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Datasheet for the decision of 25 July 2025

Case Number: T 0792/24 - 3.3.07

Application Number: 13895342.7

Publication Number: 3076972

IPC: A61K31/496, A61K31/337, A61P35/00

Language of the proceedings: EN

Title of invention:
CANCER TREATMENT WITH COMBINATION OF PLINABULIN AND TAXANE

Patent Proprietor:
BeyondSpring, Inc.

Opponent:
Synthon BV

Headword:
Combination of plinabulin and taxane / BEYONDSPRING

Relevant legal provisions:
EPC Art. 100(a), 54, 56, 83, 123(2)

Keyword:
Novelty - main request and auxiliary request 1 (yes)
Inventive step - main request (no), auxiliary request 1 (yes)
Sufficiency of disclosure - auxiliary request 1 (yes)
Amendments - allowable - auxiliary request 1 (yes)

Decisions cited:
G 0002/08, T 0779/18, T 0836/01, T 1437/21

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Case Number: T 0792/24 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 25 July 2025

Appellant: (Opponent)	Synthon BV Microweg 22 6545 GN Nijmegen (NL)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Respondent: (Patent Proprietor)	BeyondSpring, Inc. Sertus Chambers PO Box 2547 Cassia Court Camana Bay Grand Cayman (KY)
Representative:	Callaghan, Dayle Anne Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 11 April 2024 rejecting the opposition filed against European patent No. 3076972 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	Y. Podbielski

Summary of Facts and Submissions

I. European patent 3 076 972 (hereinafter "the patent") was granted on the basis of 3 claims. The independent claim of the patent as granted read as follows:

"1. Plinabulin for use in reducing the neutropenia rate of a grade 3 or 4 neutropenia in a subject being administered with 75 mg/m^2 docetaxel, wherein the plinabulin is administered intravenously at about 20 mg/m^2 to about 30 mg/m^2 wherein the plinabulin is administered within 1 h and 24 h after administering the docetaxel."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as originally filed.

III. The opposition division took the decision to reject the opposition.

IV. The decision of the opposition division, posted on 11 April 2024, cited *inter alia* the following documents:

D5: Mita *et al.*, Journal of Clinical Oncology, 2010, 28(15S), 7592
D10: Patel *et al.*, JAMA Oncology, 2017, 3(12), 1751
D11: Prescribing information Taxotere of May 2013
D16: Annex A Data filed by the patent proprietor on 29 November 2022
D22: Mohanlal *et al.*, Journal of Clinical Oncology, 2016, 34(15S), e20595

D23: Blayney *et al.*, Blood, 2016, 128(22), 2508
D24: Scientific Discussion, EMEA, 2005
D25: Harvey *et al.*, Journal of Clinical Oncology, 2006, 24(31), 4963-4970
D26: Aihara *et al.*, Annals of Oncology, 2002, 13, 286-292
D27: Mitchell *et al.*, Annals of Oncology, 2003, 14, 788-794
D28: Ji Hyun Lee *et al.*, Korean J Intern Med, 2013, 28, 314-321

V. The opposition division decided in particular as follows:

(a) Documents D22 to D28 filed by the opponent were admitted into the proceedings.

(b) The subject-matter of granted claim 1 was directly and unambiguously disclosed in the original application. The various features were disclosed as preferred in the original application and example 3 provided an additional pointer to their combination.

(c) The claimed therapeutic use, namely the reduction of the incidence of docetaxel induced neutropenia grade 3 or 4, was rendered plausible in view of the experimental results provided in example 3 of the patent (see Figure 5 and Table 9). Hence the requirement of Article 83 EPC was met.

(d) The claimed subject-matter was novel over the cited prior art, which did not unambiguously disclose plinabulin for use in the reduction of the incidence of docetaxel induced neutropenia grade 3

or 4. Also the administration time of plinabulin was not directly and unambiguously disclosed.

(e) The subject-matter of the granted claims involved an inventive step over D5 as well as over D11.

In particular, starting from D5, the distinguishing features resided in the use of plinabulin for reducing docetaxel induced neutropenia grade 3 or 4 and in the time between the administration of docetaxel and plinabulin. The first distinguishing feature resulted in a reduction of the number of patients having to reduce the docetaxel dose or to take G-CSF. The objective technical problem therefore was seen as the provision of a better tolerable docetaxel therapy. The reduction of neutropenia shown in D5 was not specific of grade 3 or 4 and the patent was the first document providing statistically reliable data on reduction of the incidence of neutropenia. As a result the claimed subject-matter was not obvious in light of the cited prior art.

VI. The opponent (appellant) lodged an appeal against the above decision of the opposition division.

VII. With its reply to the appellant's statement setting out the grounds of appeal the patent proprietor (respondent) defended its case on the basis of the patent as granted as the main request, and on the basis of auxiliary requests 1 to 3 filed therewith.

The content of the claims upon which the present decision is based can be illustrated as follows:

Claim 1 of the main request was already recited above (see I.).

Claim 1 of auxiliary request 1 read as follows:

"1. Plinabulin for use in reducing the neutropenia rate of a grade 3 or 4 neutropenia in a subject being administered with 75 mg/m² docetaxel, wherein the plinabulin is administered intravenously at about 20 mg/m² wherein the plinabulin is administered within 1 h and 24 h after administering the docetaxel."

VIII. Oral proceedings were held before the Board on 25 July 2025.

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

X. The respondent requested that the appeal be dismissed, *i.e.* that the patent be maintained as granted (main request), or that the patent be maintained on the basis of one of the auxiliary requests 1 to 3 filed with the reply to the statement setting out the grounds of appeal.

XI. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) The subject-matter of claim 1 of the main request was not novel over D5.

The claimed reduction of the neutropenia rate of a grade 3 or 4 neutropenia did not define a medical use in the sense of Article 54(5) EPC. Furthermore, the subject-matter of granted claim 1 did not define a new therapeutic application compared to

the therapeutic application disclosed in the prior art.

Even if granted claim 1 would be regarded as a specific second medical use claim, the reduction of docetaxel induced neutropenia grades 3 or 4 with plinabulin was already known from D5 in view of the common general knowledge illustrated by D24 to D28. Moreover, the administration time of plinabulin according to D5 necessarily fell within the range of time defined in present claim 1.

(b) The main request did not fulfil the requirement of Article 56 EPC. D5 represented the closest prior art. D5 already disclosed all the features of present claim 1, so that the latter could not involve an inventive step.

However, even if the administration time of plinabulin and the reduction of the rate of neutropenia of specifically grades 3 or 4 were considered as distinguishing features, no unexpected technical effect associated thereto had been demonstrated. The objective technical problem resided in the provision of a further use of plinabulin in docetaxel cancer therapy. The skilled person would have expected the reduction of the neutropenia rate reported in D5 to occur for all grades thereof, hence also for grades 3 or 4. Furthermore, since monitoring neutrophil counts was mandatory in a clinical trial such as the one of D5, the claimed subject-matter represented merely the result necessarily obtained when putting the teaching of D5 into practice.

(c) Auxiliary request 1 infringed Article 123(2) EPC. The claimed features were not directly and unambiguously disclosed in the original application in combination with each other. The claimed subject-matter resulted from the singling out of some features (in particular the use in reducing side effects of taxane, docetaxel as taxane, the specific doses of docetaxel and plinabulin, the administration time of plinabulin, the administration route of plinabulin) from the original application serving as a reservoir while omitting other features (such as the type of cancer, the tumor sizes, the administration route of docetaxel and the other side effects that can be reduced).

(d) The subject-matter of claim 1 of auxiliary request 1 was not sufficiently disclosed. The term "reducing" in the feature "reducing the neutropenia rate of a grade 3 or 4 neutropenia" was so unclear as to render the claimed subject-matter not sufficiently disclosed. In particular, since neutropenia is induced by the treatment with docetaxel and as the claim does not prescribe a pre-treatment with docetaxel, no reduction of the incidence of neutropenia could occur with the claimed therapeutic use. Furthermore, neither a comparator nor the level of reduction were defined, which prevented the skilled person from determining whether the claimed effect was indeed achieved.

(e) Auxiliary request 1 did not fulfil the requirement of Article 56 EPC. In claim 1 of auxiliary request 1, the dose of plinabulin was limited to 20 mg/m^2. D5 still represented the closest prior art and disclosed the dose of 20 mg/m^2, which did therefore

not constitute a further distinguishing feature. The same reasoning as provided for the main request therefore applied. Furthermore, no significant difference could be observed in the reduction of the rates of neutropenia grades 3 or 4 between the 20 mg/m^2 and 30 mg/m^2 doses of plinabulin according to the experimental data provided by the respondent and the original application described both doses as equivalent. There was therefore no particular effect linked to the selection of the plinabulin dose of 20 mg/m^2 in the original application. The mere selection of an optimised dose as provided in D5 could not render the claimed subject-matter inventive.

XII. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) The subject-matter of claim 1 of the main request was novel over D5.

The claimed reduction of the neutropenia rate of a grade 3 or 4 neutropenia defined a new therapeutic application.

Furthermore, D5 did not specifically disclose a reduction of the neutropenia rate of neutropenia grade 3 or 4 and it was not derivable from common general knowledge either. Moreover, D5 did not disclose the administration time of plinabulin with respect to docetaxel.

(b) The main request fulfilled the requirement of Article 56 EPC. D11 represented the closest prior art, not D5. Nevertheless, starting from D5, the claimed subject-matter differed from the one

disclosed therein in the administration time of plinabulin and in that the rate of docetaxel induced neutropenia of specifically grades 3 or 4 was reduced. The data provided in the patent in *inter alia* Table 9 and Figure 5 as well as in D16 substantiated the following associated technical effects:

- reduction of the incidence of specifically neutropenia grades 3 and 4, which were known to be more severe than neutropenia grades 2 and 1,
- fewer patients having to reduce the docetaxel dose, and
- fewer patients having to use G-CSF to reduce the incidence of neutropenia.

In particular, a better and unexpected reduction of the rate of neutropenia of grades 3 and 4 was obtained compared to grades 1 and 2. The objective technical problem resided therefore in the provision of a better tolerable docetaxel therapy. The skilled person would not have had any reasonable expectation of success of using plinabulin to reduce the rate of the clinically more relevant neutropenia grade 3 or 4 and hence solve the problem posed. In particular, the skilled person would not have expected plinabulin to be more effective in reducing the rates of neutropenia of grades 3 and 4 than the rates of neutropenia grades 1 and 2.

(c) Auxiliary request 1 met the requirement of Article 123(2) EPC. All the features of claim 1 were disclosed in the original application and their combination was directly and unambiguously derivable therefrom.

(d) The subject-matter of claim 1 of auxiliary request 1 was sufficiently disclosed. The skilled person understood that the claimed treatment was prophylactic, *i.e.* the comparator being a treatment with docetaxel alone. Furthermore, the patent contained experimental evidence of the achievement of the claimed treatment.

(e) Auxiliary request 1 fulfilled the requirement of Article 56 EPC. Starting from D5 and in addition to the distinguishing features identified for the main request, the subject-matter of claim 1 of auxiliary request 1 differed from the one of D5 in that the reduction of the rate of neutropenia was achieved with 20 mg/m^2 plinabulin. D5 did not disclose any result for this dose, since the study with 20 mg/m^2 plinabulin was still ongoing. The data provided in the patent and D16 substantiated that a better (or at least as good) reduction of the rate of neutropenia of grades 3 and 4 was achieved with this dose compared with the higher dose of 30 mg/m^2. The objective technical problem resided in the provision of a better tolerable docetaxel therapy. The skilled person would not have reasonably expected that the 20 mg/m^2 plinabulin dose would achieve a better (or at least as good effect) than the higher plinabulin dose of 30 mg/m^2.

Reasons for the Decision

Main request - granted patent

1. Novelty

1.1 In the appeal proceedings, the appellant contested the novelty of granted claim 1 in view of D5.

1.2 Second medical use

1.2.1 The appellant considered that the reduction of the neutropenia rate of a grade 3 or 4 neutropenia in a subject being administered 75 mg/m^2 docetaxel, as specified in present claim 1, did not constitute a medical use in the sense of Article 54(5) EPC. In particular, the appellant explained that, in the present case, the treatment itself would be causing neutropenia in patients that did not suffer therefrom before. In the appellant's view the claimed use in reducing the neutropenia rate of a grade 3 or 4 neutropenia would not define a new therapeutic application compared to the therapeutic application disclosed in the prior art. The criteria defined in G 2/08 for the definition of a new specific therapeutic application would not be fulfilled as in T 779/18.

1.2.2 The respondent considered that, in line with T 779/18, T 836/01 and T 1437/21, the claimed application defined a new therapeutic application. In particular, patients with neutropenia grade 3 or 4 adverse events would be physiologically distinct from patients with neutropenia grades 1 or 2. Furthermore, the claimed prophylactic treatment was to be considered as a medical use.

1.2.3 The Board considers that present claim 1 indeed defines a purpose limited product claim in the sense of Article 54(5) EPC. As stated in the impugned decision, the Board considers that the skilled person would understand the use of claim 1 as relating to the alleviation of neutropenia as a side effect of docetaxel treatment *per se*, *i.e.* in comparison to the treatment with docetaxel alone. This understanding is in line with the teaching of the description of the

patent (see *e.g.* paragraphs [0023]-[0025]). As argued by the appellant during the oral proceedings, it follows that the claimed use is prophylactic to the extent that it is administered before the side effect can be observed and reduces the occurrence thereof. In such cases, it is inevitable that potentially also patients, who would not exhibit neutropenia grade 3 or 4, will be administered the treatment. It cannot however be concluded that this disqualifies the claimed use from a medical use in the sense of Article 54(5) EPC. According to established jurisprudence, prophylactic treatments amount to methods for treatment by therapy as referred to in Article 53(c) EPC (see Case Law of the Boards of Appeal, 11th Edition, 2025, I.B.4.5.1 b)). Moreover, preventing the side effects induced by a therapy has a significant clinical value, and there is no justification for excluding this from being regarded as a form of prophylactic treatment.

1.2.4 With respect to T 779/18 referred to by both parties, the Board observes that the present case differs from the one underlying T 779/18 mainly in that the present claim defines the treatment of a specific side effect (no treatment of a side effect was directly claimed nor necessarily encompassed by the claim in the case underlying T 779/18).

1.3 The disclosure of D5

1.3.1 D5 is an abstract reporting the results of a phase II clinical study of docetaxel alone or in combination with plinabulin in patients with non-small cell lung cancer (NSCLC). The following administration scheme over a 3 week cycle was applied:

- on day 1 intravenous administration of 75 mg/m^2 docetaxel (monotherapy and combination arms) and,

- in the combination arms, intravenous administration of 30 or 20 mg/m^2 plinabulin on days 1 and 8.

1.3.2 The "methods" and "results" sections specify that:
- a total of 167 patients will be enrolled,
- the enrolment of 110 patients in the 30 mg/m^2 plinabulin dose group was complete,
- the enrolment continued in the 20 mg/m^2 plinabulin dose group, and
- 64 patients were currently evaluable.

1.3.3 The secondary endpoints included safety, and the "results" section mentions that "the incidence of neutropenia appeared lower in the combination arm (4% vs. 27%)".

1.4 Reduction of neutropenia rate, specifically of grade 3 or 4 neutropenia

1.4.1 The respondent considered that D5 did not disclose plinabulin for use in reducing docetaxel induced neutropenia of grade 3 or 4 but only for use in the treatment of cancer. The Board agrees that the treatment of cancer and the reduction of docetaxel induced neutropenia represent two different therapeutic applications. However, in the present case, while D5 is primarily aimed at the treatment of cancer, safety represented a secondary endpoint of the study and in this context the incidence of neutropenia was monitored. Contrary to the respondent's opinion, the results section of D5 unambiguously discloses the reduction of incidence of docetaxel induced neutropenia in general when administering plinabulin.

1.4.2 In this context, the respondent disputed that D5 would report a complete statistically significant study in

view of the last sentence of D5 specifying that "efficacy and safety continue to be compared in a 20 mg/m^2 plinabulin dose group to determine the optimal dose to bring into phase III testing". The Board observes that this indication is limited to the 20 mg/m^2 dose group and does not apply to the 30 mg/m^2 dose group. Furthermore, while D5 is only an abstract and does indeed not provide the detailed results and statistical analysis thereof, it remains the case that a skilled person would have no reason to question the reliability of the results from the phase II clinical study presented in D5, at least with respect to the 30 mg/m^2 dose group.

1.4.3 The appellant argued that the reduction of docetaxel induced neutropenia grades 3 or 4 with plinabulin was already known from D5 in view of common general knowledge. The appellant relied on D24 to D28 as evidence of common general knowledge at the priority date. They explained that the incidence rate reported in D5 in the monotherapy arm (27%) would correspond to levels of grade 3 and/or 4 of neutropenia usually observed according to these documents with varying doses of docetaxel (see D24, page 17, 1st paragraph, 22% incidence rate of grade 3/4 neutropenia; D25, page 4967, right column, 1st paragraph, incidence rate of grade 4 neutropenia increasing from 49.3% to 86.3% with increasing dose; D26, page 289, left column below Table 3, 51% patients experienced neutropenia and only 19% had grade 3/4; D27, page 791, Table 5, neutropenia grade 3/4 in 44% of patients; D28, page 318, left column, lines 3-5 and Table 3, 100% patients having neutropenia and 58% having grade 3/4). According to the appellant, these documents would further indicate that the incidence rate of all grades of neutropenia would be expected to be higher than those reported in D5.

As brought forward by the respondent, documents D25 to D28 are scientific articles reporting individual clinical studies, so that it is questionable whether they indeed represent evidence of common general knowledge. More importantly, as explained by the respondent and substantiated by D11 (see page 15 section 6 under "adverse reactions"), rates of adverse events depend on the situation of the clinical study and cannot be directly compared between different trials. The appellant's argument that D24 to D28 would unambiguously lead the skilled person to the conclusion that the neutropenia rates reported in D5 correspond only to neutropenia of grade 3 and/or 4 is therefore not convincing.

1.4.4 It follows that, in the absence of a specific indication regarding the neutropenia rates in D5, it has to be considered that the neutropenia rates mentioned in D5 correspond to patients having neutrophils counts below the lower limit of normal neutrophils count as a whole (1500/mL blood, see *e.g.* D10, page 1751, 1st paragraph penultimate sentence or 2000/mL blood, see *e.g.* D11, page 16, table 4), which could correspond to neutropenia of any of grades 1 to 4.

1.4.5 The appellant was finally of the opinion that the skilled person would recognise that a reduction of neutropenia would occur over all grades, hence also including grades 3 and 4. The claimed medical use would therefore be disclosed in D5 read by a skilled person in view of its common general knowledge.

1.4.6 The Board disagrees. The arguments of the appellant amount to a probable disclosure of the claimed subject-

matter in D5. However according to established jurisprudence, when assessing novelty, the gold standard of a direct and unambiguous disclosure must be applied. A finding of lack of novelty cannot be based on the mere "probability" that the claimed subject-matter was disclosed in the prior art (see Case Law of the Boards of Appeal, 11th Edition, 2025, I.C.4.1, 4th paragraph).

1.4.7 The Board comes therefore to the conclusion that there is no direct and unambiguous disclosure in D5 that plinabulin indeed reduces the rate of neutropenia of specifically grade 3 and/or 4.

1.5 Administration time of plinabulin

1.5.1 According to present claim 1 plinabulin "is administered within 1 h and 24 h after administering the docetaxel". During oral proceedings it was undisputed amongst the parties that this time range was to be considered from the beginning of the administration of docetaxel as indicated in the patent (see *e.g.* paragraphs [0051] and [0065]).

1.5.2 The appellant argued that the administration time of plinabulin according to D5 would necessarily fall within the range of time defined in present claim 1. According to the appellant, it would be standard to administer docetaxel intravenously over one hour. Furthermore, plinabulin would only be administered after the administration of docetaxel would be completed. As a result, plinabulin would necessarily be administered at least 1 hour after administering the docetaxel. Moreover, according to D5 plinabulin administration had to occur on the same day as docetaxel *i.e.* at most within 24 hours.

1.5.3 The Board observes that, as argued by the respondent, D5 does not explicitly disclose the administration time of plinabulin with respect to docetaxel. The Board nevertheless agrees with the appellant that plinabulin administration has to occur on the same day as docetaxel *i.e.* at most within 24 hours.

1.5.4 However, D5 does not disclose any minimum of time between the administration of docetaxel and the administration of plinabulin nor any duration for the administration of docetaxel *via* intravenous infusion. The fact that docetaxel was administered over a duration of 1 hour in the examples of the patent (see *e.g.* paragraphs [0065], [0122] and [0135]) does not mean that this is a universally used duration of administration. The appellant did not provide any further evidence in support of the alleged necessary duration of administration of docetaxel of 1 hour. It cannot therefore be excluded that plinabulin was administered less than 1 hour after administering docetaxel.

1.5.5 As mentioned above (see 1.4.6), the fact that the administration of plinabulin in the study of D5 probably occurred at least 1 hour after administration of docetaxel is not sufficient to support a lack of novelty.

1.5.6 Accordingly, D5 does not directly and unambiguously disclose the administration of plinabulin within 1 hour and 24 hours after administering docetaxel.

1.6 The subject-matter of claim 1 of the main request is thus novel in view of D5.

1.7 The Board observes that the appellant did not contest the finding of the opposition division that the subject-matter of the claims of the main request was novel over the remaining documents cited against novelty during the opposition proceedings.

1.8 As a consequence, the main request fulfils the requirement of novelty (Article 100(a) in combination with Article 54 EPC).

2. Inventive step

2.1 Closest prior art

2.1.1 The parties disagreed concerning the choice of the closest prior art. The appellant considered that D5 represented the closest prior art while the respondent argued that D11 should be chosen.

2.1.2 In accordance with established case law of the Boards of Appeal, when two or more pieces of prior art are feasible starting points for the assessment of inventive step, a conclusion that the subject-matter claimed is inventive can only be reached after assessing this requirement starting from all the possible pieces of closest prior art. Conversely, if the invention is obvious to the skilled person in respect of at least one of these routes, then an inventive step is lacking (see Case Law of the Boards of Appeal, 11th Edition, 2025, I.D.3.3).

2.1.3 It is established case law that the closest prior art should be directed to the same purpose or effect as the invention. As mentioned with respect to the issue of novelty, granted claim 1 relates to the use of plinabulin to reduce docetaxel induced neutropenia rate

of neutropenia grade 3 or 4. The purpose of D5 is to study the effect of plinabulin in combination with docetaxel in the treatment of cancer and the incidence of neutropenia is monitored as part of safety evaluation as a secondary endpoint. The Board considers therefore that D5 represents a suitable starting point.

2.1.4 For inventive step to be acknowledged, the claimed subject-matter must thus be non-obvious over D5 as the starting point.

2.2 Distinguishing features

2.2.1 For the reasons detailed above (see 1.), the subject-matter claimed differs from the one disclosed in D5:

(i) in that plinabulin is used in reducing the incidence of neutropenia of specifically grade 3 or 4 in a subject, and

(ii) in the specific administration time of plinabulin compared to docetaxel.

2.2.2 It was undisputed that these two features are not interrelated and can therefore be assessed separately.

2.3 Associated technical effects and objective technical problem

2.3.1 No particular effect has been brought forward for the administration time (feature (ii)). This feature was therefore arbitrarily chosen and cannot contribute to an inventive step.

2.3.2 For the reduction of the neutropenia rate of grade 3 or 4, the respondent relied on the following technical effects:

- reduction of the incidence of neutropenia of specifically grades 3 and 4, which are known to be more severe than neutropenia grades 2 and 1,
- fewer patients having to reduce the docetaxel dose, and
- fewer patients having to use G-CSF to reduce the incidence of neutropenia.

2.3.3 According to the respondent, these effects would be shown in the patent in *inter alia* Table 9 and Figure 5 as well as in D16 (reduction of incidence of neutropenia grade 3 or 4 and of the use of G-CSF).

In particular the data provided in D16 (see Table 1) would show:

- a reduction from 26% neutropenia grades 3 and 4 without plinabulin to 5% with 20 mg/m^2 plinabulin (*i.e.* a 21% drop) and a reduction from 27% to 8% with 30 mg/m^2 plinabulin (*i.e.* a 19% drop), and
- a reduction from 7% neutropenia grades 1 and 2 without plinabulin to 3% with 20 mg/m^2 plinabulin (*i.e.* a 4% drop) and a reduction from 9% to 0% with 30 mg/m^2 plinabulin (*i.e.* a 9% drop).

2.3.4 The Board observes that the reduction of the use of G-CSF and the maintenance of the docetaxel dose are, according to the reasoning of the respondent, merely an expected direct consequence of the reduction of the neutropenia rate of grades 3 or 4.

2.3.5 Moreover, the argument of the respondent concerning the greater efficacy in the reduction of grade 3 or 4 neutropenia compared to grade 1 or 2 achieved with plinabulin (see Table 9 and Figure 5 of the patent and D16) is not convincing. The Board does not share the conclusion of the respondent that a greater reduction

of incidence of neutropenia grades 3-4 compared to grades 1-2 has been evidenced. The reasons are the following:

- Table 9 of the patent only provides data regarding the rate of neutropenia grades 3 and 4. No comparison with grades 1 and 2 is provided.

- According to Figure 5 of the patent, the rate of neutropenia grade 2 in both treatment arms containing administration of plinabulin is 0%. The same is observed for neutropenia grade 1 in the treatment arm containing administration of 30 mg/m^2 plinabulin. Since the rate of neutropenia grades 1 and 2 in the corresponding arms without administration of plinabulin is around 2.75%, the reduction in terms of absolute percentage is indeed not as important as for grades 3 and 4. But a comparison of absolute percentages is in the present case not appropriate. The incidence rate of neutropenia cannot be less than 0%. Thus, as brought forward by the appellant during the oral proceedings, the incidence rate of neutropenia grades 1 and 2 has in these arms been reduced by 100%. It cannot therefore be concluded from the data in the patent that the reduction of the incidence rate is greater for grade 3 or 4 than grade 2 or 1.

- In this context, the fact that there is only little reduction of the rate of neutropenia grade 1 in the treatment arm containing administration of 20 mg/m^2 plinabulin in Figure 5 of the patent does not change this conclusion. In particular, grade 1 neutropenia appears to be of very limited clinical significance, as it was undisputed that it does

usually not require any clinical intervention. Furthermore the data in D16 report a level of neutropenia grades 1 and 2 of 3% in the arm containing administration of 20 mg/m^2 plinabulin (see table 1 of D16). This confirms that the levels reported for grades 1 and 2 are overall very low.

- The data in D16 are consistent with the data provided in the patent and do also not support the respondent's conclusion. In D16 (see Table 1), the rates of neutropenia of grades 1 and 2 after treatment with plinabulin are very low (3% and 0%, for each cohort respectively) and lower than for grades 3 and 4 (5% and 8%, for each cohort respectively). Hence, even if the reduction in terms of absolute percentage is bigger for grades 3 and 4, for the reasons explained in paragraph 2.3.5 above it cannot be concluded that the reduction of neutropenia incidence is more effective for grades 3 and 4 than grades 1 and 2.

2.3.6 It follows that, while the provided data substantiate that plinabulin is indeed effective to reduce the rate of neutropenia grades 3 and 4 as well as grades 1 and 2, no greater reduction of grades 3 and/or 4 compared to grades 1 and 2 is achieved.

2.3.7 Accordingly, starting from D5, the objective technical problem can only be formulated as the provision of a further use of plinabulin in docetaxel cancer therapy.

2.4 Obviousness of the claimed solution

2.4.1 The respondent argued that the skilled person would not have had any reasonable expectation of success of using plinabulin to reduce the rate of the clinically more

relevant neutropenia grade 3 or 4, in particular to the extent shown in the patent and D16.

2.4.2 The Board disagrees.

D5 establishes that the administration of 30 mg/m^2 plinabulin reduces docetaxel induced neutropenia to a low level, which the skilled person would recognise as clinically advantageous. The various grades of neutropenia correspond to ranges of decreasing neutrophil counts, the lower neutrophil counts corresponding to grade 3 or 4 being clinically more severe. In view of the general disclosure of D5, the skilled person would anticipate that administering 30 mg/m^2 of plinabulin would effectively mitigate the decrease in neutrophil counts in a subject in general, *i.e.* also in subjects susceptible to have decreased neutrophil counts corresponding to neutropenia grade 3 or 4. The appellant did moreover not provide any evidence that the effect of plinabulin in limiting the reduction of neutrophil count in a subject would be different depending on the level thereof. The skilled person would therefore expect that administering 30 mg/m^2 of plinabulin would also be effective in reducing the rate of neutropenia grade 3 or 4.

2.4.3 The subject-matter of claim 1 of the main request is thus not inventive when starting from D5 as closest prior art.

2.5 As a result, the main request does not meet the requirement of inventive step (Article 100(a) EPC in combination with Article 56 EPC).

Auxiliary request 1

3. Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the dose of plinabulin was limited to "about 20 mg/m^2".

4. Amendments

4.1 In the following paragraphs the cited passages of the original application are those of the A1 publication of the PCT application, WO 2015/051543 A1.

4.2 As argued by the respondent, the various features of claim 1 of auxiliary request 1 are disclosed in the original application as follows:

(a) plinabulin for use in reducing taxanes induced neutropenia rate of a grade 3 or 4 neutropenia on page 3 lines 20-21 ("10^{th} aspect" of the invention) ,

(b) docetaxel as taxane as a preferred embodiment on page 2 line 10,

(c) docetaxel dose being the standard dose used in the art as stated on page 1 lines 24 to 25 and in the examples of the patent on page 7 line 29 and in example 3,

(d) plinabulin being administered intravenously at about 20 mg/m^2 as disclosed on page 5 lines 14 to 15, wherein 20 mg/m^2 is explicitly disclosed as one of the endpoints of the narrowest range which would be understood as the preferred range by the skilled person in view of the original disclosure as a whole, and

(e) the administration time of plinabulin with respect to docetaxel as the more preferred embodiment on page 5 last paragraph.

4.3 During the oral proceedings, the appellant disputed that the claimed dose of docetaxel would be the single standard in the art. Furthermore the appellant argued that the claimed docetaxel dose would be disclosed in more specific protocols in the examples of the original application, *i.e.* only in combination with specific features such as its intravenous administration, a specific administration time and a specific plinabulin dose (see page 7 line 29 and example 3).

The Board disagrees.

While the 75 mg/m^2 docetaxel dose may not be the sole standard in the field of anti-cancer therapy, it is the only one mentioned in the original application, which is the relevant basis when assessing compliance with Article 123(2) EPC. Furthermore it is also the only dose used in the example of the patent. The fact that the claimed docetaxel dose is disclosed in the original application alongside other specific features does not mean that it is inextricably linked thereto but merely derives from the fact that it is disclosed in the context of standard experimental protocols. The skilled person would nonetheless directly and unambiguously recognise that, in view of the original application as a whole, the dose of docetaxel to be used in the context of the patent can only be 75 mg/m^2.

4.4 Furthermore, the appellant contended that the combination of these isolated features would not be directly and unambiguously disclosed in the original

application. The claimed combination of features would result from the singling out of some features from the original application serving as a reservoir while omitting other features.

In particular the following features would not be disclosed in combination:

- the combination of plinabulin and specifically docetaxel as taxane for use in the reduction of specifically grades 3 and 4 of neutropenia, and
- the specific doses of plinabulin and docetaxel, together with the administration time of plinabulin.

Moreover the following features disclosed in the original application at the same level of preference would have been omitted while selecting the claimed features:

- the type of cancer (see page 2 lines 13 to 14),
- the tumor sizes (see page 2 line 18 and page 3 lines 16 to 19), and
- the other side effects that can be reduced (see page 3 lines 3 to 4).

4.5 These arguments are not convincing.

In line with the respondent, the Board considers that the disclosure of docetaxel as the preferred taxane to be used in the first aspect of the invention on page 2 line 10 generally defines the preferred combination for all following aspects of the invention. Indeed the "first aspect" merely defines the combination of plinabulin with a taxane independently of any other feature, in particular of any therapeutic use (see page 2, lines 5 to 8). It follows that the preference for docetaxel as taxane directly and unambiguously applies

to the embodiment of page 3 lines 20 to 21 ("10th aspect" of the invention) defining the presently claimed use.

Furthermore, the features relating to the doses of plinabulin and docetaxel and the administration time of plinabulin further define separate components and aspects of the claimed therapeutic use. They individually apply to any originally disclosed embodiment, including the 10th aspect on which present claim 1 is based. In this context, the Board observes that the claimed administration time is individualised as the more preferred one and the standard docetaxel dose is the sole one disclosed in the application for administration to humans. These features do therefore not appear to require any particular selection. Even if the claimed plinabulin dose would not be considered as an individualised end-point of a preferred range, at most one selection would be required to arrive at this feature based on the embodiment on original page 5, lines 14 to 15. This does not give rise to the singling out of a combination of features not originally disclosed. Moreover, example 3 (in particular cohort 2) provides a pointer to the claimed combination of features.

Finally, the fact that other features were also disclosed in the original application but not claimed does not mean that the claimed subject-matter was not originally disclosed. These additional features are not originally disclosed in combination with or as inextricably linked to each other or to the claimed features. They merely further define other aspects of the invention. Their omission in present claim 1 does therefore not result in claiming subject-matter not originally disclosed.

4.6 During the oral proceedings, the appellant explained that the original application was only concerned with the treatment of cancer and not with the reduction of side effects resulting from the treatment with taxanes. As argued by the respondent, this argument is not conclusive since original independent claim 9 explicitly relates to the use of plinabulin for the preparation of a medicine used to reduce side effect of taxane.

4.7 Also during the oral proceedings, the appellant argued that the intravenous administration of plinabulin had to be selected from several routes of administration (see page 6, 4th paragraph). Since the original application (see page 5 lines 14 to 15) discloses the present dose of plinabulin specifically in combination with an intravenous injection, this argument is not convincing.

4.8 Finally, the appellant's argument regarding an unallowable intermediate generalisation of example 3 is not conclusive. As stated by the respondent, example 3 does not constitute the basis for the disclosure of the presently claimed features but only represents an additional pointer to their combination.

4.9 Hence, contrary to the opinion of the appellant, the combination of the claimed features is directly and unambiguously disclosed in the original application.

4.10 As a consequence, the subject-matter of claim 1 of auxiliary request 1 complies with the requirement of Article 123(2) EPC. The appellant did not raise any objection of lack of compliance with Article 123(2) EPC for the additional feature of dependent claim 2 of

auxiliary request 1. The Board is satisfied that the subject-matter of the claims of auxiliary request 1 meets the requirement of Article 123(2) EPC.

5. Sufficiency of disclosure

5.1 During the oral proceedings, the appellant contested that the subject-matter of the claims of auxiliary request 1 was sufficiently disclosed.

5.2 The Board observes that, for the same reasons as detailed for claim 1 of the main request (see 1.2.3 to 1.2.4), claim 1 of auxiliary request 1 is a purpose limited product claim. As stated in the impugned decision, the patent contains experimental evidence of the achievement of a reduction of incidence of neutropenia grades 3 and 4 when using plinabulin with docetaxel compared to docetaxel monotherapy (see paragraph [0068] and example 3, paragraph [149], Table 9 and Figure 5) with the following administration scheme over a 3 week cycle:

- on day 1 intravenous administration of 75 mg/m^2 docetaxel followed 2 hours later by intravenous administration of 30 or 20 mg/m^2 plinabulin (arm DN; 30 or 20 mg/m^2 Cohort) or placebo (arm D), and
- on day 8 intravenous administration of 30 or 20 mg/m^2 plinabulin (arm DN; 30 or 20 mg/m2 Cohort) or placebo (arm D).

5.3 The appellant argued that the term "reducing" in the feature "reducing the neutropenia rate of a grade 3 or 4 neutropenia" would be so unclear as to render the claimed subject-matter not sufficiently disclosed. According to the appellant, since neutropenia is induced by the treatment with docetaxel and as the claim does not prescribe a pre-treatment with

docetaxel, no reduction of the incidence of neutropenia can occur with the claimed therapeutic use.

5.4 This argument of the appellant is not convincing. The skilled person would understand the use of claim 1 as relating to the alleviation of neutropenia as side effect of docetaxel treatment *per se*, *i.e.* the reduction mentioned in claim 1 as being in comparison to the treatment of docetaxel alone. This is clear in view of the wording "in a subject being administered with 75 mg/m² docetaxel". As stated by the respondent, the claimed treatment is hence prophylactic.

5.5 In this context, the appellant explained during the oral proceedings that the skilled person would not be in a position to determine the reduction of neutropenia grade 3 or 4 in single subjects due to a missing comparator. This is however always the case with prophylactic treatments of the present kind. In such cases the effect could be evaluated for instance by comparing populations being administered the treatment with populations being administered a placebo. Contrary to the appellant's opinion, the skilled person would therefore be in a position to measure neutrophil counts in each population and determine whether the claimed reduction is observed or not. There is hence no such issue as a missing indication regarding the measurement of a parameter as alleged by the appellant during the oral proceedings.

5.6 During the oral proceedings, the appellant also contended that the missing indication of the level of reduction would prevent the skilled practitioner from determining whether he would be working within the scope of the claims or not. This issue, however, pertains to the evaluation of clarity rather than the

sufficiency of disclosure. In any case, the fact that no specific level of reduction is specified has to be understood in such a way that any significant reduction of neutropenia rate of neutropenia grade 3 or 4 is encompassed. As stated in the preceding paragraph, this can be determined.

5.7 Finally, it was undisputed that the data mentioned above (see 5.2) render plausible that a reduction of the rate of grade 3 or 4 neutropenia with plinabulin can be achieved with the claimed administration scheme.

5.8 Accordingly, the Board considers that auxiliary request 1 complies with Article 83 EPC.

6. Novelty

The appellant did not raise any objection of lack of novelty specific for auxiliary request 1. For the same reasons as detailed for the main request, auxiliary request 1 meets the requirement of Article 54 EPC.

7. Inventive step

7.1 Closest prior art

7.1.1 The appellant objected that the subject-matter of claim 1 of auxiliary request 1 lacked an inventive step starting from D5 as closest prior art. No further closest prior art was considered by the appellant.

7.1.2 The disclosure of D5 has already been discussed in the context of the main request (see in particular 1.3).

7.2 Distinguishing features

7.2.1 The appellant considered that there was no further distinguishing feature in addition to those considered for the subject-matter of claim 1 of the main request. D5 indeed disclosed a clinical trial with docetaxel (75 mg/m^2 intravenously administered) alone or in combination with either 30 or 20 mg/m^2 plinabulin (intravenous administration) in patients with non-small cell lung cancer (NSCLC). Hence, the treatment with the dose of 20 mg/m^2 was disclosed in D5.

7.2.2 As argued by the respondent, D5 does not unambiguously disclose a reduction of docetaxel induced neutropenia in the 20 mg/m^2 plinabulin arm, in particular because:

- the enrolment for the 20 mg/m^2 group was still ongoing,
- the conclusions of D5 indicate that efficacy and safety of the 20 mg/m^2 dose were still to be determined in comparison with the 30 mg/m^2 dose, and
- the positive results disclosed in D5 appear to concern only the 30 mg/m^2 cohort.

In addition to the distinguishing features identified for the main request (see 2.2.1), the subject-matter of present claim 1 therefore differs from D5 also in that D5 fails to disclose the effectiveness of the 20 mg/m^2 dose.

7.3 Associated technical effect and objective technical problem

7.3.1 The respondent brought forward that the data provided in the patent and the original application (see Figure 5) as well as in D16 (see Table 1) substantiated that

the reduction of the occurrence of docetaxel induced neutropenia of grades 3 or 4 with 20 mg/m^2 plinabulin was better as with 30 mg/m^2 plinabulin. In view of this technical effect associated with the dose of 20 mg/m^2 compared to the effective dose of 30 mg/m^2 disclosed in D5, the objective technical problem starting from D5 was the provision of a better tolerable docetaxel therapy.

7.3.2 The appellant countered that for both doses the incidence of neutropenia of grades 3 and 4 were very low and that no significant difference could be observed. The Board however agrees with the respondent, that the data in Figure 5 of the patent and in Table 1 of D16 show that the reduction of the occurrence of docetaxel induced neutropenia of grades 3 or 4 with 20 mg/m^2 plinabulin is at least as good as with 30 mg/m^2 plinabulin. That such an effect is achieved with the much reduced dose of 20 mg/m^2 represents an improvement which is to be taken into account for the assessment of inventive step.

7.3.3 The appellant's argument that the original application would describe both doses as equivalent and would not indicate any optimal dose is not convincing. The results relied upon already formed part of the original application (see Figure 5). The fact that both doses were considered suitable for the claimed use in reducing neutropenia grades 3 and 4 does not undermine this teaching.

7.3.4 The Board therefore considers that the objective technical problem starting from D5 resides in the provision of an optimised use of plinabulin in docetaxel cancer therapy.

7.4 Non-obviousness of the solution

7.4.1 The appellant suggested that the 20 mg/m^2 plinabulin dose had already been chosen in D5 as the optimal dose for phase III testing in view of the last sentence of the paragraph "Conclusions". The Board shares the respondent's view that the last sentence of D5 only states that the described phase II study continues with the 20 mg/m^2 dose to determine later on the optimal dose to bring in phase III trial. This sentence only means that the results of the reported phase II study are at least not complete for the 20 mg/m^2 plinabulin arm.

7.4.2 Furthermore, the appellant considered that finding the optimal plinabulin dose by carrying out the study as suggested in D5 cannot involve an inventive step. This argument is not convincing. As argued by the appellant themselves, the primary aim of D5 is to evaluate the anti-cancer activity of the combination of docetaxel and plinabulin. Safety, including reduction of the incidence of neutropenia as a whole, is merely a secondary endpoint of the study. There is no indication that the optimal dose in terms of anti-cancer therapy would be the same as in terms of specifically the reduction of incidence of neutropenia grade 3 or 4.

7.4.3 As argued by the respondent, starting from D5, the skilled person would not have expected that the 20 mg/m^2 plinabulin dose would be at least as effective as the significantly higher 30 mg/m^2 dose in reducing docetaxel induced neutropenia rates of grades 3 and 4. While the skilled person would have expected some effect in reducing docetaxel induced neutropenia grades 3 or 4 also with 20 mg/m^2 plinabulin, the extent of the

reduction obtained compared to the 30 mg/m^2 dose would not reasonably have been expected.

7.4.4 It follows that the subject-matter of claim 1 of auxiliary request 1 is inventive when starting from D5 as closest prior art.

7.5 Therefore, auxiliary request 1 meets the requirement of Article 56 EPC.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The case is remitted to the opposition division with the order to maintain the patent on the basis of auxiliary request 1 filed on 19 November 2024 and a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated