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Datasheet for the decision of 10 September 2021

Case Number: T 0325/16 - 3.3.02

Application Number: 10774734.7

Publication Number: 2431376

IPC: C07H19/06, A61K31/7068, A61P35/00

Language of the proceedings: EN

Title of invention:
NOVEL STABLE CRYSTAL OF 1-(2'-CYANO-2'-DEOXY-BETA -D-ARABINOFURANOSYL)CYTOSINE MONOHYDROCHLORIDE

Patent Proprietor:
Delta-Fly Pharma, Inc.

Opponent:
KELTIE LLP

Headword:

Relevant legal provisions:
EPC Art. 123(2), 83, 54, 56
RPBA Art. 12(4)

Keyword:
Amendments
Sufficiency of disclosure
Novelty
Inventive step
Late-filed facts
Late-filed case law

Decisions cited:
R 0017/09, T 2988/18, T 1684/16, T 1914/12, T 0777/08, T 0605/02, T 0861/93

Catchword:

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Case Number: T 0325/16 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 10 September 2021

Appellant: (Patent Proprietor)	Delta-Fly Pharma, Inc. 37-2, Nishikino, Miyajima Kawauchi-cho Tokushima-shi, Tokushima 771-0116 (JP)
Representative:	Blodig, Wolfgang Wächtershäuser & Hartz Patentanwaltspartnerschaft mbB Weinstrasse 8 80333 München (DE)
Respondent: (Opponent)	KELTIE LLP No.1 London Bridge London SE1 9BA (GB)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 21 December 2015 revoking European patent No. 2431376 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	A. Lenzen
	R. Romandini

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the patent proprietor (hereinafter: appellant) against the decision of the opposition division (hereinafter: decision under appeal) to revoke European patent No. 2 431 376 (hereinafter: patent).

II. In the proceedings before the opposition division, the opponent (hereinafter: respondent) requested revocation of the patent in its entirety on the grounds for opposition pursuant to Article 100(a) (lack of novelty and inventive step), Article 100(b) and Article 100(c) EPC.

III. The following documents, cited during the opposition proceedings, are relevant for this decision:

D1 EP 0 535 231 A1

D3 Azuma, A. *et al.*, "2'-*C*-Cyano-2'-deoxy-1-β-D-arabinofuranosylcytosine and Its Derivatives. A New Class of Nucleoside with a Broad Antitumor Spectrum", J. Med. Chem. 1993, 36, pp. 4183-4189

D5 Caira, M. R. "Crystalline Polymorphism of Organic Compounds", Topics in Current Chemistry, vol. 198, Springer Verlag Berlin Heidelberg 1998, pp. 163-208

D14 Experimental report (32 pages, filed with the notice of opposition)

D15 Byrn, S. *et al.*, "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations", Pharmaceutical Research, vol. 12, no. 7, 1995, pp. 945-954

D23 Declaration (2 pages, filed with the appellant's letter dated 16 October 2015)

IV. The opposition division's decision, in so far as it is relevant for the present decision, may be summarised as follows.

- D23 was not admitted into the proceedings.
- The grounds for opposition pursuant to Article 100(b) and 100(c) EPC did not prejudice the maintenance of the patent as granted. Its claimed subject-matter was also novel over D1 and D3 but did not involve an inventive step over D3 as the closest prior art.

V. With its reply to the statement of grounds of appeal, the respondent filed:

D25 Second experimental report (10 pages)

VI. With a letter dated 24 March 2017, the appellant filed the set of claims of the main request.

VII. In preparation for the oral hearing, which had been scheduled at the parties' request, the board issued a communication pursuant to Article 15(1) RPBA 2007.

VIII. At the oral hearing on 10 September 2021, which took place as a videoconference in the presence of both parties, the board decided to:

- confirm the opposition division's decision to not admit D23 into the proceedings
- not admit D25 into the proceedings
- admit the appellant's submission based on decision T 1684/16 into the proceedings

IX. 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 based on the set of claims of the main request filed with its letter dated 24 March 2017
- the opposition division's decision to not admit D23 into the proceedings be overturned
- D25 not be admitted into the proceedings
- its submission based on decision T 1684/16 be admitted into the proceedings

The respondent requested that:

- the appeal be dismissed, implying that the opposition division's decision to revoke the patent be confirmed
- the opposition division's decision to not admit D23 into the proceedings be confirmed
- the appellant's submission based on decision T 1684/16 not be admitted into the proceedings

X. The appellant's appeal case, where relevant for the present decision, can be summarised as follows.

- The respondent's experiments in D25 could and should have been filed earlier. D25 should not be admitted into the proceedings.

- Claim 2 of the main request was based on claims 2 and 4; page 16, lines 25 to 27; and example 3 of the application as filed. It met the requirements of Article 123(2) EPC.

- The respondent's attempts in D14 were not accurate repetitions of example 3 of the patent. There could be no doubt that the method described in example 3 yielded type II crystals of CNDAC-HCl as defined in claim 2 of the main request.

  The respondent's arguments that the method of claim 4 of the main request could not lead to type II crystals of CNDAC-HCl because the temperature of Et_2O was not specified and because the addition sequence was different in example 3 of the patent were mere unsubstantiated allegations. Example 3 provided clear guidance on the temperature of Et_2O. Moreover, when added to the solution of CNDAC-HCl in EtOH, Et_2O, regardless of its temperature, rapidly took on the temperature of the solution. The conditions of claim 4, therefore, were comparable to those of example 3 of the patent.

  Hence, the inventions as stipulated in claims 2 and 4 of the main request were sufficiently disclosed.

- Because the crystallisation conditions typically had an influence on which crystal form was eventually obtained and because neither D1 nor D3 provided any information on the crystallisation of CNDAC-HCl, their disclosures were not enabling for type I crystals. D1 and D3, therefore, were not novelty-destroying for claim 1 of the main request.

- The disclosures of D1 and D3 were comparable and could at most be considered enabling for crystalline CNDAC-HCl, of whatever form. The type I, II and III crystals of CNDAC-HCl described in the patent in examples 2 to 4 were representative

of a crystalline CNDAC-HCl. The limitation to type I and type II crystals in claims 1 and 2 of the main request was a selection from the more general teachings of D1/D3. The experimental data in the patent (paragraph [0043] and table 11, entries two and four) showed that type I and type II crystals were more stable than type III crystals. Hence, the effect linked to the selection of the type I and type II crystals in the claims of the main request was a higher stability of the crystalline CNDAC-HCl. The objective technical problem had to be seen in the provision of an anti-tumour agent containing a crystalline form of CNDAC-HCl with a higher stability. In view of the reasoning in decision T 1648/16, the solution to this problem in the form of claims 1 and 2 had to involve an inventive step.

- The board's view that arguments based on a decision of a board could not be held inadmissible was correct.

XI. The respondent's appeal case, where relevant for the present decision, can be summarised as follows.

- The experiments in D25 were carried out in response to the conclusions in the opposition division's decision on D14. They were highly pertinent to patentability and should therefore be admitted into the proceedings.

- The amended upper limit of the melting point range in claim 2 of the main request was disclosed only in example 3 of the application as filed. However, this example referred to a specific polymorph of which only a few XRPD peaks were mentioned in claim 2. This resulted in an unallowable intermediate

generalisation, and thus claim 2 did not meet the requirements of Article 123(2) EPC.

- The experiments in D14 showed that example 3 of the patent did not yield type II but type I crystals of CNDAC-HCl. Furthermore, the method of claim 4 of the main request did not mention the temperature of Et_2O, and the order of addition was also different in example 3. Consequently, the inventions as stipulated in claims 2 and 4 of the main request were not sufficiently disclosed.

- D1 and D3 taught the crystallisation of CNDAC-HCl, i.e. a known anti-tumour agent, from EtOH-Et_2O. As shown in D14, the teachings of D1 and D3 inevitably led to type I crystals. Because the combination of an API, such as type I crystals of CNDAC-HCl, with a pharmaceutically acceptable carrier was routine practice for the skilled person, the subject-matter of claim 1 did not involve an inventive step.

  Even if it were concluded that neither D1 nor D3 implicitly disclosed type I crystals, these documents nevertheless still disclosed crystalline CNDAC-HCl with a melting point of 175-176 °C. The appellant had not provided a comparison with this form. The objective technical problem could therefore only be seen in the provision of an alternative anti-tumour agent. The solution to this problem did not involve an inventive step.

  The examples of the patent showed that type I crystals of CNDAC-HCl were more stable than type II and type III crystals. However, it could not be concluded that type II crystals were more stable than type III crystals because the temperatures

under which these two crystal types were stored during the stability studies were different.

Even if it were concluded that the type I and type II crystals of CNDAC-HCl were more stable than the type III crystals and that the objective technical problem had to be formulated in more ambitious terms as done by the appellant, the solution to this problem still did not require an inventive step. This was because the common general knowledge suggested screening for polymorphs having improved properties such as improved stability. Therefore, the type I and type II crystals as defined in claims 1 and 2 of the main request would have been the inevitable consequence of this screening.

- The appellant's submission based on decision T 1684/16 was only presented at the oral hearing before the board. It was late and should not be admitted into the proceedings.

Reasons for the Decision

The subject-matter of the main request and the patent as granted

1. The set of claims of the main request consists of the following four claims:

Claim 1

"*An anti-tumor agent consisting of a type I crystal of 1-(2'-cyano-2'-deoxy-β-D-arabinofuranosyl)cytosine monohydrochloride having characteristic peaks at 13.7°, 15.7°, 16.0°, 18.6°, 20.3°, and 22.7° as diffraction angles (2θ ± 0.1°)*

measured by powder X-ray diffraction, and having a melting point of 192°C to 197°C, and a pharmaceutically acceptable carrier."

Claim 2

"*An anti-tumor agent consisting of a type II crystal of 1-(2'-cyano-2'-deoxy-β-D-arabinofuranosyl)cytosine monohydrochloride having characteristic peaks at 6.4°, 12.6°, 17.3°, and 21.7° as diffraction angles (2θ ± 0.1°) measured by powder X-ray diffraction, and having a melting point of 192°C to 196°C, and a pharmaceutically acceptable carrier.*"

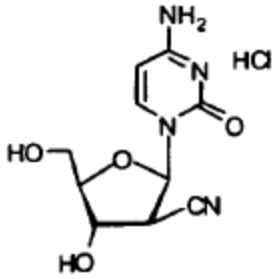
Claim 3

"*A method for production of a type I crystal as defined in claim 1, comprising the steps of dissolving under heating 1-(2'-cyano-2'-deoxy-β-D-arabinofuranosyl)cytosine monohydrochloride in ethanol, and then adding this solution dropwise into diethyl ether that has been cooled to 0 ± 5°C while stirring the mixture, to obtain the type I crystal.*"

Claim 4

"*A method for production of a type II crystal as defined in claim 2, comprising the steps of dissolving under heating 1-(2'-cyano-2'-deoxy-β-D-arabinofuranosyl)cytosine monohydrochloride or the type I crystal in ethanol, subsequently cooling this solution to 40 ± 5°C, and then adding diethyl ether dropwise to the solution while stirring the mixture, to obtain the type II crystal.*"

2. In accordance with both parties, the compound referred to in these claims, i.e. 1-(2'-cyano-2'-deoxy-β-D-arabinofuranosyl)cytosine monohydrochloride, is abbreviated as CNDAC-HCl in this decision. It has the following structure:



The patent (paragraphs [0003] to [0005], [0011] and [0012]) acknowledges, by reference to previously published documents, that this compound was known for its anti-tumour activity before the priority date of the patent.

3. Thus, claims 1 and 2 of the main request relate to anti-tumour agents consisting of a pharmaceutically acceptable carrier and different crystalline forms of CNDAC-HCl (i.e. polymorphs), namely a type I and a type II crystal, respectively. Claims 3 and 4 relate to methods for preparing these two types of crystals.

The patent discloses one further crystalline form of CNDAC-HCl, namely a type III crystal. The type I, II and III crystals of CNDAC-HCl are prepared in examples 2, 3 and 4 of the patent, respectively.

4. Claims 1, 3, 7 and 8 of the patent as granted are also of relevance for the present decision. Claims 1 and 3 are directed to the type I and type II crystals of CNDAC-HCl themselves, i.e. as defined in claims 1 and 2 of the main request. Claims 7 and 8 of the patent as

granted are virtually identical to claims 3 and 4 of the main request.

Admittance of D23

5. D23 was filed by the appellant before the opposition division. The opposition division decided to not admit this document into the proceedings. At the oral hearing, the board decided to confirm this decision. Since the outcome of this appeal is favourable to the appellant, reasons do not need to be given for this decision.

Admittance of D25

6. D25 is an experimental report filed by the respondent with its reply to the statement of grounds of appeal. The appellant requested that D25 not be admitted into the proceedings.

7. Two parts of D25 are relevant for this decision.

7.1 In the first part (section 3.2), the preparation of CNDAC-HCl is repeated according to D3.

The preparation of CNDAC-HCl and its subsequent crystallisation are described in D3 as follows (paragraph bridging pages 4187 and 4188; annotations in square brackets by the board):

> "*A solution of 6b (400 mg, 1.4 mmol)* [i.e. N-acetylated CNDAC] *in 1% HCl/MeOH (30 mL) was kept for 50 min at room temperature. The solvent was removed in vacuo and coevaporated several times with EtOH, and the resulting solid was crystallized from EtOH-Et_2O to furnish 1i·HCl* [i.e. CNDAC-HCl]

as a hydrochloride (360 mg, 89%): mp 175-176 °C; ... Annal ($C_{10}H_{12}N_4O_4 \cdot HCl \cdot ½EtOH$) C, H, N."

Thus, the preparation of CNDAC-HCl started out from N-acetylated CNDAC. Its acetyl group was cleaved in 1% HCl/MeOH to give CNDAC-HCl in solution. Solvent removal *in vacuo* and several coevaporations with EtOH completed the preparation of CNDAC-HCl. Therefore, this preparation of CNDAC-HCl entails a "first intermediate" (after removal of 1% HCl/MeOH *in vacuo*) and "further intermediates" (after each coevaporation with EtOH).

After its preparation, CNDAC-HCl is stated to have been crystallised from EtOH-Et_2O.

7.1.1 According to the respondent, D25 showed that:

- the first intermediate was composed of type II crystals
- some of the further intermediates comprised, apart from type II crystals, trace amounts of type I crystals

In its reply to the statement of grounds of appeal, the respondent put forward novelty objections to claims 1 and 3 as granted based on the first and further intermediates above.

7.1.2 However, these novelty objections had not been raised before the opposition division. The respondent justified filing these objections and the corresponding experimental data in D25 only on appeal by arguing that they were "*[i]n response to the Opposition Division's view that the prior art is silent on details of the crystallisation conditions*" (reply to the statement of

grounds of appeal, page 16, first sentence). However, before the opposition division, the respondent had only ever argued that the crystallisation from EtOH-Et_2O, i.e. the step performed in D3 after the preparation of CNDAC-HCl, i.e. after the above-mentioned first and further intermediates, inevitably led to type I crystals. This was what the opposition division did not agree with. Now, on appeal, the respondent focused on different aspects of D3, namely the preparation steps performed before the crystallisation from EtOH-Et_2O. The new objections and the corresponding data in D25 were therefore not in response to the opposition division's reasoning in the decision under appeal.

7.2 The second part of D25 (section 4) reports on the solubility of CNDAC-HCl type I crystals in EtOH and Et_2O at different temperatures.

7.2.1 According to the respondent, these data supported its sufficiency objection based on D14 (section 3.4.2, see further below).

7.2.2 However, the respondent did not explain why the solubility data of D25 were filed only on appeal.

8. The board had noted in its communication pursuant to Article 15(1) RPBA 2007 that D25 could and should have been filed before the opposition division and consequently that D25 should not be admitted into the proceedings. At the oral hearing before the board, the respondent merely referred to its previous written submission in this respect. However, none of the respondent's submissions made after the board's communication addressed the admittance of D25. Therefore, the board saw no reason to depart from its preliminary view at the oral hearing. D25 was not

admitted into the proceedings (Article 12(4) RPBA 2007).

Main request - amendments (Article 123(2) EPC)

9. Claim 2 of the main request is based, *inter alia*, on the combination of claims 2 and 4 as filed. Compared to this combination of claims, the following additional amendments have been made to claim 2 of the main request (additions are indicated by bold type, deletions by strikethrough):

> "*An anti-tumor agent* ***consisting of*** ~~*comprising*~~ *a* ***type II*** *crystal of 1-(2'-cyano-2'-deoxy-β-D-arabinofuranosyl)cytosine monohydrochloride having characteristic peaks at 6.4°, 12.6°, 17.3°, and 21.7° as diffraction angles (2θ ± 0.1°) measured by powder X-ray diffraction, and having a melting point of 192°C to* ***196*** ~~*197*~~*°C,* ***and a pharmaceutically acceptable carrier.***"

Thus, the anti-tumour agent has been further specified as consisting of an active pharmaceutical ingredient (API; in this case, a type II crystal of CNDAC-HCl) and a pharmaceutically acceptable carrier. Basis for this definition can be found on page 16, lines 25 to 27 of the application as filed.

Furthermore, the API has been specified as a type II crystal whose melting point range now has a slightly lower upper limit of only 196 °C. Basis for these amendments can be found in example 3 of the application as filed, which describes the preparation of a type II crystal. This crystal is characterised as having a melting point range of 192 to 196 °C (page 20, line 26). As correctly observed by the respondent, this

example refers to the XRPD spectrum in figure 2 of the application as filed with regard to this type of crystal and this spectrum shows more peaks than the four mentioned in claim 2 of the main request. However, example 3 expressly identifies these four peaks as "characteristic peaks" (page 20, lines 19 to 25), i.e. as peaks sufficient for characterising type II crystals and distinguishing them from other CNDAC-HCl crystals. It cannot therefore be concluded, as the respondent did, that the combination of the more limited melting point range and the four XRPD peaks in claim 2 of the main request was not directly and unambiguously disclosed in the application as filed or that their combination resulted in an unallowable intermediate generalisation. This view was already set out by the board in its communication pursuant to Article 15(1) RPBA 2007 and not challenged by the respondent at the oral hearing.

In summary, claim 2 is based on the following parts of the application as filed: claims 2 and 4; page 16, lines 25 to 27; and example 3.

10. Claim 1 of the main request was not objected to by the respondent. Its subject-matter in the board's view meets the requirements of Article 123(2) EPC. Similar to claim 2, claim 1 of the main request is based on the following parts of the application as filed: claims 1 and 4; page 16, lines 25 to 27; example 2 and more specifically page 19, lines 14 to 23, which highlights the melting point range and the characteristic XRPD peaks in claim 1 for type I crystals of CNDAC-HCl.

11. In its reply to the statement of grounds of appeal, the respondent also objected to claims 7 and 8 of the patent as granted. These objections apply *mutatis*

mutandis to claims 3 and 4 of the main request because they are virtually identical to claims 7 and 8 of the patent as granted.

Claims 7 and 8 of the patent as granted were objected to because they referred to dependent claims which allegedly did not meet the requirements of Article 123(2) EPC. Since the main request no longer contains these dependent claims, these objections have become moot.

Claim 8 of the patent as granted was also objected to because it referred to claim 3 as granted which allegedly suffered from the same deficiency as discussed above for claim 2 of the main request. However, as concluded above, claim 2 of the main request meets the requirements of Article 123(2) EPC. The objection against claim 8 of the patent as granted, in as much as it applies to claim 4 of the main request, is therefore not convincing.

Notwithstanding the above, the subject-matter of claims 3 and 4 of the main request finds a basis in the application as filed as follows:

- claim 3: page 14, lines 1 to 5 and example 2
- claim 4: page 14, lines 6 to 11 and example 3

12. In summary, the claims of the main requests meet the requirements of Article 123(2) EPC.

Main request - sufficiency of disclosure (Article 83 EPC)

13. As mentioned above, example 3 of the patent describes the preparation of type II crystals of CNDAC-HCl as defined in claim 2 of the main request. According to

this example, a solution of CNDAC-HCl in EtOH at 40 °C was added dropwise to Et_2O, heated at reflux. The resulting mixture was stirred for one hour under reflux, and the desired type II crystals were isolated by filtration.

In view of this example, the respondent argued that the inventions as stipulated in claims 2 and 4 of the main request were not sufficiently disclosed.

13.1 As regards claim 2, the respondent pointed to its attempts in D14 (sections 3.4.1 and 3.4.2) to repeat example 3 of the patent. These results showed that not type II but type I crystals were obtained when following the procedure of example 3 of the patent. Consequently, the specification of the patent failed to provide the skilled person with enough information to prepare a type II crystal of CNDAC-HCl as defined in claim 2 of the main request.

13.1.1 In the experiment described in section 3.4.1 of D14, CNDAC-HCl was dissolved in EtOH at 80 °C, the temperature of the heating bath was reduced to 70 °C, and the solution was added dropwise to Et_2O, heated at 40 °C. The resulting precipitate was analysed and turned out to be a type I crystal.

This procedure differs from example 3 of the patent at least in that the solution of CNDAC-HCl in EtOH was at a higher temperature when added to Et_2O, namely about 70 °C (D14, section 3.4.1) compared to 40 °C (patent, example 3). The board concurs with the opposition division that this cannot be regarded as an accurate repetition of example 3 of the patent (decision under appeal, point 1.2.2 on p. 8 ff).

13.1.2 In the experiment described in section 3.4.2 of D14, a solution of CNDAC-HCl in EtOH was first prepared at elevated temperature. Upon cooling to e.g. 40 °C, a precipitate was formed. Analysis of this precipitate revealed that it was made up of type I crystals.

Again, the board agrees with the opposition division that this procedure cannot be regarded as an accurate repetition of example 3 of the patent. As is clear from the summary above (point 13), example 3 requires that a solution of CNDAC-HCl in EtOH be added to Et_2O. In contrast, in the respondent's repetition in D14, the solution of CNDAC-HCl in EtOH was not added to Et_2O. While it is true that a precipitation is not described in example 3 of the patent upon cooling the solution of CNDAC-HCl in EtOH to 40 °C, the mere occurrence of such a precipitate would not have prevented the skilled person from adding only the supernatant solution to Et_2O - something the respondent deliberately chose not to do.

13.1.3 The respondent's experiments in D14, therefore, cannot challenge the sufficiency of the invention as stipulated in claim 2 of the main request.

13.2 As regards claim 4, the respondent argued that the order of addition in example 3 of the patent (as stated above, a solution of CNDAC-HCl in EtOH was added to Et_2O) was different in claim 4 (Et_2O is added to a solution of CNDAC-HCl in EtOH). Furthermore, contrary to example 3, claim 4 made no mention of the temperature of Et_2O when added to the solution of CNDAC-HCl in EtOH. In the absence of any limitation on the temperature, the method of claim 4 could give rise to a number of different crystal forms.

The board cannot accept these arguments either. As stated by the opposition division (decision under appeal, point 3.3 on page 16), the temperature of the cooled CNDAC-HCl solution in EtOH (40 °C) is essential when carrying out the process according to example 3 of the patent. Essentially the same temperature is mentioned in claim 4 (40±5 °C). The fact that the temperature of Et_2O is not specified in claim 4 is irrelevant for sufficiency in the case at issue because example 3 provides clear guidance in this respect, namely that both Et_2O and the solution in EtOH should have approximately the same temperature. In addition, as stated by the appellant (letter of 24 March 2017, page 7, point 12) and not disputed by the respondent at the oral hearing, the Et_2O quickly adopts the temperature of the solution when added dropwise to it so that the method of claim 4 involves conditions comparable to those of example 3 of the patent. Finally, the argument that the order of addition had an influence on the crystal type obtained is an unsubstantiated allegation by the respondent who bears the burden of proof. For this reason alone, it is not convincing.

14. In summary, the inventions as stipulated in the claims of the main request are sufficiently disclosed.

Main request - novelty (Article 54 EPC)

15. In its reply to the statement of grounds of appeal, the respondent objected to the lack of novelty of claims 1 and 3 of the patent as granted. As outlined above, these claims relate to the type I and type II crystals of CNDAC-HCl themselves. Since the anti-tumour agents of claims 1 and 2 of the main request contain these

crystal types, these objections are also relevant for the main request.

15.1 In a first line of argument, the respondent objected to the lack of novelty of claims 1 and 3 of the patent as granted (i.e. the type I and type II crystals of CNDAC-HCl, respectively) over the first and further intermediates disclosed in D3 (see above), arguing that these intermediates were made up of type II crystals or a mixture of type II and type I crystals as shown by D25.

However, as D25 is not part of the proceedings, these objections are unsubstantiated allegations and for this reason alone not convincing.

15.2 In a second line of argument, the respondent objected that claim 1 of the patent as granted (i.e. the type I crystals of CNDAC-HCl) lacked novelty over the crystalline end products disclosed in D1/D3, arguing that type I crystals were inevitably obtained when following the procedures of these documents for the crystallisation of CNDAC-HCl from EtOH-Et_2O.

15.2.1 The relevant part of D3 has been quoted above under point 7.1.

The relevant part of D1 (example 9) reads as follows (annotation in square brackets by the board):

> "*In 5 ml of 3% hydrochloric acid-methanol was dissolved 40 mg of the compound of Example 8* [i.e. CNDAC]*, followed by stirring at room temperature for 50 minutes. After completion of the reaction, crystallization was carried out using ethanol-ether*

to obtain 26 mg of the title compound as white crystals."

15.2.2 As is clear from the relevant parts quoted above, both D1 and D3 disclose crystallisations using EtOH and Et_2O, i.e. the same solvents used in example 2 of the patent for the preparation of type I crystals. However, further details on how these crystallisations were actually carried out are missing entirely. Since the crystallisation conditions typically have an influence on which crystal form is eventually obtained (D5: page 164, lines 18 to 24), it cannot simply be concluded, as the respondent did, that type I crystals were the inevitable result of following the procedures of D1 or D3 for the crystallisation of CNDAC-HCl from EtOH-Et_2O - simply because there are not any procedures to follow (for a similar case, see T 605/02, point 3.2.1 of the Reasons).

For the respondent's argument to be accepted, it would have to be shown that type I crystals are the inevitable result of the procedures described in D1/D3, i.e. they would have been obtained regardless of the crystallisation conditions. However, this evidence was not provided. On the contrary, the conditions chosen by the respondent for its alleged repetitions of D1 (D14: sections 3.2.4 to 3.2.6) and D3 (D14: sections 3.2.1 to 3.2.3) are all very similar as they are based on the addition of Et_2O to a solution of CNDAC-HCl in EtOH. It may be true that, as argued by the respondent, the skilled person reading D1/D3 would have readily identified EtOH as the solvent and Et_2O as the anti-solvent given the crystalline and polar nature of CNDAC-HCl. However, from this alone it cannot be concluded that the procedure used by the respondent in D14 was directly and unambiguously disclosed in D1/D3.

For these reasons, type I crystals as defined in claim 1 of the main request are not the inevitable result of the procedures disclosed in D1/D3.

15.3 It follows that the subject-matter of claim 1 of the main request is distinguished from the cited prior art D1 and D3 at least in that the anti-tumour agent comprises a type I crystal of CNDAC-HCl.

In the absence of convincing novelty objections to claim 2 of the main request, it also can be concluded that the subject-matter of claim 2 is distinguished from the cited prior art at least in that the anti-tumour agent comprises a type II crystal of CNDAC-HCl.

Furthermore, the respondent never argued that the subject-matter of claims 3 and 4 of the main request lacked novelty.

Therefore, the claimed-subject-matter of the main request is novel over the cited prior art.

Main request - inventive step (Article 56 EPC)

16. In a first line of argument, the respondent started from D3 as the closest prior art.

16.1 It was concluded above that the subject-matter of claims 1 and 2 of the main request is distinguished from D3 at least in that the anti-tumour agent comprises either a type I or a type II crystal of CNDAC-HCl, respectively.

16.2 D3 discloses crystalline CNDAC-HCl in a general form.

The appellant argued, and this was not contested by the respondent, that the specific crystal types I, II and III of CNDAC-HCl disclosed in the patent were representative of a general crystalline form of CNDAC-HCl.

Given this, below it is examined whether the selection of crystal types I and II as defined in claims 1 and 2 of the main request from the set of possible crystalline forms of CNDAC-HCl encompassed by the disclosure of D3, including the type III crystals of the patent, is linked to a technical effect.

16.3 In paragraph [0043] and table 11, the patent reports on stability studies of crystal types I, II and III of CNDAC-HCl.

Entry four in table 11 of the patent shows that type II crystals transform into type I crystals when stored at 40 °C and a relative humidity of 75%. The appellant came to the conclusion, and the respondent expressly agreed, that type I crystals are more stable than type II crystals.

Table 11 (entry two) also shows that crystals of type II are not converted into crystals of type I when stored under normal humidity, even over a longer period of time (30 days). Contrary to this, crystals of type III are converted into type I crystals after just two hours (paragraph [0043]). It is true that, as argued by the respondent, the temperature to which the type II crystals were exposed in these studies was somewhat lower than that of the type III crystals (type II: 60 °C; type III: 80 °C). However, the type II crystals proved to be completely stable over a period 360 times longer than that within which the type III

crystals transformed into type I crystals (30 days versus 2 hours). The board agrees with the appellant that this is evidence of type II crystals being more stable than type III crystals.

With type I crystals being more stable than type II crystals, and the latter being more stable than type III crystals, it can be concluded that type I and II crystals are more stable than type III crystals. Therefore, the selection of the type I and type II crystals from the set of possible crystalline forms of CNDAC-HCl embraced by D3 is linked to a higher stability.

16.3.1 The respondent argued that the disclosure of D3 was not restricted to crystalline CNDAC-HCl in a general form. More specifically, D3 disclosed a CNDAC-HCl hemi-ethanolate with a melting point (mp) of 175-176 °C. This was a direct and unambiguous disclosure of a crystalline form of CNDAC-HCl with a mp of 175-176 °C, and for the acknowledgement of a technical effect, the appellant should have compared the type I and type II crystals to this crystal form.

16.3.2 This is not convincing. The patent (paragraph [0014]) sets out that the inventors were unable to prepare the CNDAC-HCl hemi-ethanolate of D3 with a mp of 175-176 °C. The appellant concluded that the disclosure of D3 was not enabling with respect to this crystal form. The board sees no reason to doubt the correctness of this conclusion because the respondent, when trying to crystallise CNDAC-HCl from EtOH-Et_2O, allegedly according to D3, did not obtain such a hemi-ethanolate either but only crystals with a higher mp, namely the type I and type II crystals of the patent.

Therefore, the disclosure of D3 is not enabling for the CNDAC-HCl hemi-ethanolate with a melting point of 175-176 °C. A comparison with this crystal form or a comparison with another crystal form of CNDAC-HCl with a mp of 175-176 °C could not be expected from the appellant.

16.4 Based on the previous point, the objective technical problem can be seen in the provision of an anti-tumour agent containing a crystalline form of CNDAC-HCl with a higher stability.

16.5 Faced with this objective technical problem, the skilled person would not have arrived at the claimed solution in an obvious manner.

16.5.1 The respondent's position was essentially that the skilled person would have screened for different polymorphic forms as a matter of routine. The common general knowledge even suggested searching for the most stable form (D15: page 948, left column, penultimate line to right column, line 3; T 777/08, point 5.2 of the Reasons). In carrying out this screening, the skilled person would inevitably have found crystal types I and II of CNDAC-HCl. Since the combination of the known anti-tumour agent CNDAC-HCl with a pharmaceutically acceptable carrier would have been routine for the skilled person, the skilled person would have found a solution to the above-mentioned objective technical problem without inventive efforts. This argument gained even more weight given that D3 proposed the solvent system EtOH-Et_2O for crystallisation, i.e. incidentally the solvents used in the patent for the manufacture of type I and type II crystals.

16.5.2 The board does not agree. It is true that it is in the common general knowledge of the skilled person to screen for polymorphs of an API to find one having improved properties such as an improved stability. However, this alone is not sufficient to deny inventive step to a solution by which this improvement is achieved. Only if the prior art either contains a clear pointer that the claimed subject-matter solves the objective technical problem or at least creates a reasonable expectation that a suggested investigation would be successful, can an inventive step be denied. With this view, the board essentially accepts the appellant's submission based on decision T 1684/16 (point 4.3.4 of the Reasons; catchword) in which essentially the same view is expressed.

In the case at hand, there is no disclosure in the cited prior art creating any expectation, let alone containing any pointer, that the type I or type II crystals of CNDAC-HCl defined in claims 1 and 2 of the main request could be more stable than other crystalline forms of CNDAC-HCl.

There is no suggestion that the crystal types I and II of CNDAC-HCl are more stable than others. While D3 mentions the solvent system EtOH-Et_2O to be used for crystallisation, it gives no details on the stability of the crystal form obtained. The mere mention of the solvent system in D3, therefore, would not have given a reasonable expectation to the skilled person, let alone a pointer, that its use would have led to crystalline forms of CNDAC-HCl which are more stable than others.

16.6 The respondent also relied on T 777/08 in its inventive-step analysis. In this decision, the board held that the skilled person, starting from the

amorphous form of an API as the closest prior art, would have gained a clear expectation from the common general knowledge that a crystalline form of it would have provided a solution to the problem of providing a product having improved filterability and drying characteristics. This expectation was considered reasonable because, although it could not be assumed that every single crystalline form would solve the problem, it could be assumed that many of these crystalline forms would. In view of this, the board considered the provision of a specific polymorph from the group of equally suitable candidates to be arbitrary and not involving an inventive step (T 777/08, point 5.2 of the Reasons).

The current case differs not only in that the closest prior art discloses a crystalline rather than an amorphous API, but also in that the skilled person would not have gleaned from it a reasonable expectation of success in solving the problem of providing crystal forms of CNDAC-HCl that are more stable than others. This is because the mere suggestion to look for more stable forms cannot be considered a reasonable expectation to find a specific solution, let alone a pointer.

16.7 The respondent requested that the appellant's submission based on decision T 1684/16 not be admitted as it had only been presented at the oral hearing and as it was hence late filed.

In this case, the appellant's submission is a legal argument relating to the interpretation of Article 56 EPC, more specifically to the application of the problem/solution approach. It is part of this approach that if the objective technical problem resides in the

achievement of a certain effect, in this case a higher stability, a prior-art document combined with the closest prior art renders the claimed subject-matter obvious only if it contains a pointer or otherwise creates a reasonable expectation that by means of this subject-matter the effect could be achieved. This principle became part of the boards' reasoning in T 1684/16 and has been used by the appellant and relied upon by the board in the case at issue.

Since the appellant's submission is thus a legal argument, the board had no discretion to not admit it into the proceedings (T 1914/12, point 7.2.3 of the Reasons).

This consideration is fully in line with, for instance:

- T 861/93, which held that "*decisions relied on by a party in support of its arguments are never citations which can be rejected as late under the provision of Article 114(2) EPC. Arguments are not covered by that provision. Therefore, decisions to which a party refers in support of its arguments are to be considered part of those arguments and may not be rejected as late.*" (point 12 of the Reasons; translation provided by the current board)
- T 2988/18, according to which "*[a]rguments pertaining to the interpretation of law are arguments generally accepted at any stage of the proceedings*" (point 1.4 of the Reasons)
- R 17/09, where it was held that: "*The reference to decisions in a decision, even decisions not cited to the party earlier in writing or at the oral proceedings, cannot support an objection of there being a fundamental procedural violation under Article 112a(2)(c) EPC. The parties to EPO*

proceedings are presumed to know the law relating to the EPC, including the relevant decisions."

The board agrees with the case law. Since the board found the appellant's submission based on decision T 1684/16 to reflect a correct understanding of the case law, the submission was admitted and endorsed in the present decision.

17. In the alternative to D3, the respondent also considered D1 as the closest prior art. However, at the oral hearing before the board, the respondent conceded that the disclosures of D1 and D3 were comparable and that its arguments for lack of an inventive step starting from D1 were the same as those starting from D3. Indeed, as set out above when discussing novelty, the subject-matter of claims 1 and 2 differs from D1 by the same distinguishing features as from D3. Considering that the respondent's arguments are not convincing in relation to D3, the board sees no reason why they should be more convincing in relation to D1.

18. In summary, the selection of the specific type I and type II crystals of CNDAC-HCl from the disclosure of crystalline CNDAC-HCl of whatever form in D3/D1 involves an inventive step. Accordingly, the anti-tumour agents of claims 1 and 2 comprising these types of crystals and the methods of preparing these types of crystals of claims 3 and 4 also involve an inventive step.

Therefore, the claimed subject-matter of the main request involves an inventive step, and the main request is allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

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

   Claims 1 to 4 of the main request, filed with letter dated 24 March 2017

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated