is relevant for the purposes of sufficiency is not whether specific higher concentrations are not achievable, but whether therapeutically relevant concentrations are. The latter requirement is clearly fulfilled, even according to the disclosure of document (66), since solutions with concentrations approaching 40 µg/mL were obtained (cf. Tables 2, 4 and 7). It is additionally noted that other means for adjusting the amounts of FIE administered, such as drop size and number, would also be open to the skilled person.

The line of argumentation based on documents (66) and (111) suffers from further weakness owing to the focus on a specific formulation type (cf. document (66), point 4.2), based on Formulation 4 of the patent in suit. Leaving aside the issue of the omitted benzalkonium chloride, the board would like to emphasise that sufficiency of disclosure is to be assessed based on the content of the patent as a whole. Contrary to the contention of the appellant opponents, the information provided in paragraph [0020] of the patent in suit, relating to means of improving solubility, cannot be regarded as being overly broad, and further guidance of how to put this into practice is given in Formulations 2 and 6. A mere assertion that a research programme would be required in this respect is not enough to support a finding of insufficiency.

Analogous reasoning applies to the stability data provided in document (66). Moreover, as pointed out by the appellant patentee, any instability demonstrated was not on a time scale that would preclude therapeutic use.

Finally, the mere fact that further patents were subsequently filed relating to specific aspects of formulating prostaglandins, such as document (67), cannot in itself be regarded as constituting proof of insufficiency with respect to the patent in suit.

With respect to the priority document (36), the same considerations apply *mutatis mutandis*. Although Formulation 4 of the patent in suit is absent therein, an analogous example is provided for a structurally similar active ingredient (see page 17). Therefore, as set out above in point 6.2, the claimed invention is also considered to be sufficiently disclosed in document (36).

6.3.2 The appellant opponents further criticised the nature of the experimental models used in the patent in suit, and contended that results obtained did not provide convincing evidence that FIE would be suitable for treating the claimed indications. However, according to established case law, absolute proof of clinical utility in human subjects is not required, as long as the observed effects directly and unambiguously reflect the therapeutic application (see e.g. T 609/02, Reasons, point 9).

In the present case, as outlined above in point 6.2, two different models were used to assess two different aspects central to the claimed indications, namely, a guinea pig model for conjunctival hyperemia and lasered

cynomolgus monkeys for IOP-lowering effect (cf. paragraphs [0062], [0067], respectively). Similar models have been used for the same purpose in the prior art, such as document (3), wherein it is explained that the monkey eye is used for the determination of effects on IOP, since it is highly reminiscent of the human eye, but that it is unsuitable for evaluating the side effects, so that different animal models must be used for this purpose (page 10, line 21 to line 28). Therefore, in the absence of evidence to the contrary, the board sees no reason to doubt that the models employed in the patent in suit deliver meaningful results reflecting suitability for the claimed treatment.

Moreover, as set out in the decision cited above, once such evidence is available from the patent in suit, then post-published evidence may be taken into account. In the present case, product information document (54) issued by the European Medicines Agency confirms the approval of Travatan, which comprises FIE (referred to as "travoprost"), for the indications of "ocular hypertension or open-angle glaucoma" (page 2, points 2 and 4.1).

6.3.3 Finally, the appellant opponents submitted that post-published evidence represented by documents (10), (11) and (60) demonstrated that travoprost (FIE) was unsuitable for the treatment of normal tension glaucoma (NTG), which was a medical indication falling within the terms of the claims.

In this context, the appellant opponents pointed to passages in said documents according to which, in order to slow the progression of visual field loss, the target value for IOP reduction in NTG patients was 30%

(see e.g. document (10) and (11), first paragraphs of the introduction). However, the board notes that document (60) quotes an expert in the field to the effect that IOP should be lowered "as low as you can safely get it" (see page 27, middle column). Similarly, document (10) refers to a ">20% reduction in average IOP" as being "a reasonable or good response", and this benchmark is also used in document (11), whereby about a third and half the eyes examined, respectively, fell into this category (see "Conclusion" in the respective Abstracts, on the first pages of these documents). It cannot therefore be concluded from these documents, as argued by the appellant opponents, that a reduction of 30% is indispensable in order to achieve a clinical benefit, or that travoprost is ineffective in treating NTG.

The appellant opponents further emphasised the lack of predictability as to which patients would benefit from treatment, with particular reference to document (10), wherein it is stated that "the present study was unable to identify any factors that might have been useful in predicting those patients with NTG in whom a significant effect of travoprost would be expected". However, it is not necessary for sufficiency that a "significant effect" be achieved, and a variability in response is inherent in any treatment.

Support for the fact that travoprost is indeed effective in lowering IOP in NTG patients is provided by documents (117) and (118) (see "Conclusion" in the respective Abstracts, on the first pages of these documents). The appellant opponents criticised in this context that, according to the appellant patentee's own submissions, IOP reduction alone could not be equated with treatment. However, the board notes that it is

this aspect that has been challenged by the appellant opponents. Moreover, it is additionally disclosed in said conclusion of document (118) that the travoprost composition was well tolerated.

Consequently, based on the evidence provided, the board sees no reason to doubt that FIE can be seen as beneficial in the management of NTG.

6.4 Having regard to the above considerations, the board concludes that the requirement of sufficiency of disclosure is met for the invention as defined in the main request, and the objections under Article 100(b) EPC are to be rejected.

7. *Main request, Novelty (Articles 52(1) and 54 EPC)*

For the reasons set out above in point 5.2, the present disclaimer is considered to properly exclude the relevant disclosure of document (1). Moreover, in view of the conclusion that the claimed priority is valid (cf. above point 5.3), no further novelty objections were raised by the appellant opponents.

Accordingly, the subject-matter of the main request meets the requirements of novelty.

8. *Main request, Inventive step (Articles 52(1) and 56 EPC)*

8.1 In accordance with the problem-solution approach applied by the boards of appeal to assess inventive step, it is first necessary to identify the closest prior art, then to determine in the light thereof the technical problem which the claimed invention addresses and successfully solves, and finally to examine whether

or not the claimed solution to this problem is obvious for the skilled person in view of the state of the art.

Contrary to the submission of the appellant opponents, the problem-solution approach was not merely developed as an exercise in time saving, but rather in order to ensure an objective assessment of inventive step and avoid *ex post facto* analysis of the prior art (cf. "Case Law of the Boards of Appeal of the EPO", 7th edition 2013, chapter I, section D, point 2).

Accordingly, regarding the first step of choosing the closest prior art, care must be taken to identify a starting point which the skilled person would have realistically taken under the circumstances of the claimed invention. Therefore, the first consideration in this selection is whether a prior art document discloses subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention. A further consideration is the structural similarity with the claimed invention, in terms of common relevant technical features. In cases of doubt, before an inventive step can be acknowledged, the problem-solution approach should be repeated taking possible alternative starting points (Case Law, *supra*, I.D.3; cf. also T 1760/11, point 10.1, and T 967/97, point 3.2).

8.2 The patent in suit relates to the treatment of glaucoma and ocular hypertension by means of prostaglandin analogues (e.g. paragraph [0001]). It is further elaborated therein that, although naturally-occurring prostaglandins are known to lower IOP after topical application, they generally cause inflammation and conjunctival hyperemia, and that these side effects

have been observed to persist in many synthetic prostaglandins (paragraph [0004]).

In this context, document (3) is then discussed in some detail, as disclosing esterified $PGF_{2\alpha}$ analogues, synthetically modified to include a phenyl ring, and retaining the potent IOP-lowering effect of the parent $PGF_{2\alpha}$ isopropyl ester (IE), while decreasing the degree of conjunctival hyperemia. The subclass of 17-phenyl-18,19,20-trinor analogues is disclosed as being preferred and, most particularly, the 13,14-dihydro derivative (latanoprost). In contrast, 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE (i.e. compound 4 of document (3), designated as compound C in the patent in suit) is reported to still display unacceptable hyperemia (cf. patent in suit, paragraphs [0005], [0006]).

In the section "Summary of the Invention", the patent in suit highlights that "the addition of a trifluoro-methyl group to the *meta* position on the phenoxy ring at the end of the omega chain provides a compound having excellent IOP reduction without the significant side effects found with other, closely related compounds" (paragraph [0010]).

Form the foregoing, the board concludes that the patent in suit relates to the field of topical ophthalmic prostaglandin analogues for the treatment of glaucoma and ocular hypertension, and aims at providing treatments having an improved therapeutic profile.

8.3 The appellant opponents did not dispute that document (3) constitutes a suitable closest prior art. However, they maintained that document (4) represented

at least an equally suitable starting point for the assessment of inventive step. The board does not agree:

8.3.1 Document (4) is directed to investigation into the receptors involved in the ocular hypotensive activity of PGE_2 and $PGF_{2\alpha}$, and in particular into the postulate that the EP_2, EP_3 and FP receptor subtypes are discrete entities in this context (see page 545, 546, Summary and Introduction). To this end, a number of selective ligands, including the two FP-receptor agonists 17-phenyl $PGF_{2\alpha}$ and fluprostenol were investigated for the effect of single doses on IOP in dogs and monkeys (cf. Tables 1 and 2). Three ligands were then selected, including 17-phenyl $PGF_{2\alpha}$, for further studies in monkeys using a 5-day, b.i.d. dosing regimen (Figures 1 to 3). Finally, radioligand binding studies were performed with a diverse variety of prostanoids, including, 17-phenyl $PGF_{2\alpha}$ and fluprostenol (Figures 4 to 6). Based on these studies, it was concluded: "These findings also suggest that the decrease in intraocular pressure produced by EP_3- and FP-receptor agonists is indeed mediated by different receptor subtypes" (see page 552, last sentence, and page 546, last sentence of Summary).

8.3.2 Thus, as outlined above in point 8.3.1, document (4) relates to a mechanistic investigation into receptor pharmacology underlying the ocular hypotensive activity of prostanoid analogues. The structurally diverse range of ligands are selected and classified in this study according to their selectivity for the specific receptor subtypes of interest. No information is provided with respect to the side effects of the compounds tested.

However, as set out in the patent in suit, and in document (3) cited therein, the problem of side effects was known to be a serious liability, potentially limiting the practical usefulness of prostaglandins and their analogues as drugs for the treatment of glaucoma and ocular hypertension (cf. document (3), page 2, line 45 to page 3, line 3). This is also confirmed by a number of further cited prior art documents (cf. e.g. documents (14), page 241, first paragraph; (18), page 456, "Summary and Conclusions"; (20), page 510, sentence bridging left- and right-hand columns; (23), page 692, left-hand column; (27), page 243, left-hand column, third paragraph; (30), page 535, lines 10, 11; (31), page 7, "Prostaglandine", first paragraph).

8.3.3 In view of the exclusive focus of document (4) on mechanistic aspects of IOP reduction, and complete absence of any discussion of utility in glaucoma treatment, or the critical issue of side effects, it is concluded that this document cannot be considered as being a suitable candidate as closest prior art.

8.4 In contrast, as summarised above in point 8.2, document (3) discloses the use in the treatment of ocular hypertension and glaucoma of a class of phenyl-substituted prostaglandin esters, and addresses both the issues of maintaining IOP reduction and decreasing side effects. It is therefore concerned with the same field and purpose as the patent in suit, and discloses structurally closely related compounds. The fact that it can be seen as a realistic starting point for further development in the field is confirmed by the above-referenced documents (14), (23), (27), (30) and (31), which all report research into the class of compounds first disclosed in document (3).

8.5 The further arguments of the appellant opponents in favour of document (4) as closest prior art are not considered to be convincing for the following reasons:

8.5.1 With reference to documents (71), (73) and (74), the appellant opponents argued that IOP-lowering activity alone, that is, without reference to side-effect profile, was recognised as the gold standard for establishing utility in the treatment of glaucoma and ocular hypertension. However, the board does not consider that the cited documents provide support for this submission:

Document (71) relates to a comparative review with respect to the responses of eyes of different species to topically applied prostaglandins (PGs), in terms of both hypotensive effect and side effects (see page 349, title; page 362, first sentence; page 363, Table 1). The skilled reader would also be aware of the significance of the latter from a further chapter from the same book, cited in the present proceedings as document (18) and referred to above in point 8.3.2. It is therefore in this context that the skilled person would read document (71) and the concluding paragraph cited by the appellant opponents (page 364). This is also consistent with the tentative quality of the statement therein, according to which "PGs or related eicosanoids, especially their more potent esterified prodrugs, represent a new class of ocular hypotensive agents that **may** prove useful in the therapeutic control of glaucoma" (emphasis added).

Document (74), which was published in the same year as document (71) (1989), is similarly cautious in its concluding statements (see page 74, last paragraph), and the issue of side effects is repeatedly mentioned

therein, also in the context of the topical application of $PGF_{2\alpha}$-IE (see page 65, left-hand column, first paragraph, and also page 74, sentence bridging, left- and right-hand columns).

Finally, the appellant opponents referred to the following statement in document (73): "many prostaglandin derivatives are capable to decrease intraocular tension when used topically, i.e. they are useful for the treatment of glaucoma". However, this sentence is embedded in a single introductory paragraph of a patent document relating to the development of a novel process for the preparation of 13,14-dihydro-15(*R*)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ esters, as disclosed in document (46) (page 1, lines 15 to 24), which is a family member of document (3). The skilled person would therefore read said statement, in the context of the prior art cited (cf. above point 8.2), as representing an oversimplification in the interest of brevity.

Consequently, these documents cannot support the appellant opponents' contention that the issue of side effects was a secondary consideration that should be disregarded in choosing the closest prior art.

8.5.2 In terms of structure, FIE is distinguished from the closest compounds of documents (3) and (4) by a single feature, namely, in the *meta*-CF_3 substituent and an isopropyl ester group, respectively. Therefore, considerations of structural proximity cannot override the primary criterion of identity of purpose and objective, as outlined above in points 8.1 to 8.4. In this context, the appellant opponents emphasised the relationship of fluprostenol and FIE as parent and prodrug, with reference to document (15). However, the

evaluation of obviousness of structural modifications undertaken with reference to further prior art documents is a matter to be considered in the last rather than the first step of the problem-solution approach, as set out above in point 8.1.

8.5.3 Finally, the board cannot agree that the fact that document (4) is authored by employees of a pharmaceutical company is relevant in the present context. Whatever the ultimate aim of the research published might be, the skilled person would nevertheless assess the content of this document at face value, based on the information actually disclosed therein.

8.6 In view of the above, the board concludes that document (3) is a suitable closest prior art document, in accordance with the problem-solution approach, and that the skilled person would not have considered document (4) for this purpose.

Since the board does not regard document (4) to be a realistic starting point for the assessment of inventive step, the rationale behind decision T 967/97, cited by the appellant opponents, is not applicable to the present case (cf. also T 1760/11, Reasons, point 10.3.7).

Consequently, the board sees no reason to deviate from the starting point indicated in the patent in suit for the assessment of inventive step. Document (3) is therefore considered to represent the closest state of the art.

8.7 According to the problem-solution approach, it is now necessary to determine the problem which the claimed

invention addresses and successfully solves in the light of document (3).

The appellant patentee defined the problem to be solved as lying in the provision of a treatment of glaucoma and ocular hypertension with an efficacious IOP reduction, and reduced incidence of conjunctival hyperemia.

The solution as defined in the claims relates to the use of FIE, which differs from the structurally closest compound 4 of document (3), which is designated as compound C in the patent in suit, in the *meta*-CF_3 substituent at the 16-phenoxy group.

8.8 As a next step, it must be established whether it has been rendered plausible that the problem defined under point 8.6 has been successfully solved over the whole scope claimed.

With respect to the aspect of reduction in hyperemia, the appellant patentee relied on the data provided in Table 3 of the patent in suit (page 17), and in the graphic presentation thereof in Figure 1. The two curves of interest in the latter are those designated "16-phenoxy-$PGF_{2\alpha}$" and "fluprostenol", which correspond to the results in Table 3 for comparative compound C and for FIE (compound B), respectively. It can be seen that there is a higher incidence of conjunctival hyperemia for compound C than for FIE, but that the separation of curves is less marked at lower doses, and that no difference in this respect is observed at a dose of 0.03 µg per eye.

The appellant patentee argued that the failure to detect a difference was due to limitations in the

biological model employed. However, the board notes that said model is the one chosen by the appellant patentee in order to substantiate the alleged improvement. As explained in the previous paragraph, the absence of a difference in hyperemia at lower doses is also consistent with the general trends in Figure 1, and this result cannot therefore be assumed to be a mere artefact. This situation is to be distinguished from that underlying decision T 1850/10, cited by the appellant patentee, wherein an isolated deviation was observed in an otherwise consistent array of results (see Reasons 4.3).

Moreover, the relevant question is not whether the skilled person would be "particularly interested in what was happening at the extremities of the dose-response curves", but rather whether such doses can be regarded as being suitable doses, encompassed within the terms of the claimed applications. In this regard, it is noted that the dose of 0.03 µg per eye is well within the range of 0.01 to 100, indicated as being preferred in the patent in suit (paragraph [0016]). In addition, according to the appellant patentee's own submission with respect to auxiliary request 1, documents (58) and (59) provide evidence for an IOP-lowering effect at such levels (see document (58), Table 4 and associated text on page 427; document (59), Figures 1 and 4 (note: 0.0001% = dose of 0.03 µg for a drop size of 30 µL; cf. page 32, right-hand column, line 15), and page 34, left-hand column, third full paragraph).

Consequently, the data provided in Table 3 of the patent in suit cannot support a lower propensity for FIE to cause conjunctival hyperemia over the full scope claimed.

8.9 The problem to be solved must therefore be reformulated in a less ambitious manner, as lying in the provision of alternative treatment of glaucoma and ocular hypertension.

Having regard to the data provided in the patent in suit, in Examples 5 and 6, and corresponding Figures 1 and 2, the board is satisfied that this problem has been solved.

8.10 It remains to be investigated whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

As becomes evident from the summary in point 8.2 above, document (3) is focused on prostaglandin derivatives in which the omega chain has been modified to contain a ring structure, for the topical treatment of glaucoma or ocular hypertension (page 2, lines 1 to 4; claims 1, 12, 23). This group of compounds is disclosed as exhibiting the unique property of causing insignificant ocular side effects while retaining the IOP lowering effect (page 11, lines 29 to 31). The structures envisaged are disclosed in more detail on page 3, line 7 to page 4, line 30. In all the exemplified compounds (see Table 1, and page 4, lines 8 to 20), the alpha chain is an isopropyl ester, and said ring structure in the omega chain is a phenyl group (cf. also e.g. page 3, lines 30 to 40, and page 4, line 3). One of the compounds listed is compound 4, which only differs from FIE in the lack of the *meta*-CF_3 substituent at the phenyl ring (cf. above point 8.7).

Amongst the further structural modifications contemplated in document (3) is the present

substitution of the phenyl ring, and the trifluoromethyl group is specifically listed as a suitable substituent (see page 4, lines 3 to 5; claim 6). Therefore, in seeking a solution to the problem defined in point 8.9 above, it would have been obvious for the skilled person to have considered the corresponding modification of compound 4, thereby arriving at the claimed subject-matter. In other words, the skilled person would not require any inventive skill to select a compound within the general teaching of document (3) and use it in the manner suggested therein.

8.11 The appellant patentee submitted that, based on the teachings of prior art documents (3), (4) and (23), the skilled person would have expected the *meta*-CF_3 substitution of compound 4 to have a detrimental effect on IOP reduction; the comparable efficacy demonstrated in Example 6 and Figure 2 of the patent in suit would therefore establish an inventive step.

The appellant patentee firstly referred to the data for compounds 1 and 8 in Table V of document (3) as demonstrating that substitution with a *para*-OMe group led to a decrease in efficacy. However, in document (3) itself these results are commented as follows (page 11, lines 5 to 8; emphasis added): "substituting a hydrogen on the ring structure of 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE with a methoxy group eliminated much of the ocular irritating effect **preserving most of the intraocular pressure lowering effect**". Moreover, regardless how the significance of this effect is to be assessed, the board sees no logical reason why a skilled person should extrapolate a specific observation relating to substitution at a different structure, bearing a methylene group rather than an

oxygen atom adjacent to the phenyl ring (i.e. phenyl vs. phenoxy), with a different substituent type (-OMe vs. $-CF_3$), at a different position of the ring (*para* vs. *meta*).

The same applies to document (23) (see page 701, "Structure-activity relationships"), in which the effects of substitution at the phenyl ring in 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE are reported (designated as compound 2 in document (3)). Again, in view of the differences in structure, and nature and/or position of the substituents, no sound conclusion can be drawn as to the expected effect of *meta*-CF_3 substitution at the present 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE structure.

Finally, the appellant patentee pointed to document (4) as disclosing modest efficacy for fluprostenol (page 548, Table 2 and following paragraph); it was further argued, with reference to document (15), that no improvement in this respect would be expected on esterification. The board cannot accept this line of reasoning: In document (4), fluprostenol is disclosed as being a "potent ocular hypotensive" (see page 545, Abstract; page 551, "Discussion", first sentence). Based on the teaching of document (15), according to which ester derivatives of prostaglandins act as prodrugs increasing efficacy of delivery to intraocular tissues (see page 185, second complete paragraph), the skilled person would expect this activity to at least be maintained on esterification. Moreover, the skilled person would not exclude the possibility that an increase in IOP lowering activity might be observed on esterification, in the case of free acids exhibiting poor ocular delivery. It is therefore concluded that the skilled person would not derive any clear teaching

from documents (4) and (15) with respect to the expected efficacy of FIE.

8.12 Consequently, the main request is rejected for lack of inventive step.

Auxiliary request 1 filed as auxiliary request 18 with letter of 8 June 2015

9. *Auxiliary request 1, Article 84 EPC*

The assessment presented above in point 3 applies to this request *mutatis mutandis*.

In addition, an objection was raised relating to the introduction of the feature defining the dosage of FIE as being "between 0.05 and 10 micrograms per eye". However, this feature clearly defines the amount to be applied to the eye at each instance of administration, and is therefore to be read as characterising the medical use, rather than the product used. In contrast, the feature "therapeutically effective amount" relates to the amount of FIE in the composition, and thus excludes compositions comprising negligible, therapeutically inactive amounts for the purpose claimed. These two features therefore relate to different aspects of the subject-matter of claim 1, and are in no way inconsistent or in need of being reconciled. The juxtaposition thereof is not considered to lead to lack of clarity.

Therefore, the amendments introduced do not give rise to objections under Articles 84 EPC.

10. *Auxiliary request 1, Article 123(3) EPC*

The claims have been restricted with respect to the claims of the main request, and the same reasoning and conclusions apply (see above point 4). Indeed, the appellant opponents did not raise any additional objections in this respect.

Consequently, the requirement of Article 123(3) EPC is satisfied.

11. *Auxiliary request 1, Articles 100(c), 123(2) EPC*

11.1 As set out above in point I, the application as originally filed on which the patent in suit is based is on file as document (34), and the root application as document (35). These two documents differ in their claims, but have identical descriptions, as does the parent application. In the following, reference is therefore only made to document (35) when referring to the description as originally filed.

11.2 Document (35) discloses "the use of cloprostenol, fluprostenol, their analogues and their pharmaceutically acceptable salts and esters to treat glaucoma and ocular hypertension" (see e.g. page 1, lines 4 to 7), as well as the topical application of ophthalmic compositions thereof (page 4, lines 22 to 26; see also page 7, lines 10 to 12 and 19). Said analogues are further defined by means of formula (IV) (page 5, line 18 to page 7, line 2). The list of preferred compounds in the paragraph on page 7, lines 4 to 8, includes "fluprostenol isopropyl ester (compound B)". In this respect, said paragraph refers to Table 2 (page 29), wherein the corresponding structural formula now introduced into the claims is depicted. Therefore, (+)-FIE is clearly identified as one of six preferred compounds.

With respect to the dosage ranges for topical administration of the compounds of formula (IV), this is disclosed to be "generally between about 0.001 and about 1000 micrograms per eye (µg/eye) and is preferably between about 0.01 and about 100 µg/eye and **most preferably between about 0.05 and 10 µg/eye**" (page 7, lines 10 to 17, emphasis added).

The appellant opponents argued in this context that, in order to arrive at the subject-matter now claimed, an unallowable selection from two lists would be required, namely, from a first list of preferred compounds and a second list of dosage ranges.

The board cannot concur with this assessment:

As can be seen from the passage cited above, the three possible dosage ranges are not presented as equally preferred alternatives, to be selected according to the structure of the active ingredient, but rather as a hierarchical list, whereby the range now introduced into the claims is designated as most preferred. The skilled person would therefore directly and unambiguously identify the specific combinations thereof with the list of preferred compounds as constituting a preferred embodiment within the context of document (35). This is also consistent with the examples relating to FIE, that is, Examples 5 and 6, since the dosages for which IOP lowering activity was measured (0.3 µg; cf. Figure 2), and for which an advantage in hyperemia incidence over compound C is disclosed (0.1, 0.3, 1 µg; cf. Figure 1) lie within said most preferred range.

It is therefore concluded that only a single selection of FIE, from a list of six preferred active ingredients, is required in order to arrive at the subject-matter claimed.

11.3 With respect to the disclaimer introduced into the claims, the board considers that the analysis developed above in point 5 applies *mutatis mutandis*.

11.3.1 In particular, in view of the disclosure in document (1) of a dosage range of "between about 0.05 and 5 µg/eye" (page 5, lines 44 to 66), the introduction of the disclaimer remains necessary and appropriate in order to establish novelty over this document (cf. above point 5.2).

11.3.2 Moreover, the priority claim from document (36) remains valid (cf. above point 5.3), since the disclosure therein with respect to the dosage ranges envisaged is identical to that in document (35), reproduced above in point 11.2. It is further noted that Examples 5 and 6 of document (35) are also present in document (36) as Examples 1 and 2, respectively.

The appellant opponents highlighted in this context that the paragraph in the description of document (35) listing the preferred compounds (page 7, lines 4 to 8) was missing in document (36). However, as discussed above in point 5.3.1, FIE, as defined in the present claims, is directly and unambiguously identified in individualised form in document (36) as one of two specific compounds of the invention. The nature of this disclosure is to be distinguished from that of document (1), wherein FIE is only disclosed together with a particular combination of specific features (cf. above point 5.2.2). The submission of the appellant opponents

that a different standard has been used in assessing these two disclosures is not therefore considered to be justified.

11.4 Consequently, auxiliary request 1 does not contain subject-matter which extends beyond the content of the application as originally filed, or the earlier parent and root applications as originally filed.

12. *Auxiliary request 1, Article 100(b) EPC*

The reasoning and conclusions set out above in point 6 for the main request apply equally to auxiliary request 1.

In addition, as explained above in point 9, it is not considered that the features of claim 1 are in any way contradictory. Therefore, the additional sufficiency objection based on this assumption also does not hold.

Hence, it is concluded that the invention as defined in the claims is disclosed in the patent in suit in a manner sufficiently clear and complete to be carried out by a person skilled in the art.

13. *Auxiliary request 1, Novelty (Articles 52(1) and 54 EPC)*

As for the main request, it is considered that the present disclaimer excludes the relevant disclosure of document (1), and that the priority date from document (36) is validly claimed (cf. above points 7 and 11.3).

Accordingly, the subject-matter of the auxiliary request 1 meets the requirements of novelty.

14. *Auxiliary request 1, Inventive step (Articles 52(1) and 56 EPC)*

14.1 Document (3) remains the closest prior art for the reasons stated above in points 8.2 to 8.6.

14.2 The problem to be solved in the light of the closest prior art, as submitted by the appellant patentee and derivable from the patent in suit (see paragraphs [0005], [0010], [0062]), can be seen as lying in the provision of a treatment of glaucoma and ocular hypertension with an efficacious IOP reduction, and reduced incidence of conjunctival hyperemia (cf. above point 8.7).

The solution as defined in the claims relates to the use of FIE in a dosage range of between 0.05 and 10 µg per eye.

14.3 As a next step, it has to be decided whether it has been rendered plausible that the problem defined under point 14.2 has been successfully solved over the whole scope claimed.

The appellant patentee again relied on the data provided in Examples 5 and 6 of the patent in suit, and in corresponding Figures 1 and 2, with respect to FIE (compound B) and comparative compound C (compound 4 of document (3)).

In view of this data, the board is satisfied that that FIE provides an improved therapeutic profile with respect to compound C in the dosage range claimed. The problem as defined in point 14.2 is considered to have been credibly solved.

14.4 The appellant opponents challenge to the reliability and pertinence of this data is not considered to be convincing:

14.4.1 The criticism of the appellant opponents with respect to the exclusion in Figure 1 of the score of "1" in the assessment of conjunctival hyperemia is not warranted. The appellant opponents were not able to refute the explanation provided by appellant patentee, according to which this score only related to "enlargement of vessels normally visible at limbus and on superior rectus muscle" and was therefore not indicative of conjunctival hyperemia. It cannot therefore be accepted that said exclusion is arbitrary, as alleged in the declaration submitted as document (70) (cf. point 46).

14.4.2 The appellant opponents further criticised the nature of the models used and the number of data points recorded. However, as explained above in the context of assessing sufficiency for the main request (see point 6.3.2), the board sees no reason to doubt that the models chosen in the patent in suit are fit for purpose, in the absence of evidence to the contrary. Moreover, no evidence has been provided that the non-monotonic variations in the curves in Figure 1 are in any way unusual for *in vivo* models. Similarly, the allegation that the differences in hyperemia incidence are due to differences in solubility amounts to an unsubstantiated allegation. It is therefore concluded that the reliability of the data in Figure 1 has not been put into doubt.

14.4.3 With respect to Figure 1 it was additionally questioned that a lower incidence of conjunctival hyperemia could be considered plausible for the lower end of the claimed range of 0.05 µg per eye. The board

acknowledges that, at the data point of 0.03 µg, no difference is observed for compounds B and C. However, thereafter a clear separation of curves is apparent. The board therefore considers it plausible that an improvement in this respect is already present at the dosage of 0.05 µg per eye, and for the whole of the claimed range.

14.4.4 Finally, appellant opponent 5 challenged the choice of comparative compound amongst those disclosed in document (3). However, according to consistent case law of the boards of appeal, when a comparative test is submitted to demonstrate an improved effect over the closest prior art, the nature of the comparison must be such that the effect is convincingly shown to have its origin in the distinguishing feature of the invention (see T 197/86, OJ EPO, 1989, 371, Headnote). The reason for requiring comparison with compounds of greatest possible structural proximity is because it is only here that the factor of unexpectedness is to be sought (see T 181/82, OJ EPO 1984, 401, points 4 and 5).
In the present case, the comparative tests relied on fulfill these criteria, since compound 4 (compound C) chosen for comparison is the structurally closest compound disclosed in document (3), differing from FIE only in the absence of a single substituent. In contrast, for latanoprost (document (3), compound 9; designated as compound E in patent in suit), which was suggested by appellant opponent 5 as a suitable comparative compound, three structural modifications are required in order to arrive at FIE, and the path from the former to the latter leads through compound 4.

In decision T 942/98 cited by appellant opponent 5, it was questioned whether an improved effect only demonstrated at the direct interface to the prior art

was sufficient in order to demonstrate that an improvement applied for the entire breadth of the claim, that is, also for claimed embodiments further removed from said interface (see Reasons, point 4.4). This decision is not relevant to the present case wherein a single compound is employed in the therapeutic use as claimed. Therefore, there is no further claimed breadth in this respect for which an inventive step need be demonstrated.

The board therefore concludes that the comparative tests identified above in point 14.3 can be regarded as being pertinent since they reflect the impact of the distinguishing feature of the invention.

14.5 It remains to be investigated whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

14.5.1 The skilled person starting from compound 4 would have first looked to document (3) itself for pointers to a solution to the problem posed.

As was explained above in points 8.10 and 8.11, it is considered that, based on the teaching of document (3), the skilled person would have expected comparable IOP lowering effects for compounds 4 and FIE. The question that therefore remains to be decided is whether any teaching is provided in document (3) that would lead the skilled to expect the introduction of a *meta*-CF_3 group in compound 4 to lead to a product exhibiting a lower incidence of conjunctival hyperemia.

As previously set out above in point 8.10, document (3), in its broadest disclosure, identifies the common and crucial structural feature of the

prostaglandin analogues, responsible for properties of IOP reduction with the absence of significant ocular side effects, as lying in the ring in the omega chain (see page 3, lines 4 to 6; page 11, lines 29 to 31). Within this framework, a number of structural modifications are explored, as also reflected in the claims (see page 4, lines 8 to 20, in conjunction with Table 1, and claims 1 to 6); 17-phenyl-18,19,20-trinor analogues are generally designated as being most preferred (see page 4, lines 21 to 24; page 10, lines 29 to 32; page 10, line 57 to page 11, line 1; page 11, lines 34, 35; claims 7 to 10). Substitution at the phenyl ring is also generally contemplated (see page 4, lines 3 to 5; claim 6), and exemplified in the form of compound 8, which differs from compound 1 in the introduction of a methoxy group at the *para* position (cf. Table I).

The results obtained for the side effect of conjunctival hyperemia are discussed in the paragraph on page 10, lines 48 to 53, with reference to Table IV. However, the impact of phenyl ring substitution on this side effect is not mentioned therein, and all the compounds listed in Table IV are unsubstituted at this position. The skilled person would not be able to derive any useful information pointing to the present modification.

In this context, the appellant opponents cited the following sentence from document (3) (page 11, lines 31 to 33, emphasis added): "Furthermore, substituents in the ring structure and/or in the omega chain may be introduced in **certain molecules** still exhibiting some side-effects in the eye".

However, the board notes that this sentence is very broad in suggesting a wide range of possible structural variations, without specifying which side effect, that is, irritation or conjunctival hyperemia, is to be addressed. In accordance with the teaching of document (3), these two side effects are distinct, since they are addressed in separate sections (see page 10, lines 29 to 47, and 48 to 53), and different trends can be seen in the corresponding Tables III and IV. Moreover, the reference to "certain molecules" implies that no single modification type is universally applicable, but will depend on the specific structure concerned.

It is further noted that the sentence reproduced above is embedded in a concluding paragraph, summarising previous observations. The relevant disclosure relating to substitution at the phenyl ring is to be found on page 4, lines 35 to 37; page 10, lines 33 to 36 and 45 to 47; and page 11, lines 5 and 6. Each of these passages relate to substitution with a different substituent (-OMe vs. $-CF_3$), in a different molecule (16-phenyl- vs. 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE; cf. compounds 1 and 4), and the influence thereof on a different side effect (ocular irritation vs. conjunctival hyperemia).

Consequently, no clear guidance can be found in document (3) that would lead the skilled person to expect an improvement in conjunctival hyperemia to result from the present substitution.

14.5.2 Document (4) also cannot help in this respect:

The appellant opponents argued that, in view the fact that fluprostenol was known at the priority date to be

active as an ocular hypotensive, and the fact that it could readily be converted into FIE, it would have been obvious for the skilled person to simply synthesise the latter and establish its side effect by means of routine tests.

However, in the board's opinion, this approach relies on a hindsight knowledge of what is claimed. There is no mention of side effects at all in document (4), and there would therefore have been no reason for the skilled person to select the modification disclosed therein, as opposed to any of the many others encompassed by document (3), in the absence of any expectation of being able to solve the problem posed.

In decision T 777/08 (OJ EPO 2011, 633) cited by the appellant opponents, the starting point was the amorphous form of atorvastatin, and it was found that the skilled person would have a clear expectation that a crystalline form thereof would provide a solution to the problem of providing a product having improved filterability and drying characteristics; the specific polymorph claimed was found to be an arbitrary selection from a group of equally suitable candidates for solving the problem posed (see Reasons, point 5).

Similarly, in the "try and see" situation described in decision T 1364/08, it was found that the skilled person would have clearly envisaged the mutated adenovirus disclosed in the prior art as a solution to the problem posed.

These cases are therefore to be distinguished from the present, since, as explained above, the skilled person was not provided to any pointer to FIE as a solution to the problem posed.

14.6 In view of the above considerations, the board concludes that the subject-matter of auxiliary request 1 involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent with the following claims and a description to be adapted thereto:

   Claims No. 1 and 2 of auxiliary request 1 filed as auxiliary request 18 with letter of 8 June 2015 (previously filed as auxiliary request 1A' on 25 April 2014).

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated