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Datasheet for the decision of 26 September 2023

Case Number: T 1796/22 - 3.3.07

Application Number: 18155724.0

Publication Number: 3342411

IPC: A61K31/436, A61P35/00

Language of the proceedings: EN

Title of invention:
RAPAMYCIN DERIVATIVE FOR TREATING PANCREAS CANCER

Patent Proprietor:
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Opponents:
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ARROW GENERIQUES

Headword:
Everolimus and pancreatic tumours/NOVARTIS

Relevant legal provisions:
EPC Art. 100(a), 100(b), 100(c)

Keyword:
Grounds for opposition - added subject-matter (no) - insufficiency of disclosure (no) - lack of inventive step (no)

Decisions cited:
G 0002/21, T 0814/22, T 3139/19, T 1868/16

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Beschwerdekammern

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Case Number: T 1796/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 26 September 2023

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 25 July 2022 revoking European patent No. 3342411 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairman A. Usuelli
Members: J. Molina de Alba
Y. Podbielski

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's decision revoking European patent No. 3342411.

II. The documents filed during the opposition and appeal proceedings include the following:

D1 WO 02/066019 A2

D4 R.M. Hoffman, Investigational New Drugs, 17, 1999, 343-59

D11 J.J. Gibbons et al., Proceedings of the American Association for Cancer Research, 40, 1999, abstract No. 2000

D12 M. Hidalgo et al., Oncogene, 19, 2000, 6680-6

D14 R. Sedrani et al., Transplantation Proceedings, 30, 1998, 2192-4

D15 W. Schuler et al., Transplantation, 64, 1997, 36-42

D17 WO 97/47317

D18 US 6183721 B1

D19 WO 01/51049 A1

D20 S.A. Shah et al., Journal of Surgical Research, 97, 2001, 123-30

D21 WO 94/09010

D34 M. Grewe et al., Cancer Research, 59, 1999, 3581-7

D36 I. Beuvink et al., Proceedings of the American Association for Cancer Research, 42, 2001, abstract No. 1972

D38 F.J. Dumont, Current Opinion in Investigational Drugs, 2(9), 2001, 1220-34

D40 Cancer Research UK - Types of Pancreatic Cancer

D41 The EMA's Summary of Product Characteristics for Afinitor

D63 J. Alexandre et al., Bull Cancer, 86(10), 1999, 808-11

D89 EP 0663916 B1

III. The patent in suit stems from European patent application 18155724.0, which was filed as a third-generation divisional of European patent application 02719864.7, published as international patent application WO 02/066019 (D1). The patent had been granted with the following two claims.

"*1. 40-O-(2-hydroxyethyl)-rapamycin for use as the sole active ingredient in the treatment of a solid tumor, wherein the solid tumor is a pancreatic tumor and 40-O-(2-hydroxyethyl)-rapamycin is administered in a unit dosage form for oral administration comprising 0.25 to 10 mg 40-O-(2-hydroxyethyl)-rapamycin together with one or more pharmaceutically acceptable diluents or carriers.*"

"*2. 40-O-(2-hydroxyethyl)-rapamycin for use in the treatment according to the claim 1, wherein the solid tumor is advanced solid tumor.*"

The compound 40-O-(2-hydroxyethyl)-rapamycin is also known as everolimus. Other synonyms are RAD001 and SDZ RAD (D38, page 1220, first paragraph).

IV. The decision under appeal is based on the patent as granted and the claims of seven auxiliary requests.

In the decision, the opposition division concluded that the patent as granted added subject-matter because claim 1 contained a combination of features resulting from multiple selections within D1. The opposition division saw no pointer in Example B.3 of D1 for combining the treatment of pancreatic solid tumours with the oral administration of everolimus.

For the same reasons, auxiliary requests 1 to 6 also added subject-matter. Auxiliary request 7 was admitted into the proceedings but was considered to lack clarity.

V. The patent proprietor (appellant) filed an appeal against the decision and requested acceleration of the appeal proceedings.

With its statement of grounds of appeal, the appellant re-filed the claim requests on which the decision under appeal was based and filed nine additional claim requests.

VI. In their reply to the statement of grounds of appeal, opponents 1, 3, 4, 5 and 10 (respondents 1, 3, 4, 5 and 10, respectively) requested that the appeal be dismissed.

Opponents 8 and 9 (respondents 8 and 9, respectively) did not reply to the appeal.

Opponents 6 and 7 replied to the statement of grounds of appeal but subsequently withdrew their oppositions with the letters dated 22 and 24 September 2023,

respectively. Opponent 2 did not reply to the appeal and withdrew its opposition with the letter dated 25 September 2023. Therefore, opponents 2, 6 and 7 ceased to be parties to these appeal proceedings.

VII. The Board granted the appellant's request for acceleration of the proceedings and summoned the parties for oral proceedings. In a communication under Article 15(1) RPBA, the Board gave its preliminary opinion on the case.

VIII. Oral proceedings were held before the Board on 25 and 26 September 2023. At the end of the oral proceedings, the Board announced its decision.

IX. The appellant's arguments relevant to the present decision can be summarised as follows.

Amendments

The features of claim 1 as granted were disclosed in D1, both individually and in combination. On pages 1 to 3, D1 disclosed the use of the compounds of Formula I for the treatment of solid tumours, including pancreatic tumours. Everolimus, referred to as Compound A, was the preferred compound of Formula I. All the *in vitro* and *in vivo* tests in D1 were based on everolimus. Example B.3 disclosed successful pre-clinical tests in which everolimus was the sole active ingredient for treating pancreatic tumours by oral administration. The tests in Example B.3 were based on two model cell lines commonly used in research as representative of pancreatic tumours in general. D1 did not refer to any specific type of solid pancreatic tumour. Therefore, there was no basis for reading in Example B.3 a

limitation to the treatment of exocrine pancreatic tumours.

The only passage in D1 disclosing a unit dosage form for the oral administration of everolimus as the sole active ingredient was in the paragraph bridging pages 17 and 18. The preferred unit dosage form defined in that paragraph was the one in claim 1. The skilled person would have understood that this was the unit dosage form necessary for putting into practice the treatment of Example B.3 in humans.

Therefore, the subject-matter of claim 1 was clearly and unambiguously derivable from a general reading of D1 in combination with the embodiments in Example B.3 and the passage bridging pages 17 and 18.

This conclusion was compatible with decision T 3139/19, which dealt with another divisional application of D1. In T 3139/19, the Board did not find a link in D1 between the treatment of solid kidney tumours and the use of everolimus as the sole active ingredient. The case in hand was different because Example B.3 established the link between pancreatic solid tumours and the oral administration of everolimus as the sole active ingredient. D1 did not contain an equivalent example on kidney tumours.

Inventive step starting from D17

The arm of the *in vivo* assay in D17 in which mice had been treated with everolimus was not a suitable starting point. On the one hand, the assay did not show that everolimus had any antitumour effect. The respondents' calculations of how much the tumours of the control group would have grown if the animals had

not been killed was speculative; the tumours could also have plateaued. At best, the *in vivo* assay showed that everolimus had a very weak antitumour effect. On the other hand, starting from the everolimus arm went against the teaching of D17 that a therapeutically useful antitumour effect was achieved only by the combination of a rapamycin compound with a somatostatin compound.

If the everolimus arm was nevertheless considered the closest prior art, the subject-matter of claim 1 differed in the unit dosage form and in that it provided an effective treatment of solid pancreatic tumours. The objective technical problem was how to convert an ineffective therapy against solid pancreatic tumours into an effective therapy.

The obvious solution proposed in D17 was the addition of a somatostatin compound. D17 taught away from the unit dosage forms defined in claim 1 because the skilled person had no motivation to provide a dosage form for a treatment that did not work. If they nevertheless did, considering the low effect of everolimus on pancreatic solid tumours that might possibly be derived from the *in vivo* assay in D17, the skilled person would at best work in the upper part of the dose range for rapamycin compounds suggested on page 18, i.e. at least 300 mg daily. Unit dosage forms containing a maximum of 10 mg everolimus were not suitable for providing more than 300 mg daily since this would have meant the administration of at least 30 unit dosage forms daily.

Inventive step starting from D20

D20 taught that rapamycin could inhibit the growth of pancreatic tumour cells *in vitro* by inhibiting mTOR, but it did not contain any evidence *in vivo*. In fact, D20 (page 129, left-hand column, second paragraph) acknowledged that rapamycin had not been shown to have antitumour effect *in vivo*.

The subject-matter of claim 1 differed from D20 in the mTOR inhibitor and in that it disclosed a credible therapeutic treatment supported by *in vivo* data. The objective technical problem was the provision of an effective treatment for solid pancreatic tumours.

D36 did not render the subject-matter of claim 1 obvious. It taught that not all tumour cell lines were sensitive to everolimus and disclosed no information on pancreatic tumour cell lines. Furthermore, D17 demonstrated that a pancreatic cell line sensitive to everolimus *in vitro* had no or little sensitivity *in vivo*. Therefore, the skilled person could not expect everolimus to inhibit solid pancreatic tumours.

D14, D15 or D21 did not lead to the invention either. The skilled person would only turn to documents demonstrating an antitumour effect *in vivo*. D14, D15 and D21 were on immunosuppression and did not contain any antitumour data *in vivo*. Although mTOR inhibition could result in both immunosuppression and antitumour effect, *in vitro* mTOR inhibition did not necessarily translate into *in vivo* immunosuppression and/or antitumour effect (D63, abstract).

With regard to the unit dosage form, D19 proposed a dose of rapamycin compounds for immunosuppression. But D17 demonstrated that the skilled person could not expect that pancreatic tumours could be treated using a reasonable number of unit dosage forms containing 10 mg everolimus.

The appellant's arguments were not contradictory. The information provided to the skilled person in D17 was that everolimus could not inhibit pancreatic tumours *in vivo*. The patent showed for the first time that the results in D17 were wrong and that everolimus indeed was suitable for inhibiting solid pancreatic tumours.

Starting from D11 or D12

D11 and D12 disclosed that solid pancreatic tumours were sensitive to rapamycin and CCI-779. The subject-matter of claim 1 differed from the content of these documents in that the rapamycin compound was everolimus.

The objective technical problem was the provision of an effective treatment for solid pancreatic tumours.

The skilled person would not expect everolimus to be a suitable solution to the problem posed since everolimus was known to have immunosuppressive rather than antitumour effect. D15 taught that everolimus did not provide a significant antitumour effect *in vivo*. Inhibition of mTOR did not allow the conclusion that everolimus would be a suitable antitumour agent.

Starting from D21

D21 was not a suitable starting point because it did not deal with the treatment of pancreatic tumours but with the use of everolimus as an immunosuppressant. In addition, D21 did not provide any data on the inhibition of tumours *in vivo*. The skilled person could not reasonably expect that everolimus would inhibit solid pancreatic tumours in humans.

The combination of D21 with D11, D20 or D34 did not help because none of D11, D20 and D34 related to everolimus. The skilled person would not expect the antitumour activity of rapamycin and CCI-779 to also be present in everolimus.

Starting from D36

D36 was not a suitable starting point because it did not mention the treatment of pancreatic tumours. Neither did D36 provide adequate information for the skilled person to expect that everolimus could successfully treat pancreatic tumours.

The combination of D36 with D34 did not lead to the claimed subject-matter since D34 did not refer to everolimus but rapamycin and CCI-779. Everolimus could not be expected to have the same effect as rapamycin and CCI-779.

Sufficiency of disclosure

The skilled person could carry out the subject-matter of claim 1 without undue burden. Example B.3 of D1 showed a significant and consistent reduction of tumour

growth *in vivo* in rats and mice at daily and intermittent dosing regimens: the tumour size of the treated group was 20 to 30% of the tumour size of the control. In addition, D1 contained evidence that everolimus reduced growth in other solid tumour types (Examples B.1 to B.3) and that it also reduced angiogenesis (Examples A.2 and B.6). Moreover, the oral administration of everolimus was well tolerated by rats and monkeys (page 23, last paragraph). Therefore, D1 made it credible that everolimus was efficacious and safe against solid tumours in general by the oral administration of unit dosage forms as defined in claim 1. The appellant did not need to explain why the assay in D17 failed. In view of the teaching in D1, it was the respondents' duty to demonstrate that the skilled person would not be able to carry out the claimed invention without undue burden.

The treatment of endocrine pancreatic tumours with everolimus was credible from the evidence in D1. Furthermore, the efficacy and safety of the treatment by daily oral administration of 10 mg everolimus was confirmed in D41, which could be taken into consideration, in line with decision G 2/21. This case was different to the one on which T 1868/16 was based. Contrary to the case in hand, the application as filed in T 1868/16 did not contain any experimental evidence making it credible that everolimus could have an effect against endocrine pancreatic tumours.

X. The respondents' arguments relevant to the present decision can be summarised as follows.

Amendments

The combination of features in claim 1 as granted resulted from multiple selections within the general disclosure of D1, namely the active ingredient (everolimus), the tumour type (solid pancreatic tumour), the therapeutic strategy (monotherapy), the route of administration (oral) and the unit dosage form. As in decision T 3139/19, D1 did not disclose a link between the claimed tumour type and monotherapy.

Example B.3 did not serve as a pointer to the multiple selections in claim 1. On the one hand, Example B.3 was not preferred; there were examples on other tumour types and on combination therapy which were disclosed at the same level of preference. On the other hand, Example B.3 was a highly specific, isolated embodiment; it disclosed preclinical tests in rats and mice with particular cell lines and regimens of administration. The cell lines tested in Example B.3 included two that were experimental models of exocrine pancreatic tumours. There was no preference for those two cell lines which, in any case, did not support the treatment of endocrine pancreatic tumours; it was known that exocrine and endocrine pancreatic tumours were treated differently. Moreover, the oral administration in preclinical tests was not a disclosure of the oral administration to humans.

Example B.3 could not be used as a basis in itself either; it was an independent disclosure that could not be modified. As stated in decision T 3139/19 (Reasons

3.5.2), the embodiments in the examples of D1 were highly specific. The subject-matter of claim 1 could only result from an unallowable generalisation of Example B.3 in which the administration regimens had been ignored and a missing unit dosage form had been added.

Inventive step starting from D17

The everolimus arm of the *in vivo* assay in D17 was the closest prior art. This embodiment was very similar to the tests on AR42J cells in Example B.3 of D1 and shared the most technical features with claim 1. The *in vivo* assay in D17 demonstrated that everolimus had an effect against solid pancreatic tumours. This was apparent since, contrary to the mice of the control group, the mice treated with everolimus did not need to be killed after three weeks from treatment start. If the mice of the control group had not been killed, their tumours would have doubled in size in the fourth week, as taught in D18 (column 4, right-hand column, lines 5 to 8). The final tumour size of the control group would have reached 8000 mm^3. This meant that the tumour size of the mice treated with everolimus was about 45% of the tumour size in the control group, a value that revealed the therapeutic utility of everolimus according to the results observed for lung tumours in Example B.1 of D1.

The subject-matter of claim 1 differed from the closest prior art in that everolimus was administered by unit dosage forms containing between 0.5 and 10 mg everolimus. This difference did not imply an administration regimen since it did not specify how many and how frequently unit dosage forms had to be taken; the patient could receive as many unit dosage

forms as necessary and as often as needed. The claimed unit dosage form was not associated with any technical effect. Therefore, the objective technical problem was the provision of an appropriate unit dosage form of everolimus for the treatment of solid pancreatic tumours or the provision of an alternative method for the treatment of solid pancreatic tumours using everolimus.

The unit dosage form of claim 1 was obvious in light of the dose range of 0.5 to 500 mg suggested in D17 (page 18, paragraph 2) for rapamycin derivatives. This range was fully compatible with a unit dosage form containing 10 mg everolimus. In fact, D17 (page 19) illustrated capsules containing 20 mg everolimus.

Inventive step starting from D20

D20 taught that pancreatic tumour cells used the mTOR pathway for proliferation. It demonstrated that rapamycin arrested the growth of pancreatic tumour cells by inhibiting mTOR.

The subject-matter of claim 1 differed from the teaching in D20 in that the mTOR inhibitor was everolimus instead of rapamycin. This difference did not bring about any additional technical effect. The objective technical problem was the provision of an alternative compound for the treatment of solid pancreatic tumours.

In view of D36, it was obvious to replace rapamycin with everolimus. D36 referred to RAD001, which was generally known to be everolimus (D38). D36 taught that everolimus inhibited mTOR and that this resulted in an *in vitro* antiproliferative effect against a number of

human tumour cell lines. In cell lines sensitive to mTOR inhibition, the *in vitro* antiproliferative effect also translated into an *in vivo* effect against human tumour xenografts by oral administration.

The same was true for D12, which demonstrated that the antiproliferative effect of rapamycin and CCI-779 *in vitro* and *in vivo* was based on their ability to inhibit mTOR. D12 (page 6682, right-hand column, second paragraph) referred explicitly to pancreatic tumours.

D89 and D21 also rendered the replacement of rapamycin with everolimus obvious since they disclosed in claims 5 and 8, respectively, that everolimus had antitumour properties.

D14 and D15 also rendered the claimed subject-matter obvious since they showed that everolimus had a similar effect to rapamycin both *in vitro* and *in vivo*.

In addition, D19 taught that the usual dose of rapamycin and rapamycin derivatives for humans was 1 to 10 mg.

The skilled person had no reason to turn to D17, which had been published more than three years before D20. Furthermore, D17 did not teach away from the subject-matter of claim 1 since it showed that everolimus had an *in vivo* antitumour effect. The appellant's arguments were contradictory. It considered that D17 did not show that everolimus had an *in vivo* effect against pancreatic tumours, while a test on the same cell line with similar results in the patent was considered to prove that everolimus could indeed treat solid pancreatic tumours.

Starting from D11 or D12

D11 and D12 taught the *in vitro* and *in vivo* effect of rapamycin and its prodrug CCI-779 against a broad range of tumours, including pancreatic tumours. The effect was based on the ability of the rapamycin compound to inhibit mTOR.

The subject-matter of claim 1 differed in that the rapamycin compound was everolimus and in that no unit dosage form was disclosed. As these differences did not produce a technical effect, the objective technical problem was the provision of an alternative composition for the treatment of solid pancreatic tumours.

The use of everolimus was obvious from D21 or D89, which taught that everolimus was a rapamycin derivative with improved stability and bioavailability having not only immunosuppressive but also antiproliferative properties. It was also known from D15 that the immunosuppressive effect of everolimus was based on an antiproliferative effect and that it had its origin in the inhibition of mTOR. The choice of the unit dosage form was merely the result of routine experimentation by the skilled person. In addition, D21 disclosed the usual dose of everolimus. D17 did not teach away from the choice of unit dosage form.

The solution was also obvious in light of D36, which taught that the ability of everolimus to inhibit mTOR resulted in an antitumour effect both *in vitro* and *in vivo*.

Starting from D21

D21 disclosed a family of rapamycin derivatives and their use against hyperproliferative diseases. The mode of action of the new rapamycin derivatives was the inhibition of mTOR. They could be administered orally using unit dosage forms comprising 1 to 10 mg of the active ingredient. Everolimus was a preferred compound.

The subject-matter of claim 1 was obvious because D11, D20 and D34 taught that rapamycin and CCI-779 inhibited the proliferation of pancreatic tumours by mTOR inhibition.

Starting from D36

D36 disclosed that everolimus inhibited a number of human tumours by oral administration owing to its ability to inhibit mTOR.

The use of everolimus against solid pancreatic tumours was obvious in light of D34, which taught that mTOR inhibitors were a new class of compounds suitable for treating solid pancreatic tumours in humans.

Sufficiency of disclosure

The claimed subject-matter was not sufficiently disclosed for two reasons.

First, if the treatment of pancreatic tumours was not credible from D17, the same had to be concluded from D1. The appellant was the applicant of the two applications, and in both of them the pancreatic tumour cell line AR42J had been treated in an animal model

with everolimus at the same dose. The appellant had not explained the contradiction that the invention worked in D1 but not in D17. Therefore, serious doubts arose that the invention could be reproduced.

Second, the application as filed provided evidence only on the treatment of exocrine pancreatic tumours. This evidence was not valid for endocrine pancreatic tumours, which were treated differently. As the treatment of endocrine pancreatic tumours had not been made credible in D1, the post-published evidence in D41 could not be taken into consideration (G 2/21). Moreover, the Board had decided in T 1868/16 that a patent directed to the treatment of endocrine pancreatic tumours with everolimus having a filing date years later than D1 was not sufficiently disclosed.

XI. The parties' final requests relevant to the present decision were as follows.

- The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted.

- Respondents 1, 3, 4, 5 and 10 requested that the appeal be dismissed.

- Respondents 8 and 9 did not file any requests in these appeal proceedings.

Reasons for the Decision

1. Amendments (Article 100(c) EPC)

1.1 It is established case law that the standard of disclosure to be applied for the assessment of added subject-matter is the gold standard, as confirmed by the Enlarged Board of Appeal in decision G 1/16 (Reasons 17 to 20). This standard is defined as:

"*what a skilled person would derive directly and unambiguously, using common general knowledge and seen objectively and relative to the date of filing, from the whole of these documents [the application documents] as filed*"

The patent in suit stems from a third-generation divisional application. The opposition division and the parties discussed the amendments in the claims of the patent as granted for the disclosure of the earliest application as published, cited as D1. In their discussion, they assumed that the disclosure of D1 was essentially the same as that of the application as filed and the earlier applications as filed. The Board sees no reason to take another stance. Therefore, the Board has also assessed the amendments in claims 1 and 2 as granted on the basis of D1.

1.2 Claim 1 as granted is directed to the treatment of solid pancreatic tumours with everolimus as the sole active ingredient, with everolimus being orally administered in unit dosage forms that contain 0.25 to

10 mg everolimus together with one or more pharmaceutically acceptable diluents or carriers.

D1 discloses on page 1 a family of rapamycin derivatives of Formula I. The most preferred compound of Formula I is 40-O-(2-hydroxyethyl)-rapamycin, i.e. everolimus, referred to as Compound A. In the sentence bridging pages 1 and 2, D1 states that the compounds of Formula I have been found to have potent antiproliferative properties which make them useful for the treatment of solid tumours. The paragraph bridging pages 2 and 3 discloses a list of solid tumours that can be treated according to the invention. It includes tumours involving the pancreas. As taught on page 11, third paragraph, the examples in D1 were intended to demonstrate the utility of the compounds of Formula I in treating solid tumours. The examples describe *in vitro* tests (Examples A.1 and A.2), *in vivo* tests in animal models (Examples B.1 to B.7) and two proposal of clinical tests (Examples C.1 and C.2). All the examples are based on everolimus, either as the sole active ingredient (Examples A.2, B.1 to B.3, B.6 and C.1) or in combination with other active ingredients (Examples A.1, B.4, B.5, B.7 and C.2).

Example B.3 of D1 reports the effect of everolimus orally administered to rats bearing the pancreatic tumour cell line CA20948. When everolimus was orally administered at a daily dose of 2.5 mg/kg to rats bearing CA20948 cells, the final tumour size was 23% of the control (100%). The same experiment with an intermittent administration of 5 mg/kg everolimus twice per week resulted in a final tumour size of 32% compared with the control. It was concluded that everolimus significantly and consistently decreases CA20948 pancreatic tumour growth.

Example B.3 discloses additional preclinical tests in which everolimus was tested on tumour models including the human pancreatic tumour model AR42J. In this case, the daily administration of 5 mg/kg everolimus resulted in a final tumour size of 24% compared with the control. The administration twice weekly to mice transplanted with AR42J cells also provided good antitumour response.

1.3 It is clear from the general disclosure of D1 that the compounds of Formula I have an antiproliferative effect which makes them suitable for treating solid tumours, e.g. pancreatic tumours. It is also clear that everolimus is the most preferred compound of Formula I and that it can be administered alone or in combination with other active ingredients.

In light of this general teaching, the positive results obtained in the preclinical tests on pancreatic tumour cells lines in Example B.3 can only be interpreted as a disclosure of the ability of everolimus as the sole active ingredient for treating solid pancreatic tumours by oral administration. As the tests were carried out on two different pancreatic tumour cell lines and at different dosage regimens, including daily and twice weekly administration, it cannot be concluded that the success of the tests was linked to a particular dosage regime.

1.4 With regard to the unit dosage form, it is apparent that the preclinical treatment of Example B.3 needs to be adapted to the treatment of humans. D1 contains only two passages in which it discloses suitable unit dosage forms. In the paragraph bridging pages 17 and 18, D1 discloses a unit dosage form for the oral

administration of everolimus when used alone. The penultimate paragraph on page 21 discloses unit dosage forms for the oral administration of everolimus in combination with other active ingredients.

Therefore, it is clear to the skilled reader that the treatment disclosed in Example B.3 of D1, in which everolimus is administered as the only active ingredient, is to be put into practice using oral unit dosage forms as defined in the sentence bridging pages 17 and 18, namely oral unit dosage forms comprising preferably 0.25 to 10 mg everolimus together with one or more pharmaceutically acceptable diluents or carriers.

1.5 The Board therefore concludes that the subject-matter of claim 1 as granted is directly and unambiguously derivable from D1 when Example B.3 is read in the context of the whole application.

1.6 The explanation above deals with the respondents' concern that the subject-matter of claim 1 cannot be derived from Example B.3 because the dosage regimen was essential and a unit dosage form was not disclosed. But the respondents also argued that Example B.3 could not support the treatment of pancreatic tumours in general. The skilled person knew that there are two types of pancreatic tumours, namely exocrine and endocrine, which are treated differently. As the two cell lines tested in Example B.3 represented exocrine pancreatic tumours, there was no disclosure of the treatment of endocrine pancreatic tumours.

This argument is not convincing. D1 only refers to pancreatic tumours in general. The cell lines CA20948 and AR42J tested in Example B.3 are presented as models

of pancreatic tumours without further specification; no passage in D1 refers to different types of pancreatic tumours. Therefore, there is no basis in D1 for distinguishing between exocrine and endocrine tumours.

1.7 The respondents also argued that neither Example B.3 nor the pancreatic tumour cell lines tested in it were disclosed as being preferred. Therefore, multiple choices were necessary to arrive at the tests on pancreatic tumour cells in Example B.3.

This argument is not convincing either. As explained in point 1.3 above, Example B.3 and its tests on pancreatic tumour cells constitute self-contained embodiments which, read in context, disclose by themselves the treatment of solid pancreatic tumours by the oral administration of everolimus as the sole active ingredient.

1.8 Lastly, the respondents considered that, as in decision T 3139/19, D1 does not disclose a link between the treatment of solid pancreatic tumours and the use of everolimus as the sole active ingredient.

That consideration is flawed. T 3139/19 is a decision based on a divisional application of D1 directed to the treatment of solid kidney tumours with everolimus as the sole active ingredient. Kidney tumours are merely one among the numerous solid tumour types that can be treated according to the paragraph bridging pages 2 and 3 of D1. In addition, D1 discloses no preference for the use of everolimus as the sole active ingredient or in combination with other active ingredients. Therefore, the Board in T 3139/19 concluded that there was no direct and unambiguous disclosure in D1 linking

the treatment of solid kidney tumours with the use of everolimus as the sole active ingredient.

The situation in the case in hand is different because Example B.3 provides a direct and unambiguous link between the treatment of solid pancreatic tumours and the oral administration of everolimus as the sole active ingredient. D1 had no example equivalent to Example B.3 for kidney tumours. Therefore, the rationale of T 3139/19 does not apply to the case in hand.

1.9 With regard to claim 2 as granted, a basis can be found in the sentence bridging pages 1 and 2 of D1 which discloses that the antiproliferative properties of the compounds of Formula I make the compounds particularly useful for the treatment of advanced solid tumours.

1.10 The Board therefore concludes that the patent does not add subject-matter and the ground for opposition of Article 100(c) EPC does not prejudice the maintenance of the patent as granted.

2. Priority (Article 87 EPC)

The appellant did not contest that the patent does not enjoy any of the priority dates claimed. Therefore, it was undisputed that documents D20 and D36 belong to the prior art under Article 54(2) EPC.

3. Novelty (Articles 100(a) and 54 EPC)

In its reply to the statement of grounds of appeal (page 9, point 4.2), respondent 5 raised what seemed to be a novelty objection based on document D17. Under the title "Nouveauté" (novelty), respondent 5 indicated

that D17 described the antiproliferative *in vivo* effect of everolimus on pancreatic tumours.

In its communication under Article 15(1) RPBA, the Board considered that this generic statement did not substantiate a novelty objection. At the oral proceedings before the Board, respondent 5 did not wish to comment on this point. Therefore, the Board held that there was no substantiated novelty objection on file and that the patent as granted met the requirements of Article 54 EPC.

4. Inventive step (Articles 100(a) and 56 EPC)

4.1 The respondents raised multiple inventive-step objections. Most of them considered D17 or D20 the closest prior art. In addition, respondent 4 raised an objection starting from D12, and respondent 5 raised objections starting from D11, D34, D21 and D36.

4.2 Starting from D17

4.2.1 D17 (page 1, first to third paragraphs and page 13, second paragraph) is concerned with the inhibition of undesired cell proliferation by combining a compound of the somatostatin class with rapamycin or a rapamycin derivative. It was found that the combination of the two classes of compound, which act through different mechanisms, could inhibit cell proliferation in a synergistic manner. In this context, D17 described an *in vitro* (pages 14 and 15) and an *in vivo* assay (pages 15 to 17), both on the pancreatic tumour cell line AR42J. The compound referred to as "Compound B" in those assays is 40-O-(2-hydroxy)ethyl-rapamycin, i.e. everolimus (page 12, third paragraph). Octreotide is a compound of the somatostatin class.

The *in vitro* assay of D17 studied the ability of octreotide, everolimus and their combination to inhibit the growth of AR42J cells. It was found that, at the concentrations tested, octreotide and everolimus reduced cell growth to 59.8% and 63.3% of the control, respectively. Therefore, the effect that could be expected for their combination, as calculated by the Webb method, was 37.9%. However, it was observed that cell growth was reduced to 15.6% of the control, which confirmed the presence of a synergistic interaction between octreotide and everolimus.

In the *in vivo* assay, pancreatic tumour cells AR42J were subcutaneously injected into mice. When tumours reached a volume of 0.03 cm^3 (i.e. 30 mm^3), the animals were treated for three weeks with everolimus, rapamycin, octreotide, or the combination everolimus/ octreotide or rapamycin/octreotide. The control group received a placebo. The results after four weeks are reproduced below. Nevertheless, the values of the control group are after three weeks since the animals had to be killed afterwards because the tumours became excessively large.

Treatment	Volume mm^3	SE
Control	4020	579
A) Compound B, 5 mg/kg p.o.	3685	263
B) Rapamycin, 5 mg/kg p.o.	2748	325
C) Octreotide pamoate (biodegradable, sustained release formulation), 30 mg/kg, single inj.	2205	339
Compound B + octreotide (C)	130	75
Rapamycin + octreotide (C)	106	44

Based on these results, D17 (page 18, second paragraph) proposed doses that can be administered to humans when the compounds are provided in combination. The proposed daily doses were 0.5 to 500 mg for rapamycin and its derivatives and 100 µg to 10 mg for somatostatin compounds.

4.2.2 The respondents considered that the arm of the *in vivo* assay in which mice were treated with everolimus as the sole active ingredient was the closest prior art. Considering that the tumour size of the control group after three weeks was larger or at least of the same order as the tumour size of the everolimus group after four weeks, the assay demonstrated that everolimus had some effect against pancreatic tumours. This was also confirmed by the fact that, contrary to in the control group, the mice of the everolimus group did not have to be killed before the end of the assay. The respondents

also made calculations estimating the size that the tumours of the control group might possibly have reached after four weeks if the mice had not been killed.

The appellant argued that the arm of the everolimus group was not a suitable starting point for the assessment of inventive step. The *in vivo* assay in D17 did not demonstrate any antitumour effect of everolimus. The respondents' calculations were speculative, and the tumour of the control group could also have plateaued. Furthermore, that starting point was against the teaching of D17 that the rapamycin compound and the somatostatin compound had to be combined.

The Board accepts, for the benefit of the respondents, that the *in vivo* test of D17 showed that everolimus has some antitumour effect. Nevertheless, this effect was so weak that it could be questioned whether it would have any therapeutic utility. When mice were treated with the combination therapy, tumour size increased 3 to 4 times after four weeks (from 30 to 106 or 130 mm^3). In contrast, when mice were treated with everolimus only, tumour size increased more than 120 times (from 30 mm^3 to 3685 mm^3). The calculations made by the respondents on the size that the tumours of the control group would have reached if the mice had not been killed are not convincing. The observation in the example bridging columns 3 and 4 of D18 that the tumour of the control group doubled in seven days cannot be transposed to the *in vivo* test of D17 without modification. It is clear from the teaching of D17 and, in particular, from the results of the *in vivo* test, that the efficacy of everolimus was not sufficient for therapeutic treatment. For that reason, everolimus had

to be combined with a somatostatin compound. This multiplied antitumour activity by about 30 times.

4.2.3 Starting from the arm of the *in vivo* test in D17 in which mice were treated with everolimus, it was common ground that the subject-matter of claim 1 differed in the unit dosage form for oral administration comprising from 0.25 to 10 mg everolimus. The appellant argued that, in addition, the therapeutic use of claim 1 as granted was effective while the one of the closest prior art was not.

4.2.4 It was undisputed that the unit dosage form defined in claim 1 did not produce any technical effect. The respondents stressed that claim 1 did not indicate the number and frequency of everolimus unit dosage forms that should be taken for treating pancreatic tumours. Claim 1 defined a galenic form that could be used for administering everolimus but not a dosage regimen. On that basis, the respondents formulated the objective technical problem as the provision of an appropriate unit dosage form of everolimus for the treatment of solid pancreatic tumours or as the provision of an alternative method for the treatment of solid pancreatic tumours using everolimus.

The appellant, considering that D17 did not teach that everolimus was suitable for treating solid pancreatic tumours, defined the objective technical problem as how to convert an ineffective therapy against solid pancreatic tumours into an effective therapy.

When formulating the objective technical problem, the Board has assumed, for the benefit of the respondents, that it could possibly be derived from D17 that everolimus was suitable for treating solid pancreatic

tumours. The Board also agrees that the unit dosage form defined in claim 1 does not produce any technical effect. Under these circumstances, the Board agrees with the formulation of the objective technical problem as the provision of an appropriate unit dosage form of everolimus for the treatment of solid pancreatic tumours.

4.2.5 As put forward in point 5.2.1 below (sufficiency of disclosure), the Board is satisfied that the subject-matter of claim 1 as granted is a suitable solution to the objective technical problem.

4.2.6 On the issue of obviousness, it should be noted that the *in vivo* assay of D17 was carried out in mice. Therefore, the doses administered in the assay needed to be adapted to human therapy. D17 proposes on page 18, second paragraph suitable doses of rapamycin derivatives and somatostatin compounds that may be administered to patients in combination. The proposed dose for rapamycin derivatives is 0.5 to 500 mg daily as a single dose or in divided doses.

Considering that the antitumour effect of everolimus shown in the *in vivo* assay of D17 was about 30 times lower than the effect of its combination with octreotide, the skilled person would understand that the dose required when everolimus is provided as the sole active ingredient had to be in the upper part of the range proposed in D17, e.g. around 300 to 500 mg daily. If this dose had to be administered by the oral unit dosage forms defined in claim 1, even taking the forms with the highest load of everolimus (10 mg), the patient would have to swallow not fewer than 30 to 50 unit dosage forms daily. Therefore, the skilled person would conclude that a unit dosage form according to

claim 1 was not a solution to the objective technical problem. A suitable unit dosage form would need to contain a much higher load of everolimus to be administered at an acceptable pill burden.

Consequently, starting from D17, the skilled person would not have arrived at the unit dosage form of claim 1 in an obvious manner.

4.3 Starting from D20

4.3.1 D20 (abstract; paragraph bridging pages 128 and 129; page 130, last paragraph) is a study on the mechanism by which rapamycin inhibits *in vitro* the growth of two different cell lines representative of solid pancreatic tumours. It was found that rapamycin inhibited cell proliferation by blocking the mTOR signalling pathway. Therefore, it was concluded that pancreatic tumour cells require the mTOR pathway for proliferation and that mTOR inhibitors were good candidates for treating pancreatic tumours.

The appellant correctly noted that D20 (page 129, left-hand column, second paragraph) explicitly mentions that although the immunosuppressant effect of rapamycin in animals and humans was proven, its use against solid tumours *in vivo* was unknown.

4.3.2 The subject-matter of claim 1 as granted differs from the teaching of D20 in that it relates to a therapeutic treatment, including the unit dosage form needed for implementing the treatment, rather than to an *in vitro* mechanistic study. It also differs in that the mTOR inhibitor is everolimus instead of rapamycin.

4.3.3 Based on these differences, the Board agrees with the appellant that the objective technical problem is the provision of an effective treatment of solid pancreatic tumours.

4.3.4 According to the respondents, D36 rendered the solution proposed in claim 1 obvious. The Board disagrees.

D36 relates to the antitumour effect of a hydroxyethyl ether derivative of rapamycin called RAD001. The review document D38 (abstract), representative of common general knowledge, shows that RAD001 was known to be everolimus. D36 states that everolimus has *in vitro* antiproliferative activity against a number of human tumour cell lines. However, it teaches that there are also cell lines that are less sensitive or resistant to everolimus. Nevertheless, in all cases, everolimus downregulated mTOR. *In vivo*, everolimus was able to inhibit human tumour xenografts of sensitive cell lines in mice by oral administration.

Although the skilled person could derive from the combination of D20 with D36 that everolimus was a good candidate for the treatment of pancreatic tumours, they could not ignore the content of D17 in which the ability of everolimus to inhibit pancreatic tumour cell lines *in vitro* and *in vivo* had been tested. The *in vitro* tests of D17 confirmed the teaching of D20: they showed that everolimus has a moderate effect against the growth of a pancreatic cell line. However, as discussed in point 4.2.6 above, this moderate effect *in vitro* did not result in an *in vivo* antitumour effect sufficient to treat pancreatic tumours in humans with a reasonable number of the oral unit dosage forms defined in claim 1. This conclusion was compatible with D20 (page 129, left-hand column, second paragraph), which

stated that the antineoplastic effect of rapamycin against solid tumours was largely unknown.

4.3.5 The situation does not change when documents D12, D21 or D89, D14, D15 and D19 are considered.

D12 is a review on the use of the mTOR signal transduction pathway as a target for cancer therapy. D12 (abstract and conclusion) discloses that rapamycin and its ester analogue CCI-779 can arrest cell growth by inhibiting mTOR and that this results in impressive activity against a broad range of human cancers *in vitro* and *in vivo* in human tumour xenograft models. On page 6682 (left-hand column, second paragraph), D12 refers to scientific publications in which rapamycin was shown to inhibit the proliferation of several tumour cell lines in culture and xenograft models. These included two pancreatic tumour cell lines.

It is uncertain from D12 what exactly had been shown in the cited publications on the inhibition of the pancreatic tumour cell lines by rapamycin. But the mere indication of a possible effect of rapamycin on pancreatic tumour cell lines cannot counter the evidence in D17 suggesting that everolimus does not inhibit solid pancreatic tumours *in vivo* to an extent sufficient to treat patients with the unit dosage forms defined in claim 1.

D21 and D89 are patent applications belonging to the same patent family and have similar disclosures. They focus on the use of a new group of rapamycin derivatives as immunosuppressants. The preferred rapamycin derivative is everolimus (D21: page 3, last line and claim 4; D89: claim 1). The two documents claim, among other therapeutic indications, the

treatment of tumours and hyperproliferative disorders. However, neither of them contains *in vivo* tests, let alone on the inhibition of pancreatic tumours.

D14 (abstract) and D15 (abstract) evaluate the properties of everolimus as a rapamycin derivative with immunosuppressive effect by mTOR inhibition and with improved bioavailability. D15 states that when everolimus is orally administered to *in vivo* models, its immunosuppressive effect is similar to that of rapamycin.

The fact that everolimus is a potent mTOR inhibitor and that this translates into good *in vivo* immunosuppression would not lead the skilled person to conclude that everolimus also has a good antitumour effect against pancreatic tumours. On the one hand, although the inhibition of mTOR results in *in vivo* immunosuppression and antitumour effect in the case of rapamycin, this is not necessarily the case for any mTOR inhibitor. For instance, CCI-779 is an excellent mTOR inhibitor *in vitro*. This translates into an *in vivo* antitumour effect but no significant immunosuppressive effect (D63, abstract). On the other hand, even if everolimus is a good mTOR inhibitor *in vitro*, D17 showed that it was unable to inhibit pancreatic tumours to a sufficient extent. The doses suggested in D17 could not be reasonably administered using the unit dosage forms of claim 1.

D19 (abstract and page 2, last paragraph) is concerned with the treatment of lymphoproliferative disorders using rapamycin derivatives, preferably everolimus. D19 (page 16, third paragraph) suggests a daily dose of rapamycin or rapamycin derivative of 0.1 to 50 mg, preferably 1 to 10 mg.

Although the dose suggested in D19 may be the daily dose of rapamycin compounds usually administered to adult humans, D17 suggests that this dose is not sufficient for the treatment of solid pancreatic tumours with everolimus.

4.3.6 Therefore, the subject-matter of claim 1 as granted is not obvious starting from D20 as the closest prior art.

4.4 Starting from documents D11 or D12

4.4.1 As indicated above in point 4.3.5, D12 (abstract and conclusion) teaches that rapamycin and CCI-779 can arrest cell growth by inhibiting mTOR and that this results in an *in vivo* antitumour effect against a broad range of human cancers. D12 (page 6682, left-hand column, second paragraph) mentions that in the prior art, rapamycin had been shown to inhibit the growth of several tumour cell lines in culture and xenograft models, including two pancreatic tumour cell lines.

D11 is an abstract of a conference with a disclosure similar to that of D12. It also states that CCI-779 inhibits mTOR and that several tumour types, including pancreas tumours, had been found to be sensitive to CCI-779 in nude mouse xenografts.

4.4.2 It was undisputed that the subject-matter of claim 1 differs from the teaching of D11 and D12 in that the rapamycin derivative with mTOR inhibiting properties is everolimus. A second difference was in the claimed unit dosage form.

4.4.3 Example B.3 of the patent shows that everolimus is effective at its usual dose for treating solid tumours

(see point 5.2.1 below). Therefore, the objective technical problem can again be formulated as the provision of an effective treatment of solid pancreatic tumours.

4.4.4 The respondents combined D11 or D12 with D21, D89, D15 or D36. In the Board's view, none of these combinations would lead the skilled person to the subject-matter of claim 1 in an obvious manner for the same reasons given for when the documents were combined with D20 as the closest prior art.

As explained above (point 4.3.5), D21 and D89 do not disclose *in vivo* tests on the antiproliferative effect of everolimus, let alone on the inhibition of pancreatic tumours. Therefore, the skilled person could have no expectation of success, especially in view of the weak effect derivable from D17.

D36 teaches that everolimus has an *in vivo* antitumour effect, so everolimus could have been regarded as a good candidate for the treatment of pancreatic tumours. However, the skilled person could not ignore that in D17 everolimus had been tested *in vivo* and that its effect against solid pancreatic tumours was not sufficient for administration in oral unit dosage forms as defined in claim 1.

D15 states that the *in vivo* immunosuppressive effect of everolimus by oral administration is similar to that of rapamycin. This effect was due to the inhibition of mTOR. However, mTOR inhibition does not automatically translate into *in vivo* immunosuppressive and antiproliferative effects (D63, abstract). Furthermore, D17 showed that everolimus did not inhibit pancreatic

tumour growth to a sufficient extent to be administered using the unit dosage forms of claim 1.

4.4.5 Therefore, the subject-matter of claim 1 was not obvious starting from D11 or D12.

4.5 Starting from document D34, D21 or D36

4.5.1 The inventive-step objections starting from documents D34, D21 and D36 were raised by respondent 5 only (reply of respondent 5 to the statement of grounds of appeal, point 4.3.2 to 4.3.4). Respondent 5 combined D34 with D14 or D15; D21 with D11, D20 or D34; and D36 with D34. However, none of the inventive-step objections raised by respondent 5 followed the problem-solution approach. At the oral proceedings before the Board, respondent 5 did not wish to further discuss these objections.

4.5.2 The teaching of D34 (abstract) is essentially the same as that of D20, namely that human pancreatic cell lines require the mTOR signalling pathway for proliferation and that therefore their growth is inhibited by rapamycin. Like D20, the conclusion of D34 is that mTOR inhibitors are promising compounds for the treatment of solid pancreatic tumours. Therefore, for the same reasons as starting from D20, the subject-matter of claim 1 is not obvious starting from D34 in combination with D14 or D15.

4.5.3 D21 is concerned with a new group of rapamycin derivatives having immunosuppressive properties, everolimus being the preferred compound. The treatment of tumours is cited among several therapeutic indications in addition to immunosuppression. However,

the alleged antitumour effect in D21 is not supported by *in vivo* tests, let alone against pancreatic tumours.

Therefore, starting from D21, the skilled person would have no expectation that everolimus would be suitable for treating pancreatic tumours.

Respondent 5 justifies the combination of D21 with D11, D20 and D34 in that all these documents disclose compounds that act via mTOR inhibition. Therefore, they could be expected to have similar activities. As explained above, the fact that rapamycin or CCI-779 was disclosed as an antitumour agent acting by mTOR inhibition in D11, D20 and D34 did not render obvious that everolimus would have the same effect, let alone at the level required for being administered with the unit dosage forms of claim 1.

4.5.4 Starting from the teaching in D36 that everolimus had an *in vivo* antitumour effect against some tumours, the objective technical problem would be finding further tumours for which everolimus could constitute a suitable therapy. Although the mechanistic study of D34 showed that pancreatic tumour cell lines were sensitive to mTOR inhibition *in vitro*, D17 showed that these tumours could not be effectively treated with everolimus *in vivo* using the unit dosage form of claim 1.

4.6 Therefore, the subject-matter of claim 1 as granted is inventive and meets the requirements of Article 56 EPC.

4.7 The respondents also raised the issue that the Board had decided in a related case (T 814/22) that the claimed subject-matter lacked an inventive step, even with a low dosage.

However, the facts in T 814/22 differed considerably from the case in hand. In T 814/22, claim 1 of the main request was directed to the treatment of HR+ breast tumours by combination therapy of everolimus with an aromatase inhibitor. Claim 1 of auxiliary request 8 further specified that everolimus was orally administered in a unit dosage form comprising 0.25 to 10 mg everolimus together with one or more pharmaceutically acceptable diluents or carriers. The current case is on the treatment of pancreatic tumours by administering everolimus as the sole active ingredient with specific unit dosage forms. While in T 814/22 the prior art provided reasonable expectations that everolimus could treat HR+ breast cancer, in the case in hand no prior-art document provides reasonable expectations that everolimus can effectively treat pancreatic tumours, at least at the level required for using the unit dosage form of claim 1. On the contrary, it may be derived from D17 that everolimus would be not effective or just poorly effective in the treatment of pancreatic cancer with the consequence that the daily dosages suggested in that document would not be compatible with the unit dosage forms defined in claim 1. The appellant nevertheless demonstrated that, contrary to what could be expected from the prior art, everolimus was suitable as a monotherapy for treating pancreatic tumours using the unit dosage forms of claim 1. While D17 was cited as D7 in T 814/22, a teaching corresponding to D17, discouraging the use of unit dosage forms containing no more than 10 mg everolimus for treating HR+ breast tumours, was not present in T 814/22.

5. Sufficiency of disclosure (Articles 100(b) and 83 EPC)

5.1 According to the respondents, the subject-matter of claim 1 as granted could not be carried out without undue burden for two reasons. First, the *in vivo* assay in D17 was essentially the same as in D1. If it was concluded for inventive step that D17 did not show that everolimus could treat pancreatic tumours using the unit dosage form of claim 1, the same had to be derived from D1. Second, Example B.3 of D1 provided evidence on the effect of everolimus on exocrine pancreatic tumours only. As it was known that endocrine pancreatic tumours had to be treated differently, D1 did not make it credible that everolimus could treat such tumours. Furthermore, in accordance with decision G 2/21, this deficiency could not be remedied with post-published evidence. A similar situation had been dealt with in T 1868/16.

5.2 The Board does not agree with these arguments.

5.2.1 Example B.3 of D1 discloses *in vivo* assays in which everolimus was orally administered daily or twice weekly to rats and mice bearing a tumour produced by cell models of human pancreatic tumours, namely CA20948 or AR42J cells. The final tumour size of the animals treated with everolimus was in the order of 20 to 30% the tumour size of the untreated animals (control). In the Board's view, these results make it credible that solid pancreatic tumours can be treated by the oral administration of everolimus. The doses proposed in D1 (page 17, last paragraph) when everolimus is orally administered to humans as the sole active ingredient are within the range of 0.1 to 25 mg/day. This appears to be the usual dose range of everolimus when used as a

therapeutic mTOR inhibitor. There is no reason to doubt that everolimus is effective at those doses since D1 shows that pancreatic tumours are sensitive to everolimus *in vivo*. Unit dosage forms of 0.25 to 10 mg as defined in claim 1 are suitable for administering doses of 0.1 to 25 mg/day.

Therefore, D1 made it credible that everolimus can treat pancreatic tumours using the oral unit dosage form defined in claim 1.

5.2.2 The poor results for everolimus in the *in vivo* tests of D17 do not raise doubts on the effect shown in Example B.3 of D1.

The test in D17 showed some antitumour effect for everolimus, as evidenced by the fact that, contrary to the control group, the mice treated with everolimus did not have to be killed after three weeks. However, the test appeared not to be suitable for properly assessing the magnitude of the *in vivo* effect of everolimus because tumour sizes in the control group and the treated groups had been recorded at different times and a direct comparison between them was not possible. This was not a problem in D17 since the *in vivo* assay had not been designed to accurately determine the effect of the individual compounds but to show that their combination was synergistic. The control group in D17 was not the group of untreated mice but the groups treated with monotherapy. Therefore, the inaccurate results in D17 on the antitumour effect of everolimus do not raise doubts on the conclusiveness of the assay in Example B.3 of D1, which was specifically designed to assess the effect of everolimus monotherapy. Example B.3 allowed a direct comparison between the treated and untreated groups and gave consistent results at

different conditions of animal model, cell line and administration regimen.

Respondent 5 (reply to the appeal, page 6, lines 1 to 3) and respondent 1 (letter dated 29 August 2023, page 4, second paragraph) called into question the results in Example B.3 because, according to D4 (abstract, first sentence and page 346, paragraph bridging the columns), a test based on pancreatic tumours transplanted subcutaneously to the animal model would not reliably predict the effect on a pancreatic tumour in humans. However, D4 does not raise doubts on the validity of the assays in D1. Although D4 states that animal models in which tumours are grown subcutaneously do not sufficiently represent clinical cancer in humans, it appears from the passage bridging the columns on page 346 that the doubts were based on a false negative observed in a model of lung cancer implanted subcutaneously. As the results in Example B.3 of D1 are positive, a potential false negative does not affect their conclusiveness.

5.2.3 The argument that the claimed subject-matter was not sufficiently disclosed for endocrine pancreatic tumours is not convincing either.

It was undisputed that exocrine and endocrine pancreatic tumours are treated differently (see also D40, page 1, last sentence) and that the cell lines tested in Example B.3 of D1 represent exocrine pancreatic tumours only. However, D1 contains additional *in vivo* evidence which render it credible that everolimus has a general antitumour effect not limited to exocrine pancreatic tumours. Examples B.1 to B.3 demonstrate the *in vivo* effect of everolimus against several tumour types (lung, epidermoid,

pancreas and melanoma), and Example B.6 shows that everolimus also has an *in vivo* antiangiogenic effect. In view of this evidence, it could be expected from D1 that everolimus would also inhibit the growth of endocrine pancreatic tumours. In line with the principles established in decision G 2/21 (Reasons 77 and 94), this circumstance allowed the Board to consider the post-published evidence in D41, which confirmed the effect. D41 (points 2, 4.1 and 4.2) demonstrates that tablets containing 2.5, 5 and 10 mg everolimus were approved by the European Medicines Agency for the treatment of neuroendocrine tumours of pancreatic origin at a recommended dose of 10 mg everolimus once daily. The parties did not dispute that pancreatic neuroendocrine tumours (PNETS) are a synonym of endocrine pancreatic tumours (see also D40, lines below the title "Endocrine pancreatic tumours").

The respondents also referred to decision T 1868/16. The patent on which T 1868/16 was based had been filed in 2006 and was directed to the use of everolimus for treating PNETS. In T 1868/16, the Board revoked the patent for lack of sufficiency of disclosure. According to the respondents, if the use of everolimus for treating endocrine tumours was not sufficiently disclosed four years after the filing of D1, D1 could not sufficiently disclose the same therapeutic indication either.

This argument ignores the different circumstances of the case underlying T 1868/16 and the case in hand. In T 1868/16 (Reasons 4.5 and 4.8), the Board considered that the application as filed did not contain any evidence making the claimed therapeutic effect plausible. The effect was not derivable from the common general knowledge either. Therefore, post-published

evidence could not be used to remedy the insufficiency of disclosure. The case in hand was different in that, as explained above, D1 contained experimental evidence that allowed the consideration of post-published evidence. Therefore, the conclusion of T 1868/16 is not applicable to the case in hand.

5.3 Therefore, the Board concludes that the patent as granted fulfils the requirements of Article 83 EPC.

6. Squeeze between inventive step and sufficiency of disclosure

The respondents were of the view that the Board's conclusions on inventive step and sufficiency of disclosure were inconsistent. If the skilled person considered that the effect of everolimus on pancreatic tumours in D17 was not sufficient for a therapeutic use, they would also consider that the subject-matter of claim 1 lacked sufficiency since the assay in Example B.3 of D1 was essentially the same as in D17 and should be judged equally.

This argument does not take account of two aspects. First, as explained above, the assay in D17 was not adapted to assess the effect of everolimus when administered as the only active compound, while the assay in Example B.3 of D1 was specifically designed for that aim. Second, inventive step is assessed on the basis of the available prior art, while sufficiency of disclosure is assessed on the basis of common general knowledge and the evidence provided in the application as filed. Thus, for inventive step, the relevant experimental evidence available to the skilled person was the assay in D17, which was not conclusive on the magnitude of the antitumour effect of everolimus.

Furthermore, D17 suggested dosages for the administration of everolimus alone that were not compatible with the unit dosage forms of claim 1. In contrast, for sufficiency of disclosure, the skilled person had conclusive experimental evidence in D1 making it credible that everolimus could treat solid pancreatic tumours with the dosage unit forms of claim 1.

Therefore, while it was not possible to derive from the prior art that everolimus alone was therapeutically useful against solid pancreatic tumours, the evidence provided in the application as filed rendered this effect credible at the doses at which everolimus is usually administered. As argued by the respondents in the context of inventive step, such doses are usually in the order of 1 to 10 mg, as taught in D21 (page 8, last paragraph) and D19 (page 16, third paragraph).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated