Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 24 June 2024

Case Number:	T 1152/21 - 3.3.02
Application Number:	14705884.6
Publication Number:	2958916
IPC:	C07D471/04, A61K31/519, A61P35/00
Language of the proceedings:	EN

Title of invention:
SOLID FORMS OF A SELECTIVE CDK4/6 INHIBITOR

Patent Proprietor:
Pfizer Inc.

Opponents:
Galenicum Health S.L.U.
Teva Pharmaceutical Industries Ltd.
Generics (UK) Ltd

Headword:

Relevant legal provisions:
EPC Art. 56, 113, 111
EPC 1973 Art. 84
RPBA 2020 Art. 15(3), 11
EPC R. 103(1)(a), 115(2)

Keyword:
Substantial procedural violation
Reimbursement of appeal fee
Remittal
Inventive step
Claims - clarity in opposition proceedings

Decisions cited:
G 0003/14

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1152/21 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 24 June 2024

Appellant: (Patent Proprietor)	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001-2192 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Appellant: (Opponent 3)	Generics (UK) Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Party as of right: (Opponent 1)	Galenicum Health S.L.U. CL Sant Gabriel n°50 08950 Esplugues de Llobregat (ES)
Party as of right: (Opponent 2)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on**

31 May 2021 concerning maintenance of the European Patent No. 2958916 in amended form

Composition of the Board:

Chairman	M. O. Müller
Members:	S. Bertrand
	M. Blasi

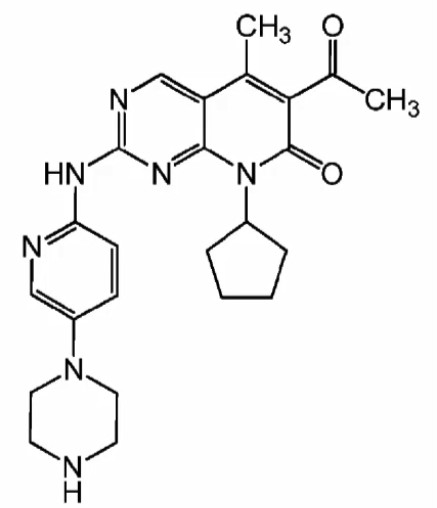
Summary of Facts and Submissions

I. The appeals by opponent 3 and the patent proprietor lie from the opposition division's interlocutory decision finding that European patent No. 2 958 916 as amended in the form of auxiliary request 10a, comprising claims which had been filed during the oral proceedings on 29 April 2021, met the requirements of the EPC.

II. Since the patent proprietor and opponent 3 are both appellants and respondents in these appeal proceedings, they are referred to as "patent proprietor" and "opponent 3" in the following. Opponents 1 and 2 are respondents for the patent proprietor's appeal. They are referred to as "opponent 1" and "opponent 2" in the following.

III. The patent is concerned with providing a crystalline form of the free base of acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one.

In the following, 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one is referred to by its common name, palbociclib. It is used (as a potent and selective inhibitor of CDK4 and CDK6) in the treatment of cell proliferative diseases such as cancer and has the following formula:



IV. The following documents are used in the present decision:

D1 WO 2005/005426 A1

D3 Assessment report published by the European Medicines Agency CHMP for IBRANCE (Palbociclib) EMA/652627/2016, London, 2016

D4 Declaration in the name of Brian Patrick Chekal filed during the examination of US application number 15/808,577, 9 November 2017

D28 Chapter 10 "Reactive Crystallization" from "Crystallization of Organic Compounds, An Industrial Perspective" (2009, Wiley)

D30 Modern Analytical Chemistry, D. Harvey, McGraw Hill Higher Education, 2000, Chapter 8 "Gravimetric Methods of Analysis", pages 233-247

D31 S. Kim et al., Organic Process Research & Development 2005, 9, pages 894-901

D39 Chemical Engineering in the Pharmaceutical Industry, second edition, P.K. Sharma, John Wiley & Sons, 2019, Chapter 35 of

"Design of filtration and drying operations", pages 799-831

D40 Protocol NCT01602887, Clinical Trials

A046 Declaration of Dr Lisa Taylor of 27 September 2021

V. In the impugned decision, the opposition division's conclusions included the following.

- The subject-matter of claim 1 according to the main request and auxiliary requests 1 to 7, 8a and 9b did not involve an inventive step starting from D1.

- The claims of auxiliary request 10a fulfilled the requirements of Articles 83, 84 and 123(2) and (3) EPC. The subject-matter of the claims according to auxiliary request 10a involved an inventive step starting from D1 (Article 56 EPC).

VI. In its statement of grounds of appeal, the patent proprietor contested the opposition division's decision. It submitted that the impugned decision amounted to a substantial violation of the right to be heard. It provided copies of the claims according to the main request, auxiliary requests 2, 4, 6, 9b and 10a filed before the opposition division, and submitted a set of claims according to auxiliary request 8b and document A046 (denoted D46 by the patent proprietor).

VII. In its statement of grounds of appeal, opponent 3 submitted that the claims of the main request did not meet the requirements of Article 56 EPC. It further submitted that the auxiliary requests were not allowable.

VIII. In their replies to the patent proprietor's grounds of appeal, opponents 1 and 2 provided counter-arguments to the patent proprietor's submissions.

IX. In its reply to opponent 3's grounds of appeal, the patent proprietor commented on opponent 3's objections. It submitted a set of claims according to auxiliary request 1A.

X. In its reply to the patent proprietor's grounds of appeal, opponent 3 contested the patent proprietor's submissions regarding the main request and the auxiliary requests.

XI. The board summoned the parties to oral proceedings as per their requests and issued a communication under Article 15(1) RPBA.

XII. Oral proceedings before the board were held by videoconference on 24 June 2024, in the presence of the patent proprietor and opponents 2 and 3. As announced beforehand in writing, opponent 1 did not attend the oral proceedings. During the oral proceedings, the patent proprietor withdrew auxiliary request 8b.

XIII. The parties' requests, where relevant to the decision, were as follows.

The patent proprietor requested:

- that the decision under appeal be set aside and that, due to substantial procedural violations of its right to be heard under Article 113 EPC, the case be remitted to the opposition division to reconsider the question of inventive step and that the appeal fee be reimbursed in accordance with Rule 103(1)(a) EPC,

- or alternatively, that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the set of claims of

- the main request or, alternatively, auxiliary request 1A filed with its reply to the grounds of appeal, further alternatively,

- one of auxiliary requests 2, 4, and 6 filed on 19 December 2019, further alternatively,

- one of auxiliary requests 9B or 10A, both filed during the oral proceedings before the opposition division on 29 April 2021.

Opponent 3 requested that the decision under appeal be set aside and that the patent be revoked in its entirety. It further requested that document A046 not be admitted into the proceedings.

Opponents 1 and 2 requested that the appeal be dismissed and that document A046 not be admitted into the proceedings.

XIV. The patent proprietor's case and the opponents' cases, in so far as relevant to the present decision, are summarised in the Reasons below.

Reasons for the Decision

Reimbursement of the appeal fee and remittal – Rule 103(1)(a) EPC, Article 111 EPC, Article 11 RPBA

1. As set out above, the opposition division concluded in its decision that the subject-matter of claim 1 of the main request did not involve an inventive step starting from D1 (point 21.6.30 of the Reasons). The opposition division held that the objective technical problem was

the provision of a crystalline form of palbociclib with improved filterability (point 21.6.19 of the Reasons). In defining the objective technical problem, it did not take into account the alleged good bioavailability of the claimed crystalline form of palbociclib (point 21.6.14 of the Reasons).

According to the patent proprietor, the opposition division failed to take into account the patent proprietor's key argument that D1 taught away from the claimed invention, despite the fact that this had been repeatedly explained during the oral proceedings as confirmed in the minutes. The patent proprietor's key argument was that D1 discouraged the skilled person from working with the free base because it had poor water solubility and low bioavailability in animal studies. The fact that any reasoning concerning this key argument was missing from the decision amounted to a substantial procedural violation of the right to be heard under Article 113 EPC since it was not apparent that the patent proprietor's oral submissions had actually been heard and considered properly. This violation of the right to be heard supported the patent proprietor's requests that the case in hand be remitted to the opposition division for it to reconsider inventive step, and that the appeal fee be reimbursed in accordance with Rule 103(1)(a) EPC.

1.1 The board does not agree with the patent proprietor for the following reasons.

Firstly, the opposition division did not consider either bioavailability or water solubility when formulating the objective technical problem (points 21.6.13, 21.6.14 and 21.6.19 of the Reasons in the decision). Hence, even if D1 did teach that the claimed compound has poor bioavailability and water solubility,

this would not deter the skilled person confronted with the objective technical problem as defined by the opposition division – which, as stated above, is unrelated to bioavailability and water solubility – from considering the claimed compound. Hence, on the basis of the position the opposition division took on the objective technical problem, there was no need for it to examine the patent proprietor's argument that D1 taught away from the claimed subject-matter.

Secondly, as submitted by the opponents, paragraph 17.2.4 of the Reasons of the opposition division's decision refers to the patent proprietor's submissions regarding inventive step starting from D1. This paragraph (in section 17 of the Reasons) relates to the patent proprietor's arguments relevant to the decision and includes the patent proprietor's argument that "[f]*urthemore the person skilled in the art, considering the poor solubility of form A of palbociclib, would not have been motivated to modify this form but would have looked for other salts*". Furthermore, paragraph 21.6.28 of the Reasons of the decision includes the inventive step reasoning starting from D1, which includes the patent proprietor's argument that "[t]*he provision of a salt was the approach followed in D1 also because the free base is known to be poorly soluble and to have low bioavailability (D1, p. 3, l. 6-8)*" (see the second sentence of paragraph 21.6.28 of the Reasons). This reasoning also states that "*the person skilled in the art would have tried to obtain larger primary particle size of the free base form A as it is known that this form is the most stable (D3, p. 18, third paragraph). As physicochemical stability is one of the most important criteria for the development of an API, it is considered that the person skilled in the art would*

have tried to modify the particle size of the crystalline form A of palbociclib. Moreover, the poor solubility of form A is not so low to preclude its use as shown in D40 (D40, Table on p. 2)" (see paragraph bridging pages 23 and 24).

It follows that the opposition division first identified the patent proprietor's argument that D1 taught away from the claimed invention in its decision in paragraph 17.2.4 of the Reasons. Furthermore the opposition division also explained in paragraph 21.6.28 of the Reasons of the decision why the argument was not convincing. Consequently, the opposition division did consider the patent proprietor's argument that D1 taught away from the claimed invention.

Therefore, for the above reasons, the opposition division's reasoning does not represent a procedural violation and does not justify reimbursing the appeal fee and remitting the case to the opposition division.

Main request

2. Claim 1 of the main request reads as follows:

"*1. A crystalline free base of 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one, having a BET Nitrogen measured specific surface area of ≤ 2 m^2/g, a volume mean diameter characterized by a D[4,3] value measured by laser diffraction of from 15 µm ± 20% to 40 µm ± 20%, and wherein the crystalline free base is a polymorph Form A of the free base having a powder X-ray diffraction pattern comprising a peaks* [sic] *at diffraction angle (2θ) of 8.0 ± 0.2, 10.1 ± 0.2 and 11.5 ± 0.2.*"

In the following, a "*volume mean diameter characterized by a D[4,3] value*" is referred to as a "D[4,3] value".

According to the patent (paragraph [0004]), using palbociclib as a potent and selective CDK4/CDK6 inhibitor is linked with challenges for pharmaceutical development. In the state of the art, the free base of palbociclib was provided by neutralisation of a salt. It formed small primary particles, which agglomerated into large, hard agglomerates that were difficult to disperse by sieving and were unsuitable for further development.

The patent is concerned with providing a crystalline free base of palbociclib having a larger particle size for improving the physicochemical and manufacturability properties (paragraph [0004] of the patent).

3. Inventive step – claim 1 – Article 56 EPC

Opponents 1 to 3 submitted that the subject-matter of claim 1 of the main request did not involve an inventive step starting from D1.

4. D1 as the closest prior art

It was common ground among the parties that D1 was the closest prior art and that example 4 of this document could be taken as the starting point for the assessment of inventive step.

Example 4 of D1 (page 22) discloses the synthesis of the isethionate salt of palbociclib. This synthesis comprises the step of neutralising the hydrochloride salt of palbociclib with NaOH (lines 24 to 26 on page 22) to give the free base. This free base is then reacted in example 4 with isethionic acid to give the isethionate salt.

Example 4 of D1 discloses that the free base of palbociclib is in the form of a "slurry" (line 24 on page 22). Example 4 of D1 does not disclose the particular specific surface area or the D[4,3] value of the free base of palbociclib.

5. Distinguishing features

It was also common ground among the parties that the claimed free base differed from the free base disclosed in example 4 of D1 on account of:

- the particular specific surface area and
- the D[4,3] value

6. Technical effect achieved by the distinguishing features and objective technical problem

The patent proprietor submitted that a reduced specific surface area and a higher D[4,3] value implied a larger particle size. A larger particle size of the compound of claim 1 of the main request resulted in (i) improved filterability and (ii) a bioavailability suitable for commercial use. These different effects are dealt with in turn in the following.

6.1 Improved filterability

The patent proprietor relied on D4.

D4 (point 22) discloses a table, which includes, *inter alia*, the D[4,3] value and the specific surface area of, *inter alia*, three experiments with Form A of the free base of palbociclib: experiments 4B, 4C and 3.

According to the notes in the table (second column), experiments 4B and 4C relate to Form A of the free base

of palbociclib prepared from palbociclib HCl salt, as disclosed in D1.

The particles of Form A of the free base of palbociclib of experiment 4B have a D[4,3] value of 201.3 ± 2.3 µm (outside the range of 15 µm ± 20% to 40 µm ± 20%, i.e. 12 µm to 48 µm, according to claim 1 of the main request) and a specific surface area of 0.676 ± 0.032 m^2/g (less than 2 m^2/g according to claim 1 of the main request). The particles of Form A of the free base of palbociclib of experiment 4B thus do not correspond to those in claim 1 of the main request and represent a comparative example.

The particles of Form A of the free base of palbociclib of experiment 4C have a D[4,3] value of 375.1 µm (outside the range of 12 µm to 48 µm according to claim 1 of the main request) and a specific surface area of 6.648 ± 0.037 m^2/g (above the range of less than 2 m^2/g in claim 1 of the main request). The particles of Form A of the free base of palbociclib of experiment 4C thus do not correspond to those in claim 1 of the main request and represent a comparative example.

According to the same notes, experiment 3 of D4 is a reproduction of example 7 of the patent application. Experiment 3 relates to large particles of Form A of the free base of palbociclib generated in situ (according to example 7 of the patent). The particles of Form A of the free base of palbociclib of experiment 3 have a D[4,3] value of 13.6 ± 0.9 µm (within the range of 12 µm to 48 µm according to claim 1 of the main request) and a specific surface area of 0.607 ± 0.035 m^2/g (less than 2 m^2/g according to claim 1 of the main request). The particles of Form A of the free

base of palbociclib of experiment 3 thus correspond to those of claim 1 of the main request.

According to the table in point 25 of D4 (bridging pages 7 and 8), particles of experiments 4B, 4C and 3 have cake filtration resistance values of 12 207, 7 237 and 139, respectively. When compared with experiments 4B and 4C, the particles of experiment 3, i.e. Form A of the free base of palbociclib exhibiting the features of claim 1 of the main request, thus have a lower cake filtration resistance value. According to point 25, this value correlates to the rate of filtration on a laboratory scale. A lower cake filtration resistance value thus implies a shorter filtration time.

Hence, as set out by the patent proprietor, it follows from the above experimental results in D4 that the particles of experiment 3 of D4, which correspond to those of claim 1, have improved handling properties, namely improved filterability, compared with the free base of D1 (experiments 4B and 4C of D4).

6.2 Bioavailability compatible with commercial use

The patent proprietor relied on D3 and A046.

D3 is an assessment report for IBRANCE®, which is the commercial name of Form A of the free base of palbociclib. The fourth paragraph of page 18 of D3, relied on by the patent proprietor, reads as follows:

"*The active substance particle size is controlled in the active substance specification. Dissolution and pharmacokinetic studies were conducted to examine the impact of particle size of palbociclib free base on the dissolution and relative bioavailability of the capsules. It was concluded that the active substance particle size does not impact finished product relative*

bioavailability, dissolution and stability within the proposed commercial active substance particle size specification."

The patent proprietor further relied on table 10 of D3.

Table 10 on pages 36 and 37 of D3 discloses clinical studies using capsules of Form A of the free base of palbociclib. In the first entry of the second part of table 10 on page 36 of D3 ("A5481022"), the D[4,3] value of the particles of Form A of the free base of palbociclib is either 16 µm or 41 µm – two values which are within the range of 12 µm to 48 µm according to claim 1 of the main request. The specific surface area of the particles of Form A of the free base of palbociclib used in that study is not disclosed.

A046 includes the characterisation of the specific surface area of three commercial batches of Form A of the free base of palbociclib used in IBRANCE® capsules. The results in the table on page 3 of this document show that the specific surface area is from 0.89 to 1.05 m^2/g, i.e. less than 2 m^2/g as required by claim 1 of the main request.

Thus, A046 shows that Form A of the free base of palbociclib used in IBRANCE® capsules, i.e. the free base used in D3, has the specific surface area required by claim 1 of the main request. Form A of the free base of palbociclib used in IBRANCE® capsules thus corresponds to claim 1 of the main request.

In view of the above-quoted passages in D3 and as set out by the patent proprietor, the relative bioavailability of the commercial palbociclib (IBRANCE® capsules), within a specific particle size range,

remains essentially the same and is compatible with commercial use.

6.3 Thus, in view of the above, the objective technical problem is, as formulated by the patent proprietor, to provide a crystalline form of palbociclib having improved filterability and a bioavailability compatible with commercial use.

7. Obviousness

7.1 Improved filterability

As submitted by the opponents, the skilled person would have expected larger particles to be more easily filtered.

This is evidenced by e.g. D30 and D31.

The second-to-last paragraph on page 240 of D30 discloses that "*[t]he size of the precipitate's particles determines the ease and success of filtration*" and that "[l]*arge, crystalline particles, however, are easily filtered*".

D31 (page 894, second paragraph under "Introduction") teaches that "[t]*he API crystallization process and crystal properties have a significant effect on downstream processing. For example, excess fines or wide particle size distribution may cause slow filtration and inefficient drying, which may be a major bottleneck of the entire manufacturing process. It is often necessary to modify the crystallization process to control particle properties to facilitate downstream operations*".

It follows that these documents teach that larger particles are more easily filtered.

A skilled person seeking to provide a free base of palbociclib with improved filterability and motivated by the above common general knowledge would have prepared such larger particles.

This was contested by the patent proprietor.

First, it submitted that there was no reasonable expectation of success. The skilled person was aware that the crystallisation of organic compounds was highly unpredictable and particularly complex. Finding appropriate crystallisation conditions in order to grow crystals is fraught with difficulty and often unsuccessful as illustrated e.g. in the last paragraph of the introduction on page 207 and at the top of page 209 of D28.

The board does not agree.

The last paragraph of the introduction on page 207 of D28 discloses that "[t]*he reader will note many uses of qualitative terms to predict the behavior of these complex systems. As in the entire field of crystallization, these wide brackets* [sic] *around possibilities (e.g., will it crystallize, will it form an oil first, will it stay amorphous, will it grow, will it nucleate, what is good mixing, what is low supersaturation, etc.?) are necessary because of the extreme species and conditions dependency of the crystallization of organic molecules*". The second full sentence at the top of page 209 of D28 reads: "*It is recognized that there are systems for which these alternative process options will not be successful in increasing particle size or improving purity.*" Both of these passages represent general statements, and as

submitted by the opponents, the main teaching of D28 is to develop process options for improving crystalline forms. Furthermore, D28, D30 and D39 teach how to achieve larger crystalline particles.

Paragraph 10.3.5 on page 215 of D28 teaches that "[s]*eeding is the key to achieving control of a reactive crystallization process. Without seeding, excessive nucleation can be expected in most systems, resulting in severe limitation on the final crystal size by creating an excessive number of particles*" and that seeds are prepared by recrystallisation from one or more suitable solvents (point 5 of paragraph 10.3.5 of D28).

The last paragraph on page 240 of D30 discloses that the precipitate's average particle size is increased by controlling the precipitation. According to this paragraph of D30, precipitation is dependent on two steps: nucleation to form new particles and then subsequent growth of those particles. The paragraph also states that larger particles form when particle growth is faster than nucleation.

D39 (paragraph 35.2.1.3.1 on page 805) describes how switching from a spontaneously nucleated batch to a seeded crystallisation batch reduces the proportion of fines with a needle-like morphology and a high aspect ratio and increases the proportion of thicker, rod-like particles.

It follows that the skilled person knew that reducing the number of nucleation sites and applying seeded crystallisation led to larger particles being obtained.

Second, the patent proprietor submitted that inventive step could be acknowledged even if the skilled person had indeed known that larger particles were easy to

filter, since the extent of the improvement in filterability achieved by the claimed particles could not have been predicted. The teaching of the prior art indicated that in cases where appropriate crystallisation conditions could be identified in order to grow crystals, the expected resulting improvement in filtration rate was about fourfold to fivefold. This was to be contrasted with the significantly faster projected filtration time of about two hours for the palbociclib particles according to claim 1 of the main request, i.e. a 12-fold to 24-fold improvement in filtration rate – much more than expected.

The board does not agree.

As submitted by the opponents, the extent of the improvement in filterability achieved by the claimed particles is not part of the objective technical problem as formulated by the patent proprietor. Irrespective of this, as set out above, a skilled person trying to improve filterability would have increased the particle size even if they were not expecting an improvement as high as achieved in the patent, and would thus have arrived at the claimed subject-matter. Thus the patent proprietor's submission is not convincing.

7.2 Bioavailability compatible with commercial use

As submitted by the opponents, the skilled person would have expected larger particles to have a bioavailability compatible with commercial use.

D40, which was publicly available before the priority date of the opposed patent, discloses phase 1 and phase 2 trials of four different palbociclib formulations (see the paragraph under "*Purpose*" on page 1). The

table on page 2 of D40 discloses the following two formulations:

- "NF1" (second row of the table), a hard capsule including the free base of palbociclib with a "small" particle size

- "NF2" (third row of the table), a hard capsule including the free base of palbociclib with a "large" particle size

D40 refers to a "*Bio-availability Study*" (page 1, under "*Study Design*").

Although the results of these trials were not available, this at least suggests that the bioavailability of the free base was acceptable for a clinical trial.

Thus, a skilled person seeking to provide a crystalline form of palbociclib having a bioavailability compatible with commercial use would have provided a free base of palbociclib with a large particle size, implying a reduced specific surface area and a higher D[4,3] value, both as required by claim 1 of the main request.

This was disputed by the patent proprietor.

First, the patent proprietor submitted that D1 encouraged the skilled person to seek new salt forms of palbociclib since the free base of palbociclib was disclosed as having poor water solubility and low bioavailability in animal studies. This was consistent with the fact that the free base of palbociclib in D1 was only disclosed as an intermediate and not as a product worthy of being made and tested itself. Rather than being encouraged by D1 to try and find a better free-base form, the skilled person was told to

disregard the free base of palbociclib and seek new salt forms instead. The inherent disadvantages of the free base would be considered to disqualify it from further consideration. According to the patent proprietor, D1 taught away from the claimed invention.

The board does not find the patent proprietor's submission convincing. Contrary to the patent proprietor's opinion, the free base of palbociclib is not only disclosed as an intermediate product. Page 13, lines 3 to 5 of D1 refers to, *inter alia*, figure 17 and discloses that the free base of palbociclib ("*the free base*") exhibits less than a 2% change in mass when exposed to humidity levels ranging from 10% RH to 90% RH at 25°C. Lastly, the passage on page 16, lines 31 to 34 of D1 discloses that compounds of formula 1, i.e. the free base of palbociclib, may be administered as crystalline or amorphous products. The low hygroscopicity of the free base of palbociclib represents an important property for the physicochemical stability of pharmaceutical products, and so the skilled person would not have disregarded the free base of palbociclib in view of the teaching of D1.

Furthermore, even if D1 did teach that the free base of palbociclib has poor bioavailability, the skilled person would have considered free-base forms of palbociclib to be worthy of further investigation in view of the clinical trial of D40. For that reason too, the skilled person would not have disregarded the free base of palbociclib disclosed in D1.

Second, the patent proprietor submitted that the skilled person was also aware that while coarser particles, at least in general terms, were easier to handle and had better manufacturing properties, poorly

soluble drugs such as palbociclib were more readily bioavailable when administered as fine particles.

The board is not convinced. As set out above, D40 discloses that the bioavailability of the palbociclib free base in both "small" and "large" particle form was studied. Thus D40 explicitly teaches larger particles as an option to provide a bioavailability compatible with commercial use, and the skilled person would not have disregarded this option.

7.3 For the reasons given above, a skilled person trying to solve the objective technical problem would have arrived at larger particles, i.e. particles having a specific surface area and D[4,3] value as claimed. The solution was therefore obvious to the skilled person. Thus, the subject-matter of claim 1 of the main request does not involve an inventive step.

8. The main request is therefore not allowable.

9. In arriving at this conclusion, the board took A046 and the effect of bioavailability compatible with commercial use into account. The opponents objected to the admittance of A046. They also contended that the effect of a bioavailability compatible with commercial use could not be taken into account in view of G 2/21.

Since the overall decision is in the opponents' favour, there is no need to provide reasons for the admittance of A046 and for taking the effect of a bioavailability compatible with commercial use into account.

Auxiliary request 1A

10. Claim 1 of auxiliary request 1A is identical to claim 1 of the main request. It follows that the reasons given for claim 1 of the main request apply *mutatis mutandis* to claim 1 of auxiliary request 1A.

11. Auxiliary request 1A is therefore not allowable.

Auxiliary requests 2, 4 and 6

12. Compared with claim 1 of the main request, claim 1 of auxiliary request 2 restricts the specific surface area to a narrower range of between 0.2 m^2/g and 2 m^2/g.

13. Compared with claim 1 of the main request, claim 1 of auxiliary request 4 specifies that polymorph A has a ^{13}C solid state NMR spectrum comprising the following resonance (ppm) values: 12.5 ppm, 112.4 ppm and 143.2 ppm ± 0.2 ppm.

14. Claim 1 of auxiliary request 6 is a combination of claim 1 of auxiliary requests 2 and 4.

15. At the oral proceedings, the patent proprietor referred to its written submissions with regard to the inventive step of the subject-matter of claim 1 of auxiliary requests 2, 4 and 6. In its statement of grounds of appeal (point 4.1.1) and the reply to opponent 3's grounds of appeal (point 2.1), it relied on the reasoning submitted in the context of claim 1 of the main request and did not comment on the relevance of the limitations of claim 1 of auxiliary requests 2, 4 and 6 identified above. In the absence of any submission on the relevance of the limitations in these auxiliary requests, the reasons given for claim 1 of the main request apply *mutatis mutandis* to claim 1 of any of auxiliary requests 2, 4 and 6.

16. Auxiliary requests 2, 4 and 6 are not allowable.

Auxiliary request 9b

17. Claim 1 of auxiliary request 9b is directed to a method of making the compound of claim 1 of the main request. It reads as follows:

"*1. A method of making a crystalline free base of 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one, having a BET Nitrogen measured specific surface area of ≤ 2 m^2/g, a volume mean diameter characterized by a D[4,3] value measured by laser diffraction of from 15 µm ± 20% to 40 µm ± 20%, and wherein the crystalline free base is a polymorph Form A of the free base having a powder X-ray diffraction pattern comprising a peaks* [sic] *at diffraction angle (2θ) of 8.0 ± 0.2, 10.1 ± 0.2 and 11.5 ± 0.2, comprising the steps of:*
(a) suspending 4-{6-[6-(1-butoxyl-vinyl)-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic acid tert-butyl ester in a mixture of water and a first solvent which is an alcohol and heating to achieve dissolution;
(b) adding an acid to produce the acid addition salt of 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2, 3-d]-pyrimidin-7-one in situ;
(c) adding a second solvent which is an aromatic solvent and an aqueous base to a pH of ≥10;
(d) separating the organic layer and heating to distill off water;
(e) ***cooling to an appropriate temperature*** *and providing seed crystals of 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one free base Form A;*

(f) gradually cooling the mixture to achieve crystallization; and
(g) isolating the resulting product" (emphasis added by the board).

18. Clarity – claim 1 – Article 84 EPC

18.1 Step (e) of claim 1 of auxiliary request 9b is a step of cooling the organic layer obtained in step (d) to an appropriate temperature (step (e)).

18.2 Opponents 2 and 3 contended that the term "*cooling to an appropriate temperature*" in claim 1 of auxiliary request 9b was not clear.

18.3 The set of claims as granted does not contain any method claim, nor does it recite the term "*cooling to an appropriate temperature*". In so far as claim 1 of auxiliary request 9b refers to this term, it is open to an assessment of clarity under Article 84 EPC (G 3/14; OJ EPO 2015, A102, order).

18.4 Pursuant to Article 84 EPC, the claims must define the matter for which the protection is sought. Hence, the purpose of this provision is to enable the scope of protection to be determined. To this end, it is necessary to determine what is covered by a claim at issue. For this, the claims have to be clear as such.

In the case in hand, the question to be answered was whether a particular temperature was an "*appropriate temperature*". The skilled person cannot make this assessment since the wording of claim 1 of auxiliary request 9b does not allow them to determine the conditions under which a temperature is an "*appropriate temperature*". Therefore, the phrase "*cooling to an*

appropriate temperature" used in step (e) of claim 1 of auxiliary request 9b is not clear.

18.5 The patent proprietor submitted that the skilled person was very familiar with heating and cooling steps, which were inherent to any (re)crystallisation process. It was a routine task for the skilled person to determine said appropriate temperature by reasonable trial-and-error experiments. Hence, the feature "appropriate temperature" of step (e) was a functional feature related to a process step which could easily be performed in order to obtain the desired result.

The board does not agree. The patent proprietor's submission is relevant for sufficiency of disclosure rather than for the clarity of the claim. As set out above, the relevant issue was what is covered by claim 1 of auxiliary request 9b, not whether the skilled person could reproduce the claimed method.

18.6 The board thus concludes that claim 1 of auxiliary request 9b is not clear and does not meet the requirements of Article 84 EPC.

19. Auxiliary request 9b is not allowable.

Auxiliary request 10a

20. Like claim 1 of auxiliary request 9b, claim 1 of auxiliary request 10a relates to a method of making the compound of claim 1 of the main request.

Steps (a) to (g) of claim 1 of auxiliary request 10a read as follows:

"*(a) suspending 4-{6-[6-(1-butoxyl-vinyl)-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl}-piperazine-1-carboxylic acid tert-butyl ester in a*

mixture of water and n-butanol and heating to ***about*** *70°C achieve* [sic] *dissolution;*
(b) adding concentrated HCl and heating at ***about*** *70°C for 4-6 hours;*
(c) adding anisole and aqueous NaOH to achieve a biphasic mixture having a pH of >10;
(d) separating the layers and heating the organic layer to ***about*** *120°C to distill off water;*
(e) cooling to ***about*** *80°C and providing seed crystals of 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one free base Form A;*
(f) maintaining the mixture at ***about*** *80°C for* ***about*** *3 hours and then gradually cooling to* ***about*** *10°C to achieve crystallization;* and
(g) filtering to isolate the resulting product" (emphasis added by the board).

21. Claim 1 – Article 84 EPC

21.1 Claim 1 of auxiliary request 10a includes the following terms: "*heating to about 70°C*", "*heating at about 70°C*", "*heating the organic layer to about 120°C*", "cooling to about 80°C", "*maintaining the mixture at about 80°C for about 3 hours*" and "*gradually cooling to about 10°C*".

21.2 Opponent 3 contended that the term "*about*" in claim 1 of auxiliary request 10a was not clear.

21.3 As set out above in the context of auxiliary request 9b, the set of claims as granted does not contain any method claim. Furthermore, the set of claims as granted does not recite the wording identified in point 21.1 above. In so far as claim 1 of auxiliary request 10a

refers to these terms, it is open to an assessment of clarity under Article 84 EPC (G 3/14; supra, order).

As already set out above in the context of claim 1 of auxiliary request 9b, claims have to be clear as such so that it can be determined what is covered by a claim at issue.

The term "*about*" in the context of claim 1 of auxiliary request 10a is associated with a specific temperature or a specific time. It may be that the term "*about*" is intended to cover measurement errors. However, measurement errors are covered for any value of any technical parameter to be measured and given in any claim (without the need for the term "*about*") since patents are in the field of technology, not mathematics, and a value can only be as precise as it can be measured according to the general technological convention. Thus, following this interpretation, the term "*about*" is superfluous and claim 1 is not concise, contrary to what is required by Article 84 EPC. Alternatively, the term "*about*" may be intended to denote a range broader than the measurement error range. Following this second interpretation, it cannot be determined how broad the range can be in claim 1 of auxiliary request 10a and what the exact limits of this range are. In this case, the term "*about*" in said claim is not clear, again contrary to what is required by Article 84 EPC.

21.4 The patent proprietor submitted that the term "*about*" was clear in light of the description of the patent since paragraph [0020] gave a clear definition of the term.

The board does not agree. As set out above, the claims have to be clear as such, i.e. without taking the description into account to interpret any unclear term. Thus, for that reason alone, the patent proprietor's submission is not convincing.

Furthermore, as submitted by opponent 3, even if the fact that the claims have to be clear as such were disregarded and it were accepted that the description could be consulted in the context of Article 84 EPC, paragraph [0020] of the patent reads as follows: "*[...], the term "about" means* ***within a statistically meaningful range of a value****, such as a stated concentration range, time frame, molecular weight, particle size, temperature or pH. Such a range can be within an order of magnitude, typically within 20%, more typically within 10%, and even more typically within 5% of the indicated value or range*" (emphasis added by the board).

Paragraph [0020] of the patent thus defines the term "*about*" as "*within a statistically meaningful range of a value*". In the board's view, the term "*statistically meaningful range*" does not clearly define a range and for that reason is unclear. When asked by the board at the oral proceedings, the patent proprietor submitted that the term "*statistically meaningful range*" was specified in the following sentence in the paragraph by relative variations in percent. Even if this were accepted too, the term would still be unclear since the following sentence contains various different percentages ("*typically within 20%, more typically within 10%, and even more typically within 5% of the indicated value or range*"). Contrary to the patent proprietor's submission that the skilled person would choose the broadest range, there is no teaching in this

following sentence to choose the percentage within 20% of the indicated value, in view of the lower preference of the term "*typically*" compared with the two other terms "*more typically*" and "*even more typically*".

21.5 Furthermore, the patent proprietor submitted that the term "*about*" was to be considered clear in light of chapter F-IV, 4.7.1 of the Guidelines for Examination in the European Patent Office, 2021 ("Guidelines").

The board is not convinced by the patent proprietor's submissions.

For post-grant proceedings, Article 84 EPC is not available unless there are amended claims. If there are none, the claims must be interpreted as they stand, e.g. to assess novelty.

In the case in hand, however, auxiliary request 10a contains claims with amendments based on the application as filed, which are therefore open to an assessment of clarity under Article 84 EPC.

The title of chapter F-IV, 4.7.1 of the Guidelines relied on by the patent proprietor is "*Interpretation of terms such as 'about', 'approximately' or 'substantially'*". This chapter relates to the interpretation of terms such as "*about*", not to the assessment of the clarity of such terms.

Thus, the patent proprietor's submission that the term "*about*" was to be considered clear in light of chapter F-IV, 4.7.1 of the Guidelines is not convincing.

21.6 In view of all the above, it is concluded that the term "*about*" in claim 1 of auxiliary request 10a does not meet the requirements of Article 84 EPC.

22. Auxiliary request 10a is thus not allowable.

23. None of the patent proprietor's requests is allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

H. Jenney M. O. Müller

Decision electronically authenticated