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Datasheet for the decision of 19 July 2023

Case Number: T 2735/19 - 3.3.07

Application Number: 06712292.9

Publication Number: 1849470

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Language of the proceedings: EN

Title of invention:
ANTICANCER DRUG CONTAINING ALPHA, ALPHA, ALPHA-TRIFLUOROTHYMIDINE AND THYMIDINE PHOSPHORYLASE INHIBITOR

Patent Proprietor:
Taiho Pharmaceutical Co., Ltd.

Opponents:
STADA Arzneimittel AG
Generics (U.K.) Limited

Headword:
TAS-102 administration/TAIHO

Relevant legal provisions:
EPC Art. 56, 83

Keyword:
Inventive step - (yes) unexpected improvement shown
Sufficiency of disclosure - (yes)

Decisions cited:
G 0003/14, G 0002/21

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Case Number: T 2735/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 19 July 2023

Appellant: (Opponent 1)	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel (DE)
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Representative:	Hartz, Nikolai Wächtershäuser & Hartz Patentanwaltspartnerschaft mbB Weinstrasse 8 80333 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 16 July 2019 concerning maintenance of the European Patent No. 1849470 in amended form**

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 interlocutory decision finding that European patent no. 1 849 470 as amended according to the main request, filed as auxiliary request 1 on 5 April 2019, and the invention to which it relates, met the requirements of the EPC.

Claim 1 of the request considered allowable by the opposition division was identical to claim 1 as granted. It read as follows:

"*1. A cancer therapeutic drug, which is a composition comprising α,α,α-trifluorothymidine (FTD) and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride in a molar ratio of 1:0.5, for use in the treatment of cancer in a human patient in need thereof by orally administering the drug at a dose, as a dose of FTD, of 20 to 80mg/m^2/day twice daily.*"

The composition defined in claim 1 was also known in the prior art as TAS-102 (patent, paragraph [0004]).

II. The documents cited by the parties during these opposition and appeal proceedings include the following:

D1 EP 0763529

D4 S. Dwivedy et al., Proceedings of ASCO, 20, 2001, abstract No.386

D5 M.B. Thomas et al., Proceedings of AACR, 43, 2002, abstract No.2754

D6 T. Emura et al., International Journal of Molecular Medicine, 13, 2004, 249-55

D7 M.C. Green et al., Journal of Clinical Oncology, 24(18suppl), 2006, 10576

D10 Declaration of A. Mita

D11 Summary of clinical data filed on 19 March 2018

D14 EMA summary of product characteristics relating to Lonsurf

D16 Summary of clinical data in D11 with additional data on continuity

D17 Table summarising data in D16

D22 Declaration of A. Ohtsu

III. In the decision, the opposition division concluded that the main request met the requirements of Articles 123(2), 83, 54 and 56 EPC.

IV. Opponent 1 (appellant 1) and opponent 2 (appellant 2) each filed an appeal against the decision. The patent proprietor is respondent to these appeal proceedings.

V. In their statements of grounds of appeal, the appellants explained why the decision under appeal should be set aside and the patent revoked in its entirety.

VI. With its reply to the statements of grounds of appeal, the respondent filed two auxiliary requests and, among other documents, D22.

VII. The Board scheduled oral proceedings, in line with the parties' requests, and gave its preliminary opinion on the case.

VIII. Oral proceedings were held before the Board on 19 July 2023. At the end of the oral proceedings, the Board announced its decision.

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

Substantial procedural violation

According to appellant 1, the decision under appeal was not sufficiently reasoned in points 4.1, 7.3 and 7.4. This constituted a substantial procedural violation that justified reimbursement of the appeal fee.

Admittance of D16, D17 and D22

D16 and D17 were filed in the opposition proceedings but the respondent had not explained why they were filed and why they were relevant. D16 and D17 were not relevant at first glance because they contained data already presented in D11.

D22 was not relevant either. It merely confirmed the decision under appeal without providing additional information. D22 could have been filed in the opposition proceedings.

Interpretation of claim 1

The definition of the dose in claim 1 was unclear and had to be construed in light of the description and figures of the patent. It could be derived from paragraphs [0020], [0034] and [0035] and Figure 2 that the composition of claim 1 was to be administered daily as two doses containing 20 to 80mg/m^2 FTD each. This interpretation made technical sense since the EMA had

authorised the use of TAS-102 (Lonsurf) for the treatment of metastatic colorectal cancer at doses of up to 160mg/day (D14, point 4.1 and Table 1).

Added subject-matter

Claim 1 added subject-matter because it required that TAS-102 be administered daily as two doses containing 20 to 80mg/m^2 FTD each, while the daily dose in the application as filed was of 20 to 80mg/m^2 FTD, divided for twice daily administration.

Sufficiency of disclosure

The clinical trials in the patent and documents D7 and D11 did not demonstrate that the subject-matter of claim 1 was sufficiently disclosed. On the one hand, the use of claim 1 was not suitable for treating all cancer types; the evidence on file related only to solid tumours, which were treated differently to blood cancer. Furthermore, D11 demonstrated that the use according to claim 1 did not always stop cancer progression. On the other hand, it had not been demonstrated that TAS-102 could treat cancer at any dose within the range of claim 1; D7 reported that doses at the upper end of the range were not safe.

Appellant 1 put forward three additional reasons that allegedly prevented the skilled person from carrying out the invention without undue burden. First, the parameter "20 to 80 mg/m^2/day twice a day" was ill-defined. Second, the skilled person would not know how to distribute the total daily dose into two partial doses. Third, the claimed therapeutic effect was not credible because claim 1 was not limited to the dosage regime applied in Example 2 of the patent; according to

Exhibit Q of D10, a washout period was necessary for reducing side-effects.

Novelty over D1

Appellant 1 argued that the treatment with test solutions 11 to 15 in Test 3 of D1 anticipated the subject-matter of claim 1.

Inventive step starting from D4

D4 was the closest prior art. The subject-matter of claim 1 differed from the teaching of D4 in that TAS-102 was administered twice daily instead of once daily. This difference did not bring about any technical effect. The examples in the patent did not allow a comparison between the treatments involving once and twice daily administration. The patients treated had different cancer types and TAS-102 had been administered at different daily doses. The results of clinical studies presented in D11 did not demonstrate that twice daily administration produced an improved effect either. On the one hand, D11 showed that the administration of TAS-102 twice daily was not always successful. For instance, on page 4 of D11, a group of nine lung cancer patients were treated at a dose of $70mg/m^2$/day but the disease could not be controlled. On the other hand, D11 did not contain comparable groups having the same number of patients, the same cancer type and receiving the same daily dose of TAS-102.

The respondent had not shown an improvement over thrice daily administration either. The examples in the patent, D11 and D10 did not demonstrate that twice daily administration was advantageous, let alone for every cancer type or every daily dose within the range

of claim 1. In fact, the application as filed presented twice daily and thrice daily administration as equivalent embodiments.

D16 and D17 did not show that twice daily administration was safer either. Furthermore, FTD was known to be very toxic and it was not credible that every treatment scheme was safe. D14 could not be generalised; it was an authorisation for the treatment of metastatic colorectal cancer only and its effect could not be extended to the whole breadth of claim 1. In this context, expert opinion D22 was not independent because the expert had a conflict of interest.

Therefore, the objective technical problem was the provision of an alternative dosage regimen of TAS-102 for the treatment of cancer.

The solution proposed in claim 1 was obvious. First, it was known at the priority date that FTD had a short half life (patent, paragraph [0003]). It was obvious that administering it twice daily would extend FTD half life and its anticancer effect compared with once daily administration. Second, D1 (page 21, lines 2 and 3) suggested the administration of TAS-102 once a day or in two to four portions a day. Twice daily administration was an arbitrary choice. It was also obvious with regard to equally valid alternatives of multiple administration that twice daily was preferable for patient compliance. Third, D6 (abstract; page 249, right-hand column, first paragraph; page 254, right-hand column, penultimate paragraph) taught that, compared with once daily administration, multiple daily dosing of TAS-102 resulted in improved antitumour effect without additional side effects. It concluded that the most effective regimen would be administering

TAS-102 every eight to ten hours, which meant twice daily.

Inventive step starting from D5

According to appellant 1, D5 could also be regarded as the closest prior art. The subject-matter of claim 1 differed from D5 in that TAS-102 was administered twice daily instead of once daily. This difference did not bring about any technical effect, meaning that the objective technical problem remained the provision of an alternative dosage regimen for TAS-102. The solution proposed in claim 1 was obvious in light of the combination of D5 with D1 or D6.

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

Admittance of D16, D17 and D22

D16 and D17 were filed in the opposition proceedings. They should be considered to be on file in accordance with Article 12(4) RPBA 2007.

D16 supplemented the efficacy data of D11 with safety data. In multicentre international clinical tests, safety data were not so easy to gather and process as efficacy data. Therefore, they could not be provided earlier, i.e. in D11. It was apparent that the data in D16 were relevant to inventive step because they showed the improved safety of the dosage regimen according to claim 1.

D17 was merely a summary of continuity data presented in D16.

D22 was the opinion of an expert in the field of clinical oncology which confirmed specific aspects of the decision contested by the appellants. Therefore, D22 was a response to the statements of grounds of appeal.

Interpretation of claim 1

It was clear to the skilled person that claim 1 required the administration of a total daily amount of FTD of 20 to 80mg/m^2 and that this amount had to be divided for twice daily administration. This was also the interpretation derivable from the description of the patent, especially from paragraphs [0007] and [0024]. The disclosure in paragraphs [0020], [0034] and [0035] was in line with the respondent's interpretation.

Added subject-matter

The added-matter objection raised by appellant 1 was based on a wrong interpretation of claim 1. Claim 1 disclosed the same dosage of TAS-102 as the application as filed.

Sufficiency of disclosure

The subject-matter of claim 1 was sufficiently disclosed. TAS-102 and the mode of action of its active ingredients were known in the art (patent, paragraph [0003]). As their physiological activity was not limited to a specific cancer cell, their beneficial effect could be expected for any type of cancer, including blood cancer. It was common general knowledge that many anticancer drugs were effective against both solid and blood cancers because both types of cancer

had the same mechanism of abnormal proliferation. With regard to the clinical tests in the patent and D11, these provided extensive evidence that the therapy of claim 1 was effective against a broad range of tumours in patients not responding to standard therapy or for which no curative therapy existed. Under such circumstances, a treatment is normally considered effective if the disease remains stable in a significant portion of patients, even if it progresses in others. In addition, the treatments in D11 in which no effect had been observed could still be improved by increasing the dose.

With regard to the dose range, the skilled person could adjust the dose without undue burden depending on the circumstances of each patient. It was not derivable from D7 that a patient could not be safely treated with a dose at the upper end of the range in claim 1.

As to the additional reasons put forward by appellant 1, the following was noted.

The feature "20 to 80mg/m^2/day twice daily" was clear and reproducible, as discussed for the interpretation of claim 1. Appellant 1 had not demonstrated that in spite of the teaching of the application as filed the skilled person would not know how to divide the daily dose or that the specific administration regime of Example 2 (i.e. five-day administration followed by a two-day rest) was essential.

Novelty over D1

In Test 3 of D1, TAS-102 solutions 11 to 15 were administered to mice once a day. The tests were neither

carried out on human patients nor involved twice daily administration.

Inventive step starting from D4

D4 was not a promising starting point. It disclosed intermediate results of a clinical study which gave disappointing results from which it could not be expected that TAS-102 would be suitable for treating cancer. D4 found that the efficacy of TAS-102 against gastrointestinal cancer, at doses found to be safe when administered once daily, was anecdotal. No objective responses were observed and only one patient demonstrated stable disease for more than three months.

The subject-matter of claim 1 differed from D4 in that TAS-102 was administered twice daily. The effect of this difference was demonstrated in the patent and documents D11 and D16. They presented the results of clinical trials on cancer patients for whom standard therapy had failed or no curative therapy existed, i.e. they were critically ill. The results showed that the administration of TAS-102 twice daily at doses ranging between 20 and 80mg/m^2/day resulted in higher efficacy and lower toxicity compared with once daily administration. This effect had been shown in particular for the case of colorectal cancer but it could be expected for every cancer type since the mode of action of FTD impaired DNA replication. The slight side effects could also be expected to occur generally because they resulted from the interaction of TAS-102 with healthy cells; they were independent of cancer type. This point was confirmed in D22 (point 4) by an expert in oncology.

The fact that a group of nine patients with small cell lung cancer on page 4 of D11 did not respond to the treatment did not invalidate the conclusion that twice daily administration was advantageous. Small cell lung cancer was one of the most aggressive and difficult-to-treat cancer types and the patients had not responded to previous treatments. In such critical cases, a conclusion on the benefit of the treatment could not be drawn from a group of only nine patients. Even if a tumour continued to evolve, the treatment could still provide an extension of life expectancy. Moreover, D11 also reported on page 4 that a test on a group of five patients with lung cancer resulted in a control rate of 40%.

Based on the effects shown, the objective technical problem was the provision of a measure for a drug containing FTD to achieve excellent anti-cancer effect and controlled side effects so that the treatment might be continued for a longer period of time.

This problem was solved by the subject-matter of claim 1 in a non-obvious way. It could not be expected from the prior art that twice daily administration of TAS-102 at doses at which it had been proved to be ineffective when administered once daily would result in an enhanced incorporation of FTD into the DNA while improving the control of side effects.

D1 was not concerned with a new dosage regimen for humans but with animal tests for finding the best FTD/thymidine phosphorylase inhibitor ratio. D1 disclosed many compounds and suggested their administration once a day or two to four times a day. In in the experimental part of D1, however, FTD was only administered once daily. There was no suggestion

that twice daily administration could be advantageous over other dosage regimens.

D6 did not lead to the invention either. It was based on a mouse model meaning that the phosphorylase and the TAS-102 doses involved differed from those applicable to humans. Even if D6 suggested that multiple daily dosing of TAS-102 could possibly result in better clinical benefits when compared with single daily dosing, twice daily dosing was neither mentioned nor tested. In Table I, D6 showed that thrice daily dosing produced a higher anticancer effect than once daily dosing. Contrary to the appellants' submissions, D6 did not conclude that the most effective regimen was administering TAS-102 every eight to ten hours. The conclusion was that thrice daily dosing could be administered at three hour intervals, i.e. within a period of approximately ten hours. This provided repeated contact of tumour cells with FTD and was possibly the best strategy for producing a potent antitumour effect.

D16 and its summary D17 showed that the choice of twice daily administration was particularly advantageous. In fact, this was the regimen recommended by the regulatory authorities (D14, point 4.2). The respondent had found that the administration of TAS-102 twice daily was not only more effective but also safer than thrice daily. This was surprising since twice daily administration implied the provision of larger amounts of TAS-102 in each dose, and this could be expected to increase the occurrence of side effects. Contrary to the appellants' contention, the application as filed showed that twice daily administration was advantageous. This could be derived from Example 2, in which twice daily administration resulted in a higher

control rate and a higher number of treatment courses than thrice daily administration.

The fact that a safe way to treat of cancer with FTD had not been found in 50 years since the discovery of this compound points to the inventive step of the claimed dosage regimen. The subject-matter of claim 1 allowed the treatment of patients that could not be treated prior to the invention.

Inventive step starting from D5

The situation starting from D5 was analogous to that starting from D4. Therefore, for the same reasons the subject-matter of claim 1 was inventive starting from D5.

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

The appellants requested that the decision under appeal be set aside and that the patent be revoked. They also requested that documents D16, D17 and D22 not be admitted into the appeal proceedings. In addition, appellant 1 requested that the appeal fee be reimbursed because of an alleged substantial procedural violation.

The respondent requested that the appeals be dismissed (main request). The respondent also requested that documents D16, D17 and D22 be admitted into the appeal proceedings.

Reasons for the Decision

1. Alleged substantial procedural violation - reimbursement of the appeal fee (Rule 103(1)(a) EPC)

1.1 According to appellant 1, the opposition division had committed a substantial procedural violation which justified reimbursement of the appeal fee. Appellant 1 argued that the opposition division had not reasoned the decision under appeal in two respects.

- In point 4.1, the decision referred to point 3 to substantiate that the claimed subject-matter was sufficiently disclosed. However, point 3 dealt with the ground of added subject-matter and therefore it could not be used for reasoning that the requirement of sufficiency was met.

- Points 7.3 and 7.4 of the decision were inconsistent. The former concluded that the claimed subject-matter was obvious while the latter stated that it was inventive.

1.2 In point 3 of the decision, the opposition division construed the feature in claim 1 "20 to 80mg/m^2/day twice daily" as defining the total daily dose, which had to be divided for twice daily administration. Following this interpretation, claim 1 did not add subject-matter.

In point 4.1, the opposition division stated that, for the reasons set out in point 3, the invention related to twice daily administration of a total daily dose of 20 to 80mg/m^2. On this basis, the opposition division then reasoned why the subject-matter of the main

request was sufficiently disclosed. Therefore, point 4.1 does not rely on point 3 to substantiate that the claimed subject-matter is sufficiently disclosed. It merely confirms the interpretation of claim 1 put forward in point 3. Consequently, the objection of appellant 1 referring to these points is unfounded.

1.3 With regard to points 7.3 and 7.4 of the decision, it is apparent from the reasoning in 7.3 that the opposition division held that the claimed subject-matter was not obvious. This was confirmed not only in point 7.4 but also in the conclusion drawn in the last sentence of point 7.3 that D6 did not lead the skilled person to the claimed dosage regime in an obvious manner. It is clear that the word "not" was missing in the first sentence of point 7.3, which states "*the prior art does lead the skilled person in an obvious manner to*...". This obvious mistake does in no way affect the quality of the decision reasoning or its outcome.

1.4 Therefore, the contention of appellant 1 that the decision under appeal was insufficiently reasoned is factually wrong. Appellant 1 has not demonstrated that the opposition division committed a substantial procedural violation and therefore there is no basis for reimbursing the appeal fee under Rule 103(1)(a) EPC.

2. Admittance of D16, D17 and D22

Documents D16, D17 and D22 were filed by the respondent with its reply to the statements of grounds of appeal. As the latter were filed in 2019, the relevant provision is Article 12(4) RPBA 2007 (see also Article 25(2) RPBA 2020).

D16 and D17 were first filed on 18 March 2018, i.e. at the outset of the opposition proceedings. Although the respondent had not explicitly indicated the relevance of the documents, it was apparent that they contained safety data intended to show the superiority of the administration of TAS-102 twice daily over thrice daily. Therefore, the Board sees no reason to hold D16 and D17 inadmissible.

As to D22, the Board considers that it is an adequate response to the statements of grounds of appeal, which called into question technical facts presented by the opposition division in the decision under appeal. In particular, D22 confirms the interpretation of claim 1 by the opposition division as well as conclusions that may be derived from the experimental data on file. Therefore, D22 is also admissible.

3. Interpretation of claim 1 of the main request

In claim 1, the dose of the composition is defined in relation to its FTD content as being "20 to 80mg/m^2/day twice daily". The meaning of this feature was controversial because it refers to the twice daily administration of a daily dose and two interpretations are possible. According to the respondent, the total daily dose of FTD was of 20 to 80mg/m^2. This daily dose was to be divided for twice daily administration. In contrast, the appellants contended that claim 1 required the daily administration of two doses containing 20 to 80mg/m^2 FTD each.

The Board holds that the skilled person would understand from the wording of claim 1, which refers to "day" after specifying the amount of 20 to 80mg/m^2,

that the TAS-102 daily dose based on its FTD content is of 20 to 80mg/m^2 and that this dose must be divided for twice daily administration. This interpretation is in line with the general teaching of the patent as presented in paragraphs [0007] and [0024]. Paragraph [0007] explains that the administration of TAS-102 once daily required a dose of 100mg/m^2 FTD. Nevertheless, the inventors found that when TAS-102 is administered twice daily, the total daily dose can be reduced to 20 to 80mg/m^2 FTD and still exhibit a remarkable anticancer effect. Similarly, paragraph [0024] teaches that even if the dose according to the invention is lower than the one conventionally administered once daily, twice daily administration provides an excellent anticancer effect and facilitates the control of side effects.

Paragraphs [0020] and [0034] use the same wording as claim 1, indicating that the daily dose is to be administered twice daily. The appellants correctly noted that paragraph [0035] discloses TAS-102 doses of 50 and 60mg/m^2 FTD that are administered twice daily. However, this is an obvious mistake in light of the general teaching of the patent and the specific disclosure in paragraph [0034] referring to doses of 50 and 60mg/m^2/**day** FTD.

The appellants' argument that their interpretation is technically sensible because the EMA authorised the use of TAS-102 at doses of up to 160mg/day (D14, Table 1) is irrelevant and flawed: Table 1 of D14 discloses total daily doses of up to 160mg not 160mg**/m^2**.

4. Added subject-matter - claim 1 of the main request

Appellant 1 raised an added-matter objection based on its interpretation of claim 1 that TAD-102 was administered daily as two doses of 20 to 80mg/m^2 FTD each. As the Board concluded that this interpretation of claim 1 was flawed, the appellant's objection is irrelevant.

Consequently, the main request fulfils the requirements of Article 123(2) EPC.

5. Sufficiency of disclosure - claim 1 of the main request

5.1 The appellants questioned whether the skilled person could carry out the subject-matter of claim 1 without undue burden. They argued that the use defined in claim 1 could not credibly treat every type of cancer, let alone at any dose within the range defined in claim 1. The Board disagrees.

5.2 As acknowledged in paragraphs [0004] and [0005] of the English translation of the application as filed, which correspond to paragraphs [0003] and [0004] of the patent, the combination of FTD with 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride in a molar ratio of 1:0.5 was known in the art as TAS-102. The mode of action of the two active compounds constituting the composition was also known. Through its incorporation into DNA, FTD inhibited DNA replication. This mechanism circumvented the sensitivity problems arising from fluorouracil-based antitumour agents, which act on RNA. The main limitation of FTD was its fast degradation by thymidine phosphorylase. This limitation could be overcome by adding the thymidine phosphorylase inhibitor 5-

chloro-6-(1-(2-iminopyrrolidinyl)methyl) uracil hydrochloride, which extended FTD half-life.

Example 2 and Figure 2 (Trials 3 and 4) of the English translation of the application as filed showed that the oral administration of TAS-102 at a total daily dose of 60 or 50mg/m^2 FTD, provided in two daily doses, effectively treated more than 70% of breast cancer patients for whom standard therapy had not worked. In this context, effectively treating meant that at least tumour progression was stopped and the disease remained stable.

The Board agrees with the respondent that, due to the direct action of FTD on DNA, TAS-102 could be expected to have a general effect on tumours and not to be limited to a single cancer type. Therefore, the consideration of the post-published evidence in document D11 confirming this effect on additional tumour types was in line with the principles established in G 2/21 (Reasons 77 and 93), namely that the purported effect is encompassed by the technical teaching of the application as filed and that it is embodied by the same originally disclosed invention.

D11 demonstrates that TAS-102 is able to treat a broad range of cancer types in a significant proportion of patients. The appellants tried to cast doubt by focusing on particular embodiments in D11 in which the disease control rate was of 0%. However, the embodiments selected by the appellants appeared to involve a very low number of patients and could not be considered to be statistically relevant. In the Board's view, a correct analysis of the data in D11 has to be based on the benefit provided by the anticancer agent to a population of patients, not to individual patients

or a small group of them. A better overview of the data in D11 is presented on page 42 of the respondent's reply to the appeals, in which the results of the clinical trials according to claim 1 were summarised in a table. The content of this table was not contested by the appellants and is reproduced here below.

	N	Disease control rate
Colorectal Cancer	718	45 96%
Gastric Cancer	290	44 14%
Esophagus Cancer	45	26 67%
Pancreatic Cancer	18	22 22%
Hepatic Cancer	2	50 00%
Duodenal cancer	1	100 00%
Breast Cancer	9	77 78%
Lung Cancer	14	14 29%
Cervical Cancer	3	33 33%
Renal Cancer	2	100 00%
Head and Neck Cancer	1	100 00%
Prostate Cancer	1	100 00%
Thymic cancer	1	100 00%
Uterine Cancer	1	100 00%
Unknown	12	33 33%

In the table, N is the number of patients treated. Considering that trials involving too low a number of patients cannot be taken into consideration because they are not statistically relevant, the table shows that the therapeutic use of claim 1 is suitable for treating a significant portion of patients having colorectal, gastric, oesophageal, pancreatic, breast and lung cancer. The existence of non-responders in these trials is not a reason to deny sufficiency of

disclosure. It is common in the treatment of cancer that a substantial portion of patients do not respond to the treatment. The cases of lung, pancreatic and oesophageal cancers are well known to be particularly difficult to treat, so that even a low portion of patients responding to the treatment may be considered to constitute a significant technical contribution. This is even more the case for patients at an advanced stage of the disease or who had not responded to previous treatments, as was the case for the patients in D11.

Therefore, in view of the common general knowledge on the mode of action of the active ingredients of TAS-102 and the evidence in the application as filed and D11, it is credible that the therapeutic use of claim 1 is generally suitable for treating cancer. The fact that there is no available evidence on blood cancer does not raise serious doubts since the interference in DNA replication exerted by FTD can also be expected to work in blood tumours.

5.3 With regard to the dosage range, it is common practice in oncology to adjust the dose depending on the circumstances of each patient. This does not entail an undue burden (see also expert opinion D10, page 3, first paragraph).

The appellants considered that post-published document D7 raised serious doubts that a patient can be treated with a dose at the upper end of the range of claim 1. D7 reports the results of a phase I study on the safety of TAS-102 administered twice daily to patients with metastatic breast cancer. It states that the recommended dose is that causing a limiting toxicity in no more than one third of patients, which in this case

was 50mg/m^2/day. As D7 states that the dose of 80mg/m^2/day caused toxicity in two thirds of patients, the appellants argued that this dose could not be used.

This argument is not correct. The fact that a dose of 80mg/m^2/day administered in two daily doses causes higher toxicity than the recommended dose does not exclude this dose. It could be used depending on the circumstances since the skilled person would be able to adjust the dose to each patient's needs. As one third of patients did not experience toxicity, at least that third of patients could potentially benefit from the higher dose.

5.4 Appellant 1 raised three additional sufficiency objections, namely that: (i) the parameter "20 to 80 mg/m^2/day twice a day" was ill-defined; (ii) the skilled person would not know how to distribute the total daily dose between two partial doses; (iii) the therapeutic effect of claim 1 was not credibly achieved because the claim was not limited to the dosage regime applied in Example 2 of the patent - according to D10, a washout period was necessary for reducing side-effects.

The Board does not agree with appellant 1 on any of these three points.

The objection of point (i) is not a sufficiency but a clarity objection. As claim 1 is identical to claim 1 as granted, a clarity objection cannot be raised in opposition or its subsequent appeal proceedings (G 3/14, Order). Furthermore, as explained in point 3 above, the parameter "20 to 80 mg/m^2/day twice a day" is clear to the skilled person, who would know how to apply it in the context of claim 1.

The objection of point (ii) is not convincing. The Board finds it is difficult to imagine that the skilled person would not know how to divide the total daily amount of TAS-102 for twice daily administration. Appellant 1 has not provided any evidence casting doubt in this respect.

With regard to objection (iii), the situation is similar to that of the adaptation of the dosage. The skilled person would be able to determine, depending on the nature and intensity of the adverse effects experienced by the patient, whether a washout period is needed and of which length. Contrary to the opinion of appellant 1, this view is in line with the teaching in Exhibit Q, point 1.2, of D10, which explains how to manage adverse effects by introducing a washout period between treatment courses. Appellant 1 has not explained why in light of Exhibit Q a washout period of two days would be unavoidable.

5.5 The Board therefore concludes that the appellants did not raise serious doubts that the skilled person could carry out the subject-matter of claim 1 without undue burden. Consequently, claim 1 of the main request fulfils the requirements of Article 83 EPC.

6. Novelty over D1 - claim 1 of the main request

Appellant 1 argued that the subject-matter of claim 1 was not novel over the treatment with test solutions 11 to 15 in Test 3 of D1 (pages 54 to 56).

This argument is flawed. Test 3 of D1 studies the antitumour effect of thirty solutions containing FTD or combinations of FTD with Compound 29. Compound 29 is

5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride (D1, page 25, line 19). In particular, solutions 11 to 15 have a molar ratio FTD:Compound 29 of 1:0.5 (page 55, line 11 and page 56, lines 21 to 26). In other words, solutions 11 to 15 of D1 are solutions of TAS-102.

In the description of how Test 3 was carried out, D1 states that the test was conducted in a similar manner to Test 2 except for the use of solutions 1 to 30 (page 55, line 35). Looking at the description of Test 2 (page 54, line 12 and 13), it appears that the solutions were orally administered to mice once a day. Therefore, the solutions of TAS-102 in Test 3 were neither administered to humans nor twice daily. For these reasons alone, D1 does not anticipate the subject-matter of claim 1.

7. *Inventive step starting from D4 - claim 1 of the main request*

7.1 The invention relates to the treatment of cancer by oral administration of TAS-102 at an FTD dose of 20 to 80mg/m^2/day, wherein the dose is divided for twice daily administration.

The appellants cited D4 as the closest prior art. D4 is the abstract of a poster presented at an annual meeting of the American Society of Clinical Oncology. It reports the results of a phase I clinical trial of TAS-102 and the preliminary results of an on-going phase II clinical trial. In both trials, TAS-102 was orally administered once daily. The maximum tolerated dose found in the phase I trial was 50mg/m^2/day. In the phase II trial, it was intended to increase the dose by introducing rest periods within the administration

regimen: for two weeks, TAS-102 was provided for five consecutive days followed by a two-day rest. The treatment was repeated every four weeks. Six gastrointestinal cancer patients were treated with TAS-102 at doses of 70 and 80mg/m^2/day. Nevertheless, no objective responses were observed. Only one patient demonstrated stable disease for more than three months.

7.2 The parties did not dispute that the subject-matter of claim 1 differs from D4 in that TAS-102 is administered twice daily instead of once daily. They disagreed on the technical effect brought about by this difference. According to the respondent, the data in the patent examples and in D11 demonstrate that twice daily administration provides an improvement over once daily in the efficacy and safety of TAS-102 irrespective of cancer type. The appellants maintained that no effect had been demonstrated.

In the following, the Board will explain that the evidence on file does indeed make it credible that TAS-102 administered twice daily provides an enhanced anticancer effect and lower levels of side effects than once daily administration.

7.2.1 Regarding the anticancer effect aspect, the Board agrees with the appellants that the results of the clinical trials in the patent do not allow any conclusion to be drawn as to the relative efficacy of once and twice daily administration of TAS-102. This is true solely because the patients in the once daily regimen trial (Trial 1) had a different cancer type from the twice daily regimen trials (Trials 3 and 4).

With regard to the results of the clinical tests in D11, the appellants argued that they could not be

compared with each other because they had not been carried out under the same conditions. The Board does not deny that a comparison of the data in D11 is not straightforward. However, comparative tests on patients having a serious illness cannot be carried out in a discretionary manner; they are subject to ethical concerns and are often not even feasible. In the case in hand, the Board holds that the tests in D11 at least show a tendency allowing the conclusion to be drawn that the administration of TAS-102 twice daily indeed results in a higher efficacy compared with once daily administration.

7.2.2 The appellants focused on the result for individual patients to argue that the claimed treatment did not work. But such an approach does not make technical sense since, as explained with regard to sufficiency of disclosure (point 5.2), in the treatment of cancer it cannot be expected that all patients will respond. The technical contribution to the art lies rather in the response of a significant portion of patients.

On page 6 of D11, three groups involving a total of 28 patients with colorectal cancer were treated at doses of the order of 100mg/m^2/day administered once daily. The disease control rate was on average about 35%. Similar results were obtained for the over 140 patients with colorectal cancer on pages 8 and 9 of D11, who were treated once daily at FTD doses ranging from 50 to 180mg/m^2/day. In contrast, the over 700 colorectal cancer patients treated with TAS-102 twice daily at FTD doses of 30 to 70mg/m^2/day on pages 1 to 5 and 11 to 15 of D11 experienced an average disease control rate of about 45% (see also the table on page 42 of the respondent's reply to the appeals).

Therefore, D11 shows that the treatment of colorectal cancer with TAS-102 administered twice daily provides better disease control than when it is administered once daily, even if the doses of the once daily regimen are considerably higher. This finding is consistent with the fact that TAS-102 has been approved by the EMA for the treatment of metastatic colorectal cancer with a dosage regimen as defined in claim 1 (D14, points 4.1 and 4.2).

7.2.3 At the oral proceedings before the Board, the appellants did not contest this improvement. Their position was rather that the improvement had been demonstrated for colorectal cancer only and that it was not credible for other cancer types.

As discussed with regard to sufficiency of disclosure, TAS-102 can be expected to have a general effect on tumours and not to be limited to a single cancer type due to the direct effect of FTD on DNA. Furthermore, the appellants relied in their discussion of obviousness on the teaching in D6 (abstract and last paragraph on page 254) that FTD incorporates into DNA in a time-dependent manner, this implying that dividing the daily dose increases the contact time of FTD with DNA and can be expected to produce a more potent anticancer effect. Therefore, the Board finds it credible that twice daily administration does indeed enhance the anticancer effect of TAS-102 over once daily administration irrespective of cancer type.

7.2.4 On the aspect of safety, as taught in the patent (paragraph [0007]) and demonstrated in D11, the administration of TAS-102 twice daily produces an anticancer effect at doses considerably lower than those required when the product is administered once

daily (see point 7.2.2 above). Therefore, the occurrence of side effects may credibly be expected to be reduced accordingly.

7.3 On the basis of these effects, the objective technical problem may be defined, in line with the respondent's proposal, as the provision of measures for improving the anticancer efficacy and the safety of TAS-102.

7.4 The appellants argued that the combination of D4 with the teaching of documents D1 or D6 rendered the subject-matter of claim 1 obvious. The Board disagrees.

7.4.1 D4 itself does not point to the solution in claim 1 since it proposes improving the anticancer efficacy of TAS-102 by introducing rest periods that could possibly allow the maximum-tolerated dose to be increased beyond 50mg/m^2/day. The document does not suggest any administration regimen other than once daily.

7.4.2 D1 (abstract and page 3, lines 5, 6, 38 and 39) is directed to a family of compounds that inhibit human-derived thymidine phosphorylase, and to the use of these compounds as potentiators of antitumour agents. 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride, referred to as Compound 29, is one of the preferred compounds in D1 (page 6, line 27 and page 25, line 31). As discussed in point 6 above, Test 3 of D1 evaluates the antitumour effect of solutions containing combinations of FTD with Compound 29 in different ratios, including TAS-102 (solutions 11 to 15 on page 56). D1 generally states on page 21, lines 2 and 3 that the preparations according to the invention can be administered once a day or in about 2 to 4 portions per day. However, this general statement does not suggest in any way that twice daily administration

could improve the efficacy or the safety of TAS-102. In fact, all the *in vivo* tests in D1 are based on the administration of preparations according to the invention once daily.

Therefore, the combination of D4 with D1 would not lead the skilled person to the subject-matter of claim 1 in an obvious manner.

7.4.3 D6 (title, abstract and introduction) discloses a study on the optimal schedule for TAS-102 administration, based on its intracellular metabolism and its incorporation into DNA. In the study, it was found that the incorporation of FTD into DNA was not concentration- but time-dependent, and that administering the daily dose of TAS-102 in thrice daily doses resulted in an enhanced antitumour effect without increasing side effects compared with once daily administration. This result was confirmed in mice for three different human tumour xenografts (Table I on page 253). D6 concluded that multiple daily dosing could result in better clinical benefits of TAS-102 when compared with single daily dosing, because dividing the dose was expected to enhance the time of contact of FTD with DNA and would produce a more potent antitumour effect. The optimum regimen proposed in D6 was the administration of TAS-102 thrice daily at three-hour intervals, i.e. within a period of eight to ten hours. This proposal was misunderstood by the appellants, who interpreted that TAS-102 was to be administered every ten hours.

In view of the teaching of D6, it was obvious to the skilled person that the anticancer effect of TAS-102 could be improved by dividing the daily dose and administering it multiple times daily. It should

nevertheless be noted, that D6 refers to multiple daily dosing and that the regimen tested and proposed as being optimum is thrice daily. Although twice daily administration is encompassed by the expression "multiple dosing", it is not explicitly mentioned in D6. It may also be derived from the principles outlined in D6, namely that the antitumour effect is enhanced by extending the time of contact between FTD and DNA, that the more divided the dose the greater the antitumour effect. Therefore, it could be expected from D6 that twice daily administration would not improve the anticancer effect of TAS-102 as much as thrice daily. In addition, in line with expert declaration D10 (point 5), considering that twice daily administration implies the provision of a higher amount of active ingredient in each dose compared with thrice daily, it could also be expected that twice daily administration would cause a higher level of side effects. Surprisingly, the respondent has demonstrated that what happens is the opposite: twice daily administration provides an efficacy of the same order while reducing the level of side effects compared to thrice daily administration. This is apparent from documents D11, D16 and D17, as explained in the paragraphs below.

7.4.4 On anticancer efficacy, D11 discloses on pages 7, 10 and 11 the results of administering TAS-102 to more than 30 patients having colorectal cancer thrice daily at a dose based on FTD of 60 to 80mg/m^2/day. The disease control rate observed was about 60%. As discussed above (point 7.2.2), the result for twice daily administration of 30 to 70mg/m^2/day was about 45%. Taking account of the difference in doses, it can be concluded that the anticancer effect of the two regimens is of the same order.

As to safety, D16 and D17 demonstrate that, contrary to what could be expected, the administration of TAS-102 twice daily is safer than thrice daily.

D16 shows continuity data of clinical trials in D11. The data in D16 relevant to safety in relation to twice and thrice daily administration are summarised in D17. The appellants argued that a conclusion cannot be drawn from D17 because it does not take account of the cancer type treated. But the Board agrees with the respondent (reply to the statements of grounds of appeal, page 18, points 5.2.4 to 5.2.6 and 6.2) and expert opinion D22 (point 4) that, as a rule, the side effects of TAS-102 are not closely related to cancer type because they are caused by the interaction of FTD with healthy cells. At the oral proceedings before the Board, appellant 2 questioned the independence of the opinion in D22 because the expert who drafted it allegedly had a conflict of interest: as director of a clinical centre that had collaborated with the respondent, the expert had an interest in the respondent carrying out further clinical tests at his centre. The Board considered this allegation unfounded. Therefore, the data in D17 were considered to be suitable for comparison. They are reproduced here below.

Ref clinical trial	Number of divided portions	Dosage mg/m^2/day	Dose reduction in any courses	Number of patients
9805	**Thrice** a day	60	**100%**	3
		70	**100%**	6
		80	**83.33%**	6
9804	Twice a day	60	71.43%	7
10040010	Twice a day	60	0%	3
10040010	Twice a day	70	50%	6
10040030	Twice a day	70	20%	112
10040040	Twice a day	70	31.25%	12
TPU-TAS-102-102	Twice a day	70	13.63%	24
TPU-TAS-102-103	Twice a day	70	20.45%	44
TPU-TAS-102-104	Twice a day	70	6.25%	46
Recourse	Twice a day	70	13.70%	534
TAGS	Twice a day	70	11%	335
9804	Twice a day	80	66.67%	3

In the table of D17, the column "dose reduction in any courses" shows by how much a dose had to be reduced in any of the courses of the treatment due to the occurrence of side effects. Therefore, the data in the column reflect the level of side effects of the treatment. The table shows that twice daily administration in most cases required a dose reduction of less than 20% and only in the worst cases was this about 70%. In contrast, the administration of equivalent doses thrice daily required dose reductions ranging from 80% to 100%. Thus, D17 shows that, contrary to what could be expected, the level of side effects caused by a dose of TAS-102 administered twice daily is considerably lower than when it is administered thrice daily. This conclusion is also supported by the fact that TAS-102 was approved by the EMA for the treatment of metastatic colorectal cancer by twice daily administration (D14, points 4.1 and 4.2).

7.4.5 In summary, the skilled person wanting to improve the efficacy and safety of the therapeutic indication disclosed in D4 would turn to D6. This combination would lead them to provide TAS-102 in multiple doses as an obvious solution. In particular, the skilled person would administer TAS-102 thrice daily, which is the regimen found in D6 to be optimum. The skilled person would have expected that administration twice daily, which was neither disclosed nor explicitly suggested in D6, would not be as good as thrice daily. It is even less likely that they would have expected twice daily administration to exhibit a comparable level of anticancer efficacy while considerably reducing the level of side effects. Therefore, the solution to the objective technical problem proposed in claim 1 was not obvious from the combination of D4 with D6. It constituted the selection of an undisclosed embodiment which was unexpectedly advantageous.

7.4.6 The appellants argued that it would have been obvious to select twice daily administration over thrice daily administration because administration twice daily would improve patient compliance. This argument is not convincing, since according to the objective technical problem, the skilled person's focus was on improving the efficacy and safety of the treatment in D4. They had no motivation to deviate from this primary aim due to considerations of patient compliance. The appellants' argument is based on hindsight.

8. Inventive step starting from D5 - claim 1 of the main request

8.1 In its statement of grounds of appeal (pages 44 and 45, point 5.2), appellant 1 raised an additional inventive-

step objection starting from D5 as the closest prior art. At the oral proceedings before the Board, the appellant did not wish to discuss this objection further.

Like D4, D5 is an abstract presented at a conference on cancer research. D5 would appear to be a continuation of the research on which D4 was based. It reports on a clinical test for finding the maximum tolerated dose of TAS-102 when administered orally once daily for five days every three weeks to patients having solid tumours. The aim of D5 was to provide a more dose-intensive regimen than in previous phase I studies which found that the maximum tolerated dose was 50mg/m^2/day. In D5, the doses ranged from 100 to 140mg/m^2/day and, as in D4, no objective responses were observed. Only two patients demonstrated stable disease for more than four months and one patient for more than six months.

The subject-matter of claim 1 differs from the teaching of D5 not only in that TAS-102 is administered twice daily instead of once daily but also in the daily dose administered. For the reasons explained with regard to D4, the objective technical problem is the provision of measures for improving the anticancer efficacy and safety of TAS-102. Also for the reasons explained for D4, the combination of D5 with D1 or D6 would not lead the skilled person to the solution proposed in claim 1 in an obvious manner.

9. Consequently, the Board concludes that the subject-matter of the main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated