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Case Number: T 1507/11 - 3.3.01

Application Number: 05784925.9

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Title of invention:
COMBINATIONS OF PKC ACTIVATORS AND PKC INHIBITORS FOR ALZHEIMER'S DISEASE TREATMENT AND COGNITIVE ENHANCEMENT

Applicant:
Blanchette Rockefeller Neurosciences Institute

Headword:
Bryostatin with α-tocopherol/BRNI

Relevant legal provisions:
EPC Art. 56
RPBA Art. 13(1)

Keyword:
Inventive step (no): obvious combination of active ingredients
Auxiliary request 4: admitted (no)

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Case Number: T 1507/11 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 4 August 2016

Appellant: (Applicant)	Blanchette Rockefeller Neurosciences Institute 8 Medical Center Drive Morgantown, WV 26505-3409 (US)
Representative:	Kador, Utz Ulrich Kador & Partner Corneliusstrasse 15 80469 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 18 February 2011 refusing European patent application No. 05784925.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	L. Seymour
	M. Blasi

Summary of Facts and Submissions

I. The present appeal lies from the decision of the examining division refusing the European patent application No. 05 784 925.9, based on an international application published as WO 2006/031337.

II. Of the documents cited during the examination/appeal proceedings, the following are referred to below:

(1) WO 2004/004641

(5) P F Hickman et al., Brit. J. Cancer, 1995, 72, 998 - 1003

(7) C McLoughlin et al., Anaesthesia, 1992, 47, 202 - 206

(8) W Eriksen, Med. Hypotheses, 2004, 62(5), 721 - 726

(10) S-E Bursell, G L King, Diabetes Res. Clin. Pr., 1999, 45, 169 - 182

(11) C K Chow, Biol. Signals Recept., 2001, 10, 112 - 124

(13) K. Yamada et al., Eur. J. Neurosci., 1999, 11, 83 - 90

(14) M-K Sun, D L Alkon, Eur. J. Pharmacol., 2008, 584, 328 - 337

(16) C W Mahoney, A Azzi, Biochem. Bioph. Res. Co., 1988, 154(2), 694 – 697

(17) V W DeLaGarza, American family physician, 2003, 68(7), 1365 - 1372

(18) PubMed abstract of R A Floyd, K Hensley, Neurobiol. Aging, 2002, 23(5), 795 - 807

(19) PubMed abstract of J A Luchsinger et al., Arch. Neurol., 2003, 60(2), 203 - 208

(20) PubMed abstract of E T Klatte et al., Alzheimer Dis. Assoc. Disord., 2003, 17(2), 113 - 116

(21) PubMed abstract of L A Boothby, P L Doering, Ann. Pharmacother., December 2005, 39(12), 2073 - 2080

(23) D Boscoboinik et al., J. Biol. Chem., 1991, 266(10), 6188 - 6194

(24) R Ricciarelli et al, Biochem. J., 1998, 334, 243 - 249

(25) D Goti et al., J. Neurochem., 2001, 76, 498 - 508

III. The decision under appeal was based on the main and sole request filed with letter dated 22 December 2010, claims 1 and 10 of which read as follows:

"1. A composition comprising:

a) a PKC activator;

b) a PKC inhibitor; and

c) a pharmaceutically acceptable carrier

wherein the PKC inhibitor is a vitamin E, calphostin C, a thiazolidinedione, ruboxistaurin or combinations thereof.

...

10. The composition of claim 9, wherein the vitamin E is α-tocopherol."

IV. In its decision, the examining division focused on the subject-matter of claim 10. The closest prior art was identified as being document (1), which disclosed the use of protein kinase C (PKC) activators such as bryostatin for treating cognitive impairment of a neurological disease. The problem to be solved was defined as lying in the provision of a composition having improved activity. The proposed solution related to the co-administration of α-tocopherol. In view of the results reported in document (14), the examining division was not satisfied that an enhancement of the cognitive abilities had been demonstrated over the whole scope claimed. With respect to the improvement relating to the reduction of side effects, in particular myalgia, it was noted that neither the application as filed nor document (14) contained any evidence for this effect. Based on the cited prior art, such as documents (5), (7), (8), (10), and (11), it was nevertheless considered to be plausible that side effects could be reduced. However, the same prior art also rendered the claimed subject-matter obvious. Finally, the examining division was of the opinion that the cited prior art did not support the existence of a prejudice that would have dissuaded the skilled person from combining α-tocopherol and the PKC activator.

V. The appellant (applicant) lodged an appeal against this decision. With its statement of grounds of appeal, the appellant filed an amended main request, claim 1 of

which differed from that underlying the decision under appeal in that it was specified that the PKC activator was "in an amount effective to reduce neuro-degeneration, reduce the loss of cognitive ability, and/or enhance cognitive ability" and that "the PKC inhibitor is α-tocopherol" (cf. above point III, claims 1 and 10).

VI. In reply to a communication of the board sent as annex to the summons to oral proceedings, the appellant filed, with letter dated 4 July 2016, a new main request and three auxiliary requests, which were subsequently replaced, with letter dated 5 July 2016, by corresponding requests containing an amendment to claim 20.

Claim 1 of the main request is identical to that filed with the statement of grounds of appeal (cf. above point V).

Claim 1 of auxiliary request 1 corresponds to that of the main request with the additional limitation that "the PKC activator is a macrocyclic lactone".

In claim 1 of auxiliary request 2, the PKC activator was further limited to "bryostatin-1".

Claim 1 of auxiliary request 3 is worded as a purpose-limited product claim pursuant to Article 54(5) EPC, and reads as follows:

"1. A composition for use as a medicament for reducing neurodegeneration, reducing the loss of cognitive ability, and/or enhancing cognitive ability, comprising:

a) a PKC activator in an amount effective to reduce neurodegeneration, reduce the loss of cognitive ability, and/or enhance cognitive ability;

b) a PKC inhibitor; and

c) a pharmaceutically acceptable carrier

wherein the PKC activator is bryostatin-1 and the PKC inhibitor is α-tocopherol and wherein the bryostatin-1 is administered in a dose of between 5 and 200 $\mu g/m^2$."

VII. Oral proceedings were held before the board on 4 August 2016.

During the course of the oral proceedings, the appellant filed a further auxiliary request, as auxiliary request 4. Claim 1 of this request differed from that of auxiliary request 3 in the insertion at the end of the claim of the feature "and the α-tocopherol is administered in a dose of between 15 and 2,000 IU per day".

VIII. The appellant's arguments on the issue of inventive step, insofar as they are relevant to the present decision, may be summarised as follows:

Starting from document (1) as closest prior art, the appellant defined the problem to be solved as lying in the provision of a composition which enhanced cognitive ability, and reduced the side effect of myalgia, without negatively affecting the enhancement of cognitive ability. As taught in the application in suit, the problem had been solved by the the addition of the PKC inhibitor α-tocopherol to the known

compositions comprising a PKC activator such as bryostatin-1. Confirmation was further provided by document (14), which demonstrated that bryostatin-1 in combination with α-tocopherol improved learning over the control to at least a similar extent as bryostatin-1 administered alone, independently of dose. It was further discussed therein that much of the oxidant-related adverse effects observed with PKC activators, such as myalgia, could be eliminated or attenuated by co-administration of a powerful antioxidant, such as vitamin E. Hence, it was also plausible that a reduction in myalgia was achieved with the compositions according to claim 1.

Regarding the aspect relating to the side effect myalgia, document (1) itself merely taught a maximum tolerated dose of 40 $\mu g/m^2$ for bryostatin-1, and therefore suggested a reduction in dose in order to address this problem, rather than the combination with further active agents. Certainly, α-tocopherol was not mentioned therein.

The usefulness of α-tocopherol in reducing myalgia induced by a PKC activator could also not have been predicted from the remaining prior art cited in the decision under appeal, namely, documents (5), (7), (8), (10) and (11). These documents concerned different fields of research, and would not therefore have been consulted by the skilled person seeking to reduce myalgia in the present context. Specifically, document (5) disclosed the anti-neoplastic activity of bryostatin-1, and suggested using vasodilators to reduce myalgia. Documents (7), (8), (10) and (11) related to uses of vitamin E and α-tocopherol, but not in the form of combination drugs. Moreover, although documents (7) and (8) addressed the issue of myalgia,

this was associated with suxamethonium administration and work-related exposures, respectively, rather than PKC activation. Documents (10) and (11) did not even mention myalgia.

Should the board come to the conclusion that the effect of myalgia reduction had not been plausibly demonstrated, the problem to be solved would then be defined as lying in the provision of an alternative composition for enhancing cognitive ability. As previously set out, document (14) provided evidence that this problem had successfully been solved. Here again, the claimed solution would not have been obvious:

Contrary to what was implied in document (13), the beneficial effect of α-tocopherol in improving cognition had not been consistently established at the priority date of the application in suit, as was confirmed by documents (17) to (19). The appellant further referred to document (21) in this context, as recommending against the use of α-tocopherol, owing to the increased mortality and morbidity observed with long-term daily doses of greater than 400 IU; although post-published, this document should be taken into account since the literature evaluated therein was, for the most part, pre-published. Therefore, when taken as a whole, the state of the art at the present priority date indicated that the success of using α-tocopherol alone or in combination with other agents for improving cognition was not predictable.

In any case, even if the skilled person had been aware of a potential beneficial effect of α-tocopherol on neurodenerative disease when used alone, he would also have known that the therapeutic properties of an agent

could be altered through use in combination with another agent, as exemplified in document (20). In particular, he would have been deterred from combining α-tocopherol with a PKC activator, such as bryostatin-1, by the knowledge that the former acted as a PKC inhibitor, as disclosed, for example, in documents (10), (11), (16), (23), (24) and (25). The skilled person would have been further discouraged by the disclosure in document (1) that the PKC inhibitor staurosporin eliminated the effect of the PKC activator bryostatin-1.

Contrary to the opinion expressed in the decision under appeal, the skilled person would indeed have assumed that α-tocopherol would be delivered to the brain and exhibit PKC inhibitory activity therein. The expectation of passage through the blood-brain barrier had been confirmed by document (25).

The appellant concluded that α-tocopherol would have been expected to inhibit PKC activation in the brain, thereby abolishing the effect of the PKC activator, such as bryostatin-1, in enhancing cognitive ability. The fact that no such interaction had been observed, as had been demonstrated in document (14), was therefore surprising.

With respect to auxiliary requests 1 to 3, the appellant submitted that the same arguments in favour of inventive step applied as for the main request. The additional limitations in these requests had been introduced in order to more closely reflect the experiments provided in document (14). It was therefore all the more evident that the problem of enhancing cognitive ability had been plausibly solved for the full scope claimed.

Finally, the appellant argued that auxiliary request 4 should be admitted into the proceedings, since it had been filed in reaction to the board's conclusion on inventive step for the higher-ranking requests. With respect to auxiliary request 3 previously on file, dependent claim 5 had merely been incorporated into claim 1, in order to further support the claimed breadth with respect to document (14).

IX. The appellant requested that the decision under appeal be set aside, and that a patent be granted on the basis of the claims of the main request or, alternatively, of auxiliary requests 1 to 3, all filed with letter dated 5 July 2016, or further alternatively, of auxiliary request 4 filed during the oral proceedings of 4 August 2016.

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

Reasons for the Decision

1. The appeal is admissible.

2. *Admission of auxiliary request 4 (Article 13(1) RPBA)*

Auxiliary request 4 was filed at an advanced stage of the appeal proceedings, namely towards the end of the oral proceedings before the board, after the discussion on inventive step of the main request and auxiliary requests 1 to 3 had been completed. No new aspects were raised during oral proceedings before the board, beyond those already addressed in the decision under appeal and during the subsequent written phase of the appeal proceedings. Moreover, the intention indicated by the appellant in filing auxiliary request 4 was to address an aspect that had not been challenged by the board (cf. above point VIII, last two paragraphs, and point 4 below). Therefore, its filing cannot be seen as a timely or appropriate reaction to developments during oral proceedings. Consequently, the board decided not to admit auxiliary request 4 into the appeal proceedings.

3. *Main request, inventive step (Articles 52(1), 56 EPC)*

3.1 Claim 1 of the main request is directed to a composition comprising a PKC activator, α-tocopherol, and a pharmaceutically acceptable carrier. α-Tocopherol is a major active component of vitamin E (see e.g. application in suit, paragraph [37]). In a preferred embodiment the PKC activator is bryostatin-1 (see e.g. claim 6; application in suit, paragraphs [45] (last line) and [46]; examples). Such compositions are

disclosed as being useful in reducing neurodegeneration, reducing the loss of cognitive ability, and/or enhancing cognitive ability (see e.g. claims 9, 12, and 16).

3.2 The board considers, in agreement with the appellant and the examining division, that document (1) represents the closest state of the art.

Document (1) is concerned with methods and corresponding compositions for enhancing cognitive ability by administration of a PKC activator in a pharmaceutically acceptable carrier; in a preferred embodiment bryostatin-1 is used (see e.g. claims 1 and 5; page 6, line 25 to page 8, line 2). This compound is discussed in more detail on page 19, line 29 to page 20, line 17, as having previously been investigated as an anti-cancer agent, whereby the main adverse reaction is myalgia, limiting the maximum dose to 40 $\mu g/m^2$ (note: erroneously designated as 40 mg/m^2). Experimental evidence is provided that bryostatin-1 significantly improves rats' performance in the Morris Water Maze task (page 24, lines 28 to 31; page 35, lines 1 to 3; Example II).

3.3 The appellant defined the problem to be solved, in the light of document (1), as lying in the provision of a composition which enhanced cognitive ability, and reduced the side effect of myalgia, without negatively affecting the enhancement of cognitive ability.

The solution proposed in claim 1 relates to a composition characterised in that it additionally comprises α-tocopherol.

As a next step according to the problem-solution approach, it is necessary to establish whether said problem has plausibly been solved.

3.4 In this regard, it will first be discussed whether it has been rendered plausible that supplementation with α-tocopherol ameliorates the side effect of myalgia induced by a PKC activator.

3.4.1 In this respect, the appellant firstly pointed to the application in suit, and specifically to paragraph [77], which starts with the following statement:

"The compositions of the present invention increase the tolerable dose of the PKC activator administered to a patient and/or ameliorate the side effects associated with PKC activation by attenuating the activation of PKC in peripheral tissues. Specifically, PKC inhibitors inhibit PKC in peripheral tissues or preferentially inhibit PKC in peripheral tissues."

It can be seen that this statement is very general in nature and merely proposes a theoretical approach as to how the problem of side effects associated with PKC activation might be addressed.

The only other information provided in paragraph [77] is the following reference to literature relating to vitamin E (emphasis added):

"Vitamin E, for example, has been shown to normalize diacylglycerol-protein kinase C activation in the **aorta of diabetic rats** and cultured rat smooth muscle **cells exposed to elevated glucose levels**. (Kunisaki *et al.* (1994) Diabetes 43(11): 1372-1377). In a double-blind trial of vitamin E (2000 IU/day) treatment in patients

suffering from moderately advanced **Alzheimer's Disease**, it was found that vitamin E treatment reduced mortality and morbidity, but did not enhance cognitive abilities. (Burke *et al.* (1999) *Post Graduate Medicine* 106(5): 85-96)."

It is immediately apparent (see in particular passages emphasised in bold) that neither of these references relate to the present context of the pathogenesis or treatment of myalgia induced by a PKC activator.

Consequently, it is concluded that paragraph [77] cannot be viewed as providing support for the plausibility of the asserted effect with respect to vitamin E.

3.4.2 The appellant further relied on post-published document (14), which includes a study into the effect of co-administration of bryostatin-1 and α-tocopherol on spatial learning and memory in rats. In this document, adverse effects of PKC ativators are discussed, including myalgia as the main dose-limiting toxicity of bryostatin-1 (see, in particular, page 335, right-hand column; cf. also page 329, left-hand column, central paragraph). Reference is made to "Hickman et al., 1995" (document (5)) as disclosing that myalgia "may be due to muscular mitochondrial dysfunction". It is then further suggested that this is "a condition commonly contributing to an increased generation of oxidants", and that, "by co-administering a powerful antioxidant, much of these oxidants-related adverse effects with PKC activators may be eliminated or attenuated" (see page 335, right-hand column, lines 25 to 27 and lines 39 to 41).

As is apparent from the summary in the preceding paragraph, document (14) merely elaborates a further alternative hypothesis to that outlined above in point 3.4.1 with respect to a possible mechanism by which α-tocopherol may alleviate bryostatin-induced myalgia. The speculative character of these considerations is reflected in the cautious nature of the language used in the passages reproduced above. However, no concrete basis is provided that would plausibly establish a relationship between oxidant formation and myalgia. As acknowledged by the appellant, the cited document (5) does not propose such a link, but discloses evidence suggesting vasodilators such as nifedipine as a promising avenue for reducing bryostain-induced myalgia (cf. page 998, Summary, in particular, last line).

Therefore, document (14) also does not lend plausibility to the asserted effect.

3.4.3 Concerning the further prior art documents analysed in the decision under appeal as summarised above in point IV, the board agrees with the appellant that these cannot impart plausibility to the effect in question. In particular, documents (7) and (8) relate to the treatment of myalgia resulting from a different cause to the present, and documents (10) and (11) make no mention of this side effect (cf. above point VIII, fourth paragraph).

3.4.4 Finally, it is noted that the application in suit acknowledges that "the etiology of bryostatin-induced myalgia is uncertain" (see paragraph [75], last line). Indeed, as discussed in document (5) (see page 998, introductory section), "the consequences of PKC activation in animal muscle appear to be relatively

diverse". Similarly, α-tocopherol was known at the priority date of the application in suit to exhibit numerous possible modes of action, in addition to its well-documented antioxidant property (see e.g. document (11), page 113, left-hand column, last paragraph; document (23), page 6188, paragraph bridging left- and right-hand columns). Therefore, in view of the multiple processes potentially at play in the present case, a simple theoretical global selection and matching of molecular mechanisms of the two active agents of the present composition, without providing any more concrete or sound basis for supposing that the asserted effect is truly displayed in the relevant context, cannot be considered to be sufficient to render it plausible that α-tocopherol does indeed ameliorate the bryostatin-related side effect of myalgia.

3.4.5 Consequently, the board concludes it has not been rendered plausible that the problem as defined above in point 3.3 has been successfully solved.

3.5 The problem to be solved must therefore be reformulated in a less ambitious manner, as lying in the provision of an alternative composition for enhancing cognitive ability.

Having regard to the experimental results reported in document (14), the board is satisfied that this problem has been solved. In particular, spatial learning and memory in rats upon chronic co-administration of bryostatin-1 and α-tocopherol was found to be improved over the the control group, and at least comparable to the group receiving bryostatin-1 alone (see page 330 to 333, Results, points 3.1 and 3.2).

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

As set out above in point 3.2, document (1) already discloses compositions comprising a PKC activator, in particular bryostatin-1, as well as suitability for the stated use. Starting from these compositions and faced with the problem posed, the skilled person would also have been aware of the possibility of combination with further active substances relevant to the overall therapeutic effect (see document (1), page 9, lines 1, 2).

In this context, the skilled person would also have been aware of the fact that relevant beneficial effects had been ascribed to vitamin E and α-tocopherol. For example, document (11) describes vitamin E as being "an essential nutrient necessary for the optimal development and maintenance of human nervous system integrity and function", and that "increased intake is associated with reduced risk of cardiovascular disease, Parkinson's disease, Alzheimer's disease and other degenerative disorders" (page 113, left-hand column, first complete paragraph; see also document (25), page 498, first line of Abstract). Similarly, in document (13), it is concluded that the use of α-tocopherol prevents learning and memory deficits and that it should be investigated for the treatment of Alzheimer's disease (see page 89, right-hand column, last paragraph).

Consequently, it would have been obvious for the skilled person to have considered supplementing the compositions taught in document (1) with α-tocopherol,

as a solution to the problem defined above in point 3.5.

3.7 The appellant's submissions that the skilled person would have been deterred from such a combination do not hold for the following reasons:

3.7.1 The appellant firstly argued, with reference to documents (17) to (19) and (21), that there was no consistent teaching in the prior art with respect to the beneficial effects of α-tocopherol.

In document (17), the efficacy of various pharmacologic treatments of Alzheimer's disease is reviewed, and it is concluded, "Benefit for vitamin E ... has been suggested, but supporting evidence is not strong" (see page 1365, Abstract; and page 1367). However, the board notes that, in Table 4 (page 1369), vitamin E is disclosed as being a recommended drug by four of the six organisations listed. In abstract (18), it is stated that "Vitamin E supplementation did not show major beneficial effect on cognitive functions". In abstract (19), an investigation into the relationship between Alzheimer's disease (AD) and the intake of vitamin E is summarised as having found that intake of vitamin E "was not related to a decreased risk of AD". Document (21) refers to contradictory studies with respect to the effect of the combined use of vitamins C and E on the incidence of AD.

Thus, it can be seen from the previous paragraph that, although these additional citations (17) to (19) and (21) moderate the disclosures summarised above in point 3.6 to a certain extent, in particular with respect to the magnitude of the effect to be expected, they are certainly not uniform in negating any relevant

beneficial effect of vitamin E. Therefore, taking this information as a whole, together with that summarised above in point 3.6, the skilled person would certainly have been provided with sufficient motivation to pursue this avenue with a reasonable expectation of success.

3.7.2 Moreover, the board cannot accept the appellant's submissions according to which the prior art would have led the skilled person to expect adverse interactions on combining a PKC activator with α-tocopherol.

Certainly, as reflected in document (20), the skilled person would generally be aware of the potential for interactions, positive or negative, when combining any two active agents. However, the question to be answered in the present case is whether, as argued by the appellant, the skilled person would have expected α-tocopherol to limit or abolish the beneficial effect of the PKC activator, such as bryostatin-1, in enhancing cognitive ability.

The appellant pointed in this context to several documents disclosing a PKC inhibitory activity for α-tocopherol, namely, documents (10), (11), (16), (23), (24) and (25). However, none of these documents concern the role of this activity in the context of cognitive or neurodegenerative processes in the brain. Document (25) does provide evidence of delivery of α-tocopherol to the brain. However, on page 506 of this document (right-hand column), numerous possible mechanisms are presented by which α-tocopherol might exert its effect once there. *Inter alia*, the role of microglia activation is discussed, and it is speculated that "it seems **conceivable** that some of the modulatory properties of αTocH during monocyte activation **could be extrapolated to microglia activation**" (emphasis added);

this is followed by citations relating to "inhibition of PKC activity by αTocH ... in human monocytes". It can therefore be derived from document (25) that the mechanisms by which α-tocopherol exerts its effect in the brain are complex and not fully understood. In the absence of any more concrete teaching to this effect, the skilled person would not have been deterred by an expectation of adverse interactions between α-tocopherol and a PKC activator.

The disclosure in document (1) that the PKC inhibitor staurosporin completely abolishes the effect of bryostatin also cannot help in establishing a deterrent. Apart from the fact that staurosporin is structurally remote from α-tocopherol, said finding lacks relevance since it is based on *in vitro* experiments, specifically designed to demonstrate mechanistic aspects of bryostatin activity (see page 10, line 26 to page 11, line 6; page 20, lines 14 to 17; page 32, lines 1 to 8).

3.7.3 Finally, the appellant pointed to potential problems of toxicity arising from the use of therapeutic PKC inhibitors in general (see document (10), page 177, left-hand column, last two sentences of first complete paragraph), and the suggestion that long-term daily doses of α-tocopherol of greater than 400 IU were associated with increased mortality and morbidity (see document (21)). However, the board notes that such doses are not excluded from the present claims (cf. claims 20 to 22). Moreover, the potential for toxicity and consequent adjustment of dose is something that the skilled person would always have to consider as a matter of routine when formulating compositions.

3.8 In view of the above analysis, it is concluded that the skilled person would not require any inventive skill in order to arrive the subject-matter of claim 1, and would not have been deterred from doing so. Consequently, the appellant's main request is rejected for lack of inventive step.

4. *Auxiliary requests 1 to 3, inventive step (Articles 52(1), 56 EPC)*

The amendments introduced into claims 1 of auxiliary requests 1 and 2, namely, the definition of the PKC activator as "a macrocyclic lactone" and "bryostatin-1", respectively, as well as the reformulation of claim 1 of auxiliary request 3 as a second medical use claim in which the dosage range of of bryostatin-1 was defined as being "between 5 and 200 $\mu g/m^2$" (cf. above point VI) were all introduced as a precautionary measure, in order to preempt potential objections as to whether the problem defined above in point 3.5 had been plausibly solved for the full scope claimed (cf. above point VIII, penultimate paragraph). However, in the event, this question was not material to the present decision (cf. above point 3.5, second paragraph), and no additional arguments in favour of inventive step were submitted by the appellant for these requests. Indeed, in view of the fact that the closest prior art document (1) already discloses the macrocyclic lactone bryostatin-1 as a preferred embodiment, and a dose range substantially overlapping with that specified in auxiliary request 3 (cf. above point 3.2), the reasoning and conclusions set out in point 3 apply *mutatis mutandis* to the subject-matter of claims 1 of auxiliary requests 1 to 3.

Hence, auxiliary requests 1 to 3 are also rejected for lack of inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated