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**Datasheet for the decision
of 4 October 2016**

Case Number: T 2506/12 - 3.3.07
Application Number: 05803151.9
Publication Number: 1827500
IPC: A61K47/48, A61K31/704,
A61K31/4995, A61K45/06,
A61P35/00
Language of the proceedings: EN

Title of invention:

PEGYLATED LIPOSOMAL DOXORUBICIN IN COMBINATION WITH
ECTEINESCIDIN 743

Patent Proprietors:

Pharma Mar S.A., Sociedad Unipersonal
Ortho Biotech Products L.P.

Opponent:

Teva Pharmaceutical Industries Ltd.

Relevant legal provisions:

EPC Art. 54, 56

Keyword:

Novelty - second (or further) medical use (yes)
Inventive step - reasonable expectation of success (yes)

Decisions cited:

T 1859/08, G 0005/83, G 0002/08



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Case Number: T 2506/12 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 4 October 2016

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Decision under appeal:

**Interlocutory decision of the Opposition
Division of the European Patent Office posted on
25 October 2012 concerning maintenance of the
European Patent No. 1827500 in amended form.**

Composition of the Board:

Chairman D. Semino
Members: R. Hauss
 D. T. Keeling

Summary of Facts and Submissions

- I. European patent No. 1 827 500 was granted on the basis of twenty-six claims.

Claims 1 and 2 read as follows:

"1. The use of ET-743 in the preparation of a medicament for an effective treatment for cancer of the human body by combination therapy employing an effective therapeutic amount of ET-743 with an effective therapeutic amount of Pegylated Liposomal form of the anthracycline Doxorubicin ("PLD").

2. The use of PLD in the preparation of a medicament for an effective treatment for cancer of the human body by combination therapy employing an effective therapeutic amount of PLD with an effective therapeutic amount of ET-743."

As explained in paragraphs [0003] and [0004] of the patent specification, the term "ET-743" stands for "Ecteinascidin 743", also called "trabectedin" or "Yondelis". Furthermore, a specific pegylated liposomal form of doxorubicin hydrochloride is marketed as "Doxil" (see paragraph [0018] of the patent specification and document D16a (as identified in point III below), page 2419).

- II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step and extended beyond the content of the application as filed (Articles 100(a) and (c) EPC).
- III. The documents cited during the opposition and appeal proceedings included the following:

D1: Zeltia Group Annual Report 2002

D2: Zeltia Junta General de Accionistas 2003

- D2a: English translation of document D2
- D3: Annals of Oncology 13, 1737-1742 (2002)
- D4: Annals of Oncology, 15(3), 440-449 (March 2004)
- D7: Drugs 62(8), 1185-1192 (2002)
- D8: Anti-Cancer Drugs 13, 381-393 (2002)
- D12: Clinical Cancer Research 7, 3251-3257 (2001)
- D16: Tibotec Therapeutics, Doxil Product Information, printed 2/2005
- D16a: Physicians' Desk Reference, 57th edition 2003, 2419-2423, published 23 December 2002
- D19: Breast Cancer Research and Treatment 77, 185-188 (2003)
- D20: Annals of Oncology 10, 1113-1116 (1999)
- D22: Clinical Cancer Research 7, 3040-3046 (2001)
- D29: Annals of Oncology 19, 1802-1809 (2008)
- D34: Eur J. Cancer, 48(15), 2361-2368 (2012), in press <http://dx.doi.org/10.1016/j.ejca/2012.04.001>
- D35: V.T. DeVita et al. (ed.): Cancer - Principles & Practice of Oncology, 6th edn. Philadelphia 2001, page 217
- D50: Expert Statement by José Maria del Campo, 25 March 2015, filed by the patent proprietors with letter of 7 July 2015
- D56: Journal of Clinical Oncology 28(19), 3107-3114 (2010)
- D57: Assessment Report for Yondelis, EMEA/640507/2009

IV. The decision under appeal is the interlocutory decision of the opposition division, announced on 26 September 2012 and posted on 25 October 2012, rejecting the patent proprietors' amended main request and auxiliary requests I to III and finding that the

patent as amended in the form of auxiliary request IV met the requirements of the EPC.

- V. In the decision under appeal, the opposition division came to the conclusion that, while certain dependent claims of the main request contained added subject-matter, that objection was overcome in auxiliary request I. As in the main request, the claims of that request related to a specified medical use involving the combination of ET-743 and PLD for treating cancer in the human body. Prior-art citations D1 and D2 disclosed that a clinical phase I trial of Yondelis (ET-743) in combination with Doxil (PLD) was in progress, but did not provide any information about the success of the treatment. Hence the subject-matter of the claims of auxiliary request I was novel over the disclosure of documents D1 and D2, because the achievement of a clinical benefit had to be taken into account as a technical feature in the assessment of novelty. Starting from the teaching of document D1, the objective technical problem was thus the provision of a safe and effective treatment of cancer. Since there was a reasonable expectation of success that the combination therapy of PLD and ET-743 would solve that problem, especially in view of the teaching of documents D1 and D12, the claimed solution did not involve an inventive step.

The same reasoning with regard to inventive step applied to auxiliary request II, since claim 1 of that request was identical to claim 1 of auxiliary request I, and to auxiliary request III, since the additional mandatory technical features present in the claims of that request did not contribute to inventive step.

The claims of auxiliary request IV specified exact dosages for each drug. As far as auxiliary request IV was concerned, the objective technical problem in relation to the teaching of document D1 was the provision of a dosage of a combination of two anti-cancer drugs that was effective and safe in the treatment of cancer. The solution to that technical problem as defined in the claims of auxiliary request IV was not obvious, since the skilled person, due to safety concerns, would not have considered combining the two drugs at the relatively high therapeutic dosages claimed.

VI. Both the patent proprietors and the opponent lodged an appeal against that decision. For the sake of simplicity, the appellants will continue to be designated as "patent proprietors" and "opponent" in this decision.

VII. With their statement setting out the grounds of appeal, the patent proprietors filed a main request and auxiliary request I.

Claims 1 and 2 of the **main request** are identical to claims 1 and 2 as granted (see point I above).

Claims 1 and 2 of **auxiliary request I** differ from the corresponding claims of the main request by indicating upper limits for the dosages of PLD ("up to 50 mg/m² ") and ET-743 ("up to 1.3 mg/m² ").

VIII. With their reply to the opponent's statement setting out the grounds of appeal, the patent proprietors filed auxiliary requests II to IV.

The claims of **auxiliary request II** correspond to those of former auxiliary request IV, held to be allowable in

the decision under appeal. Claims 1 and 2 are identical to claims 1 and 2 of the main request but further specify that PLD is employed at a dosage of 30 mg/m² and ET-743 is employed at a dosage of 1.1 mg/m².

Claims 1 and 2 of **auxiliary request III** correspond to claims 1 and 2 of auxiliary request II with the following additions:

- in claim 1: *"...wherein said effective therapeutic amount of PLD is to be administered prior to the administration of said effective therapeutic amount of ET-743."*

- in claim 2: *"...wherein said effective therapeutic amounts of ET-743 and PLD are provided as separate medicaments and wherein said effective therapeutic amount of PLD is to be administered prior to the administration of said effective therapeutic amount of ET-743."*

Claims 1 and 2 of **auxiliary request IV** correspond to claims 1 and 2 of auxiliary request II, with the following addition in both claims:

"...wherein said effective therapeutic amount of PLD is to be administered over an infusion time of about 1 hour followed by said effective therapeutic amount of ET-743 over an infusion time of about 3 hours and wherein the infusions are to be carried out at an interval of 3 weeks."

IX. In a communication issued in preparation for oral proceedings and advising the parties of the board's preliminary opinion, the board mentioned *inter alia* that the prior art disclosed that a combination of ET-743 and PLD was indeed considered by the person skilled in the art, since it was reported in documents

D1 and D2 that clinical trials of that combination were in progress. Thus the question whether the combination of those two drugs "would" have been considered had already been answered in the prior art. The general consideration that any clinical trial might still fail due to unforeseen effects was not sufficient to establish inventive step.

- X. With letter dated 1 September 2016, the patent proprietors filed **amended versions of auxiliary requests I to III**. The amendments did not affect the wording of claims 1 and 2 of those requests.
- XI. Oral proceedings were held on 4 October 2016 in the presence of both parties.
- XII. The arguments of the patent proprietors may be summarised as follows:

Novelty - main request

While it was mentioned in documents D1 and D2 that clinical phase I trials of Yondelis (ET-743) in combination with other chemotherapy agents, including Doxil (PLD), were in progress, it was contested that said prior-art documents disclosed the therapeutic indication of treating cancer in human patients as an actual therapeutic effect or benefit.

Firstly, when medical-use claims were being considered and novelty was to be derived from the therapeutic indication, the mere statement in a prior-art citation that a certain therapy was being explored or that clinical trials were in progress did not amount to a novelty-destroying disclosure. Reference was made in that context to the established case law of the Boards of Appeal, and in particular to decision T 1859/08 of 5 June 2012 concerning a case involving combination

therapy. Documents D1 and D2 did not provide any information regarding the outcome of the relevant clinical trial and the efficacy or toxicity associated with the combination of ET-743 and PLD.

Secondly, while it was not contested that PLD was known to be an approved drug authorised for the treatment of cancer, including ovarian cancer, that was not the case for ET-743. At the publication date of documents D1 (2002) and D2 (2003) it had not been established that ET-743 could provide safe and effective treatment for any type of cancer, since that could only have been shown in a clinical phase III study. No such study had been published. It was thus not known whether both drugs had the desired activity coupled with an acceptable toxicity profile, and it could not be argued on that basis that the therapeutic benefit of the combination was implicitly disclosed in documents D1 and D2.

Inventive step

Documents D1 or D2 could be regarded as the closest prior art. The technical problem was the provision of a safe and effective treatment of cancer. It was not challenged that, based on the disclosure of those documents, combination treatment with ET-743 and PLD would have been considered by the person skilled in the art. Such treatment would not, however, have been considered with a reasonable expectation of success, because myelosuppression was a dose-limiting toxicity of ET-743 and it was furthermore known, e.g. from document D16 (supported by the clinical results reported in documents D19, D20 and D22), that PLD could potentiate myelosuppression in other drugs when administered in combination with them. This known risk taught away from the claimed invention. Apart from

that, the success rate in oncology trials was generally very low, as mentioned in the expert declaration D50 (page 2, bottom paragraph), and favourable data obtained in preclinical studies did not necessarily give an indication of success. Since extensive testing on humans was required, the person skilled in the art would have refrained from a mere "try-and-see" approach. Thus the invention of claims 1 and 2 of the main request was based on the surprising finding that the envisaged combination was acceptable in terms of safety. The envisaged combination therapy with ET-743 and PLD also had reduced side effects in comparison with the combined administration of ET-743 and doxorubicin, as well as increased efficacy in comparison with monotherapy.

It was even more surprising that both drugs could be administered at or near each drug's maximum tolerated therapeutic dosage, as specified in claims 1 and 2 of all auxiliary requests, viz. up to 1.3 or at 1.1 mg/m² in the case of ET-743, and up to 50 or at 30 mg/m² in the case of PLD.

It was further specified in claims 1 and 2 of auxiliary requests III and IV that PLD was to be administered prior to the administration of ET-743, which was preferable to co-administration. According to data reported in document D57, co-administration entailed a slower clearance of ET-743 from the plasma and thus a higher exposure to ET-743 than when it was administered as a single agent.

The definition of claims 1 and 2 of auxiliary request IV included a dosage regimen which was particularly effective in maximising activity and minimising toxicity, as shown by the data reported in

example 1 of the patent in suit and confirmed by post-published evidence D29, D34 and D56.

XIII. The arguments of the opponent may be summarised as follows:

Novelty - main request

Phase I studies for anti-cancer agents were carried out with human patients suffering from cancer, typically having a tumour previously shown at least in animal and *in vitro* studies to be sensitive to the relevant compounds. According to document D2, a combination study was carried out with patients suffering from ovarian cancer, and both PLD and ET-743 were known at that time to be effective against ovarian cancer. In particular, document D1 mentioned favourable preliminary results of clinical phase II trials of ET-743 for ovarian cancer. Document D7 disclosed *in vitro* activity of ET-743 against a wide range of solid tumour cell lines including ovarian carcinoma, as well as favourable results of clinical phase II multicentre trials primarily in patients with advanced soft tissue sarcoma, and also mentioned the fact that ET-743 was generally well tolerated. Since both drugs were known to be effective for treating the same disease, the person skilled in the art reading documents D1 or D2 would infer that their combination must have been effective for treating the disease as well.

A finding of lack of novelty would not deviate from established case law, since the circumstances of the present case were different. In the case underlying decision T 1859/08, the board had not been convinced that the prior-art document cited against novelty

actually disclosed a clinical trial with human patients involving the combination of the two relevant drugs.

Inventive step

The objective technical problem with regard to claims 1 and 2 of the main request could be defined as providing an effective treatment for cancer of the human body. It was known from documents D1 and D2 that the combination of ET-743 and PLD was eligible for clinical studies, from which it could be inferred that preclinical data had been favourable. Since the drugs had overlapping efficacy against cancer, it was implicit that their combination must also provide the desired efficacy. Although it could never be excluded that a combination might fail in clinical tests due to unexpected interactions of its components, the person skilled in the art choosing the combination of ET-743 and PLD for testing would have had a reasonable expectation of success in view of the general principles governing the use of combination therapy, as shown, for instance, in document D35, since those drugs were known to have different mechanisms of action and different dose-limiting toxicities, and PLD was furthermore known to be less toxic than other anthracyclines. Thus there was a reasonable expectation that good efficacy coupled with acceptable toxicity could be achieved. Even considering the possibility that increased myelotoxicity of E-743 might occur in combination with PLD, the skilled person would have expected to lower that risk by working at somewhat reduced dosages, as was typical for combination therapy, while still obtaining the desired therapeutic efficacy, but would not have been discouraged by an expectation of failure of the combination at all dosages.

Technical advantages which were allegedly obtained in comparison with monotherapy or with a combination of ET-743 and unencapsulated doxorubicin could not be relevant to the assessment of inventive step, since they were not based on a technical feature distinguishing the claimed subject-matter from the closest prior art.

The addition of upper limits for the dosage of each drug in claims 1 and 2 of auxiliary request I did not provide any contribution to inventive step. It was not surprising that the dosages employed in combination therapy did not exceed the dosages suitable for monotherapy.

As far as auxiliary requests II to IV were concerned, finding suitable dosages by clinical trial did not require inventive skill and was routinely accomplished by dosage escalation. It was typical for combination therapy to employ dosages lower than those used for each agent in monotherapy, and the dosages defined in auxiliary requests II to IV confirmed that expectation.

It had not been shown that a dosage regime involving sequential administration of PLD and ET-743 or specific infusion times and intervals, as defined in auxiliary requests III and IV, provided any surprising technical effect which could support inventive step.

XIV. The appellants (patent proprietors) requested that the decision under appeal be set aside and the patent maintained on the basis of the main request as filed with their statement setting out the grounds of appeal, or, in the alternative, on the basis of one of auxiliary requests I, II or III, as filed by letter of 1 September 2016, or auxiliary request IV as filed by

letter of 6 September 2013 with the reply to the opponent's grounds of appeal.

- XV. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

1. Patent in suit

1.1 The patent in suit seeks to provide medicaments for the combination treatment of cancer of the human body, and proposes a combination of the drugs ET-743 and PLD, as defined in claims 1 and 2 of the present main request.

1.2 The claims are backed up in example 1 of the patent in suit (see paragraphs [0051] ff of the patent specification) by data from a clinical phase I trial involving thirty patients suffering from various cancers.

The objectives of the study were to determine the maximum tolerated dose of ET-743 in combination with PLD 30 mg/m² administered every 21 days and to evaluate the safety profile and pharmacokinetics of the drugs when given in combination (paragraph [0051]).

In the dose-finding trial, a fixed PLD dose of 30 mg/m² was administered intravenously over one hour followed immediately by one of six doses of ET-743 (0.4, 0.6, 0.75, 0.9, 1.1 and 1.3 mg/m²) administered intravenously over three hours. This treatment was repeated every 21 days (paragraph [0052]).

It is reported that five patients, three with soft tissue sarcoma, and one each with ovarian and head and

neck cancer, had a partial response. Fourteen additional patients (five with sarcoma, and one each with carcinoid tumour, pancreatic, bladder, head and neck, thyroid, breast, gastric, SCLC and ovarian cancer) showed disease stability for longer than three months (paragraph [0059]).

From the results obtained it was concluded that the concomitant administration of PLD did not have an impact on the pharmacokinetics of ET-743, and that the maximum tolerated dose, and recommended dose, of ET-743 was 1.1 mg/m² when administered in combination with PLD 30 mg/m² (paragraphs [0060] to [0062]).

1.3 No objection under Article 100(b) EPC was raised during the opposition and appeal proceedings.

2. Novelty - main request

2.1 Independent claims 1 and 2 of the main request concern the further therapeutic application of ET-743 (claim 1) or of PLD (claim 2) in the treatment of cancer of the human body by combination therapy employing an effective therapeutic amount of ET-743 with an effective therapeutic amount of PLD.

2.2 Both claims are in "Swiss-type" format, i.e. directed to the use of a substance for the manufacture of a medicament for a specified therapeutic application.

The novelty of the subject-matter of such a claim can be derived not only from the novelty of the substance or of the method of manufacture, but also from the novelty of the therapeutic application, which is regarded as a functional technical feature, as established by decision G 5/83 of the Enlarged Board of Appeal (OJ EPO 1985, 64, order: point 2, reasons: point 21; also see Case Law of the Boards of

Appeal of the European Patent Office, 8th edition 2016, I.C.7.2.1).

This special concept of a purpose-limited process claim also applies in the present case, since the patent in suit was granted before the publication of decision G 2/08 of the Enlarged Board of Appeal, which abolished the Swiss-type format but had no retroactive effect (see G 2/08, OJ EPO 2010, 456, order: question 3, reasons: point 7.1.4).

- 2.3 Since both substances intended for the combination therapy were already known, and claims 1 and 2 of the main request do not define any specific manufacturing step, it follows that novelty may only be derived from the therapeutic application

"for an effective treatment for cancer of the human body by combination therapy employing an effective therapeutic amount of PLD with an effective therapeutic amount of ET-743",

as per the wording of claim 2, and analogous wording in claim 1.

This was not contested among the parties.

For the purpose of assessing novelty, it thus has to be examined whether the claim features which define the therapeutic application are anticipated in documents D1 or D2, and in particular whether it is directly and unambiguously derivable from at least one of those documents that a therapeutic effect, or clinical benefit, in the treatment of cancer is obtained in humans by administration of the combination therapy.

- 2.4 Documents D1 and D2 disclose that Yondelis (ET-743) had shown efficacy in the treatment of soft-tissue sarcoma and that its efficacy as sole agent in further

types of cancer was being evaluated in twenty phase II studies (see D1: page 9, columns 3 and 4; D2a: slide 12, slide 19).

Both documents disclose that Yondelis monotherapy showed efficacy in advanced ovarian cancer in a phase II trial with data obtained from 55 patients (see D1: page 9, column 4; D2a: slides 12 and 21).

Both documents also disclose that the combination of Yondelis (ET-743) and Doxil (PLD) was being tested in a clinical phase I trial for the treatment of cancer (see D1: page 9, column 3; D2a: slide 17).

Document D2 further specifies that the medical indication targeted in that combination trial was ovarian cancer (see D2a: page 8, slide 17).

2.5 Since clinical phase I trials of anti-cancer medication are carried out on human cancer patients, it can be affirmed that the purpose of treating cancer of the human body is indeed disclosed in documents D1 and D2. Both documents also disclose that the study was designed to test ET-743 and PLD in combination (see point 2.4 above).

Hence it is decisive for the question of novelty to establish whether an effective treatment with effective amounts of each drug is disclosed in D1 and/or D2.

2.6 As neither document mentions further details or results of the phase I combination trial, no explicit disclosure of these elements can be found. It must therefore be examined whether there is an implicit disclosure, meaning that the person skilled in the art, in the light of common general knowledge, when reading the respective document at its publication date would have understood an effective treatment (i.e. the

achievement of the desired clinical benefit), with effective amounts of each drug, to be part of its information content.

These considerations are in keeping with decision T 1859/08 cited by the patent proprietors, according to which a mere statement that a combination therapy is "currently being explored", or that a medicament is being evaluated in clinical studies, does not amount to a disclosure of the achievement of a clinical benefit in human patients. It is also not decisive whether the clinical benefit, or therapeutic effect, is inherent in the prior-art disclosure. The relevant criterion is whether it is accessible, i.e. disclosed, rather than "hidden" (see T 1859/08, reasons: points 13, 14).

- 2.7 With regard to this issue, the opponent took the position that, since both ET-743 and PLD were already known to have efficacy in the relevant therapeutic application, it would have been directly and unequivocally implicit to the reader of documents D1 and D2 that the combination treatment, too, must have the desired efficacy. The patent proprietors argued that it had not, however, previously been known that ET-743 used alone provided efficacy combined with acceptable safety; nor was it disclosed in documents D1 and D2 that the combination treatment provided efficacy combined with acceptable safety.
- 2.8 It is self-evident that, for a treatment to be effective, it must show efficacy in treating the targeted disease. The board agrees, however, with the patent proprietors' argument that an effective medical treatment has to meet not only the criterion of efficacy but also that of acceptable safety. A treatment which caused unacceptable harm to patients

would not be considered an effective treatment within the usual meaning of the term.

Thus the aspects of both efficacy and safety have to be taken into account to determine whether an effective treatment is (implicitly) disclosed in the prior-art citations.

The board considers moreover that this concept of effective treatment would also apply if the claims only referred to a treatment without explicitly mentioning the word "effective".

2.9 It was not disputed by the patent proprietors that, at the time of the publication of documents D1 and D2, PLD in the form of Doxil was an approved drug authorised for the treatment of cancer, including ovarian cancer (see also document D16a, page 2420, "indications and usage"). Thus it was part of the common general knowledge of the person skilled in the art that PLD as a single agent provided efficacy, and also acceptable safety, in the treatment of cancer, in particular ovarian cancer.

2.10 As far as ET-743 is concerned, both document D1 and document D2 report favourable preliminary results of clinical phase II studies obtained with Yondelis in the treatment of advanced ovarian cancer in 55 human patients, with a global response rate of 26% (D2) or 28% (D1) in patients resistant to platins-taxanes and a response rate of 54% in refractory patients. While toxicity is not discussed in that context, it is not mentioned either that any safety concerns precluding such treatment were identified.

2.11 Since PLD and ET-743 were both known to be effective as monotherapy anti-cancer agents, in particular in the

treatment of ovarian cancer, the person skilled in the art would have inferred from the disclosure of document D2 (where it is mentioned that the combination study targeted ovarian cancer) that a combination treatment carried out as a phase I trial with Yondelis (ET-743) and Doxil (PLD) would provide clinical efficacy in the treatment of ovarian cancer. The possibility that each drug might cancel out the other's pharmacological activity is remote and would not have been considered a realistic outcome without actual experimental evidence. Thus, assuming it can be inferred from the wording of document D2 that the combination treatment was carried out (see however point 2.14 below), there is some merit in the opponent's argument that the therapeutic efficacy of the claimed combination in the treatment of ovarian cancer was implicitly disclosed at least in document D2.

2.12 However, nothing was known or disclosed about the safety of the combination therapy. Phase I studies are normally carried out precisely for the purpose of identifying side effects and safe dosage ranges, and documents D1 and D2 do not mention any experimental results in that regard. Based on the available information, the person skilled in the art reading document D1 or D2 would thus not have been able to exclude the possibility that ET-743 and PLD might interact to produce unacceptable adverse effects, and in combination might reach dose-limiting toxicity before reaching the threshold of pharmacological efficacy.

2.13 Taking into account the criteria established in point 2.8 above, it cannot therefore be confirmed that documents D1 or D2 implicitly disclose an effective treatment by combination therapy (irrespective of the

question whether these documents disclose effective therapeutic amounts of each drug).

2.14 An additional point concerns the actual wording used in documents D1 and D2 with regard to the combination trial. The relevant text passages read as follows:

D1: "There are ten additional Phase I trials in combination with other chemotherapy agents (...)"

D2: "abiertos 10 estudios de fase I en combinación con otros agentes", translated as: "10 Phase I studies in progress in combination with other substances" (D2a).

Since a clinical trial also involves a preliminary set-up stage required for organisational matters, it can, arguably, not be inferred with absolute certainty that the combination treatment of human patients had already been carried out at the time of writing or publication of documents D1 and D2.

2.15 For these reasons, the board finds that the therapeutic application as defined in claims 1 and 2 of the main request is not disclosed in documents D1 and D2, and that therefore the subject-matter of these claims is novel having regard to the disclosure of documents D1 and D2 (Articles 100(a), 52(1) and 54(1) and (2) EPC).

3. Inventive step - main request

3.1 The issue of inventive step will be considered according to the problem-and-solution approach generally employed by the boards for assessing inventive step. That approach involves

(a) identifying the closest prior art,

(b) assessing the technical effects achieved by the claimed subject-matter when compared with the closest prior art,

(c) defining the objective technical problem on the basis of the technical effects actually achieved,

(d) examining whether or not the person skilled in the art, having regard to the state of the art within the meaning of Article 54(2) EPC, would have suggested the claimed combination of technical features in order to solve the objective technical problem.

Starting point in the prior art

3.2 The parties have regarded documents D1 or D2 (without particular preference) as the closest prior art. The board has no reason to select a different starting point for the assessment of inventive step.

3.3 The relevant information content of both documents is very similar. As already mentioned, both documents disclose that the combination of ET-743 and PLD was being tested in a clinical phase I study for the treatment of cancer. For the sake of simplicity, the following analysis will refer to document D2 only.

Technical problem and solution

3.4 It has been established above that the disclosure of document D2 differs from the subject-matter of claims 1 and 2 of the main request in that D2 does not disclose the effective treatment of cancer of the human body by the envisaged combination therapy.

3.5 Consequently, the technical problem to be solved in view of that starting point is the provision of a combination treatment for cancer of the human body with adequate efficacy and safety (see point 2.8 above).

3.6 This technical effect is expressed as a feature of claims 1 and 2 (the therapeutic application, or medical

indication), which means that non-working embodiments are excluded from the scope claimed.

- 3.7 The patent proprietors contended that the envisaged combination therapy with ET-743 and PLD also achieved a reduction in side effects in comparison with the combined administration of ET-743 and non-liposomal doxorubicin, as well as increased efficacy in comparison with monotherapy using each drug alone. However, irrespective of whether these further alleged technical effects are actually achieved, they cannot be taken into account in the formulation of the objective technical problem, since they have no basis in a comparison of the claimed subject-matter with the disclosure of the closest prior art (see point 3.1. (b) and (c) above). The appropriate starting point for the assessment of inventive step within document D2 is neither monotherapy nor the combination of ET-743 with non-liposomal doxorubicin, but the disclosure of the combination of ET-743 with PLD, which comes closest to the claimed subject-matter.

Obviousness of the solution

- 3.8 According to the principles generally known to be useful in the selection of drugs for combination chemotherapy (see document D35, page 292, column 1, bottom paragraph), only drugs known to be (partially) effective against the same tumour when used alone should be selected for use in combination. When several drugs of a class are available and are equally effective, a drug should be selected on the basis of toxicity that does not overlap with the toxicity of other drugs to be used in the combination. Although such selection leads to a wider range of side effects, it minimises the risk of a lethal effect caused by

multiple insults to the same organ system by different drugs and allows dose intensity to be maximised.

- 3.9 As mentioned above (see points 2.9 to 2.11), it was known that both ET-743 and PLD had shown efficacy in the treatment of ovarian cancer. Both ET-743 and doxorubicin were also known to have shown efficacy against soft-tissue sarcoma (see D1, D2 and D12). This knowledge would give rise to an expectation of efficacy of the combination treatment employing both drugs. ET-743 and PLD also belong to different chemical classes, which is commonly regarded as favourable from the viewpoint of efficacy, as it may provide different mechanisms and thus a broader range of interaction between drugs and cancer cells.
- 3.10 Document D2 discloses that a clinical phase I study assessing the combination treatment of cancer with Yondelis (ET-743) and Doxil (PLD) was in progress. Thus, at the publication date of D2, the information was available that the envisaged combination treatment was considered by pharmaceutical researchers with an expectation of success sufficient to justify a clinical phase I trial. In this context it is pointed out that drug compounds to be used in a clinical trial with human subjects are not selected based on a general "try-and-see" attitude, but based on existing favourable scientific data, for both ethical and economical reasons. Thus a clinical trial is not a mere screening exercise.
- 3.11 Contrary to what was argued by the patent proprietors, there is no other information on file which would have caused the person skilled in the art to change that assessment and to come to believe, at the priority date of the patent in suit, that there was, after all, no

reasonable expectation of success for the combination treatment involving ET-743 and PLD.

3.12 It was known that both drugs were well tolerated in monotherapy of human patients (see D16a for PLD; D2 and D7: pages 1189 and 1190 for ET-743) and had different dose-limiting toxicities for most cancer types. This information at least did not speak against combining the drugs, since it is advantageous to choose substances with different dose-limiting side effects to obtain a benefit from a combination treatment (see point 3.8 above and D35: page 292). While experimental data relating to the safety of the combination were not available, the mere absence of such information would not have been a reason for the person skilled in the art to expect the combination to fail.

3.12.1 The patent proprietors argued in this respect that the success rate in oncology trials was generally very low, at about 5% (as disclosed in the expert declaration D50: page 2), and it was therefore surprising that the studies they had conducted showed that the combination treatment could be carried out successfully at safe dosage levels.

3.12.2 The board observes that the statement in document D50 cited by the patent proprietors regarding low success rates of oncology drugs refers to tests carried out on individual new drugs rather than to combination treatments with known anti-cancer drugs.

In any case, the patent proprietors' argument cannot succeed, since the general consideration that any clinical trial might fail does not throw additional doubt on the particular combination treatment envisaged and is therefore not sufficient to establish an inventive step. The reason why clinical studies are

carried out at all is that they have uncertain outcomes. But they are routine tests and the fact that their outcome is uncertain does not in itself turn their results into an invention.

- 3.13 The patent proprietors furthermore submitted that it was known that myelosuppression (bone marrow suppression) was a dose-limiting side effect of ET-743. While myelosuppression was not a dose-limiting side effect of PLD (except in the case of AIDS-related Kaposi's sarcoma), it was however known that Doxil (PLD) may potentiate the toxicity of other anticancer therapies, and that hematologic toxicity may be more severe when Doxil is administered in combination with other agents that cause bone marrow suppression.

While the patent proprietors referred in this regard to document D16 (page 8, column 1, first paragraph), which is a product information leaflet published after the priority date of the patent in suit, the same information is contained in pre-published document D16a (Physicians' desk reference, page 2421, column 1, "myelosuppression"), and the opponent did not contest that the warning against the potentiation of myelosuppression was known. The board considers that documents D19, D20 and D22, which were also cited by the patent proprietors in that context, do not contain any further relevant information, since none of them relates to a combination of PLD with ET-743.

The patent proprietors concluded that, because of the known risk of increased myelosuppression, the person skilled in the art would not have had a reasonable expectation of success when considering a combination therapy using ET-743 and PLD.

3.14 The board does not arrive at the same conclusion, for the following reasons:

It was not actually known whether (and to what extent) PLD potentiates the risk of myelosuppression when combined specifically with ET-743. Even taking that possibility into account, the person skilled in the art would not have been deterred from, or prejudiced against, testing the combination treatment. It is typical for combination treatments that interactions between the drugs may give rise to increased toxicities, which may in many cases be balanced by employing reduced dosages of each drug. Thus, while alerted to the possibility of undesirable interaction between the two drugs, the person skilled in the art would still have been motivated to explore, with a reasonable expectation of success, whether adequately safe combinations of dosages existed.

3.15 The upshot is that the combination of ET-743 and PLD as disclosed in D2 looked promising in terms of efficacy, and that the aspect of safety of the combination treatment had yet to be assessed. While the outcome of a clinical trial could be success or failure, no particular reason was known which would have discouraged the person skilled in the art from carrying out an experimental evaluation to confirm the usefulness of the combination treatment. Finding out in this straightforward manner that useful dosage combinations providing both efficacy and safety indeed existed cannot be regarded as an invention.

3.16 As a consequence, the subject-matter of claims 1 and 2 of the main request does not involve an inventive step within the meaning of Article 56 EPC.

4. Inventive step - auxiliary request I
 - 4.1 Claims 1 and 2 of auxiliary request I differ from the corresponding claims of the main request by specifying upper limits for the dosages of PLD and ET-743 of 50 mg/m^2 and 1.3 mg/m^2 respectively.
 - 4.2 Based on these technical features and starting from the teaching of documents D1 or D2, the technical problem is the provision of a combination treatment for cancer of the human body with adequate efficacy and safety, including the determination of suitable drug dosages.
 - 4.3 If that problem is solved by claims 1 and 2 of auxiliary request I, that solution is, however, not unexpected, since it is well known that it is typical for combination therapies in cancer treatment to employ dosages lower than those used in monotherapy of each drug, usually for reasons of safety. It was also known that PLD when administered alone can be used at a dosage of 50 mg/m^2 (see D4: abstract), and ET-743 when administered alone can be used at dosages of 1.5 or 1.65 mg/m^2 (see D7: page 1187, column 2, lines 1, 7; D8: abstract). Thus the upper dosage limits defined in claims 1 and 2 unsurprisingly reflect typical dosages used in monotherapy, or lower.
 - 4.4 The patent proprietors contended that the claimed subject-matter was inventive because it was surprising that both drugs could be safely employed at or near full dosage.
 - 4.5 This argument cannot succeed, since the claims under consideration do not require, as a mandatory feature, that both or even one of the drugs be employed at the dosage which is defined as the upper limit. The alleged

surprising result is therefore in any case not obtained over the entire scope claimed.

It may be added that 1.3 mg/m² is not in fact the full dosage of ET-743 in monotherapy, and the patent in suit does not provide experimental data for combination treatment involving a dosage of 50 mg/m² PLD. Thus it has not been shown that both drugs may be safely employed at or near full dosage.

- 4.6 As a consequence, the subject-matter of claims 1 and 2 of auxiliary request I does not involve an inventive step within the meaning of Article 56 EPC.
5. Inventive step - auxiliary request II
- 5.1 Claims 1 and 2 of auxiliary request II differ from claims 1 and 2 of the main request in that they specify that a dosage of 30 mg/m² PLD and a dosage of 1.1 mg/m² ET-743 are to be employed in the combination therapy.
- 5.2 As in the case of auxiliary request I, the technical problem is the provision of a combination treatment for cancer of the human body with adequate efficacy and safety, including the determination of suitable drug dosages.
- 5.3 The patent proprietors argued that it was surprising that both drugs could be safely employed at or near full dosage. Identifying the most suitable dosages was not a "one-way-street" situation, since the dosages of both drugs were variables of the combination treatment, and extensive clinical research was involved in arriving at the proposed solution.

5.4 The board does not reach the same conclusion, for the following reasons:

The person skilled in the art carrying out clinical trials in respect of the envisaged combination treatment would have identified suitable dosages in a routine dose-finding trial.

The fact that a clinical trial may be laborious and time-consuming does not mean it is an undue burden if it is the only appropriate test, and therefore routine work. In this framework, varying the dosages of both drugs, if required, in order to identify a suitable dosage combination cannot be considered an excessive burden. In fact, since Doxil was a well-established drug with a known dosage range and toxicity profile, it would have been obvious to select a fixed effective dose of PLD at a medium dosage level and vary the dosage of ET-743 to find the tolerated maximum dose, as was indeed done by the patent proprietors according to example 1 of the patent in suit.

The claimed dosages are also lower than the highest dosages of each drug known to be used in monotherapy, which in view of common general knowledge is not surprising.

Even if it had been found that the dosage combination identified as suitable in the clinical trial involved surprisingly high dosages, such a finding could not be considered more than a bonus effect once it was obvious for the person skilled in the art to test the combination of ET-743 and PLD.

5.5 As a consequence, the subject-matter of claims 1 and 2 of auxiliary request II does not involve an inventive step within the meaning of Article 56 EPC.

6. Inventive step - auxiliary request III
 - 6.1 Claims 1 and 2 of auxiliary request III indicate the same dosages for ET-743 and PLD as the corresponding claims of auxiliary request II, with the additional requirement that PLD is to be administered prior to ET-743.
 - 6.2 According to the patent proprietors' argumentation, it can be seen from the section "Discussion on Clinical Pharmacology" in document D57 (bridging pages 11 and 12) that the clearance of ET-743 from the plasma is slower when it is co-administered with PLD than when it is administered in monotherapy, causing a higher exposure of the patient to the ET-743 and the potential toxic side effects that might result from this. As a consequence, administration of PLD prior to ET-743 is to be preferred.
 - 6.3 The board finds that this alleged advantage cannot be taken into consideration in the formulation of the objective technical problem, because such an advantage is not mentioned or taught in the patent in suit and the application as filed. The experimental data reported in the patent in suit were obtained exclusively with sequential administration of PLD followed by ET-743, and no comparison with a dosage regime involving concurrent administration of the two drugs was carried out.

It has in any case not been shown, nor can it be derived from post-published document D57, that a technical advantage exists. Document D57 mentions in the relevant section that two studies provided contradictory results and that it cannot be excluded that the pharmacokinetic profile of ET-743 is changed with co-administration of PLD, concluding: "The

clinical meaning of this fact is, for the time being, unknown". Since it had not been established at the time of publication of D57, i.e. five years after the priority date of the patent in suit, whether the pharmacokinetic profile was in fact changed and what the implication of that might be, the patent proprietors' remarks about side effects are at best speculative.

- 6.4 Thus the technical problem with regard to claims 1 and 2 of auxiliary request III is the provision of a combination treatment for cancer of the human body with adequate efficacy and safety, including the identification of suitable drug dosages and a suitable dosage regime.
- 6.5 The issue of obviousness with regard to the combined dosages of 30 mg/m² PLD and 1.1 mg/m² ET-743 has been discussed in the context of auxiliary request II (see point 5.4 above).
- 6.6 With regard to the sequence of administration, one of three possibilities (administration of PLD prior to ET-743, administration of both drugs at the same time and administration of ET-743 prior to PLD) was chosen. According to example 1 of the patent in suit, that choice turned out to be effective. It has not been argued or shown by the patent proprietors that there is anything in the prior art or common general knowledge which would prejudice the person skilled in the art against testing the sequence defined in auxiliary request III. Thus the order of administration cannot provide a contribution to inventive step.
- 6.7 As a consequence, the subject-matter of claims 1 and 2 of auxiliary request III does not involve an inventive step within the meaning of Article 56 EPC.

7. Inventive step - auxiliary request IV
- 7.1 Claims 1 and 2 of auxiliary request IV indicate the same dosages for ET-743 and PLD as the corresponding claims of auxiliary request II, with the additional requirements that PLD is to be administered over an infusion time of about one hour, followed by ET-743 over an infusion time of about three hours, and that the infusions are carried out at an interval of three weeks.
- 7.2 This corresponds to the dosage regime which was tested according to example 1 of the patent in suit.
- 7.3 The patent proprietors argued that the dosage regime specified in the claims of auxiliary request IV was the most effective regime.
- 7.4 The data obtained according to example 1 of the patent in suit were exclusively obtained in the manner described in claims 1 and 2 of auxiliary request IV, viz., a fixed PLD dose of 30 mg/m² was administered intravenously over one hour followed immediately by one of six doses of ET-743 administered intravenously over three hours, and this treatment was repeated every 21 days (see point 1.2 above). No direct comparison has been provided with other ways of administering the combination treatment, and it has not been shown that the claimed dosage regime has an unexpected technical effect.
- 7.5 Hence the technical problem is the same as in the case of auxiliary request III, namely the provision of a combination treatment for cancer of the human body with adequate efficacy and safety, including the identification of suitable drug dosages and a suitable dosage regime.

- 7.6 Obviousness with regard to the dosages and sequence of administration has been discussed in the context of auxiliary requests II and III (see points 5.4 and 6.6 above).
- 7.7 It was known that infusion times of one hour for PLD and of three hours for ET-743 were not unusual durations, nor is it uncommon to repeat the treatment every three weeks (see D3, page 1738, "Treatment" with PLD 35 mg/m² administered over one hour in a combination treatment with paclitaxel and D8, page 392, column 1, recommending administration of ET-743 as a three-hour infusion every three weeks). It has not been argued or shown by the patent proprietors that there is anything in the prior art or common general knowledge which would prejudice the person skilled in the art against testing the dosage regime defined in auxiliary request IV.
- 7.8 As a consequence, the subject-matter of claims 1 and 2 of auxiliary request IV does not involve an inventive step within the meaning of Article 56 EPC.
8. In view of this outcome, a decision on the other claims of the present requests or on other substantive issues is not required.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



S. Fabiani

D. Semino

Decision electronically authenticated