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Datasheet for the decision of 18 March 2022

Case Number: T 2963/19 - 3.3.07

Application Number: 13731230.2

Publication Number: 2861210

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Language of the proceedings: EN

Title of invention:
METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN

Patent Proprietor:
Ipsen Biopharm Ltd.

Opponent:
Teva Pharmaceutical Industries Ltd

Headword:
Liposomal irinotecan/IPSEN

Relevant legal provisions:
EPC Art. 87(1), 83, 56

Keyword:
Priority - same invention (no)
Sufficiency of disclosure - plausibility (yes)
Inventive step - (no) - closest prior art - reasonable expectation of success of clinical trial

Decisions cited:
T 0116/18, T 0096/20, T 0239/16, T 2506/12, T 2154/14

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Case Number: T 2963/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 18 March 2022

Appellant: (Patent Proprietor)	Ipsen Biopharm Ltd. Ash Road Wrexham Industrial Estate Wrexham LL13 9UF (GB)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Opponent)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 28 August 2019 revoking European patent No. 2861210 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	A. Jimenez

Summary of Facts and Submissions

I. European patent 2 861 210 ("the patent") was granted on the basis of five claims.

Independent claim 1 of the patent as granted defined:

"Liposomal irinotecan for use in a method of treating pancreatic cancer in a human patient, wherein the patient exhibits evidence of recurrent or persistent pancreatic cancer following primary chemotherapy and wherein the patient has failed prior treatment with gemcitabine or become resistant to gemcitabine, the method comprising co-administration of an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU) and leucovorin to the patient in at least one cycle wherein the cycle is a period of 2 weeks and, for each cycle:
(a) liposomal irinotecan is administered to patients not homozygous for the UGT1A 1 *28 allele on day 1 of each cycle at a dose of 80 mg/m^2 and to patients homozygous for the UGT1A1 *28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of 60 mg/m^2 or 80 mg/m^2;
(b) 5-FU is administered at a dose of 2400 mg/m^2; and
(c) leucovorin is administered at a dose of 200 mg/m^2 (l form) or 400 mg/m^2 (l+d racemic form);
and wherein in each cycle, the liposomal irinotecan is administered prior to the leucovorin, and the leucovorin is administered prior to the 5-FU.

II. The patent was opposed on the grounds that its subject-matter lacked inventive step and that the claimed invention was not sufficiently disclosed. The appeal

was filed by the patent proprietor (appellant) against the decision of the opposition division to revoke the patent.

The decision under appeal was *inter alia* based on the main request, in which claim 1 as granted was amended by deletion of the terms "or 400 mg/m^2 (l+d racemic form)" and by addition of the feature:"and wherein the liposomal irinotecan is irinotecan sucrose octasulfate salt liposome injection".

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

D1 : FDA label (Highlights of Prescribing Information) for FUSILEV (levoleucovorin) (2008)
D1b : Leucovorin calcium product label, November 2011
D2 : Gebbia V et al., Am J Clin Oncol (2008) 33:461-464
D3 : Zaniboni A et al., Cancer Chemother Pharmacol (2012) 69:1641 -1645
D4 : Neuzillet C et al., World J Gastroenterol (September 2012) 18(33):4533-4541
D5 : Yoo et al., BrJ Cancer (2009) 101 :1658-1663
D6 : Taieb Jet al ., Ann Oncol (2007) 18:498-503
D7 : Chen Let al., .J Clin Oncol (2008) 26:2565
D8 : Infante et al., Cancer Chemother Pharmacol (2012) 70(5), 699
D10 : FDA label (Highlights of Prescribing Information) for CAMPTOSAR {irinotecan) (2012)
D12 : Ko AH et al. , J Clin Oncol (2011) 29(15), 4069
D13 : Tsai C-S et al., J Gastrointest Oncol (2011) 2{3):185-194
D15b: "Study of MM-398 With or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin in

Patients With Metastatic Pancreatic Cancer", Clinical Trials Identifier: NCT01494506 (25 January 2013)
D17 : Commission Implementing Decision and Annexes {Summary of Product Characteristics for Onivyde®)
D18 : "FDA approves new treatment for advanced pancreatic cancer' (2015), FDA News Releases
D19 : "'Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOlI-1): a global, randomised, open-label, phase 3 trial", Lancet, 2016 Feb 6; 387(10018):545-57
D22 : L.Chen, et al., "Phase I study of liposome irinotecan (PEP02) in combination with weekly infusion of 5-FU/LV in advanced solid tumours", Journal of Clinical Oncology, 2010, 28:15 suppl, e13024

IV. The opposition division came to the following conclusions:

(a) The patent sufficiently disclosed the invention as claimed according to the main request. The suitability of the defined treatment regimen for the defined indication was plausible in view of examples 6 and 7 of the patent and having regard to the known effectiveness of similar combination treatment involving non-liposomal irinotecan as mentioned in the the patent and reported in documents D2, D3, D5 and D6, the so-called "FOLFIRI regimen".

(b) The priority document of 13 June 2012 ("PD1") described the administration of leucovorin at a dose of 200 mg/m^2 without specifying whether the leucovorin was in the l-form or in the racemic form. The subject-matter as defined in accordance with the main request was therefore not entitled to

this priority. Documents D4, D8, D10 and D15b were therefore prior art.

(c) Document D15b represented the closest prior art. It described a protocol for a Phase 3 clinical study involving liposomal irinotecan (MM-398), alone or in combination with fluorouracil and leucovorin for use in treating metastatic pancreatic cancer in patients with failed gemcitabine based therapy. The combined dosage regimen proposed in document D15b further differed from the dosage regimen defined in claim 1 of the main request in that the order of administration was not specified and in that it involved administration of 400 mg/m² of leucovorin instead of 200 mg/m² of the l-form.

The problem to be solved was the provision of effective and safe treatment for the defined indication. In view of the triple treatment described in the prior art any advantage of triple treatment over monotherapy could not be taken into account. Moreover, improvement over monotherapy was not plausibly derivable from the application as filed.

Document D15b did not present any results of the described treatment, but the report that the triple dosage regimen was tested in a clinical study provided for a reasonable expectation of success. The skilled person was not discouraged from carrying out the therapeutic protocol by any particular reason and the confirmation that the dosage regimen of the clinical trial provided both efficacy and safety of treatment could not be regarded as inventive.

The defined sequence of administration corresponded to the order of administration of irinotecan, leucovorin and fluorouracil as described in documents D2-D6 and therefore represented an obvious option. Furthermore, equivalence of the 400 mg/m^2 leucovorin with the 200 mg/m^2 of the l-form was not contested.

Document D15b did not explain the meaning of "MM-398", but from document D13 "MM-398" was known to be nanoliposomal irinotecan. The application as filed further acknowledged that the particular form of liposoamal irinotecan as defined in claim 1 was known from US8147867.

Claim 1 of the main request did therefore not meet the requirement of inventive step.

V. The following additional documents were cited during the appeal proceedings:

D23 : Declaration of Amy McKee, M.D.
D23A: Hoos et al., J Clin Oncol 31:3432-3438
D23B: Clinical Development Success Rates 2006-2015, published by Biotechnology Innovation Organization (BIO)
D24 : Declaration of Bruce Belanger, Ph.D.

D15c: EU clinical trial database for NAPOLI-1 study from 12 October 2012
D25 : Pin-Yuan Chen et al, Neuro-Oncology 15(2):189–197 (December 2012)
D26 : Drummond DC et al, Cancer Res 2006; 66: 3271–3277 (2006)
D27 : Roy AC et al, Annals of Oncology 24(6): 1567-1573 (February 2013)

D28 : Svenson S, Current Opinion in Solid State and Materials Science, 16(6) pp 287-294 (October 2012)
D29 : Makrilia N et al, JOP. Journal of the Pancreas, 12(2) pp 110-113 (2011)
D30 : Chen LT et al, Journal of Clinical Oncology, 30(4 Suppl) pp 613-613 (February 2012)
D31 : Cunningham D et al, Journal of Clinical Oncology 29 (4 Suppl): 6-6 (2011)
D32 : Gerber DE, Journal of Thoracic Oncology 7(12) Supplement 5_ S387-S389 (December 2012)
D33 : Noble et al, Cancer Res 2006; 66: (5). March 1, 2006
D34 : Krauze MT et al, Neuro-Oncology 9(4): 393-403 (2007)
D35 : Mullard A, Nature Reviews Drug Discovery, vol. 17, page 777 (2018)
D36 : The Medicines for Human Use (Clinical Trials) Regulations (MHCTR) 2004.

D37 : Expert declaration of Carla Schoonderbeek
D37A: Directive 2001/20/EC
D38 : Expert declaration of Grant H. Castle, Ph.D.
D38A: Communication from the Commission 2010/C 82/01

Documents D23-D24 and D37-D38A were filed by the appellant with its statement of grounds of appeal and its further submission of 30 June 2021, respectively.

Documents D15c and D25-D36 were filed by the respondent (opponent) with its reply of 27 July 2020.

VI. In a communication pursuant to Article 15(1) RPBA issued on 9 August 2022 the Board informed the parties of its preliminary opinion, that the patent did not seem to disclose a technical contribution resulting from the distinguishing features with respect to

document D15b. In this context the Board questioned whether on the basis of the post-published document D19 the problem to be solved could be formulated as the provision of improved treatment with respect to monotherapy.

The appellant's letter of 21 December 2021 was filed in response to this communication and in preparation of the oral proceedings.

Oral proceedings by videoconference were held on 18 March 2022.

VII. The arguments of the appellant relevant to the present decision can be summerized as follows:

(a) Requests relating to G 2/21

The content of post-published documents, in particular document D19, supported the appellant's arguments regarding sufficiency and inventive step. The referral G 2/21 specifically concerned the question whether post-published documents may be taken into consideration. The outcome of G 2/21 was therefore relevant to the present proceedings. The postponement of the oral proceedings or the stay in the proceedings pending G 2/21 allowed to take the outcome of G 2/21 into account and thereby served the interest of procedural economy.

(b) Admittance of documents

Documents D23, D23A, D23B and D24 were filed in reaction to the findings in the decision under appeal. Documents D37 and D38 were filed in reaction to the respondent's submission of

documents D15c, D35 and D36. The documents supported the maintained argument that document D15b did not provide a reasonable expectation of success for the triple treatment. The filing of these documents during the appeal proceedings did not compromise the respondent's right to be heard.

Documents D25-D34 were filed by the respondent to support the argument that agent "MM-398" corresponded to the particular type of liposomal irinotecan defined in claim 1 of the main request. Claim 4 of the patent as granted already defined this type of liposomal irinotecan. Documents D25-D34 should therefore already have been filed during the first instance proceedings.

(c) Priority

The agent "leucovorin" was described in document PD1 to act as a biochemical cofactor for 1-carbon transfer reactions. As evidenced by documents D1 and D1b it was common knowledge that only the l-form of leucovorin is pharmaceutically active. The skilled person would therefore understand that in PD1 the term "leucovorin" referred to the l-form of leucovorin. If the term "leucovorin" in PD1 were not considered to relate specifically to "l-leucovorin", it could only relate to the l-form or the racemate. In that case the definition of the l-form in claim 1 of the main request represented merely a selection from two disclosed alternatives, which did not affect the priority entitlement. The subject-matter of claim 1 of the main request was therefore implicitly disclosed in PD1.

(d) Sufficiency

The patent reported that the promising results from the Phase 1 trial regarding the efficacy and safety of triple therapy presented in example 6 warranted the exploration of triple therapy in the Phase 3 study of example 7, which involved the same dosage regimen as defined in claim 1 of the main request. No serious doubts based on verifiable facts had been raised regarding the suitability of the defined dosage regiment for the defined indication. The maximum tolerated dose of 80 mg/m^2 liposomal irinotecan reported for triple therapy in document D22 indicated that from the prior art the claimed dosage regimen was not obvious to the skilled person, but did not imply that with the teaching of the patent at hand the skilled person would seriously doubt the suitability of the defined dosage regimen for the defined therapeutic indication.

(e) Inventive step

Document D15b did not represent a suitable starting point in the prior art, because this document did not disclose any results of treatment of gemcitabine refractory pancreatic cancer. Moreover, document D15b referred the use of "MM-398" without further identification of this agent. In contrast, document D13 referred to results from treatment of patients with gemcitabine refractory pancreatic cancer involving the administration of liposomal irinotecan and therefore represented a more promising starting point in the prior art. Similar considerations as in T 2154/14 and T 96/20 applied. The availability of a more promising starting point

distinguished the present case from the facts underlying T 239/16 and T 2506/12.

Document D15b described a dosage regimen involving administration of "MM-398" in monotherapy as well as in triple therapy. Monotherapy had previously been reported as save and efficacious. No such data existed with respect to the triple dosage regimen of document D15b. This was confirmed by the declaration in document D24. The dosage regimen for monotherapy therefore represented a more promising starting point than the dosage regimen for triple therapy.

The relevant differences between the subject-matter of claim 1 of the main request and the triple dosage regimen described in document D15b concerned (i) the required safety and efficacy of the claimed treatment therapy and (ii) the definition of irinotecan sucrose octasulfate liposome salt injection in stead of "MM-398".

The results of example 6 of the patent indicated that the claimed triple dosage regimen provided safe treatment of gemcitabine refractory pancreatic cancer, which was more effective than monotherapy. The results reported in document D19 confirmed that the claimed triple dosage regimen presented a solution to the problem of providing such superior safe and effective treatment.

The mere disclosure of the protocol of the clinical trial in document D15b did not provide the skilled person with a reasonable expectation of safe and effective treatment. As declared in document D24, the claimed dosage regimen had not been previously

tested in patients with gemcitabine refractory pancreatic cancer. As further explained in documents D23, D37 and D38 any approval of clinical trials was based on the evaluation of the risks for the patients against the potential rather than expected benefits of treatment. In the case of the clinical trial for treatment of gemcitabine refractory pancreatic cancer described in document D15b, which represented a particularly difficult challenge as illustrated by documents D23A and 23B, such approval would reflect a hope to succeed rather than a reasonable expectation of success.

Documents D7, D12 and D13 reported successful treatment of patients with gemcitabine refractory pancreatic cancer involving administration of the maximum tolerated dose (MTD) of 120 mg/m^2 of liposomal irinotecan in monotherapy. In contrast, no previous report on the efficacy of the 80 mg/m^2 dose of liposomal irinotecan in combination treatment of such patients existed. At the same time document D22 disclosed for liposomal irinotecan in combination therapy with 5-FU and leucovorin a MTD of 80 mg/m^2 when administered once in three weeks. The prior art thereby actually dissuaded the skilled person from an expectation of successful treatment from the triple dosage regimen described in document D15b, which involved administration of 80 mg/m^2 liposomal irinotecan at the higher frequency of once every two weeks.

Moreover, the mere reference in document D15b to "MM398" did not lead the skilled person towards "irinotecan sucrose octasulfate salt liposome injection" as defined in claim 1 of the main request. In this context the skilled person could

not rely on document D25 as common knowledge. At the same time the skilled person would derive from documents D13 and D27 that "MM398" represented some liposomal formulation of irinotecan hydrochloride (CPT-11) instead of irinotecan sucrose octasulfate salt.

The skilled person would therefore not have arrived at the claimed subject-matter as solution to the problem of providing safe and effective treatment of gemcitabine refractory pancreatic cancer, let alone as solution to the problem of providing treatment which was more effective than monotherapy.

VIII. The arguments of the respondent relevant to the present decision can be summerized as follows:

(a) Requests relating to G 2/21

It was not evident that the outcome of G 2/21 was determinative for the decision in the present appeal proceedings. The postponement of the oral proceedings or the stay in the proceedings pending G 2/21 was contrary to the interest of legal certainty.

(b) Admittance of documents

Documents D23, D23A, D23B , D24 and D37 and D38 were filed in support of a line of argument presented for the first time during the appeal proceedings, namely that the mentioned triple dosage regimen in document D15b would not provide a reasonable expectation of successful therapy. These documents should have been filed during the first

instance proceedings, in which the appellant essentially argued that the triple dosage regimen therapy D15b did not represent the closest prior art. Documents D23A, D24B and D24 further lacked relevance, because these documents did not represent prior art.

Documents D25-D34 supported the argument that the skilled person was aware of the constitution of MM-398, which had only been contested for the first time by the appellant during the oral proceedings before the opposition division.

(c) Priority

The disclosure in PD1 required a dose of 200 mg/m^2 of "leucovorin" without any reference to the l-form of leucovorin as defined in claim 1 of the main request. The term "leucovorin" related according to its established meaning to the racemic mixture of the l- and d-form. As the skilled person was aware that the l-form and the racemate required different dosing, the term "leucovorin" used in PD1 could not be considered to relate to the racemic mixture as well as the l-form. The subject-matter of claim 1 of the main request could therefore not be directly and unambiguously derived from the disclosure in PD1.

(d) Sufficiency

The patent provided no experimental results of the the defined triple therapy involving the administration of 80 mg/m^2 liposomal irinotecan once in two weeks. The results reported in example 6 concerned triple therapy in which the frequency

of administration of the 80 mg/m^2 liposomal irinotecan remained undisclosed. At the same time document D22 indicated for triple treatment a maximum tolerated dose (MTD) of 80 mg/m^2 liposomal irinotecan once every three weeks. As acknowledged in the appellant's submission of 21 December 2021 the skilled person would on the basis of this MTD described in document D22 seriously doubt whether administration of 80 mg/m^2 liposomal irinotecan at the increased frequency of once every two weeks would be safe. The patent therefore failed to sufficiently disclose the suitability of the defined therapeutic regimen for the defined therapeutic indication.

(e) Inventive step

Document D15b represented a realistic starting point in the prior art by describing the protocol of a clinical trial for treatment of gemcitabine refractory pancreatic cancer involving the administration of 80 mg/m^2 "MM-398" once in two weeks in combination with 5-FU and leucovorin. With the reference to "MM-398" document D15b disclosed inherently the "irinotecan sucrose octasulfate salt liposome injection" defined in claim 1 of the main request, as was evident from documents D13 and D25-D34. This realistic starting point could not be disregarded merely on the basis of the availability of allegedly more promising prior art.

Document D15b did not disclose the therapeutic benefit resulting from the described treatment with the triple dosage regimen. The problem to be solved could be seen in the provision of safe and

effective treatment for gemcitabine refractory pancreatic cancer treatment.

As explained in T 239/16 and T 2506/12 the disclosure of a protocol for a clinical trial, in particular in case of a Phase 3 trial, implied a reasonable expectation of success of the investigated treatment based on results from prior investigations. In the case of the Phase 3 clinical involving the triple therapy described in document D15b this expectation of success was supported by results from prior investigations reported in documents D2-D6, D7, D12, D13, D22, and D30. The results reported in the patent, in particular example 6, did essentially not go beyond these results already reported in this prior art.

The skilled person would therefore have expected the triple treatment of claim 1 to be safe and effective and thus have arrived at the claimed subject-matter in an obvious manner. The higher level of effectiveness with respect to monotherapy did not result from a difference with respect to the triple therapy described in document D15b and could therefore not contribute to any inventive merit. Such higher level of effectiveness represented a mere bonus effect from what was obvious in view of the prior art.

IX. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed with the statement of grounds of appeal, which corresponded to the main request on which the decision under appeal was based.

The appellant also requested that the oral proceedings be postponed pending the decision of the Enlarged Board of Appeal in case G2/21, or that the proceedings be interrupted and stayed before any negative finding of the Board on Article 83 and 56 EPC.

The appellant further requested that documents D25-D34 not be admitted into the appeal proceedings, that documents D37, D37A, D38 and D38A be admitted into the proceedings in case the Board intended to admit documents D15c, D35 and D36, that documents D23, 23A D23B and D24 be admitted into the proceedings and if not, that documents D15c, D35 and D36 not be admitted into the proceedings.

X. The respondent requested that the appeal be dismissed.

The respondent further requested that the oral proceedings not be postponed.

The respondent also requested that documents D23, D23A, D23B, D24, D37, and D38 not be admitted into the appeal proceedings and that documents D25-D34 be admitted into the proceedings.

Reasons for the Decision

1. Admittance of documents filed during the appeal procedure

1.1 Documents D23, D23A, D23B and D24 concern expert declarations with annexes filed by the appellant with its statement of grounds of appeal to further support the argument that contrary to the finding in the decision under appeal (see section 5.7.3) the protocol

for the Phase 3 clinical trial in document D15b did not provide the skilled person with a reasonable expectation of success.

The Board considers the filing of documents D23, D23A, D23B and D24 a legitimate response to the decision under appeal and therefore does not hold these documents inadmissible (Article 12(4) RPBA 2007). Accordingly, these documents are part of the appeal proceedings.

1.2 Documents D25-D34 were filed by the respondent with its reply to the appeal to support its argument that the product name "MM-398" was at the time of publication of document D15b well known to relate to liposomal irinotecan, in particular irinotecan sucrose octasulfate salt liposome injection. In the statement of grounds of appeal the appellant maintained its argument, which it had first presented during the oral proceedings before the opposition division, that document D15b only referred to "MM-398" and that no prior art then on file identified MM-398 as irinotecan sucrose octasulfate salt liposome injection.

Documents D15c, D35 and D36 were filed by the respondent with its reply to the appeal to argue that contrary to opinion expressed in document D23 the international Phase 3 clinical trial to which document D15b related provided a reasonable expectation of success.

The Board considers the filing of documents D25-D34, D15c, D35 and D36 a legitimate response to the statement of grounds of appeal and therefore does not hold these documents inadmissible (Article 12(4) RPBA

2007). Accordingly, these documents are part of the appeal proceedings.

1.3 Documents D37, D37A, D38 and D38A were filed by the appellant in support of the argument that the report of the Phase 3 clinical trial as in documents D15b and D15c did not provide the skilled person with a reasonable expectation of success. The Board considers the filing of documents D37, D37A, D38 and D38A as a legitimate response to the reply to the appeal and has therefore admitted these documents into the appeal proceedings (Article 13(1) RPBA 2020).

2. Priority

The appellant did not dispute that the disclosure in PD1 (see for instance claim 3) required a dose of 200 mg/m^2 of "leucovorin" without any explicit reference to the l-form of leucovorin as defined in claim 1 of the main request.

Documents D1 and D1b present product labels describing levoleucovorin and leucovorin. These documents represent common general knowledge and have been relied upon as such by both parties. According to document D1 (see paragraph 11) the term "levoleucovorin" relates to the l-form, whereas the term "leucovorin" designates according to document D1b the racemic mixture of the l- and d-form. Whilst document D1b states that the l-form is the biologically active compound, the document nevertheless refers to "leucovorin" as not requiring reduction in order to participate in reactions (see D1b, page 1, left column, under "CLINICAL PHARMACOLOGY"). Document D1b thereby demonstrates that in references to the biological activity the term "leucovorin" may be used in an ambivalent manner .

Having regard to the meaning and use of the terms "levoleucovorin" and "leucovorin" in documents D1 and D1b the skilled person could therefore not directly and unambiguously derive from document PD1 that the leucovorin actually intended for the described use in a dose of 200 mg/m^2 was the l-form in stead of the racemic mixture. This assessment is not affected by the mere reference in document PD1 to biological effects of "leucovorin" ("*Leucovorin acts as biochemical cofactor for 1-carbon transfer reactions...*";see PD1, page 11, lines 9-17 and page 31, line 26 to page 32 line 3), because in such context the term "leucovorin" may be well be used in an ambivalent manner as demonstrated in document D1b.

Moreover, based on the common knowledge that the l-form is the biologically active compound the skilled person would realize that for a desired biological effect the racemic mixture requires a different dose than the l-form. Accordingly, the skilled person could not directly and unambiguously derive from the dosage regimen involving a dose of 200 mg/m^2 of "leucovorin" described in document PD1 that actually two alternatives were intended, namely a dose of of 200 mg/m^2 of leucovorin as racemic mixture and a dose of 200 mg/m^2 of leucovorin in the l-form.

Accordingly, the Board considers that the subject-matter of claim 1 of the main request involving the definition of a dose of 200 mg/m^2 of leucovorin (l-form) is not entitled to the priority of PD1.

Documents D4,D8, D10 and D15b, which became available after the claimed first priority, but before the claimed second priority, therefore represents prior art under Article 54(2) EPC.

3. Sufficiency of disclosure

The patent teaches that the defined triple therapy regimen is suitable for treatment of gemcitabine resistant pancreatic cancer and presents the design for a Phase 3 trial as disclosed in example 7 of the patent (see paragraphs [0083]-[0177] by which this teaching can be verified. The Board does not recognize that this teaching is compromised by any serious doubt based on verifiable facts.

To the contrary, the Board considers that this teaching is plausible taking account of:

- the efficacy of administration of 80 mg/m^2 MM-398 in combination with 5-FU and leucovorin in treatment of patients with pancreatic cancer during the Phase 1 trial reported in example 6 of the patent (see paragraphs [0081]-[0082])

- the known efficacy of the triple combination of non-liposomal irinotecan with 5-FU and leucovorin in treatment of patients with gemcitabine-refractory pancreatic carcinoma in the so-called FOLFIRI regimen as reported in documents D2, D3, D5 and D6 and referred to in the patent (see paragraph [0003], see also the application as filed page 1).

The respondent argued that document D22 indicated a MTD for liposomal irinotecan in triple therapy of 80 mg/m^2 administered only once every three weeks and thereby justified according to the appellant's own admission serious doubts whether the administration of the liposomal irinotecan at a dose of 80 mg/m^2 in triple therapy once every two weeks would be tolerable. This

argument is not considered convincing, because the triple therapy reported in document D22 involved administration of liposomal irinotecan once every three weeks with weekly administration of 5-FU and leucovorin and thus substantially differed from the triple dosage regimen of claim 1 of the patent. This assessment of the relevance of the actual content of document D22 with respect to the issue of sufficiency of disclosure in the patent is not affected by any argument by the appellant that having regard to the MTD reported in document D22 the suitability of the claimed dosage regimen for the defined treatment was not obvious from the prior art.

In line with the principles established in the jurisprudence of the Boards of appeal of the EPO (see Case Law of the Boards of Appeal of the EPO, 9th Edition 2019, sections II.C.7.1.4, II.C.7.2 and II.C.9) the Board therefore concludes that the main request complies with the requirement of Article 83 EPC.

4. Inventive step

4.1 Starting point in the prior art

4.1.1 In the decision under appeal the subject-matter of claim 1 of the main request is denied an inventive step starting from document D15b as closest prior art.

Document D15b describes a randomized, open label Phase 3 study of "MM-398" in monotherapy (arm A, experimental monotherapy) or "MM-398" in combination with 5-Fluorouracil (5-FU) and Leucovorin (arm C, experimental triple therapy) versus therapy with 5-FU and Leucovorin (Arm B, active comparator) in treatment of patients with metastatic pancreatic cancer who have failed prior

gemcitabine-based therapy. Arm A involves administration of 120 mg/m^2 "MM-398" once in three weeks and Arm C involves administration of 80 mg/m^2 "MM-398", 2400 mg/m^2 5-FU and 400 mg/m^2 leucovorin every two weeks.

The appellant contested the finding in the decision under appeal that the triple therapy described in document D15b represents a suitable starting point in the prior art, because document D15b failed to disclose effective treatment of pancreatic cancer and merely referred to "MM-398" as one of the agents to be used. In its view document D13 represented a more pertinent starting point, because it reported the actual efficacy of liposomal irinotecan by reference (30) to the Phase 2 study of monotherapy involving administration of 120 mg/m^2 liposomal irinotecan every three weeks as described in document D12.

4.1.2 The Board recalls that the problem solution approach implies that in case an inventive step can be recognized starting from a particular item of prior art which is convincingly identified as most promising starting point and thus represents the closest prior art, attempts to argue a lack of inventive step starting from less promising starting points are bound to fail. However, in case an inventive step is denied starting from a realistic particular item of prior art, the mere argument that the claimed subject-matter nevertheless involves an inventive step in view of an allegedly closer prior art, may not be persuasive, because in such case the allegedly closest prior art may well represent a starting point that is in fact not more promising.

4.1.3 The patent describes in example 7 a protocol for a Phase 3 trial for assessing the claimed triple dosage regimen in treatment of gemcitabine refractory pancreatic cancer. It is not in dispute that the patent itself does not present experimental results from this Phase 3 trial.

The patent reports in example 6 merely beneficial results from administration of 80 mg/m^2 liposomal irinotecan in combination with 5-FU and leucovorin in patients with pancreatic cancer in the context of a Phase 1 trial without mention of the frequency of administration. As acknowledged by the appellant with the filing of document D24, the claimed specific triple dosage regimen involving administration of liposomal irinotecan, 5-FU and leucovorin once every two weeks had, as a matter of fact, not been tested prior to the Phase 3 trial ("NAPOLI-1"). The prior testing of triple therapy with liposomal irinotecan in a Phase 1 trial actually involved administration of liposomal irinotecan once every three weeks with weekly administration of 5-FU and leucovorin (see D24, sections 6-8).

In view of the fact that the patent itself does not present experimental results specifically demonstrating the therapeutic effect of the claimed triple dosage regimen involving administration once every two weeks the Board considers that the disclosure of the triple dosage regimen in document D15b cannot be disqualified as a realistic starting point in the prior art on the ground that it does not report results of the described treatment. The facts of the present case differ in this respect from the facts in decisions T 2154/14 and T 96/20, in which the original disclosure did present experimental results specifically demonstrating the

therapeutical effect of the defined treatment. The Board further observes that in decisions T 239/16 and T 2506/12 protocols for clinical trials without disclosure of results were regarded as suitable starting points in the prior art. In view of the considerations in section 4.1.2 above the Board finds the applicant's argument, that in contrast to the present case in T 239/16 and T 2506/12 no further starting points were under consideration, not persuasive.

The Board further observes that the triple therapy of Arm C of document D15b is evidently closer to the claimed triple dosage regimen than the monotherapy of arm A.

Document D15b exclusively uses the code-name "MM-398" for one of the agents to be administered in the trial. However, at the time of publication of document D15b the skilled person was able to identify "MM-398" as a known and available product, namely the liposomal formulation containing nano-sized irinotecan crystals complexed with sucrose octasulfate corresponding to the liposomal irinotecan defined in claim 1 of the main request. This is evident from document D25 and the reference (15) therein to document D26 describing its preparation (see D25 page 190 right column under "Investigational Agent"). The Board considers that when confronted with the teaching of document D15b the person skilled would thus be aware of the identity of "MM-398", if not by direct knowledge of document D25 then at least by the ability to find the information in document D25 (see Case Law of the Boards of Appeal of the EPO, *supra*, section I.C.2.8.4). The use code-name "MM-398" in document D15b does therefore not further

affect the status of this document as a realistic starting point in the prior art.

Accordingly, the Board agrees with the finding in the decision under appeal that the triple therapy of arm C described in document D15b represents a realistic starting point in the prior art.

4.2 Problem to be solved

4.2.1 The differences between the claimed subject-matter and arm C of the trial protocol described in document D15b concern

(a) the actual effective and safe treatment of the patients

(b) specification of the order in which the drugs are administered

(c) the distinction in the starting dose of liposomal irinotecan depending on the status of the UGT1A1*28 allele and

(d) the definition of the l-form in claim 1 of the main request.

The appellant did not submit arguments regarding the relevance of the above identified differences b), c) and d) to contest the conclusion in the decision under appeal that the claimed subject-matter lacked an inventive step. In stead, the appellant relied on the definition of liposomal irinotecan as irinotecan sucrose octasulfate liposome salt injection as an additional difference relevant for the assessment of inventive step. However, as explained in section 4.1.3

above, the skilled person who is confronted with the teaching of document D15b would be aware that "MM-398" corresponds to irinotecan sucrose octasulfate liposome salt injection. The definition of the type of liposomal irinotecan in claim 1 does therefore not represent a difference with the prior art.

In view of the difference that document D15b describes a protocol for treatment without reporting the results of the treatment the Board considers that the problem to be solved may be formulated as the provision of actually effective and safe treatment of the defined patients suffering from pancreatic cancer.

4.2.2 The Board appreciates that the post-published document D19 (see abstract) indicates for the claimed triple dosage regimen favourable efficacy, including a longer median overall survival rate (6.1 months versus 4.9 months), in comparison with monotherapy as described in arm A of document D15b. However, as explained in section 4.1.3 above, the triple dosage regimen described for arm C in document D15b represented already a realistic starting point in the prior art. The actual level of efficacy of the claimed dosage regiment has not been shown to be influenced by any difference with respect to the triple dosage regimen of arm C in document D15b. The Board therefore considers that the level of efficacy described in document D19 does not allow to further qualify the problem to be solved.

4.3 Assessment of the solution

4.3.1 As explained in document D23 (see D23, page 5, section 27), the development of therapy of gemcitabine refractory pancreatic cancer represents a particular

challenge taking account of the poor prognosis and low success rates of clinical trials (see documents D23A and D23B). Documents D37 and D38 confirm in this context that the approval of a clinical study depends on the assessment of the foreseeable risks in relation to the anticipated benefit in terms of relevance of the findings, which does not necessarily imply an expected positive outcome and does not represent a scientific advice on the development programme of the investigational product tested (see D37 page 6, section 28; see D38, page 4 under "Final comments" with reference to document D38A paragraph 18). The Board is therefore not convinced that the mere fact that document D15b reports the testing of the dosage regimen in a Phase 3 clinical trial already by itself provided the skilled person with a reasonable expectation that the treatment under investigation would be safe and effective. The considerations in T 239/16 regarding the expected success following the approval of a clinical trial (see section 6.5) are evidently closely linked to the further circumstances of the case decided therein and cannot be extrapolated to the present appeal case. The same applies with respect to similar considerations in T 2506/12 (see section 3.15).

4.3.2 However, the presentation of the triple dosage regimen in document D15b is not to be considered by itself, because the publication of document D15b was preceded by reports of beneficial triple treatment of gemcitabine refractory pancreatic cancer patients involving non-liposomal irinotecan with 5-FU and leucovorin, the FOLFIRI regimen, in Phase 2 studies (see documents D2-D6) as well as the report of benefits from treatment of such patients with liposomal irinotecan with or without 5-FU and leucovorin in Phase 1 investigations (see documents D12 and D13).

In this context the Board takes the view that in as far as the patent proposes the claimed dosage regimen to be safe and effective in view of considerations based on information which was essentially already available, the same considerations apply in the assessment whether following the presentation of the clinical trial in document D15b a positive outcome for the described triple therapy could reasonably be expected.

The patent makes reference to the known FOLFIRI regimen involving triple treatment including non-liposomal irinotecan (see paragraph [0003]). The patent further relies on the promising efficacy and safety of triple combination treatment in the Phase 1 trial of example 6 to propose the Phase 3 study of example 7 involving the claimed dosage regimen (see paragraph [0083]). However, example 6 does not mention the dose of the administered 5-FU and leucovorin nor the two weekly dosing cycle of the defined drugs. As acknowledged in document D24 no clinical testing of the actually claimed dosage regimen had, as a matter of fact, taken place before the Phase 3 trial. According to the Board the patent thus proposes the claimed dosage regimen in view of considerations based on information which was essentially already available. Based on the same considerations the skilled person would also have expected the triple treatment of document D15b to be safe and effective and by consequence consider the subject-matter of claim 1 of the main request obvious in view the prior art.

The appellant's argument that the skilled person would be dissuaded from expecting safe and effective treatment with the triple dosage regimen of document D15b in view of the information in document D22 is not

considered convincing. Document D22 discloses for liposomal irinotecan a MTD of 80 mg/m^2 when administered once in three weeks in combination with weekly administration of 5-FU and leucovorin. The triple dosage regimen described in document D15b indeed involves administration of 80 mg/m^2 liposomal irinotecan at the higher frequency of once every two weeks. However, the triple dosage regimen of document D15b further involved administration of 5-FU and leucovorin at a reduced frequency with respect to document D22. Taking account of these differences the skilled person would in view of document D22 not have expected excessive toxicity of the triple dosage regimen of document D15b, which is in line with the status of the investigation described in document D15b as a Phase 3 study.

Accordingly, the Board concludes that in view of the prior art the skilled person would have arrived at the claimed subject-matter in an obvious manner and that the subject-matter of claim 1 of the main request does therefore not involve an inventive step.

5. Requests relating to G 2/21

5.1 In T 116/18 the following questions were referred to the Enlarged Board of Appeal:

If for acknowledgement of inventive step the patent proprietor relies on a technical effect and has submitted evidence, such as experimental data, to prove such an effect, this evidence not having been public before the filing date of the patent in suit and having been filed after that date (post-published evidence):

- Should an exception to the principle of free evaluation of evidence be accepted in that post-published evidence must be disregarded on the ground that the proof of the effect rests exclusively on the post-published evidence?

- If the answer is yes (the post-published evidence must be disregarded if the proof of the effect rests exclusively on this evidence), can the post-published evidence be taken into consideration if, based on the information in the patent application in suit or the common general knowledge, the skilled person at the filing date of the patent application in suit would have considered the effect plausible (ab initio plausibility)?

- If the answer to the first question is yes (the post-published evidence must be disregarded if the proof of the effect rests exclusively on this evidence), can the post-published evidence be taken into consideration if, based on the information in the patent application in suit or the common general knowledge, the skilled person at the filing date of the patent application in suit would have seen no reason to consider the effect implausible (ab initio implausibility)?

The referral is pending as G 2/21.

5.2 The Board has rejected the appellant's request to postpone the oral proceedings pending G 2/21, because it was not evident on beforehand that answers to the referred questions formulated in T 116/18 would be determinative to the decision in the present appeal proceedings.

5.3 As explained in section 3 above, the Board concludes that the main request meets the requirement of sufficiency of disclosure taking account of the teaching in the patent and without reliance on any post-published documents. This conclusion is not affected by answers to the referred questions, which concern the consideration of post-published evidence for an technical effect relied upon in support of acknowledgement of inventive step.

As explained in section 4 above, the Board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step irrespective whether or not the post-published documents relied upon by the appellant, in particular document D19, are considered as evidence for the level of efficacy of the claimed dosage regimen. This conclusion is therefore also not affected by answers to the referred questions

Taking account of the interest of procedural economy as well as the interest of legal certainty the Board has therefore rejected the appellant's request for an interruption and stay of the proceedings before any negative finding of the Board on Article 83 and 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated