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Datasheet for the decision of 21 October 2021

Case Number: T 1806/18 - 3.3.01

Application Number: 10781781.9

Publication Number: 2501384

IPC: A61K31/506, A61P35/00, A61K9/00, C07D239/69

Language of the proceedings: EN

Title of invention:

METHOD OF TREATING PROLIFERATIVE DISORDERS AND OTHER PATHOLOGICAL CONDITIONS MEDIATED BY BCR-ABL, C-KIT, DDR1, DDR2 OR PDGF-R KINASE ACTIVITY

Patent Proprietor:

Novartis AG

Opponents:

Fresenius Kabi Deutschland GmbH
Hamm&Wittkopp Patentanwälte PartmbB
TEVA PHARMACEUTICAL INDUSTRIES, LTD.
Intas Pharmaceuticals Ltd.
Generics (U.K.) Limited

Headword:

Nilotinib for treating chronic myeloid leukemia / NOVARTIS

Relevant legal provisions:
EPC Art. 54, 56
RPBA Art. 12(4)
RPBA 2020 Art. 13(2)

Keyword:
Main request - novelty (yes)
Main request - inventive step - reasonable expectation of success (no)
Late-filed documents - admitted (no)

Decisions cited:
T 0056/87, T 0158/96, T 2436/10, T 2506/12, T 0239/16

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Beschwerdekammern

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Case Number: T 1806/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 21 October 2021

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 17 May 2018 revoking European patent No. 2501384 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: S. Albrecht
L. Bühler

Summary of Facts and Submissions

I. European patent No. 2 501 384 ("the patent") was granted with three claims.

II. Opposition proceedings were based on the grounds for opposition under Article 100(a) EPC for lack of novelty and lack of inventive step and under Article 100(b) and (c) EPC.

III. The following documents, cited during the opposition and appeal proceedings, are referred to below:

D1: European Medicines Agency, "P/60/2009: European Medicines Agency decision of 27 March 2009 on the agreement of a Paediatric Investigation Plan and on the granting of a deferral and on the granting of a waiver for nilotinib (Tasigna) (EMEA-000290-PIP01-08) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended", 18 May 2009 (11 pages in total)

D3: V. Niblett, "A Nurse's Guide to Dosage Calculation: Giving Medications Safely", Lippincott Williams & Wilkins, 2006, pages xvii-xxi and 127-31

D4: C. Simpson and P. Hall, "Rx: Reading and Following the Directions for all Kinds of Medication", 1st edition, New York, The Rosen Publishing Group, 1994, table of contents and pages 42-3

D5: M. A. Koda-Kimble *et al.*, "Handbook of Applied Therapeutics", 8th edition, Lippincott Williams & Wilkins, 2007, pages viii-xi and 91.1

D6: U.S. Department of Health and Human Services, Food and Drug Administration, "Guidance for Industry. Food-Effect Bioavailability and Fed Bioequivalence Studies", December 2002 (12 pages in total)

D18: O. Q. P. Yin *et al.*, "Effects of Yoghurt and Applesauce on the Oral Bioavailability of Nilotinib in Healthy Volunteers", J Clin Pharmacol 51, 2011, 1580-6

D21: Tasigna® (nilotinib) capsules, United States Prescribing Information, August 2009, 2-22

D36: EMEA, Scientific Discussion of Tasigna®, 2007, 1-52

D58: B. D. Damle *et al.*, "Effect of Food on the Oral Bioavailability of Didanosine from Encapsulated Enteric-Coated Beads", J Clin Pharmacol 42, 2002, 419-27

D61: Copy of decision T 2506/12 of 4 October 2016

D65: Official journal of the European Union of 27 December 2006, "Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006", pages L 378/1, 378/7 and 378/8

D65a: Official journal of the European Union of 27 December 2006, "Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006", pages L 378/1 to L 378/19

D70: Copy of decision T 239/16 of 13 September 2017

D71: Expert opinion of Carla Schoonderbeek

D72: European Medicines Agency, "Note for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99)", January 2001, 1-13

D74: Official journal of the European Union of 24 September 2008, "Communication from the Commission - Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of compliance check and on criteria for assessing significant studies", pages C 243/1 to C 243/12

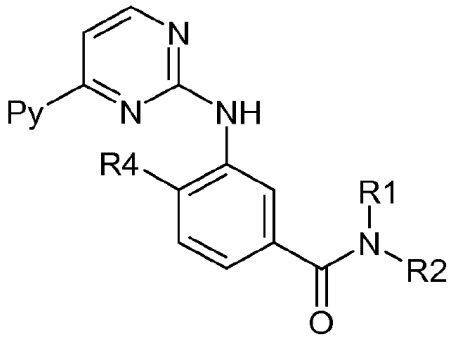
D75: A. M. Tamboli *et al*., "An Overview on Bioequivalence: Regulatory Consideration for Generic Drug Products", Journal of Bioequivalence & Bioavailability 2(4), 6 September 2010, 086-92

D76: I. Kanfer and L. Shargel, "Generic Drug Product Development. International Regulatory Requirements for Bioequivalence", Taylor & Francis Group, 2010, pages xviii-xix, 3-5, 77, 172 and 195

IV. The opposition division's decision to revoke the patent was based on a single set of claims filed as a main request on 21 February 2018.

Claim 1 of this request reads:

"1. A pyrimidylaminobenzamide of formula (I)



(I),

wherein
Py denotes 3-pyridyl,
R_1 represents hydrogen,
R_2 represents 5-(4-methyl-1 H-imidazol-1-yl)-3-(trifluoromethyl)-phenyl; and
R_4 represents methyl;
or a pharmaceutically acceptable salt thereof, for use in the treatment of chronic myeloid leukemia (CML), wherein the compound of formula (I) or a pharmaceutically acceptable salt thereof and, optionally, pharmaceutically acceptable carriers, is orally administered dispersed in apple sauce."

The pyrimidylaminobenzamide of formula (I) recited in this claim is also known by the international non-proprietary name "nilotinib".

In the appealed decision, the opposition division found, *inter alia*, that the claimed subject-matter was novel over document D1 but lacked an inventive step based on document D21 as the closest prior art.

V. The patent proprietor ("appellant") lodged an appeal against the opposition division's decision.

VI. With the statement setting out the grounds of appeal, the appellant requested that the decision under appeal

be set aside and that the patent be maintained inamended form on the basis of the set of claims of themain request underlying the impugned decision or, alternatively, on the basis of the set of claims filed as the first auxiliary request with the statement setting out the grounds of appeal.

VII. With their replies to the statement of grounds of appeal, all five opponents ("respondents") requested that the appeal be dismissed.

VIII. In a communication pursuant to Article 15(1) RPBA 2020 dated 28 September 2020 ("communication"), the board drew the parties' attention to the points to be discussed during the oral proceedings and provided a preliminary opinion acknowledging novelty of claim 1 of the main request.

IX. Oral proceedings took place before the board on 21 October 2021 as a mixed-mode hearing. All five respondents attended the proceedings via videoconference; the appellant and the board were physically present. At the end of the oral proceedings, the Chair announced the board's decision.

X. The appellant's written and oral submissions relevant to the present decision may be summarised as follows.

Admittance of documents D65a, D71 and D74 (filed by the appellant)

These documents were to be admitted. Documents D71 and D74 had been filed at the first possible opportunity in reaction to the discussion of safety issues based on document D65 which had taken place for the first time

during the oral proceedings before the opposition division.

The filing of the full regulation (EC) No 1901/2006 as document D65a was justified in view of the fact that document D71 referred to parts of this regulation not contained in document D65.

Admittance of documents D75 and D76 (filed by respondent III)

These documents were not to be admitted under Article 13(2) RPBA 2020. Respondent III did not provide any cogent reasons why there were exceptional circumstances justifying the late filing of these documents.

Main request - claim 1 - novelty over document D1

The opposition division was correct in finding the claimed invention novel over the disclosure of the paediatric investigation plan in document D1, annex I, section C ("PIP of document D1"). The only clinical study of this plan involving the use of nilotinib dispersed in apple sauce was a bioavailability study to be conducted with healthy volunteers, not in patients afflicted with CML.

Main request - claim 1 - inventive step

The claimed invention would not have been obvious starting from document D21 as the closest prior art or, as argued by the respondents, starting from the bioavailability study of the PIP of document D1 as the closest prior art.

Starting from the respondents' choice of the closest prior art, the technical problem to be solved was the provision of an effective treatment of CML. In line with decision T 2506/12, the term "effective" implied that the medical treatment must not cause unacceptable harm.

The solution proposed in claim 1 would not have been obvious in light of the cited prior art. It was well known that the concomitant administration of Tasigna® nilotinib capsules with food could cause serious, life-threatening complications in CML patients. For this very reason, documents D21 and D36 evidencing common general knowledge instructed against taking these capsules with food. From common general knowledge, the skilled person was also aware of the fact that food could alter the bioavailability of drugs by various means and that the relative direction and magnitude of such food effects on the bioavailability of drugs like nilotinib were next to impossible to predict without conducting a fed bioequivalence study. In light of these facts and absent any bioequivalence study using apple sauce as food, the skilled person would not have had any expectation on the relative direction and magnitude of the food effect of apple sauce on nilotinib. As a consequence, document D1 combined with common general knowledge would not have led the skilled person to reasonably expect that nilotinib dispersed in apple sauce would solve the technical problem posed.

Concerning the legal framework of the PIP of document D1, the opposition division was incorrect in assuming that the European Medicines Agency ("EMA") had made a safety assessment before approving this PIP. Contrary to the respondents' view, the EMA's approval of this

PIP would not have created a reasonable expectation of success.

Regarding decision T 239/16 relied upon by the respondents, the circumstances of the case underlying this decision were not comparable to those of the case at issue. Hence, the conclusions reached in this decision did not apply.

XI. The respondents' written and oral submissions relevant to the present decision may be summarised as follows.

Admittance of documents D65a, D71 and D74

These documents should be rejected as late-filed. Safety issues had been discussed in the appellant's reply to the notices of opposition. Issues concerning document D65 could have been addressed by the appellant in writing within the two-month period prior to the oral proceedings before the opposition division.

Admittance of documents D75 and D76

These documents were common general knowledge documents submitted in reply to the appellant's letter of 19 July 2019. They did not raise any new issues and were therefore to be admitted.

Main request - claim 1 - novelty over document D1

Respondent I

The subject-matter of claim 1 lacked novelty over the disclosure of the PIP in section C of annex I of document D1.

Respondent II

Document D1 implicitly disclosed the subject-matter of claim 1 in annex I, section C. The fact that the therapeutic efficacy of the claimed medical use was not mentioned in this document did not alter this finding, the reasons being as follows.

(a) The disclosure of the patent did not go beyond the content of document D1. Both described the administration of nilotinib dispersed in apple sauce, and in both cases the skilled person relied on the prior art for the therapeutic effect.

(b) The claimed subject-matter was not directed to a further indication for nilotinib but to a different route of administration. In line with decision T 2436/10 (point 4.3 of the Reasons), it was not necessary that document D1 present any experimental results to be novelty-destroying for the claimed subject-matter.

Main request - claim 1 - inventive step

Document D1 as the closest prior art

Starting from the bioavailability study of the PIP of document D1, the technical problem to be solved was the provision of a medical use for the described mixture of nilotinib and apple sauce. Alternatively, the technical problem could be seen as the provision of an effective, easy-to-swallow treatment of CML or as the provision of an effective treatment for children with CML having difficulties swallowing intact nilotinib capsules.

The solution proposed in claim 1 would have been obvious for the following reasons.

(a) Disclosure of document D1 combined with common general knowledge

At the priority date of the patent, nilotinib was authorised for the treatment of CML. Accordingly, the skilled person would have clearly expected that the formulation of nilotinib in apple sauce proposed in the PIP of document D1 would be effective in the treatment of CML. In this regard, the facts of the case at issue were similar to those considered by the competent board in decision T 239/16, in which it was held that regulatory authorities would only authorise trials that had a reasonable expectation of success.

The unpredictability of the food effect of apple sauce on nilotinib bioavailability relied upon by the appellant had been removed by the disclosure of the results of the food-effect study in document D36. The trend emerging from these results led to a reasonable expectation that the food effect of apple sauce on nilotinib bioavailability would be trivial.

Should the skilled person nevertheless have considered the possibility of apple sauce causing serious adverse events in CML patients by increasing the bioavailability of nilotinib, they would have simply halved the dose of nilotinib.

(b) Legal framework of the PIP of document D1

The claimed subject-matter would moreover have been obvious when considering the PIP of document D1 in the context of its legal framework set out in document D65a.

(c) Identity of the PIP applicant

The fact that the PIP applicant was the originator of the Tasigna capsule formulation would have led the skilled person to reasonably expect that the formulation of nilotinib in apple sauce proposed in the PIP of document D1 would be effective in the treatment of CML.

Document D21 as the closest prior art

The solution proposed in claim 1 would furthermore have been obvious when starting from document D21 as the closest prior art.

XII. The parties' final requests relevant for the present decision were as follows.

The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the set of claims of the main request underlying the impugned decision or, alternatively, on the basis of the set of claims filed as the first auxiliary request with its statement setting out the grounds of appeal. The appellant further requested that documents D65a, D71 and D74 be admitted into the proceedings and that documents D75 and D76 not be admitted into the proceedings.

The respondents requested that the appeal be dismissed and that the first auxiliary request not be admitted

into the proceedings. Respondent III additionally requested that documents D65a, D71 and D74 not be admitted into the proceedings.

Reasons for the Decision

2. The appeal is admissible.

Procedural issues

3. Admittance of documents D65a, D71 and D74 into the proceedings

3.1 In the current case, the statement setting out the grounds of appeal was filed before 1 January 2020, the replies being filed in due time. Thus, Article 12(4) RPBA 2007 applies.

3.2 In point 1.3 of its communication, the board indicated its intention not to exclude these documents from the appeal proceedings under Article 12(4) RPBA 2007 and gave reasons.

3.3 At the oral proceedings, the respondents did not present any arguments on this issue.

3.4 As a consequence, the board sees no reason to deviate from its preliminary opinion. Therefore, documents D65a, D71 and D74 form part of the basis of the appeal proceedings (Article 12(4), second half-sentence, RPBA 2007).

4. Admittance of documents D75 and D76 into the proceedings - Article 13(2) RPBA 2020

4.1 With its submission of 5 August 2020, respondent III filed documents D75 and D76, i.e. after notification of the summons to oral proceedings.

4.2 At the oral proceedings, respondent III explained that documents D75 and D76 were common general knowledge documents that had been submitted in reply to the appellant's letter of 19 July 2019. Their filing merely served to support arguments that had been presented in the reply to the statement of grounds of appeal on the meaning of the term "bioequivalence". Hence, these documents did not raise any new issues and should be admitted.

4.3 The board considers the filing of documents D75 and D76 to be an amendment of respondent III's appeal case within the meaning of Article 13(2) RPBA 2020, thus giving the board discretion as to their admittance.

4.4 The board notes that documents D75 and D76 were submitted more than a year after the appellant's letter of 19 July 2019. In the absence of any justification from respondent III why these documents could not have been filed earlier, exceptional circumstances within the meaning of Article 13(2) RPBA 2020 cannot be acknowleged.

4.5 The board therefore decided not to admit documents D75 and D76 into the appeal proceedings in accordance with Article 13(2) RPBA 2020.

Main request

5. The subject-matter of claim 1

5.1 Independent claim 1 is a purpose-limited product claim within the meaning of Article 54(5) EPC. The product is a dispersion of the active ingredient nilotinib or a pharmaceutically acceptable salt thereof ("nilotinib (salt)") in apple sauce, as correctly noted by the opposition division (see point 8.9.2.1. of the impugned decision). The claimed purpose is the oral treatment of CML.

5.2 Hence, the subject-matter of claim 1 is a medical use claim requiring, i*nter alia*, the oral administration of nilotinib (salt):

(a) in the form of a dispersion in apple sauce

(b) to patients afflicted with CML

6. Novelty (Article 54 EPC)

6.1 In the opinion of respondents I and II, the disclosure of the PIP in annex I, section C, of document D1 anticipates the subject-matter of claim 1.

Content of document D1

6.2 Document D1 discloses the EMA decision of 27 March 2009 ("EMA decision") on the agreement of a PIP and on the granting of a deferral and on the granting of a waiver for nilotinib (Tasigna) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended ("PIP regulation"). Tasigna is the trade name for a hard capsule containing nilotinib as the pharmaceutically active ingredient ("Tasigna capsule").

6.3 The EMA decision comprises two main parts:

(a) the text of the decision itself (see pages 2 to 4 of document D1)

(b) the opinion of the Paediatric Committee ("PDCO") on the agreement of the PIP of document D1 and a deferral and a waiver (see pages 5 and 6) together with two annexes, including annex I on the measures and timelines of this PIP and the subset(s) of the paediatric population and condition(s) covered by the waiver (see pages 7 to 9)

6.4 Annex I is subdivided into sections A, B and C. Section C sets out the details of the PIP in a bullet list containing the following five items:

- item 1, identifying CML as the condition to be investigated

- item 2, defining the proposed PIP indication as the treatment of Philadelphia chromosome-positive CML

- item 3, stating that the subset(s) of the paediatric population concerned by the paediatric development are paediatric patients from birth to less than 18 years

- item 4, describing the formulation(s) used, i.e. "Capsule, 200 mg and 50 mg, unmanipulated or contents dispersed with yoghurt or applesauce, oral use"

- item 5, setting out the details of the proposed measures in a table (reproduced below)

Area	Number of studies	Description
Quality		Not applicable
Non-clinical	1	Oral (gavage) juvenile development study in rats
Clinical	3	Randomized, open-label, three-period crossover study comparing the bioavailability of nilotinib when administered as intact capsule or the capsule content mixed with yogurt or apple sauce in adult healthy volunteers Multiple-dose, open-label, single-agent, non-controlled trial to evaluate pharmacokinetics, pharmacodynamics, safety and activity in paediatric patients from birth to less than 18 years with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic or accelerated phase who are imatinib-intolerant or in whom the disease is imatinib-resistant, or with refractory or relapsed Philadelphia chromosome-positive acute lymphoblastic leukaemia. Multiple-dose, open-label, single-agent, non-controlled, multi-centre trial to evaluate pharmacokinetics, safety and activity in paediatric patients from birth to less than 18 years with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic or accelerated phase who are imatinib-intolerant or in whom the disease is imatinib-resistant or with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase.

The subject-matter of claim 1 is novel over the disclosure of the PIP of document D1

6.5 As can be seen from this table ("table of section C"), the PIP of document D1 proposes three clinical studies in human subjects.

Clinical study 1 of the PIP of document D1

6.6 The clinical study first mentioned in this table ("study 1 of the PIP of document D1") involves the use of the following three nilotinib formulations (see table of section C in conjunction with item 4 of section C):

(a) intact, unmanipulated Tasigna capsule ("Tasigna capsule formulation")

(b) mixture of the content of a Tasigna capsule with apple sauce ("nilotinib/apple sauce formulation")

(c) mixture of the content of a Tasigna capsule with yoghurt ("nilotinib/yoghurt formulation")

6.7 It is undisputed that the nilotinib/apple sauce formulation is a dispersion of nilotinib in apple sauce in accordance with claim 1.
This formulation is to be administered to healthy adult volunteers instead of CML patients (see table of section C). Hence, the disclosure of study 1 of the PIP of document D1 does not anticipate the subject-matter of claim 1.

Clinical studies 2 and 3 of the PIP of document D1

6.8 The two clinical studies ("studies 2 and 3 of the PIP of document D1") listed below study 1 of the PIP of document D1 are to be carried out in paediatric CML patients. Unlike for the disclosure of study 1, however, the table of section C does not further specify the nilotinib formulations to be employed in studies 2 and 3 of the PIP of document D1.

6.9 The board agrees with respondents I and II that the paediatric population concerned by studies 2 and 3 of the PIP of document D1 includes paediatric patients of a very young age unable to swallow the Tasigna capsule formulation.

6.10 However, this fact does not allow concluding with certainty that this patient subset will receive the nilotinib/apple sauce formulation.

6.10.1 As convincingly argued by the appellant, studies 2 and 3 are follow-up studies of study 1 of the PIP of document D1. The overall aim of this first study is to establish whether the nilotinib/apple sauce formulation and the nilotinib/yoghurt formulation have oral bioavailabilities comparable to that of the Tasigna capsule formulation (see table of section C above). If this would indeed be so for one or both of these formulations, then this/these formulation(s) would be considered suitable for use in the paediatric CML patients in the follow-up studies 2 and 3 of the PIP of document D1 and consequently employed in these studies. In other words, the type of nilotinib formulation to be used in studies 2 and 3 hinges on the outcome of study 1 of the PIP of document D1.

6.10.2 Undisputedly, this outcome was not known at the publication date of document D1. It follows that the oral administration of the nilotinib/apple sauce formulation to CML patients in the context of studies 2 and 3 of the PIP is not directly and unambiguously derivable form the disclosure of document D1, explicitly or implicitly.

6.11 As a consequence, respondent II's argument that document D1 implicitly disclosed to the practitioner - i.e. parents of very young children afflicted with CML - that nilotinib can be administered to their offspring dispersed in apple sauce or yoghurt, must fail, and its arguments on the non-mentioning of the therapeutic efficacy of the claimed medical use (see section XI. above) need not be considered further.

6.12 Respondent I based its lack of novelty objection on items 2 and 4 of section C of annex I of document D1 (see point 6.4 above), arguing that the selection of

the nilotinib/apple sauce formulation from the single list of nilotinib formulations disclosed in item 4 of section C could not confer novelty to the subject-matter of claim 1 over document D1. Respondent I also presented arguments in favour of the plausibility of the claimed therapeutic effect, citing documents D1, D3 to D5 and D21 and the principles set out in decision T 158/96 (see catchword, point 3.5, second paragraph of the Reasons) to support its case.

6.13 The board does not concur.

6.13.1 Under the boards' settled case law, the technical disclosure in a prior-art document must be considered as a whole (see T 56/87, OJ 1990, 188). Individual sections of a document cannot be considered in isolation from the others but must be seen in their overall context.

6.13.2 Applied to the current case, this means that items 2 and 4 of section C of annex I of document D1 must be read in conjunction with the remaining items of this section including item 5 setting out the details of the agreed PIP (see point 6.4 above).

6.13.3 In doing so, the board arrives at the conclusion that section C of annex I does not anticipate the claimed subject-matter (see points 6.4 to 6.10.2 above).

6.14 As a consequence, respondent I's novelty objection must fail, and its arguments on the plausibility of the claimed therapeutic effect need not be considered further.

Overall conclusion on novelty

6.15 In light of the above considerations, the board concludes that respondent I and II's objections under Article 54 EPC against claim 1 of the main request do not prejudice the maintenance of the patent on the basis of the set of claims of the main request.

7. Inventive step

Document D1 as the closest prior art

7.1 In agreement with the respondents, the board considers the disclosure of study 1 of the PIP of document D1 to be a suitable starting point for assessing inventive step of claim 1.

7.2 The claimed subject-matter differs from this disclosure in that the claimed dispersion of nilotinib in apple sauce is administered to patients with CML instead of healthy volunteers (see points 6.5 to 6.10.2 above).

Objective technical problem and solution

7.3 To formulate the objective technical problem, it is necessary to establish the technical effect(s) achieved by the aforementioned distinguishing feature.

7.4 Under point 5.4.2 of its communication, the board observed that the experimental data presented in example 2 of the patent (see table 1, bottom half) credibly showed that the single oral administration of 400 mg nilotinib, with two 200 mg nilotinib capsules content, each dispersed in one teaspoon of apple sauce, gives rise to a similar systemic exposure of nilotinib in healthy human volunteers compared with the single oral administration of 400 mg nilotinib given as two

intact capsules. This has not been contested by the respondents.

7.5 Equally undisputed is the fact that the oral administration of 400 mg of nilotinib in the form of two intact Tasigna capsules is an approved treatment for CML in adult patients, as evidenced by document D21, which represents the skilled person's common general knowledge at the priority date of the patent.

7.6 In light of the above facts, the board considers it credible that the oral administration of a dispersion of nilotinib (salt) in apple sauce to patients with CML would result in an effective treatment of this condition.

7.7 As a consequence, the board accepts the appellant's formulation of the objective technical problem as the provision of an effective treatment of CML.

7.8 Respondents III and V argued that solely the issue of efficacy should be taken into account in the inventive-step analysis starting from document D1. Safety issues of the claimed treatment should not be considered part of the objective technical problem because such issues were related to the use of apple sauce and not to the distinguishing feature, i.e. the therapy.

7.9 The board does not endorse the respondents' views. It instead agrees with the appellant's argument with reference to the decision T 2506/12 (see document D61, Reasons, point 2.8) that for a treatment to be effective, it must meet not only the criterion of efficacy but also that of acceptable safety. The board acknowledges that claim 1 does not contain any limitation to specific doses of nilotinib. However, in

the absence of any evidence to the contrary, the board is satisfied that the technical problem has been solved over the whole extent claimed, both for the criterion of efficacy and that of acceptable safety.

7.10 The proposed solution to this problem is the oral administration of a dispersion of nilotinib (salt) in apple sauce.

Obviousness of the proposed solution

7.11 The following facts belonged to the skilled person's common general knowledge at the priority date of the patent.

(a) Nilotinib administered orally in the form of Tasigna capsules is effective in the treatment of adult CML patients (see point 7.5 above).

(b) Apple sauce is a soft food (see document D6, page 8, second full paragraph).

(c) Apple sauce is commonly used in the art for administering medicinal products to patients unable to swallow intact capsules, e.g. CML patients of a very young age targeted, *inter alia*, by the PIP of document D1 (see point 6.9 above).

Respondents' first line of argument

7.12 In a first line of argument, the respondents contended that the proposed solution would have been obvious based on the disclosure of the PIP of document D1 read in light of the common general knowledge.

Respondents III and V argued that in light of the known effectiveness of the Tasigna capsule formulation in the treatment of CML, the skilled person would have expected the nilotinib/apple sauce formulation of document D1 to be effective in the treatment of CML as well. Similarly, respondent I held that the teaching of document D1 would have encouraged the skilled person to select apple sauce and yoghurt as carriers for nilotinib and to test these in routine experiments. Likewise, respondent II argued that starting from study 1 of the PIP of document D1 as the closest prior art, the skilled person only needed to verify the efficacy of the nilotinib/apple sauce formulation in the treatment of CML, and in view of the problems some patients experienced with swallowing solid dosage forms, the skilled person would have been very motivated to do so.

7.13 The board does not agree. As evidenced by document D6, it was common general knowledge at the priority date of the patent that:

(a) food can alter the bioavailability of a drug by various means, including:

(i) delay gastric emptying
(ii) stimulate bile flow
(iii) change gastrointestinal (GI) pH
(iv) increase splanchnic blood flow
(v) change luminal metabolism of a drug substance
(vi) physically or chemically interact with a dosage form or a drug substance

(see document D6, page 2, first paragraph)

(b) "*[f]or other immediate-release drug products (BCS Class II, III, and IV) and for all modified release drug products, food effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In these cases,* ***the relative direction and magnitude of food effects on formulation BA [bioavailability] and the effects on the demonstration of BE [bioequivalence] are difficult, if not impossible, to predict without conducting a fed BE study.***"

(see document D6, page 2, last paragraph; emphasis added by the board)

7.14 To illustrate this lack of predictability in the absence of a fed bioequivalence study, the appellant referred to document D58.

7.14.1 This prior-art document discloses a food-effect oral bioavailability study for didanosine administered orally in the form of encapsulated, enteric-coated beads (i.e. a modified release drug product in accordance with the teaching of document D6 mentioned under point 7.13(b) above). The different foods tested were a high-fat meal, a light meal, two tablespoons of yoghurt and two tablespoons of apple sauce.

7.14.2 The effects of these foods on the Cmax and the AUC of didanosine were as follows (see abstract of document D58).

(a) Apple sauce and the light meal decreased the Cmax of didanosine in a similar manner (Cmax decreases of 24% and 22% respectively). This decrease was

significantly lower than the Cmax decrease observed with a high-fat meal (46%).

(b) By contrast, in terms of AUC decrease, apple sauce was similar to the high-fat meal, lowering the AUC by 19% and 18% respectively.

7.14.3 These study results are analysed in more detail in the section entitled "Discussion" (see page 424, right-hand column, first paragraph of document D58). In this section, the authors explain that they had anticipated the observed lower Cmax for the high-fat meal compared to the light meal. By contrast, they had not expected that small amounts of apple sauce such as two spoonfuls would cause significant delays in gastric emptying and were therefore surprised to observe a similar Cmax decrease for apple sauce (24%) and the light meal (22%).

7.15 In view of these facts and findings, the board accepts the results disclosed in document D58 (see abstract) as confirmation of the principle established in document D6 that for immediate-release drug products of BCS Class II, III and IV and for all modified release drug products, food effects cannot be predicted in the absence of a fed bioequivalence study (see point 7.13(b) above).

7.16 Turning to the case at hand, it was common general knowledge at the priority date of the patent that nilotinib is a BCS Class IV drug (see document D36, page 3, last sentence). Accordingly, the skilled person would have considered the aforementioned principle laid down in document D6 to be applicable to the nilotinib/apple sauce formulation (and the nilotinib/yoghurt formulation) proposed in the PIP of

document D1. In line with this principle, and absent any results in the cited prior art of a food-effect bioavailability study or a fed bioequivalence study for an orally administered nilotinib formulation using apple sauce as food, the skilled person would not have made any predictions on the relative direction and magnitude of the food effect of apple sauce, if any, on the oral bioavailability of nilotinib when administered orally as nilotinib/apple sauce formulation in study 1 of the PIP.

7.17 Several respondents submitted that the unpredictability taught in document D6 had been removed by document D36's disclosure of the results of a food-effect study in healthy subjects receiving three treatments of a single 400 mg oral dose of nilotinib under fasting, high-fat meal and light meal conditions (see page 17, first full paragraph, Table 8). In this study, the intake of a high-fat meal 30 minutes before nilotinib administration significantly increased the bioavailability (expressed as AUC_{0-t}) and the peak serum concentration (expressed as Cmax) of nilotinib. The same results were obtained for a light meal, albeit to a lesser extent. Noting the decreased level of food effect of the light meal relative to the high-fat meal, the skilled person would have expected this level to be even lower for apple sauce because of the small meal size, the absence of fat and the low total caloric content. As a matter of fact, the exact same trend had been expected by the authors of document D58 (see page 424, right-hand column, section entitled "Discussion").

7.18 The board does not endorse the respondents' view.

7.18.1 Document D6 (see page 8, chapter VI.A., first paragraph) states that for the labelling of drug

products to recommend that the product be sprinkled on soft foods, such as apple sauce, additional in vivo relative bioavailability studies should be performed.

7.18.2 The skilled person would have inferred from this teaching that the food effect of apple sauce on the oral bioavailability of a drug product such as the Tasigna capsule content (see document D1) cannot be reliably predicted on the basis of results (or a trend observable in them) emerging from a food-effect bioavailability study using a different type of food, e.g. the high-fat and the light breakfasts tested in the food-effect study of document D36. As a consequence, even if - as submitted by respondent V - it is correct that document D1 post-dates documents D6, D21 and D36 and that it is therefore reasonable to assume that Novartis in proposing apple sauce (and yoghurt) as a candidate carrier for nilotinib in the PIP of document D1 would have taken all the technical information contained in these documents into account, it remains that the food effect of apple sauce on the oral bioavailability of nilotinib would not have been predictable based on the effects observed with different types of food (e.g. high-fat meals, light meals and other kinds of ingredients with nutritional value including lactose monohydrate used as the excipient for nilotinib in the Tasigna capsule formulation).

7.18.3 As regards the authors' expectations in document D58, these are based on the principle that the rate of gastric emptying is mainly dependent on the type and caloric content of the meal, a light meal causing a lesser delay in gastric emptying and thus having a less marked influence on the Cmax compared to a high-fat meal (see page 424, right-hand column, first

paragraph). However, the delay of gastric emptying is only one of various mechanisms by which food can alter the oral bioavailability of a drug (see point 7.13(a) above). Accordingly, the disclosure of the authors' expectations in document D58 does not support the respondents' case either.

7.19 The same holds true for respondent V's argument according to which the expectation that a small amount of apple sauce would have no significant food effect was consistent with document D18, in which the patent's inventors expressed the view that they expected the nilotinib in apple sauce formulation to be bioequivalent to intact nilotinib capsules. As convincingly argued by the appellant, document D18 is post-published and can therefore not be relied on as evidence of the skilled person's expectations before the priority date of the patent.

7.20 Respondent IV, for its part, submitted at the oral proceedings that the alleged unpredictability of the food effect of apple sauce on the oral bioavailability of nilotinib was irrational. It was absolutely excluded to have a trial-and-error approach when performing studies with human beings.

7.21 The board agrees that in the case at issue the skilled person would not have adopted a try-and-see attitude in solving the posed technical problem. However, this does not make the unpredictability of the food effect irrational. The fact that a clinical study is announced in a prior-art disclosure does not automatically mean that its outcome was predictable and that a reasonable expectation of success had to be acknowledged. Whether this is indeed so, depends on the facts and circumstances of each case.

7.22 In the case at issue, the appellant has convincingly shown that the skilled person would not have been able to predict the outcome of study 1 of document D1. As a consequence, the skilled person, starting from study 1 of the PIP of document D1, would not have made any prognosis or had any expectation for the relative direction and magnitude of the food effect of apple sauce on the bioavailability of nilotinib after oral administration of the nilotinib/apple sauce formulation to adult healthy volunteers in study 1 of the PIP of document D1.

7.23 What is more, the skilled person would have been alarmed by the fact that Tasigna capsules can cause significant prolongation of the cardiac ventricular repolarisation as measured by the QT interval on the surface ECG ("QT prolongation") in a concentration-dependent manner when inappropriately taken with food (see document D21, page 6, section 5.2). This QT prolongation can give rise to serious, potentially life-threatening adverse events (see the above-mentioned reference in document D21).

7.24 For this reason, document D21 warns against taking Tasigna capsules with food and stipulates that no food should be consumed for at least two hours before the nilotinib dose is given until at least one hour after (see e.g. page 2, left-hand column, warning box and second paragraph; page 4, warning box; page 7, section 5.8; and page 18, sections 17.1 and 17.5).

7.25 Document D36 gives further insights into the QT prolongation effect of nilotinib in the presence of food. On page 20, first paragraph of this document, it is stated that in a study involving healthy volunteers,

the oral administration of nilotinib after a high-fat meal produced statistically significant increases in the QT interval compared to the oral intake of nilotinib under fasting conditions.

7.26 Even if in light of the considerable differences between a high-fat meal and apple sauce in terms of fat content, total caloric content and meal size the skilled person did not consider the study results reported in document D36 with a high-fat meal to be directly transferable to apple sauce, it remains that the food effect of apple sauce on orally administered nilotinib was unpredictable at the priority date of the patent. The skilled person would also have taken account of the finding on page 17 of document D36, first full paragraph, that a light meal increased the Cmax of nilotinib significantly, reporting a 55% increase. In view of these facts and the multitude of mechanisms by which food can alter the bioavailability of a drug (see point 7.13(a) above), the skilled person would have seriously contemplated the possibility of apple sauce triggering serious adverse events of QT prolongation by increasing the plasma concentration of nilotinib through a different mechanism than a high-fat meal.

7.27 Respondent III submitted that to the extent that the skilled person would have foreseen this possibility, they would have simply reverted to common general knowledge (e.g. documents D21 and D36) and halved the dose of nilotinib.

7.28 This argument cannot succeed for the following reasons.

7.28.1 It is undisputed that document D21 (see page 5, penultimate paragraph in conjunction with page 12,

section 7.2, first paragraph) recommends to halve the dose of nilotinib when patients must be co-administered a strong inhibitor of CYP3A4, i.e. an enzyme involved in the metabolism of nilotinib. In this way, a significant increase of the systemic exposure to nilotinib caused by the CYP3A4 inhibitor can be avoided. Equally undisputed is the commonly known fact that some foods can increase the oral bioavailability of nilotinib, either by inhibiting CYP3A4 (see document D21, page 7, section 5.8) or by other means (see food-effect study disclosed in document D36, page 17).

7.28.2 In contrast, the food effect of apple sauce on the systemic exposure to nilotinib has not been laid out in the prior art. The unpredictability of this effect left the skilled person entirely uncertain as to whether apple sauce increases or decreases the AUC and Cmax of orally administered nilotinib and to what extent. While considering the possibility that apple sauce indeed raises the AUC and Cmax of oral nilotinib, the skilled person would also have contemplated that apple sauce does the exact opposite and decreases the AUC and Cmax of oral nilotinib, in which case halving the dose would be detrimental to the efficacy of the nilotinib treatment. As a result, the skilled person would not have applied the solution offered in document D21 in the absence of any knowledge on the relative direction and magnitude of the food effect of apple sauce on orally administered nilotinib.

7.29 From the above, the board arrives at the overall conclusion that document D1, when read in light of the common general knowledge, would not have led the skilled person to implement study 1 of the PIP of document D1 in the expectation that the nilotinib/apple

sauce formulation would be comparable to the Tasigna capsule formulation in terms of nilotinib bioavailability and thus be effective in the treatment of CML.

Respondents' second line of argument

7.30 In a second line of argument, the respondents considered that the solution proposed in claim 1 would have been obvious in light of the legal framework of the PIP set out in document D65a (PIP regulation).

A. Respondent IV - "One-way-situation inevitably leading to the claimed subject-matter"

7.31 Respondent IV took the position that document D1 disclosed a "one-way situation" leading directly to the proposed solution when considering the legal framework of the PIP of document D1, specifically Articles 15(2) and 20 of the PIP regulation. Study 1 of the PIP of document D1 represented a standard, routine approach usually applied in the art to obtain the required scientific information. In the current case, it served to establish whether the nilotinib/apple sauce formulation and the nilotinib/yoghurt formulation, intended for use in the paediatric population, fulfilled certain requirements in terms of bioavailability. Considering the timeline between the date of publication of document D21 and the date of publication of D1, the skilled person would have seen that fundamental developments had been going on in the meantime and that there was the option to take nilotinib with apple sauce. Otherwise, the PIP of document D1 would not have been granted. As a consequence, the skilled person would have concluded that once study 1 of the PIP of document D1 would have

been successfully completed and the required scientific information obtained, these same formulations would be automatically employed in the subsequent studies 2 and 3 involving CML patients.

7.32 Article 15(2) of the PIP regulation stipulates that:

"*[t]he paediatric investigation plan shall specify the timing and the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. In addition, it shall describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.*"

7.33 These measures are defined in document D74 - a guideline from the European Commission on the PIP regulation - as including "*studies, trials, data and pharmaceutical development proposed to generate new scientific information aiming at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population including the development of age appropriate formulation in all subsets of the paediatric population affected by the condition, as specified in a paediatric investigation plan*".

7.34 Article 20 of the PIP regulation, in turn, concerns deferrals in relation to the PIP and reads as follows:

"1. At the same time as the paediatric investigation plan is submitted under Article 16(1), a request may be made for deferral of the initiation or completion of some or all of the measures set out in that plan. Such

deferral shall be justified on scientific and technical grounds or on grounds related to public health.

In any event, a deferral shall be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population or when studies in the paediatric population will take longer to conduct than studies in adults."

7.35 In the case of the PIP of document D1, the EMA granted such a deferral for studies 2 and 3 with a projected date of completion "By September 2015" (see penultimate row of annex I of document D1). This means that study 1 of the PIP of document D1 (comparing the bioavailability of nilotinib when administered as intact capsule or the capsule content mixed with yoghurt or apple sauce in adult healthy volunteers) had to be conducted first and thus represents a necessary stepping stone to the envisaged studies 2 and 3, i.e. the outcome of study 1 determines the conduct of the further studies.

7.36 The board is, however, unable to find any evidential support in the aforementioned provisions of the PIP regulation or any other prior art relied on by the respondents for respondent IV's assumption of a successful completion of this pre-study for the nilotinib/apple sauce formulation. In the absence of such evidence, respondent IV's argument is based on hindsight and must, thus, be dismissed.

B. Respondents' contention that the skilled person would have had a reasonable expectation that the nilotinib/apple sauce formulation would solve the posed technical problem when considering the legal framework of the PIP of document D1

7.37 In a different approach, the respondents submitted that the skilled person would have inferred from the fact that the PDCO had recommended to agree to the proposed PIP and that the EMA had decided to follow this recommendation that the PDCO and the EMA had at very least a reasonable expectation that the treatment of CML patients with the nilotinib/apple sauce formulation would be safe and effective.

7.38 To support their case, the respondents argued as follows.

(a) Before delivering its opinion on the PIP of document D1, the PDCO had assessed whether the clinical trials proposed in it were appropriate, as confirmed by the expert opinion D71, page 4, paragraph 23, first sentence. This assessment comprised an investigation of the safety of the formulations of the PIP, including in the particularly vulnerable paediatric population, as evidenced by Article 17(1) and Article 19 in conjunction with Article 11(1)(a) of the PIP regulation. In carrying out its tasks, the PDCO had taken into account ethical considerations, as reflected in document D72 (see sections 1.4, 2.6 and 2.6.4) and had considered in accordance with Article 6(2) of the PIP regulation whether the clinical studies proposed in the PIP of document D1 could be of significant therapeutic benefit to and/or fulfil a therapeutic need of the paediatric population (see document D71, paragraph 26).

(b) The fact that following this assessment the PDCO adopted a positive opinion on the PIP of document D1 therefore indicated that:

(i) the clinicians of the PDCO did not have any safety concerns with the proposed formulations

(ii) the PDCO had considered the proposed studies to be of significant therapeutic benefit to and/or fulfil a therapeutic need of the paediatric population

(iii) this opinion was based on favourable scientific data

7.39 The board does not endorse the respondents' view.

B.1. No evidence for the PDCO's alleged safety assessment in the cited provisions of the PIP regulation (see point 7.38(b)(i) above)

7.40 Under Article 6(1) of the PIP regulation, the PDCO is tasked, *inter alia*, with the assessment of the content of any paediatric investigation plan for a medicinal product submitted to it in accordance with the PIP regulation and to formulate an opinion.

7.41 Further details on this assessment are provided, *inter alia*, in Article 17(1) of the PIP regulation. This article specifies that the PDCO shall adopt an opinion, *inter alia*, on whether the proposed studies will ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets of it. In other words, the PDCO investigates whether the proposed studies are appropriate for generating the necessary data to assess if and how the proposed formulations may be used safely and efficaciously to treat the

paediatric population. Hence, the topic of investigation of the PDCO under Article 17(1) of the PIP regulation is the design of the proposed studies, and not - as contended by the respondents - the safety (and efficacy) of the formulations proposed in the PIP.

7.42 The provisions of Article 19 read in conjunction with Article 11(1)(a) of the PIP regulation do not provide evidence for such a safety assessment by the PDCO either. The reasons are as follows.

7.42.1 Article 19 of the PIP regulation reads as follows:

"If, having considered a paediatric investigation plan, the Paediatric Committee concludes that Article 11(1)(a), (b) or (c) applies to the medicinal product concerned, it shall adopt a negative opinion under Article 17(1).

In such cases, the Paediatric Committee shall adopt an opinion in favour of a waiver under Article 12, whereupon the procedure laid down in Article 25 shall apply."

7.42.2 In accordance with Article 11(1)(a) of the PIP regulation, the PDCO shall grant a waiver when there is evidence showing that the medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population.

7.42.3 In the case at issue, the PDCO did not recommend to waive studies 2 and 3 of the PIP of document D1 for the paediatric population unable to swallow capsules. However, as correctly pointed out by the appellant, this fact does not constitute proof of the opposite, i.e. that the PDCO had assessed the safety of the

formulations proposed in this PIP and concluded that these were likely to be safe (and effective) in paediatric CML patients. Only once the three studies (including study 1, i.e. the bioavailability study in healthy adults) have been conducted and the necessary data generated and only at the request of the Committee for Medicinal Products for Human Use does the PDCO make a quality, safety or efficacy assessment of the medicinal product for use in the paediatric population (see Article 6(1), under (d) of the PIP regulation), as confirmed by Carla Schoonderbeek in paragraphs 25 to 27 of document D71, the content of which has not been disputed by the respondents.

B.2. Respondents' arguments based on Article 6(2) of the PIP regulation (see point 7.38(b)(ii) above)

7.43 Article 6(2) of the PIP regulation stipulates that:

"[w]hen carrying out its tasks, the PDCO shall consider whether or not any proposed studies can be expected to be of significant therapeutic benefit to and/or fulfil a therapeutic need of the paediatric population. The Paediatric Committee shall take into account any information available to it, including any opinions, decisions or advice given by the competent authorities of third countries."

7.44 Likewise, Article 17(1) of the PIP regulation specifies that the PDCO shall adopt an opinion on whether the expected therapeutic benefits justify the studies proposed.

7.45 In the case at issue, the PDCO adopted a positive opinion on the PIP of document D1. It thus appears correct to say that the PDCO did indeed expect the

studies proposed in this PIP to provide a significant therapeutic benefit to and/or fulfil a therapeutic need of the paediatric population.

7.46 However, these expected benefits are subject to the condition that the nilotinib/apple sauce formulation and/or the nilotinib/yoghurt formulation would be found in study 1 of the PIP of document D1 to have oral nilotinib bioavailabilities comparable to that of the Tasigna capsule formulation and that studies 2 and 3 confirm safety and efficacy of nilotinib found in adult CML patients also for the paediatric population. Absent any evidence that the outcome of study 1 was known at the priority date of the patent, it cannot be inferred from the PDCO adopting a positive opinion on this PIP that the PDCO had a reasonable expectation that these two formulations would be reasonably safe and efficacious in the paediatric population.

7.47 The board has no doubt that the PDCO, in assessing the content of the PIP of document D1, took into account ethical considerations (see sections 1.4, 2.6 and 2.6.4 of document D72). As convincingly argued by the appellant, it is for this very reason that the EMA granted a deferral of studies 2 and 3 in accordance with Article 20(1), second paragraph of the PIP regulation. Specifically, conducting study 1 of the PIP of document D1 in the less vulnerable adult population first and awaiting its outcome before initiating studies 2 and 3 of this PIP protected the particularly vulnerable paediatric population targeted by this PIP against undue risk associated with the unknown effect of apple sauce and yoghurt on the bioavailability of nilotinib.

7.48 Accordingly, the arguments of the respondents based on Article 6(2) of the PIP regulation are not convincing.

B.3. No evidence that the PDCO's positive opinion on the PIP of document D1 is based on favourable scientific data

7.49 Absent any evidential support for respondent II's contention that the PDCO's positive opinion on the PIP of document D1 was based on favourable scientific data on the efficacy and safety of the nilotinib/apple sauce formulation, this argument must fail. For this reason, respondent II's written argument in relation to the statement made in decision T 2506/12, Reasons 3.10 that "drug compounds to be used in a clinical trial with human subjects are not selected based on a general 'try-and-see' attitude, but based on existing favourable scientific data, for both ethical and economical reasons" need not be considered further.

7.50 In light of the preceding considerations, the board concludes that the provisions of the PIP regulation relied on by the respondents do not contain any indication on the basis of which the skilled person would have interpreted the EMA's agreement on the PIP of document D1 and the PDCO's positive opinion on it as implying that both the EMA and the PDCO had a reasonable expectation that the treatment of CML patients with the nilotinib/apple sauce formulation would be safe and effective.

Further arguments by the respondents on obviousness of the solution proposed in claim 1

7.51 In a further line of argument, several respondents submitted that the skilled person would have found the

disclosure of document D1 highly credible given that the PIP applicant of document D1 was the originator of the Tasigna capsule formulation, i.e. Novartis. The respondents further contended that the PIP applicant had relied on its own scientific knowledge on the Tasigna capsule formulation when preparing the PIP and selecting the measures proposed. As a consequence, the skilled person would have interpreted the fact that the clinicians of the PIP applicant - despite being aware of the common general knowledge reported in documents D6, D21 and D36 - had proposed to conduct study 1 of the PIP of document D1 with nilotinib dispersed in apple sauce as implicit confirmation that these clinicians did not have any safety concerns about administering this formulation to humans and that they themselves had a reasonable expectation that the proposed study plan would pass the PDCO's and the national ethics committees' investigations. Otherwise, the PIP applicant would not have put forward the proposed study plan, for both ethical and economic reasons.

7.52 The board does not doubt the credibility of the content of document D1. The board also accepts it as credible that the clinicians of the PIP applicant would have taken the common general knowledge reflected by documents D6, D21 and D36 into account when preparing the PIP and that they were hoping for the desired outcome, i.e. that the nilotinib formulations proposed in the PIP of document D1 would have comparable oral nilotinib bioavailability to that of the Tasigna capsule formulation. However, as set out under point 7.21 above, whether the announcement of a clinical study in a prior-art disclosure leads to a reasonable expectation of success depends on the facts and circumstances of the case. In the case at issue, the

respondents did not explain why the clinicians of the PIP applicant - despite being aware of the known unpredictability of the food effect of apple sauce on nilotinib - would still have had a reasonable expectation that the nilotinib/apple sauce formulation would exhibit an oral nilotinib bioavailability in healthy human adults comparable to that of the Tasigna capsule formulation. Absent any such explanation, the respondents' argument cannot convince the board.

Considerations set out in decision T 239/16 of Technical Board of Appeal 3.3.01 do not apply to the case at hand

7.53 To further support their cases, the respondents referred to decision T 239/16, submitted as document D70.

7.53.1 In the case underlying this decision, the claimed subject-matter was directed to an active agent of the group of bisphosphonates for use in a method of treating osteoporosis by means of a specified dosage regimen. The closest prior art was a document providing information on a planned, phase II clinical study to patients afflicted with osteoporosis. This study included five equivalent arms on different dosage regimens of which the fifth represented the most promising point for the assessment of inventive step. The claimed subject-matter differed from this disclosure in the failure of the former to directly and unambiguously disclose the effective treatment of osteoporosis. The deciding board defined the objective technical problem as the provision of an effective treatment of osteoporosis.

7.53.2 In terms of obviousness, the deciding board held, *inter alia*, that the disclosure of the five study arms in the closest prior art:

"*leads to an expectation of success, due to the fact that clinical studies are based on data obtained by pre-clinical testing both in vitro and in animals and require authority approval which takes ethical considerations into account. This means in the present case that the skilled person would expect all study arms to treat osteoporosis effectively, unless he was dissuaded from this by the prior art*" (see point 6.5 of the Reasons, second paragraph).

Having analysed whether the skilled person's expectation based on the closest prior art was diminished by any disclosure of the prior art invoked by the parties, the deciding board also noted that:

"*there remained a residual doubt that the desired treatment would be obtained, which however did not diminish the prospects of success to such an extent that the reasonable expectation turned into a mere 'hope to succeed'. Clinical trials in humans are planned scientific investigations. They require authority approval, which is only given after a risk/benefit evaluation. For ethical (but also economic) reasons it has to be ensured that research risks are minimised and are reasonable in relation to any potential benefits. Ethical and economical considerations require that the 'benefit' will arise with reasonable certainty and will not only 'be hoped for'. This has to be taken into consideration as part of the technical circumstances when assessing the level of confidence of the skilled person in making rational*

predictions about achieving the envisaged treatment" (see point 6.6 of the Reasons, fifth paragraph).

7.53.3 In other words, in decision T 239/16, the competent board acknowledged a reasonable expectation of success on the basis of a prior-art disclosure of a planned phase II clinical study after having carefully analysed the technical circumstances underlying this case, with particular focus on pharmaceutical and regulatory aspects of clinical studies. Key points leading to the board's conclusion of a reasonable expectation of success in T 239/16 include the following.

(a) The closest prior art was a phase II clinical study on dosage regimens. The relevant fifth regimen was not presented as a further control in addition to the placebo group, but as a study arm of interest.

(b) Phase II clinical studies were known to be based on earlier preclinical studies.

(c) The skilled person's expectation arising from the suggestion of the closest prior art was not diminished by the relevant state of the art knowledge.

7.53.4 The technical circumstances underlying the current case differ from those underlying decision T 239/16 to the extent that the findings and reasons developed in this decision are not transferable.

7.53.5 The clinical study representing the closest prior art in the case at hand (i.e. study 1 of the PIP of document D1) is a pharmacokinetic study in healthy adult volunteers forming part of an agreed PIP and not, as in the case underlying decision T 239/16, a phase II

clinical study in patients belonging to the claimed patient group. The board has not been made aware of any evidence that study 1 of the PIP of document D1 is built on scientific data obtained from preclinical development suggesting that the nilotinib/apple sauce formulation is likely to exhibit an oral nilotinib bioavailability in healthy human adults comparable to that of the Tasigna capsule formulation.

7.53.6 Moreover, in following the instructions set out in the clinical study representing the closest prior art in decision T 239/16, the skilled person obtains results for the patient group addressed by the claimed invention immediately and the skilled person's expectation arising from the suggestion of the closest prior art is not diminished by the relevant state of the art knowledge. In the case at issue, however, the situation is different. As explained under point 6.10.1 above, the outcome of study 1 (which was not known at the priority date of the patent) is decisive for the selection of the type of nilotinib formulation to be used in studies 2 and 3. Hence, to obtain the instructions necessary to perform the clinical studies in patients belonging to the patient group recited in claim 1, the skilled person is required to perform study 1 of the PIP first and await its outcome. In view of the unpredictability of this outcome, the claimed invention would not have - as contended by respondent V - come out as a result of simply following the PIP of document D1.

7.53.7 In view of the foregoing, the respondents' arguments based on decision T 239/16 cannot succeed.

Conclusion on inventive step based on document D1 as the closest prior art

7.54 In light of the above considerations, the board concludes that the respondents' objection under Article 56 EPC against claim 1 of the main request starting from document D1 as the closest prior art does not prejudice the maintenance of the patent on the basis of the set of claims of the main request.

Inventive step based on document D21 as the closest prior art

7.55 In the impugned decision, the opposition division identified document D21 as the closest prior art. As outlined in point 7.6 above, this document discloses the oral administration of 400 mg of nilotinib in the form of two intact Tasigna capsules as an approved treatment for CML in adult patients.

7.56 The claimed subject-matter differs from this disclosure in that nilotinib takes the form of a dispersion in apple sauce.

Objective technical problem and solution

7.57 The technical effects achieved by the aforementioned distinguishing feature are:

(a) easier swallowing of the nilotinib formulation

(b) similar bioavailability (AUC_{0-t}) and peak serum concentration (Cmax) relative to a single oral dose of nilotinib given as two intact Tasigna capsules, as evidenced by table 1 of the patent

7.58 The objective technical problem to be solved by the claimed invention vis-à-vis the Tasigna capsules of document D21 is therefore the provision of a nilotinib

composition which has similar effectiveness in the oral treatment of CML but which is easier to swallow.

7.59 The proposed solution to this problem is a dispersion of nilotinib (salt) in apple sauce.

Obviousness of the proposed solution

7.60 The respondents referred to their arguments submitted for document D1 representing the closest prior art. Accordingly, for the same reasons as those provided above starting from document D1 as the closest prior art, the board considers that the claimed subject-matter would not have been obvious based on document D21 as the closest prior art.

7.61 It follows that the respondents' objections under Article 56 EPC against claim 1 of the main request starting from document D21 as the closest prior art must fail.

Overall conclusion on the main request

8. The board finds that none of the grounds for opposition invoked by the respondents prejudice the maintenance of the patent on the basis of the set of claims of the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is remitted to the opposition division with the order to maintain the patent with the following claims and a description to be adapted thereto:

claims 1 and 2 of the main request filed by letter dated 21 February 2018

The Registrar: On behalf of the Chair (according to Art.8(3) RPBA):

M. Schalow L. Bühler

Decision electronically authenticated