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Datasheet for the decision of 31 October 2023

Case Number: T 1379/21 - 3.3.07

Application Number: 07711417.1

Publication Number: 1983984

IPC: A61K31/436, A61K31/365, A61K31/351, A61P35/00, A61P25/00

Language of the proceedings: EN

Title of invention:
TUBEROUS SCLEROSIS TREATMENT

Patent Proprietor:
Novartis Pharma AG

Opponents:
Intas Pharmaceuticals Ltd.
Teva Pharmaceutical Industries Ltd.
Stada-Arzneimittel Aktiengesellschaft
Cooke, Richard

Headword:
Tuberous sclerosis / NOVARTIS

Relevant legal provisions:
RPBA 2020 Art. 12(4)
EPC Art. 56, 123(2)

Keyword:

Amendment to case - complexity of amendment - amendment admitted (no)
Inventive step - main request (no) - auxiliary requests 1-3, 6, 7, 7B (no)
Amendments - auxiliary requests 4, 5, 7A, 8 - allowable (no)

Decisions cited:

T 1320/13

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Beschwerdekammern

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Case Number: T 1379/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 31 October 2023

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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted on 16 July 2021 concerning maintenance of the European Patent No. 1983984 in amended form.

Composition of the Board:

Chairwoman Y. Podbielski
Members: M. Steendijk
J. Lécaillon

Summary of Facts and Submissions

I. European patent 1 983 984 ("the patent") was granted on the basis of four claims.

The patent as granted related to 40-O-(2-hydroxyethyl)-rapamycin for use in the treatment of disorders mediated via the Tuberous Sclerosis Complex (TSC) or symptoms thereof wherein 40-O-(2-hydroxyethyl)-rapamycin is administered orally in dosages from 2.5 mg up to 15 mg.

The compound 40-O-(2-hydroxyethyl)-rapamycin is also referred to as RAD001, RAD and everolimus.

II. Four oppositions had been filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed. The four opponents filed appeals against the interlocutory decision of the opposition division that the patent as amended in accordance with the proprietor's main request met the requirements of the EPC. This main request had originally been filed as auxiliary request 1 on 1 July 2019.

Claim 1 of the main request defined:

"40-O-(2-hydroxyethyl)-rapamycin for use in the treatment of disorders mediated via the Tuberous Sclerosis Complex, wherein the disorders are renal angiomyolipomas (AML), lymphangioleiomyomatosis (LAM), and/or subependymal giant cell astrocytomas (SEGAs);

wherein 40-O-(2-hydroxyethyl)-rapamycin is administered orally in dosages from 2.5 mg up to 15 mg."

In its decision the opposition division cited *inter alia* the following documents:

D1: Annals of Neurology, 2006, 59(3), 490-498
D5: Cancer Investigation, 2004, 22(4), 588-603
D7: Curr. Opinion in Cell Biol., 2005, 17, 596-603
D10: Nephrol. Dial. Transplant, 2004, 19(10), 2606-2614
D11: Clin. Pharmacokinet., 2004, 43(2), 83-95
D14: Expert. Opin. Investig. Drug, 2005, 14(3), 313-328
D15: Medicinal Research Reviews, 2006, 26(2), 160-180
D16: Oncogene, 2004, 23, 3138-3144
D17: J. Clin. Oncology, 2005, 23(16S), 3007
D26: Certican package leaflet
D31: Summary of Product Characteristics for Votubia
D32: Lancet, 2016, 388, 2153-2163
D33: Neurology, 2016, 87, 1011-1018
D34: Brit. J. Pharmacology, 2001, 133, 875-885
D35: Transplantation Proceedings, 2001, 33, 514-515
D36: J. Clin. Pharmacol., 1997, 37, 405-415
D37: Br. J. Clin. Pharmacol., 48, 694-703
D38: Transplantation, 1997, 64(1), 36-42
D39: Hematol. Oncol. Clin. N. Am., 2002, 16, 1101-1114
D40: Proc. Am. Ass. Cancer Res., 1999, 40, Abstract #2000

The opposition division arrived at the following conclusions:

(a) The application as filed disclosed the treatment of the defined TSC-conditions as a preferred aspect of the claimed invention and specifically disclosed for the preferred active agent everolimus a suitable oral dosage of 0.1 mg to 15 mg, including

for instance 2.5 mg. The main request therefore complied with Article 123(2) EPC.

(b) The statements in the patent concerning the reduction of growth of TSC1 and TSC2 null cells and the reduction of kidney and liver tumours in TSC1+/- and TSC2+/- mice supported the suitability of everolimus for the defined therapeutic purpose. The opponents had not raised serious doubts substantiated by verifiable facts regarding the effectiveness of the defined treatment and the defined treatment did not go against prevailing principles. The main request thus complied with Article 83 EPC.

(c) Document D14 discussed the hypothesis that rapamycin and its derivatives could prove to be effective in the treatment of patients suffering from Tuberous Sclerosis (TS), but failed to disclose the utility of everolimus in the treatment of AML, LAM or SEGAs. The main request therefore met the requirement of novelty.

(d) Document D1 represented the closest prior art, because it described rapamycin as effective in the treatment of SEGAs and thus aimed at the same objective as the claimed invention.

The claimed subject-matter differed from the teaching in document D1 in the definition of everolimus instead of rapamycin as the agent to be used. The efficacy of everolimus in the treatment of the claimed disorders was credible on the basis of the data reported in the patent and confirmed by the post-published document D31. Documents D32 and D33 did not demonstrate an improvement over

treatment with rapamycin. The problem to be solved concerned the provision of an effective alternative treatment of AML, LAM and SEGAs.

Document D1 discussed mTOR inhibition as a mechanism of action for the efficacy of rapamicin in the treatment of SEGAs, but explicitly stated that the reported findings did not prove the efficacy of mTOR inhibition in the treatment of SEGAs and indicated possible additional mechanisms of action. The skilled person could therefore not reasonably expect from document D1 that everolimus, a known immunosuppressive rapamycin-analog and mTOR inhibitor, would be effective in the treatment of SEGAs like rapamycin. The disclosure in document D16 that everolimus is investigated in Phase I clinical trials for treatment of TSC syndrome provided in the absence of any reported results on efficacy no relevant guidance towards the claimed utility.

The main request therefore met the requirement of inventive step.

III. During the appeal proceedings the following further documents were filed:

D43: Blood, 2005, 105(11), 4463-4469
by opponent O4 with the statement of grounds of appeal,

D44: T 3139/19
by opponent 1 with the statement of grounds of appeal,

D45: Orphanet J. Rare Dis., 2021, 16, 299
by the proprietor with the reply to the appeals.

IV. With the reply to the appeal the patent proprietor upheld the main request on which the decision under appeal was based and filed auxiliary requests 1-7, 7A, 7B and 8.

Claim 1 of auxiliary request 1 defined with respect to claim 1 of the main request the everolimus dosages to range from 2.5 mg up to 10 mg.

Claim 1 of auxiliary request 2 defined with respect to claim 1 of the main request the everolimus dosages as 2.5 mg, 5 mg or 10 mg.

Claim 1 of auxiliary request 3 limited with respect to claim 1 of the main request the disorders to be treated by deletion of LAM.

Claim 1 of auxiliary request 4 defined with respect to claim 1 of the main request the dosage from 2.5 mg up to 15 mg as a daily dosage.

Claim 1 of auxiliary request 5 limited with respect to claim 1 of the main request the disorders to be treated to AML by deletion of LAM and SEGAs.

Claim 1 of auxiliary request 6 defined with respect to claim 1 of the main request the everolimus dosage as a dosage of 10 mg.

Auxiliary requests 7 and 7B were limited to single claims which correspond, respectively, to the independent claims of auxiliary requests 2 and 6; auxiliary request 7A was limited to the independent claim of auxiliary request 2 with further restriction of the disorders to be treated to AML by deletion of LAM and SEGAs.

Auxiliary request 8 was limited to a single claim which restricted with respect to claim 1 of the main request the disorders to be treated to AML by deletion of LAM and SEGAs and the everolimus dosage as a dosage of 10 mg.

V. In its communication pursuant to Article 15(1) RPBA the Board expressed *inter alia* the preliminary opinion that

- the main request complied with Articles 123(2), 83 and 54 EPC,

- document D45 was not to be admitted,

- document D1 represented the closest prior art for the assessment of inventive step, in view of which the objective technical problem was formulated as the provision of alternative effective treatment of AML, LAM and SEGAs.

VI. Oral proceedings were held on 31 October 2023.

VII. The arguments of the opponents relevant to the present decision are summarized as follows:

The subject-matter of the main request extended beyond the content of the original disclosure due to the combined selection of the dosage range, the disorders to be treated and the nature of the treatment. Moreover, in line with the considerations in T 1320/13 the dosage range itself had not been originally disclosed, because it resulted from the combination of an end point of a range with a specific value selected from a list of individual values.

The subject-matter of the main request did not involve an inventive step in view of document D1 as closest prior art, which described the treatment of SEGAs with rapamycin instead of everolimus. The patent provided no indication of any particular effect resulting from the difference with the prior art. Particular effects allegedly demonstrated in post-published documents should therefore not be taken into account. The filing of document D45 represented a complex amendment to the proprietors case which should not be admitted. The results reported in documents D32 and D33 and document D45 were anyway not suitable to show any relevant advantage of the treatment with everolimus as claimed over the treatment with rapamycin as known from document D1. The objective technical problem underlying the claimed invention could at best be seen in the provision of an alternative treatment of TSC mediated disorders such as SEGAs.

Document D1 itself pointed at compelling circumstantial evidence for the efficacy of mTOR inhibition in the treatment of SEGAs. Actual proof of the efficacy of mTOR inhibitors would not be required for a relevant expectation of success. The skilled person's expectation regarding the effectiveness of mTOR inhibitors was further supported by the teaching in documents D5, D7, D15 and D16. Possible further mechanisms of action of rampamycin mentioned in document D1 were anyway according to document D43 also related to its mTOR inhibition. As everolimus was known from documents D1, D14, D15, D16, D17 and D38 as a rapamycin analogue with mTOR inhibiting activity the skilled person had a reasonable expectation that everolimus

would be useful in the treatment of TSC mediated disorders as defined in claim 1 of the main request.

The definition of the dosage did not contribute to an inventive step, because the patent provided no substantiation regarding the significance of the defined dosages and because in the absence of a definition of a dosing frequency the actually administered therapeutic dose remained anyway undefined. Moreover, the defined dosing of everolimus had been described in documents D10, D14 and D17 and the determination of relevant dosages would anyway represent routine practice.

The auxiliary requests 1-3, 6, 7 and 7B did not meet the requirement of inventive step for the same reason as the main request.

The definition of the daily dose in auxiliary request 4 and the combined selection of AML and the dosage in auxiliary requests 5, 7A and 8 did not comply with Article 123(2) EPC.

VIII. The arguments of the patent proprietor relevant to the present decision are summarized as follows:

The subject-matter of the main request was adequately based on the original disclosure of the defined therapeutic indications for everolimus and the originally disclosed dosages of everolimus. The application as filed indicated the treatment of the defined TSC mediated disorders as preferred and specifically disclosed for everolimus a suitable dosage range of 0.1 mg to 15 mg, including a dosage of 2.5 mg.

Document D1 described the treatment of patients with SEGAs by oral administration of rapamycin. The activity of everolimus in cell-lines and in animal models reported in the patent demonstrated that everolimus is useful for effective treatment of TSC mediated disorders as defined in the claims. This was confirmed in the post-published document D31. The further post-published documents D32/D33 and D45 should be taken into account as evidence of the improved effect of everolimus in treatment of TSC mediated disorders as compared to rapamycin. Document D45, which had only become available after the decision under appeal, should be admitted into the appeal proceedings as a direct response to the finding in the decision under appeal that documents D32 and D33 did not indicate any relevant improvement associated with the claimed subject-matter over the prior art.

Document D1 reported only preliminary results for the treatment of SEGAs with rapamycin, which still required confirmation by prospective trials. The results in document D33 confirmed that rapamycin was not particularly effective in the treatment of TSC related seizures.

Any beneficial effect reported for the single individual agent rapamycin could not be extrapolated to the class of mTOR agents in general, in particular taking account of the additional mechanisms of action of rapamycin explicitly mentioned in document D1. Effective therapy of TSC mediated disease from inhibition of mTOR activity could further not be predicted on the basis of a link between mTOR activity and

manifestations of TSC mentioned in the prior art, in particular in view of the reference in document D5 to additional factors that are likely to be involved in the development of TSC mediated diseases.

Further, from documents D10, D11 and D35-D38 rapamycin and everolimus were known to differ significantly in their pharmacokinetic and pharmacodynamic characteristics. The shared mTOR inhibitory activity of rapamycin derivatives did not allow for the prediction of their therapeutic utility. This was illustrated by the mTOR inhibitor temsirolimus for which documents D39 and D40 indicated utility in cancer treatment, but not in immunosuppressant therapy.

Moreover, document D1 disclosed the effectiveness of rapamycin at concentrations typically used in immunosuppressive therapy. In line with the instructions in document D26 immunosuppressive therapy with everolimus involves oral administration with a dose of 1.5 mg/day. Document D1 provided therefore no motivation to consider the higher dosing of everolimus as mentioned in document D17.

The reference to combination treatment of rapamycin with gamma-interferon in document D1 and the more advanced stage of development of temsirolimus, a rapamycin prodrug, would furthermore lead the skilled person away from the claimed utility of erverolimus.

Accordingly, the skilled person could not derive from the prior art any reasonable expectation for

the effectiveness of everolimus in the treatment of TSC mediated disorders as defined in the claims of of the main request. The claimed subject-matter was therefore not obvious to the skilled person as solution to the problem of providing effective alternative treatment of TSC mediated disorders.

The definition of the daily dose in claim 1 of auxiliary request 4 was based on the general reference to daily dosing in the application as filed, which the skilled person would understand as also pertaining to the subsequently described oral dosages for everolimus.

The 10 mg dosage defined in claim 1 of auxiliary request 6 was remote from any immunosuppressive dosing of everolimus and therefore not obvious from the use of rapamycin in the immunosuppressive concentrations reported in document D1.

The definition of AML as the disorder to be treated in auxiliary requests 5, 7A and 8 did not give rise to subject-matter extending beyond the original disclosure, because this definition corresponded to an embodiment which had been originally described as preferred and merely resulted from the deletion of alternative indications.

IX. The opponents requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

The opponents further requested that document D45 and auxiliary requests 5, 6, 7A, 7B and 8 not be admitted into the appeal proceedings.

X. The patent proprietor requested that the appeals be dismissed.

As an auxiliary measure the proprietor requested that the patent be maintained on the basis of one of auxiliary requests 1 to 7, 7A, 7B and 8, all filed with the reply to the statements of grounds of appeal.

Reasons for the Decision

1. Main request: amendments

1.1 The application as originally filed discloses in claim 1 the utility of macrocyclic compounds of a defined general structural formula for the treatment of neurocutaneous disorders. The TSC mediated disorders AML, LAM and SEGAs are disclosed in claim 4 of the application as filed. The compound 40-O-(2-hydroxyethyl)-rapamycin (everolimus) is defined in claim 7 of the application as filed as the agent to be used.

1.2 The application as filed highlights (see page 14, lines 3-8) the utility of everolimus, describing for this compound a suitable dosage range for oral administration of 0.1 mg to 15 mg, including a specific dosage of 2.5 mg:

"E.g. everolimus may be administered, e.g. orally, in dosages from 0.1 mg up to 15 mg, such as 0.1 mg to 10 mg. e.g. 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2.5 mg, 5 mg, or 10 mg, more preferably from 0.5 mg to 10 mg, e.g. in the form of (dispersible) tablets; e.g. comprising everolimus in the form of a solid

dispersion; e.g. a weekly dosage may include up to 70 mg, e.g. 10-70 mg..."

The narrowing of the general dosage range for everolimus in claim 1 of the main request by replacement of the lower limit of the originally disclosed range 0.1 mg by the specifically disclosed value of 2.5 mg does not go beyond a one dimensional restriction by selection of the disclosed value of 2.5 mg, which is *per se* not considered to introduce subject-matter extending beyond the original disclosure. The considerations in T 1320/13 (see points 11-15 of the reasons) are not pertinent for the present case, in which the original disclosure specifically presents the dosage of 2.5 mg in the context of the range for suitable dosages of 0.1 mg to 15 mg and thereby provides a basis for the combination of the dosage values in the defined range of 2.5 mg up to 15 mg.

1.3 The application as filed (see page 7, lines 17-26) further describes the treatment of TSC mediated disorders as a preferred aspect of the disclosed invention with specific reference to AML, LAM and SEGAs and does not express any similar preference regarding other specific therapeutic indications. In view of this pointer towards the treatment of TSC mediated disorders AML, LAM and SEGAs the Board considers that the definition of the treatment of these TSC mediated disorders in claim 1 of the main request does not introduce a further aspect of selection that would in combination with the definition of the dosage range result in subject-matter extending beyond the original disclosure.

1.4 The Board therefore concludes that the main request complies with Article 123(2) EPC.

2. Main request: inventive step

2.1 The claimed invention as presented in the patent

The patent presents in paragraphs [0040] to [0046] the experimental basis for the claimed utility of everolimus in the treatment of TSC medicated disorders. Paragraphs [0040] to [0043] describe how the activity of the compound to be used may be shown by *in vitro* methods involving Tsc1-/-, Tsc2-/- and control MEF cell lines. Paragraph [0044] reports that it can be demonstrated that everolimus (Compound A) significantly reduces growth under all conditions and blocks any growth response of the cells to IGF1. Paragraph [0045] discusses trials in mouse models of TSC involving Tsc1+/- and Tsc2+/- mice. Paragraph [0046] reports that it can be demonstrated that everolimus has a dramatic effect in reducing kidney and liver tumors in Tsc1+/- and Tsc2+/- mice.

2.2 The objective technical problem

2.2.1 Document D1 describes the regression of SEGAs in patients with TSC following oral administration of up to 7 mg rapamycin daily (see D1, pages 492-496, under "Results"). The difference of the claimed subject-matter with this prior art concerns the use of everolimus in the defined dosage range instead of rapamycin.

2.2.2 The Board considers that the patent provides with the mentioned report on the activity of everolimus in experimental models a credible indication for the

effectiveness of everolimus in the treatment of TSC mediated disorders such as AML, LAM and SEGA's as defined in the claims of the main request. This effectiveness is confirmed by the post-published document D31, which represents the Summary of Product Characteristics for Votubia and indicates the authorized approval of relevant dosages of everolimus for the treatment of AML and SEGAs (see D31, pages 2-3).

2.2.3 The proprietor relied on the post-published documents D32 and D33 to substantiate that everolimus provides for improved therapy of TSC mediated disorders compared to rapamycin.

Document D32 reports a significant reduction of seizure frequency with a tolerable safety profile in patients with TSC having treatment-resistant seizures following treatment with everolimus (see D32, abstract). Document D33 reports that no significant benefit could be shown for treatment of epilepsy in children with TSC with sirolimus (=rapamycin) in spite of an observed decrease in seizure frequency (see D33, summary).

The Board observes that documents D32 and D33 report on studies of entirely different design involving different patient groups. The study of document D32 included patients aged between 2-65 years, whereas the study of document D33 only involved children aged between 1.8-10.9 years. Already for this reason alone the Board agrees with the finding in the decision under appeal that the results reported in documents D32 and D33 are not suitable to show an improvement for treatment of TSC mediated disorders with everolimus as compared to treatment with rapamycin.

2.2.4 Admittance of D45

The proprietor further relied on the post-published document D45 as evidence that everolimus provides for improved therapy of TSC mediated disorders compared to rapamycin.

Document D45 reports the results of a study comparing the effect of the treatment of AML associated with TSC with a daily oral dose of 10 mg everolimus with that of the treatment with 2 mg sirolimus (=rapamycin), indicating better therapeutic efficacy of everolimus, in particular in terms of AML volume reduction (see D45, abstract).

Document D45 was filed with the proprietor's reply to the appeals and thus represents an amendment to the proprietor's case under Article 12(4) RPBA in the form of new evidence.

During the first instance proceedings the proprietor had argued that the claimed subject-matter represented an improvement over the prior art based on the effects of treatment with everolimus compared to rapamycin on seizures in TSC patients as reported in documents D32 and D33. With the filing of document D45 the proprietor argued during the appeal proceedings that the improvement associated with the claimed subject-matter is demonstrated by the better efficacy of everolimus in the treatment of AML. With the filing of document D45 the proprietor did thus not contest the finding in the decision under appeal regarding the relevance of documents D32 and D33 *per se*, but relied on evidence regarding a different aspect of treatment which had not been considered during the first instance proceedings.

The proprietor argued that D45 could not have been filed earlier, because it was only published after the opposition division's decision had been taken. The Board does not doubt this sequence of events. However, whilst this argument may be relevant when assessing whether a document should have been filed in the first instance proceedings (Article 12(6) RPBA), it does not lead to an automatic admittance under Article 12(4) RPBA. Instead, when assessing whether the amendment to the proprietor's case should be allowed, the Board exercises its discretion in view of *inter alia* the criteria set out in Article 12(4) RPBA. These include the complexity of the amendment, the suitability of the amendment to address the issues which led to the decision under appeal and the need for procedural economy.

The proprietor's argument that document D45 demonstrates an improvement for the claimed subject-matter raises a plurality of new issues to be dealt with for the first time during the appeal proceedings. These issues include the question whether the effect of a better efficacy of everolimus in the treatment of AML as reported in document D45 should be considered encompassed by the technical teaching of the application as filed and embodied by the same originally disclosed invention, and the question whether an improvement of treatment with 10 mg everolimus over 2 mg rapamycin in the treatment of AML as reported in document D45 is at all suitable to demonstrate an improvement for the use of everolimus as defined in claim 1 of the main request with respect to the use of up to 7 mg rapamycin in the treatment of SEGAs as described in document D1. These issues are of high complexity and, in addition, cast doubt on whether

D45 is suitable to address the issues which led to the decision under appeal.

In view of the above, the Board has exercised its discretion under Article 12(4) RPBA not to admit document D45 into the appeal proceedings.

2.2.5 In view of the activity of everolimus in experimental models reported in the patent and in the absence of suitable evidence of an improvement from use of everolimus as defined in the claims with respect to the known use of rapamycin the Board concludes that starting from document D1 the objective technical problem is to be defined as the provision of an alternative treatment of a TSC mediated disorder, in particular the treatment of SEGAs.

2.3 Assessment of the claimed solution

2.3.1 Document D1 describes the regression of SEGA's in TSC patients following treatment with the mTOR inhibitor rapamycin in the context of the role of constitutive activation of mTOR activation in the development of the hamartomatous lesions in TSC patients (see D1, page 491, left column and figure 1). Document D1 points out that the observed effectiveness of rapamycin at concentrations typically used in transplantation medicine is consistent with the known action of rapamycin on mTOR causing a reduction in cell size or apoptosis (see D1, page 496, bridging section from left to right column). Whilst document D1 observes that there may be additional mechanisms of action and that the reported preliminary findings do not by themselves prove the efficacy of mTOR inhibition for the treatment of tuberous sclerosis-associated SEGA's, the document explains that the observed results from treatment with

rapamycin provide compelling circumstantial evidence to this effect (see D1, page 496, right column).

Document D1 itself refers to everolimus (RAD001) as a rapamycin derivative acting on mTOR in a similar fashion as rapamycin, which is in clinical development in a number of therapeutic indications, including oncology (see page 491, right column and figure 1). Faced with the objective technical problem of providing alternative treatment starting from document D1 the skilled person would therefore take account of document D17, which presents the results of a phase 1 study with tumor pharmacodynamic evaluation of dose and schedule of the oral mTOR inhibitor everolimus in patients with advanced solid tumors. Document D17 reports that the oral administration of everolimus achieves substantial intratumoral inhibition of mTOR signaling recommending a daily dosage of 10 mg everolimus for further development.

The Board considers that the information indicating the efficacy of mTOR inhibition in the treatment of SEGAs, which is qualified in document D1 as compelling circumstantial evidence, together with the information from document D17, that substantial intratumoral mTOR inhibition can be achieved by administration of an oral dosage of everolimus in the range of 10 mg, provides the skilled person with a reasonable expectation that oral administration of everolimus in the dosage range as defined in the claims of the main request allows for effective treatment of SEGAs. The claimed solution was therefore obvious to the skilled person in view of the prior art.

2.3.2 The references in document D1 to the preliminary nature of its findings and to required confirmation by

subsequent prospective trials (see D1, page 496, right column and page 498, left column) do not affect the report in document D1 regarding the actually observed regression of SEGAs in patients with TSC following oral administration of rapamycin. Document D1 specifically explains in this context why the reported changes may indeed be attributed to the administration of rapamycin (see D1, page 497, right column). The teaching in document D1 regarding the efficacy of rapamycin in the treatment of SEGAs is further not compromised by the results reported in the post-published document D33, because these results concern only the treatment of seizures in children with TSC.

The proprietor's argument that no reasonable expectation concerning the utility of everolimus could be based on the teaching of document D1 due to the preliminary nature of the results reported for rapamycin is therefore not considered convincing.

2.3.3 The proposition in document D1 regarding the efficacy of mTOR inhibition in the treatment of SEGAs is not based on a mere speculative extrapolation from the observed effects of a single agent, but is justified in document D1 on the basis of the efficacy of the mTOR inhibitor rapamycin against the background of the role of mTOR inhibition in the development of SEGAs (see D1, page 491). Alternative activities of rapamicin (the reduction of VEGF or intratumoral thrombosis) are only mentioned in document D1 as possible additional mechanisms of action (see D1, page 496, right column). Moreover, it remained uncontested that these alternative activities had anyway been described as still originating from its mTOR inhibition in document D43 to which document D1 refers (see D43, abstract and figure 8). Document D5 merely states in the context of

tumor prevention that mTOR may be necessary but not sufficient to cause the disease (see D5, page 597, left column) and further supports the proposition in document D1 by attributing the encouraging results demonstrated by rapamycin in preclinical testing in models of TSC to its mTOR inhibitory activity.

Contrary to the proprietor's arguments the Board does therefore not consider the proposition in document D1 regarding the efficacy of mTOR inhibition in the treatment of SEGAs unreasonable.

2.3.4 Rapamyin and everolimus were known to differ in their pharmacokinetic properties (see D10, page 1, right column; D11, page 93, "Conclusion"; D35, page 514, concluding sentence; D36, abstract; D37, abstract) and to exhibit certain differences in their pharmacodynamic effects (see D34, abstract; D38, page 40 passage bridging left and right column). However, notwithstanding these known differences everolimus was still commonly known as an orally administered rapamycin derivative which is effective as mTOR inhibitor (see D1, page 491; D14, page 322; D15, page 162; D16, page 3142; D17, "Background"; D38, page 37, left column).

Document D39 indicates that rapamycin and its derivatives everolimus (RAD) and temsirolimus (CCI-779) are in spite of many shared properties developed for different therapeutic application (see D39, page 1105, "Clinical development"). Document D40 confirms that temsirolimus showed in contrast to its persisting effect on tumor growth no prolonged effect on immune function after drug withdrawal (see D40, abstract). The Board observes, however, that documents D39 and D40 do not indicate any specific different indication for mTOR

inhibition by rapamycin and everolimus. Moreover, the observation that the specific pharmacologic properties of a rapamycin derivative may favour its development for a specific therapeutic indication does not affect the proposition in document D1 regarding the efficacy of mTOR inhibition in the treatment of SEGAs nor the teaching in document D17 that oral administration of everolimus achieves intratumoral mTOR inhibition.

Contrary to the proprietor's arguments the Board therefore considers that the differences in pharmacology between rapamycin and everolimus do not affect the skilled person's expectations based on the information in documents D1 and D17.

2.3.5 The experiments in document D1 involved the oral administration of daily dosages of up to 7 mg of rapamycin giving rise to serum concentrations in the range of 10 ng/ml (see D1, pages 492-496, "Results"). These serum concentrations are described as typical for the use of rapamycin in transplantation medicine (see D1, page 496, left column). Document D26 describes for the use of everolimus as an immunosuppressant tablets comprising up to 1 mg (see D26, page 1) and a typical starting dose of 1.5 mg/day (see D26, page 3). Such a dose of 1.5 mg/day for immunosuppressive treatment is not remote from the lower amount of 2.5 mg in the dosage range defined in claim 1 of the main request. Moreover, document D26 refers to the 1.5 mg/day only as a starting dose and does therefore not dissuade the skilled person from the higher dosages in the range of 2.5-15 mg, in particular when taking account of the teaching in document D17, which reports substantial intratumural inhibition of mTOR from the oral administration of everolimus recommending a daily dosage of 10 mg everolimus for further development.

Contrary to the proprietor's argument the reference in document D1 to immunosuppressant concentrations does therefore not affect the skilled person's expectations from the information in documents D1 and D17.

2.3.6 The reference to combination treatment of rapamycin with gamma-interferon in document D1 and the advanced development of the rapamycin prodrug temsirolimus in phase 3 clinical trials in cancer patients (see D16, page 3142) only indicate that other developments may also have been obvious the skilled person. This does not in any way affect the skilled person's expectations with respect to the suitability of the oral administration of everolimus for treatment of SEGAs as an alternative to rapamycin based on documents D1 and D17.

2.4 The Board therefore concludes that the subject-matter of claim 1 of the main request does not involve an inventive step.

3. Auxiliary requests

3.1 Admittance of the auxiliary requests

The auxiliary requests involving the restriction of the dose or the therapeutic indication as defined in the auxiliary requests represented a justified response by the proprietor to the appeals filed by the opponents.

The Board has therefore admitted the auxiliary requests into the appeal proceedings.

3.2 Auxiliary requests 1-3, 6, 7 and 7B: inventive step

3.2.1 The independent claims of auxiliary requests 1-2, 6, 7 and 7B define with respect to the main request the dosage of everolimus more restrictively as 2.5-10 mg, 2.5/5/10 mg or ultimately 10 mg. As explained above in sections 2.3.1 and 2.3.5 document D17 reports substantial intratumural inhibition of mTOR from the oral administration of everolimus and recommends a daily dosage of 10 mg everolimus for further development. The skilled person would therefore reasonably expect that such a 10 mg dosage of everolimus would also be suitable for treatment of SEGAs as an alternative to rapamycin described in document D1. The reasons for lack of inventive step set out for the main request therefore also apply with respect to auxiliary requests 1-2, 6, 7 and 7B.

3.2.2 The amendment in claim 1 of auxiliary request 3 concerns the deletion of LAM. This amendment does not introduce any additional difference with respect to the teaching of document D1. The reasons for lack of inventive step set out for the main request therefore equally apply with respect to auxiliary request 3.

3.2.3 Accordingly, the Board concludes that the subject-matter of auxiliary requests 1-3, 6, 7 and 7B does not involve an inventive step.

3.3 Auxiliary requests 4, 5, 7A and 8: amendments

3.3.1 Claim 1 of auxiliary request 4 introduces with respect to claim 1 of the main request the feature that the orally administered everolimus dosage of 2.5-10 mg is a daily dosage.

The application as originally filed (see page 13, lines 23-31) only refers to daily dosages in an explicit manner as follows:

"For such treatment, the appropriate dosage will, of course, vary depending upon, for example, the chemical nature and the pharmacokinetic data of a compound used, the individual host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage includes a range
- from about 0.0001 g to about 1.5 g, such as 0.001 g to 1.5 g;
- from about 0.001 mg/kg body weight to about 20 mg/kg body weight, such as 0.01 mg/kg 30 body weight to 20 mg/kg body weight,
for example administered in divided doses up to four times a day."

The only explicit disclosure of a daily dosage in the application as filed therefore refers to a wide dosage range for the described class of compounds in general and not the specific daily oral dosage for everolimus as defined in claim 1 of auxiliary request 4.

The subsequent paragraph in the application as filed (see pages 13-14, bridging section) states that a compound of the invention may be administered as appropriate, for instance in dosages which are known for the defined compounds of the invention by any administration route such as enterally, orally or parenterally. The paragraph continues with the passage cited in section 1.2 above, in which for everolimus an oral dosage in the range of 0.1-15 mg, such as 2.5 mg,

and a weekly dosage of up to 70 mg, such as 10-70 mg, is described.

This passage in the application as filed regarding the oral dosages of everolimus does not explicitly refer to these dosages as daily dosages.

The disclosure in the application as filed is not considered to implicitly disclose the oral dosage as defined in claim 1 of auxiliary request 4, because it cannot be concluded from the cited passages of the application as filed that the described oral dosages for everolimus necessarily concerned daily dosages.

The subject-matter claimed in auxiliary request 4 can therefore not be directly and unambiguously derived from the application as filed.

3.3.2 The claims of auxiliary requests 5, 7A and 8 define the disease to be treated as AML in combination with the definition of the dosage respectively as 2.5-15 mg, 2.5/5/10 mg or 10 mg.

As explained in section 1.2 above in the context of the main request the definition of the dosage as 2.5-15 mg in auxiliary request 5 represents a one dimensional restriction including the selection of the disclosed value of 2.5 mg. The definition of the dosages in auxiliary requests 7A and 8 also represent selections from the suitable values listed in the application as filed (see page 14, lines 3-5).

As discussed in section 1.3 above in the context of the main request the application as filed describes the treatment of TSC mediated disorders as a preferred aspect of the disclosed invention with specific

reference to AML, LAM and SEGAs. However, the application as filed provides no further preference for treatment of AML. The definition of the disease to be treated in the claims of auxiliary requests 5, 7A and 8 thus represents a further aspect of selection by singling out AML from the original disclosure.

The application as originally filed provides no further pointer to this combination of the selection of the dosage and the selection of the disorder to be treated.

The subject-matter claimed in auxiliary requests 5, 7A and 8 can therefore not be directly and unambiguously derived from the application as filed.

3.3.3 The Board therefore concludes that the auxiliary requests 4, 5, 7A and 8 do not comply with Article 123(2) EPC.

Order

For these reasons it is decided that:

4. The decision under appeal is set aside.

5. The patent is revoked.

The Registrar: The Chairwoman:

S. Sánchez Chiquero Y. Podbielski

Decision electronically authenticated