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Datasheet for the decision of 7 December 2020

Case Number: T 2730/16 - 3.3.02

Application Number: 07784499.1

Publication Number: 2069374

IPC: C07H7/04, A61K31/70, A61P3/10

Language of the proceedings: EN

Title of invention:
CRYSTALLINE SOLVATES OF (1S)-1,5-ANHYDRO-1-C-(3-((PHENYL) METHYL) PHENYL)-D-GLUCITOL DERIVATIVES WITH ALCOHOLS AS SGLT2 INHIBITORS FOR THE TREATMENT OF DIABETES

Patent Proprietor:
AstraZeneca AB

Opponent:
LEK Pharmaceuticals d.d.

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)
Reasonable expectation to solve objective technical problem (no)

Decisions cited:
T 1684/16, T 0488/16, T 1422/12, T 0643/12, T 0094/11, T 1067/08, T 0777/08, T 0724/08, T 0933/04, T 0440/91, G 0007/93

Catchword:

Europäisches Patentamt
European Patent Office
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Case Number: T 2730/16 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 7 December 2020

Appellant: (Opponent)	LEK Pharmaceuticals d.d. Verovskova 57 1526 Ljubljana (SI)
Representative:	Maiwald Patent- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Respondent: (Patent Proprietor)	AstraZeneca AB 151 85 Södertälje (SE)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 24 November 2016 concerning maintenance of the European Patent No. 2069374 in amended form.**

Composition of the Board:

Chairman	M. O. Müller
Members:	A. Lenzen
	P. de Heij

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the opponent (appellant) against the opposition division's interlocutory decision (decision under appeal), according to which European patent No. 2 069 374 (patent in suit) in amended form meets the requirements of the EPC.

II. The following documents, cited during the opposition proceedings, are relevant for the present decision:

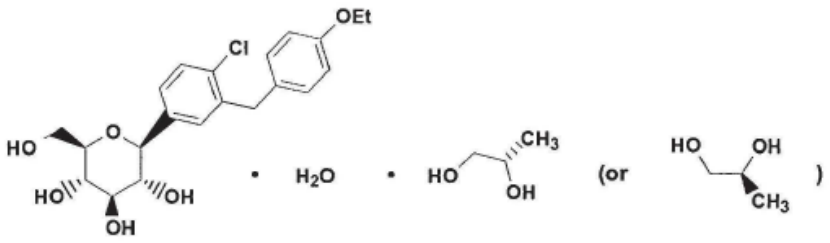
D1 WO 2004/063209 A2
D2 WO 02/083066 A2
D3 WO 03/099836 A1
D4 WO 2004/060347 A2
D5 Rubino, J. T. et al. (1990): Influence of solvent composition on the solubilities and solid-state properties of the sodium salts of some drugs, International Journal of Pharmaceutics, 141, 1990, pages 141 to 145
D6 US 3,970,651
D7 CA 1,101,840
D10 Byrn, S. et al. (1995): Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations, in: Pharmaceutical Research, vol. 12, no. 7, pages 945 to 954
D11 Huang, L.-F., Tong, W.-Q. (2004): Impact of solid state properties on developability assessment of drug candidates, in Advanced Drug Delivery Reviews, vol. 56, pages 321 to 334
D12 Declaration of Li Tao
D13 WO 2015/117538 A1
D13a English translation of D13
D14 European Medicines Agency, Assessment report of

Forxiga, 18 September 2012

III. In its notice of opposition the appellant requested that the patent in suit be revoked in its entirety based on the ground for opposition pursuant to Article 100(a) EPC (lack of an inventive step).

IV. The decision under appeal is based on the main request pending before the opposition division. It comprises only one claim (in the following simply: claim 1), which reads as follows:

"*A crystalline structure of a compound having the formula Ia,*



Compound Ia

characterized by one or more of the following:

a) unit cell parameters substantially equal to the following:
Cell dimensions:
a = 11.2688(8) Å
b = 4.8093(3) Å
c = 46.723(3) Å
α = -degrees
β = -degrees
γ = -degrees
Space group = $P2_12_12_1$
Molecules/asymmetric unit = 1
wherein measurement of said crystalline structure is at room temperature and which is characterized by fractional atomic

coordinates substantially as listed in Table 4;

b) *a powder x-ray diffraction pattern comprising 2Θ values (CuKα λ = 1.5418 Å) selected from the group consisting of 3.8 ± 0.1, 7.6 ± 0.1, 8.1 ± 0.1, 8.7 ± 0.1, 15.2 ± 0.1, 15.7 ± 0.1, 17.1 ± 0.1, 18.9 ± 0.1 and 20.1 ± 0.1, at room temperature;*

c) *a solid state ^{13}C NMR spectrum having substantially similar peak positions at 16.2, 17.6, 39.3, 60.9, 63.3, 69.8, 76.9, 78.7, 79.4, 113.8, 123.6, 129.3, 130.5, 132.0, 135.7, 139.1 and 158.0 ppm, as determined on a 400MHz spectrometer relative to TMS at zero;*

d) *a differential scanning calorimetry thermogram having an endotherm in the range of about 50°C to 78°C or as shown in Figure 7;*

e) *thermal gravimetric analysis curve with about 18.7% weight loss from about room temperature up to about 240°C or as shown in Figure 5; or*

f) *having a proton NMR having substantially similar peak positions as listed Table 1A.*"

The compound on the left side of formula Ia above, 1-C-(6-chloro-4'-ethoxydiphenylmethane-3-yl)-β-D-glucopyranose, is commonly known as dapagliflozin. Thus, claim 1 relates to a crystalline solvate of dapagliflozin with water and (*S*)-propylene glycol which comprises these three compounds in equimolar amounts (1:1:1 molar ratio). In the following, in accordance with the patent in suit and both parties, this crystalline solvate of claim 1 is referred to as the "SC-3 form". Furthermore, the following abbreviations are used:

PG for propylene glycol
API for active pharmaceutical ingredient

V. The opposition division held that the subject-matter of claim 1 involved an inventive step over a combination of the closest prior art D1 with D4. The reasoning was essentially as follows:

- D1 disclosed amorphous dapagliflozin and a crystalline complex of dapagliflozin. Over these two embodiments, no technical effect could be derived from D12 for the SC-3 form from claim 1. The objective technical problem had to be considered that of providing an alternative crystalline form of dapagliflozin.
- While providing a crystalline form of a known pharmaceutically active compound was, in the absence of any unexpected property, usually not regarded as involving an inventive step, the crystallisation of dapagliflozin appeared to have been an issue on the priority date of the patent in suit. Thus, providing the SC-3 form appeared to have required more than mere routine screening.
- Moreover, the teaching of D4 was very broad and unspecific and would not have given the skilled person a reasonable expectation of success, i.e. a reasonable expectation of obtaining a crystalline form of dapagliflozin.

VI. By letter of 20 December 2017, the appellant filed:

D15 ICH Guideline, Impurities: Guideline for Residual Solvents

VII. The board issued a communication pursuant to Article 15(1) RPBA 2020 in preparation for the oral proceedings, which had been scheduled upon the parties' requests.

VIII. By letter of 11 September 2020, the patent proprietor (respondent) filed:

D16 Braga, D., Grepioni, F., Chem. Comm. 2005, pages 3635 to 3645
D17 Braem A., Top. Med. Chem. 2014, 12, pages 73 to 94

IX. On 7 December 2020, oral proceedings before the board took place, at the end of which the board pronounced its decision.

X. The parties' requests relevant for this decision were as follows.

- The appellant requested that the decision under appeal be set aside and that the patent in suit be revoked in its entirety. It also requested that D13 be admitted into the proceedings and that D16 and D17 not be admitted into the proceedings.

- The respondent requested that the appeal be dismissed. It also requested that D13 not be admitted into the proceedings.

XI. The appellant's arguments, insofar as they are relevant for the present decision, can be summarised as follows.

Admittance of D13

D13 (and its English translation D13a) should not be considered as being late filed as it was responsive to the respondent's response to the notice of opposition. It could not have been filed during the nine months opposition period, since it was not yet published. The document was also *prima facie* relevant.

Admittance of the inventive-step objection based on D2 as the closest prior art

During the opposition proceedings, the appellant had never actively withdrawn its objection based on D2 as the closest prior art. It therefore could not be concluded that it had been abandoned. This objection was still part of the proceedings.

Inventive step

D1 was the closest prior art. In Examples 20 and 13, it disclosed amorphous dapagliflozin and a crystalline complex of dapagliflozin with L-phenylalanine, respectively. Each of these two forms of dapagliflozin was a suitable starting point for the assessment of inventive step.

Stability testing of tablets containing amorphous dapagliflozin had shown that the tablets were stable irrespective of the presence of a desiccant. D14 also disclosed that the SC-3 form transformed into anhydrous amorphous dapagliflozin upon long exposure to high temperature and also that the SC-3 form was susceptible to oxidative degradation. It therefore had to be concluded that the SC-3 form did not offer any advantages over amorphous dapagliflozin and even that amorphous dapagliflozin was more stable. Lastly, it was not at all clear whether or not D12, allegedly showing

superior properties of the SC-3 form, used the same amorphous form of dapagliflozin as D1. Therefore, it could not be inferred from D12 that the SC-3 form was less hygroscopic than amorphous dapagliflozin. Furthermore, the effect of higher stability of the SC-3 form could not be derived from the application as filed.

Starting from amorphous dapagliflozin as disclosed in D1, the objective technical problem had to be considered that of providing a crystalline form of dapagliflozin.

The solution to this problem was obvious in view of D4 and T 777/08. Furthermore, even if a lower hygroscopicity had been accepted as a technical effect and the objective technical problem had been considered that of providing a crystalline form of dapagliflozin that was less hygroscopic, the skilled person would still have found a solution to this problem in D4. This was because, according to D4, a PG solvate of an API was not only crystalline but also less hygroscopic than the particular API itself. By following the teaching of D4, the skilled person would inevitably have obtained the SC-3 form. Example 7 showed that celecoxib sodium PG solvate took up water from the environment; however, because there was no comparison with the corresponding reference compound celecoxib sodium, it could not be concluded that the hygroscopicity of celecoxib sodium was not reduced. D4 stated that moisture sorption studies had been used to characterise the PG solvates of D4. As also shown by D12, such studies were commonly used to examine the hygroscopicity of a compound. Therefore, it was clear that the API PG solvates of D4 were of lower hygroscopicity than the corresponding APIs themselves.

As far as D1 disclosed a crystalline complex of dapagliflozin with L-phenylalanine, no technical effect could be inferred from D12 for the SC-3 form. Consequently, starting from this complex, the objective technical problem had to be considered that of providing an alternative crystalline form of dapagliflozin.

In practice, the skilled person would not have used the complex as such and would not have tried to crystallise it according to D4. Nevertheless, the solution to the objective technical problem was obvious in view of D4. The complex could be regarded as a composition comprising dapagliflozin and L-phenylalanine and the transformation of this complex to the SC-3 form was comparable to a situation in which one component (L-phenylalanine) of a composition (the complex) was replaced by a different component (PG and water).

Therefore, the subject-matter of claim 1 was not inventive over a combination of D1 with D4.

XII. The respondent's arguments, insofar as they are relevant for the present decision, can be summarised as follows.

Admittance of D13

The opposition division carefully assessed the late filing of D13 and gave sound reasons why it did not admit it into the proceedings. The document was available more than a year before it was filed by the appellant and was not *prima facie* relevant.

Admittance of the inventive-step objection based on D2 as the closest prior art

The respondent shared the board's view that the appellant's objection based on D2 as the closest prior art should not be admitted into the proceedings.

Inventive step

D1 was the closest prior art. D12 showed that the SC-3 form was less hygroscopic than amorphous dapagliflozin, as disclosed in Example 20 of D1. The appellant's testing of tablets comprising amorphous dapagliflozin and its arguments based on D14 were not convincing because they addressed the decomposition, i.e. chemical stability, of the forms in question. This, however, was different from their physical stability in terms of hygroscopicity. Lastly, the amorphous dapagliflozin in D12 was prepared in essentially the same way as that in D1. It therefore could not simply be asserted that both were different.

With regard to amorphous dapagliflozin as disclosed in D1, the objective technical problem had to be considered that of providing a crystalline form of dapagliflozin which was more stable, i.e. less hygroscopic.

Even if the skilled person had taken D4 into consideration when trying to provide a solution to this problem, they would not have had a reasonable expectation of success. This was because the formation of solvates and their properties were highly unpredictable. Furthermore, Example 7 of D4 cast serious doubt on whether a lower hygroscopicity was achieved as universally as suggested by D4. This

document disclosed that celecoxib sodium PG solvate took up water to form celecoxib sodium PG trihydrate. Since water uptake occurred at very low relative humidities, celecoxib sodium PG solvate had to be classified as very hygroscopic according to D4's own classification scheme.

Even if it had been accepted that Example 13 of D1 disclosed a crystalline complex of dapagliflozin with L-phenylalanine, and also that the objective technical problem had to be considered merely that of providing an alternative crystalline form of dapagliflozin, the subject-matter of claim 1 would still have involved an inventive step. This was because the skilled person would not have used the complex from D1 as such in crystallisation attempts according to D4. Instead, the skilled person would have had to resort to the precursor of the complex, i.e. amorphous dapagliflozin, as also disclosed in D1. The SC-3 form, however, involved an inventive step over amorphous dapagliflozin. Consequently, the SC-3 form also had to involve an inventive step over the crystalline complex of dapagliflozin with L-phenylalanine.

Therefore, the subject-matter of claim 1 was inventive over a combination of D1 with D4.

Reasons for the Decision

Admittance of D13 and D13a

1. D13 is a document in Japanese, D13a is its English translation. These documents were filed by the appellant during the opposition proceedings but outside the nine month opposition period. The opposition

division did not admit D13 into the proceedings (decision under appeal, page 11, point 3)

- because D13 was late-filed,
- because D13 was post-published and thus no prior art,
- because D13 did not relate to a propylene glycol solvate of dapagliflozin and was thus not *prima facie* relevant,
- because D13 was not representative of common general knowledge at the priority date of the patent in suit.

There were opposing requests by both parties as to whether D13 should be admitted into the appeal proceedings or not. In its communication pursuant to Article 15(1) RPBA 2020 the board had explained that it considered these requests to also relate to D13a.

It is noted that a board of appeal should only overrule the way in which a department of first instance has exercised its discretion when deciding on a particular case if it concludes that it has done so according to the wrong principles, or without taking into account the right principles, or in an unreasonable way, and has thus exceeded the proper limits of its discretion (G 7/93 (OJ 1994, 775), point 2.6 of the reasons). The appellant argued in this context that D13 was filed in response to the patent proprietor's filing of D12. It was not late-filed. D13 served to "*refute the Proprietor's allegation based on D12 that dapagliflozin was difficult to crystallize at the priority date of the opposed patent*" (the appellant's letter dated 20 December 2017, page 2, paragraph 3), i.e. the allegation which was decisive for the opposition

division when arriving at its decision. For that reason it was also *prima facie* relevant.

This is not convincing. Although the filing of D13 could, in view of the reason given by the appellant, indeed be regarded as a reaction to the filing of D12, this does not mean that D13 necessarily had to be admitted by the opposition division. In this context it also had to be considered whether D13 was at all suitable to prove the fact for which D13 was submitted as evidence. In this regard, the appellant's contention that "*D13 reflects the skilled person's knowledge at the priority date of the opposed patent with regard to crystallization methods of dapagliflozin*" (letter dated 20 December 2017, page 3, paragraph 3) cannot be accepted on account of the facts

- that D13 is a patent document and not e.g. a well-known standard textbook. D13 cannot therefore be representative of common general knowledge.
- that the priority date of D13 (10 February 2014) is more than seven years later than the earlier priority date of the patent in suit (28 June 2006).

Based on the above reasoning, the board in its communication pursuant to Article 15(1) RPBA 2020 expressed the preliminary view that D13 and D13a should not be admitted into the appeal proceedings. In the further course of the written appeal proceedings (letter of 6 October 2020, point 2) and also during the oral proceedings, the appellant explicitly chose not to comment on this aspect. Therefore, during the oral proceedings, the board saw no reason to deviate from its preliminary view and decided not to admit D13 and

D13a into the appeal proceedings (Article 25(2) RPBA 2020 in conjunction with Article 12(4) RPBA 2007).

Admittance of D16 and D17

2. D16 and D17 were filed by the respondent. At the request of the appellant at the oral proceedings, the board decided not to admit D16 and D17 into the proceedings. In view of the fact that the respondent is not adversely affected by the final decision, there is no need to give further reasons for this decision.

Main request - Inventive step (Article 56 EPC)

3. The respondent's main request was that the appeal be dismissed. The main request thus corresponds to the patent in suit as held allowable by the opposition division.

4. Closest prior art

4.1 The appellant considered both D1 and D2 to be suitable as the closest prior art.

4.2 D2 as the closest prior art

During the written opposition proceedings, the appellant initially argued on the basis of D1, D2 or D3 as the closest prior art. In the annex to the summons to oral proceedings (page 11, penultimate paragraph), the opposition division took the preliminary view that D2 could not constitute the closest prior art. In its subsequent letter in response to the summons, the appellant put forward inventive-step objections based on D1 and D3 only. Then, at the oral proceedings before the opposition division, the appellant agreed to D1

being the closest prior art - see minutes page 2 - and apparently did not put forward inventive-step objections based on D2 or D3. Consequently, the decision under appeal (page 11 f., point 4) only discusses the objection based on D1, but not those based on D2 or D3.

The course of the proceedings described above shows that the appellant did not actively maintain its objection based on D2 as the closest prior art during the oral proceedings before the opposition division and that it did indeed abandon it, thereby preventing it from being discussed in the decision under appeal. However, in its statement of grounds of appeal, the appellant again put forward an objection based on D2 as the closest prior art.

In its communication pursuant to Article 15(1) RPBA 2020 the board expressed its preliminary view that this objection should not be admitted into the appeal proceedings pursuant to Article 25(2) RPBA 2020 in conjunction with Article 12(4) RPBA 2007 because, *inter alia*, the appeal proceedings were judicial in nature, meaning that the decision of a board of appeal should in principle be based on the substance of the dispute before the department of first instance; see T 724/08 (point 3 of the Reasons) and Article 25(1) RPBA 2020 in conjunction with Article 12(2) RPBA 2020.

At the oral proceedings before the board the appellant did not argue in substance in this matter. Instead, it referred to its written submissions. In its letter of 6 October 2020, the appellant had contested the board's preliminary view and argued that it had not actively withdrawn or abandoned the inventive-step attack starting from D2 as the closest prior art in the

opposition proceedings, and also that the decisions to which the board referred were not applicable to the present case. The conclusion drawn by the board in its communication was therefore incorrect.

This reasoning cannot be accepted. It may be that the appellant had not withdrawn its inventive-step objection based on D2 verbatim during the opposition proceedings; however, as explained above, the course of the opposition proceedings and the decision under appeal show that such a withdrawal had occurred (at least) implicitly. In this connection, it is also noted that the appellant did not at any time request a correction of the minutes, nor did it claim that the decision under appeal was erroneous in that it did not deal with the appellant's objection based on D2.

The two decisions cited by the board in its communication (T 1067/08 (points 6 and 7 of the Reasons) and T 933/04 (point 2 of the Reasons)) concern cases in which a patent proprietor was responsible for the fact that the opposition division had not made a decision on requests filed by the patent proprietor on appeal. In the board's view, these cases were indeed applicable, *mutatis mutandis*, to the present case, in which the appellant must be held responsible for having abandoned its objection based on D2 before the department of first instance. Thus, during the oral proceedings, the board decided not to admit the appellant's objection based on D2 as the closest prior art into the proceedings.

4.3 Based on the two previous points, this decision will assess only the appellant's objections based on D1 as the closest prior art.

D1 as the closest prior art

4.4 Claim 1 essentially relates to a crystalline solvate ("SC-3 form") of dapagliflozin with water and (*S*)-propylene glycol ("(*S*)-PG") (for the exact wording of claim 1, see point IV above).

4.5 D1 (page 1, lines 5 to 13 and page 35, lines 13 to 20) is directed to a process of producing 1-C-(substituted diphenylmethane-3-yl)-β-D-glucopyranose compounds, such as dapagliflozin in particular. It also relates to crystalline complexes of these C-aryl glucoside compounds formed with an amino acid complex forming agent such as L-phenylalanine.

D1 describes the stepwise synthesis of dapagliflozin. In the last step of the synthesis, dapagliflozin is obtained "*as a glassy off white solid*" (Example 20). It was common ground between the parties that this should be understood as a reference to **amorphous dapagliflozin**.

Furthermore, according to the appellant, D1 disclosed the preparation of a crystalline complex of dapagliflozin with L-phenylalanine (Example 13). Both parties disagreed on whether or not this disclosure was enabling. In the following, it is accepted in the appellant's favour that the approach taken in Example 13 of D1 is enabling and that it does in fact disclose **a crystalline complex of dapagliflozin with L-phenylalanine**.

The appellant put forward inventive-step objections starting from both forms of dapagliflozin disclosed in D1, i.e. amorphous dapagliflozin and the crystalline complex of dapagliflozin with L-phenylalanine.

Both of the appellant's objections are assessed in the following.

5. Amorphous dapagliflozin as the starting point

5.1 The subject-matter of claim 1, i.e. the SC-3 form, differs from amorphous dapagliflozin in that it is a crystalline form further comprising (*S*)-PG and water.

5.2 D12 is a declaration submitted by the respondent. It is a summary of the respondent's efforts made in the course of developing a pharmaceutically acceptable form of dapagliflozin. Points 4 and 12 of this declaration relate to amorphous dapagliflozin and to the SC-3 form of claim 1, respectively. These points read as follows (emphases added):

> "*4. [...] After complete solvent removal, an amorphous glassy foam was formed inside the reactor vessel. This amorphous glassy material was* ***physically unstable. It transformed to a gel on exposure to relative humidities >33% at room temperature within a day,*** *thereby posing significant handling issues.*"
>
> "*12. [...] the mixed solvate SC-3 (dapagliflozin + 1 (S)-propylene glycol + 1* H_2O*) was found to be* ***physically stable under ambient temperature and humidity****. Results from moisture sorption-desorption studies indicated that SC-3 was* ***non-hygroscopic*** *at 25 °C (Fig. 2).*"

The above two statements are clear and nothing was apparent that could have cast doubt on their accuracy. Contrary to the view expressed in the decision under appeal, they allow a direct comparison to be made

between the SC-3 form and amorphous dapagliflozin and it has to be concluded that the SC-3 form has a higher stability, i.e. a lower hygroscopicity, than amorphous dapagliflozin.

5.3 The appellant contested the conclusion drawn from D12, namely that the SC-3 form was more stable, i.e. less hygroscopic, than amorphous dapagliflozin. It put forward the following arguments.

5.3.1 The appellant reported on experimental tests in which tablets containing amorphous dapagliflozin were stored with and without desiccant under different conditions of temperature, relative humidity and duration. Before and after the tests, the tablets were analysed for the presence of amorphous and/or crystalline forms of dapagliflozin and for the presence of impurities. In these tests, the tablets containing the amorphous form of dapagliflozin were found to be stable regardless of the presence of a desiccant. These tests proved that the SC-3 form did not offer any advantages over the amorphous form in terms of stability.

This is not convincing for several reasons. Firstly, these tests only examined the stability of amorphous dapagliflozin against decomposition (determined by the content of impurities) and against transformation into a crystalline form. From D12 it was concluded that the SC-3 form and amorphous dapagliflozin differ from each other in terms of their hygroscopicity. However, the hygroscopicity of a compound, i.e. its propensity to bind water from the environment, is different from its stability against decomposition and its stability against conversion into a crystalline form. Secondly, the appellant's tests examined the stability of the amorphous form contained in a tablet. In a tablet,

however, the API is not only diluted, but the API is also shielded from the environment, at least to some extent. A result obtained for a tablet containing dapagliflozin therefore cannot be compared with a result obtained for dapagliflozin in substance, as was the case in the respondent's studies as summarised in point 4 of D12.

5.3.2 The appellant also referred to D14 (page 14, paragraphs 1 and 5 from the bottom). It disclosed that the SC-3 form was susceptible to oxidative degradation and that the SC-3 form transformed into the amorphous anhydrous form upon long exposure to high temperature. This again showed the lack of stability of the SC-3 form and even proved that amorphous dapagliflozin was thermodynamically more stable than the SC-3 form.

As noted in the previous point, the stability of a compound to decomposition, e.g. oxidative degradation, is different from its propensity to bind water from the environment, i.e. its hygroscopicity. Similarly, stating that the hydrous SC-3 form was converted to anhydrous amorphous dapagliflozin upon long exposure to high temperature is equivalent to saying that the SC-3 form decomposed to an anhydrous form (dehydration induced by high temperature). These observations do not allow any conclusion to be drawn about the hygroscopic properties of the compounds in question.

5.3.3 The appellant also argued that both D1 and D12 referred to amorphous dapagliflozin; however, detailed instructions for its preparation were only disclosed in D1. Therefore, it was possible that the two amorphous forms did not correspond to each other or that the modification was not the same in both cases. In this context, it was quite conceivable that dapagliflozin

showed polyamorphism, i.e. that there were several amorphous modifications. It was also not demonstrated in D12 that the amorphous form described therein was completely amorphous and that it did not contain residual solvent(s).

This is not convincing. According to point 4 of D12, amorphous dapagliflozin is obtained "*[a]fter* ***complete solvent removal***" (emphasis added). Without any apparent reason to doubt this statement, it cannot simply be asserted that amorphous dapagliflozin, as referred to in D12, contains residual solvent(s). Further, amorphous dapagliflozin is obtained in D1 and D12 in essentially the same way, namely by removing the solvent from a solution of dapagliflozin. Although the solvent used is not specified in D12, this alone, at least in the absence of evidence to the contrary, does not support the allegation that the two amorphous forms of D1 and D12 could be different in any way. This conclusion is also supported by the fact that, as pointed out by the respondent, the appellant itself did not indicate how it had obtained the amorphous dapagliflozin used in its tablet studies (see point 5.3.1 above).

5.4 Thus, in line with the respondent, the objective technical problem can be considered that of providing a crystalline form of dapagliflozin which is more stable, i.e. less hygroscopic.

5.4.1 The appellant argued that the effect inferred from D12 could not be derived from the application as filed (e.g. from paragraph [0062]) and that it therefore should not have been taken into account for formulating the objective technical problem.

This is not persuasive. The application as filed (paragraphs [0005] ff.) relates to solid forms of dapagliflozin such as, *inter alia*, the SC-3 form from claim 1. It not only discusses the stability of polymorphic forms in general (paragraph [0062]), but also indicates that stable forms of dapagliflozin can be crystallised as solvates (paragraph [00115] in conjunction with paragraph [0005]). Undoubtedly, hygroscopicity is an important stability aspect in the pharmaceutical field. This is evidenced not only by D4 (page 3, paragraph 2 and the more extensive discussion below) but also, for example, by D11 (page 327, third paragraph under point 3.3) and some of the decisions cited by the respondent in this appeal (T 1684/16 (point 4.3.4 of the Reasons), T 94/11 (point 3.2 of the Reasons) and T 643/12 (point 5.3 of the Reasons)). Therefore, the formulation of the objective technical problem as that of providing a crystalline form of dapagliflozin which is more stable, i.e. less hygroscopic, falls within the framework of the invention as disclosed in the application as filed (T 1422/12, point 2.3.3 of the Reasons; T 440/91, points 4.1 to 4.3 of the Reasons) and the effect inferred from D12 can be taken into account.

5.4.2 The appellant also argued that the application as filed did not plausibly demonstrate that the effect(s)/ problem(s) relied on by the respondent at the time, such as an alleged superior stability, in particular, had actually been solved on the effective date (letter of 20 December 2017, point 3). The post-published evidence D12 should therefore have been disregarded altogether for the assessment of inventive step and the formulation of the objective technical problem based on e.g. T 488/16 (point 4.2 of the Reasons).

Nonetheless, in this respect the appellant only referred to the thermal stability of the dapagliflozin forms in the application as filed, but not to stability in the sense of reduced hygroscopicity (see letter of 20 December 2017, point 3.1.1). In addition, at the oral proceedings, the appellant expressly emphasised that it was not discussing plausibility when comparing the stability of the different forms of dapagliflozin. Therefore the plausibility of the effect of increased stability in the sense of reduced hygroscopicity in the application as filed was no longer contested at the oral proceedings and as a consequence, there is no reason not to take D12 into account.

5.5 As regards obviousness, the appellant pointed to D4.

5.5.1 D4 relates to PG solvates of APIs. In particular, D4 (page 4, paragraph 4; page 3, paragraphs 2 and 3) states quite generally

(i) that the formation of PG solvates makes it possible to obtain crystalline compounds from APIs which are difficult to crystallise

(ii) that the API PG solvates are more stable and less hygroscopic than the APIs themselves.

5.5.2 The appellant argued that the skilled person would have consulted D4 and would have taken its teaching into account. This was because D4 offered solutions to the problem of providing a crystalline form of an API as well as to the problem of providing a form that is less hygroscopic. Furthermore, it was clear from Example 7 of D4, describing the manufacture of a mixed PG/water solvate of the API celecoxib, that not only PG solvates

as such but also mixed PG/water solvates were in accordance with the invention in D4. The SC-3 form from claim 1 with a 1:1:1 molar ratio of dapagliflozin, PG and water would inevitably have been obtained when trying to crystallise dapagliflozin according to D4. Consequently, the subject-matter of claim 1 did not involve an inventive step over a combination of D1 and D4.

5.5.3 Even if it were assumed in the appellant's favour that an attempt to crystallise dapagliflozin according to D4 would inevitably have resulted in the SC-3 form, the argument that the skilled person would have consulted D4 when trying to solve the objective technical problem is not sufficient. For this argument to be correct, the skilled person, in order to take the teaching of D4 into account, would also have had to have a reasonable expectation of success, i.e. a reasonable expectation that this teaching would actually have solved the objective technical problem. Whether or not this is the case will be assessed in the following.

5.5.4 On pages 45 to 296, D4 gives a very long list of APIs whose PG solvates are said to be covered by the invention in D4. Among these compounds is also T-1095 (page 267, entry 4), i.e. a compound which is structurally similar to dapagliflozin. In view of points 5.5.1 (i) and (ii) above, this list amounts to D4 pretending to have found an almost universal solution to the problem of providing a crystalline form of an API and in particular to the problem of providing a form of an API which is less hygroscopic. This alone would not have given the skilled person a reasonable expectation of success, i.e. a reasonable expectation of obtaining a crystalline form of dapagliflozin which is less hygroscopic than amorphous dapagliflozin. The

reason is that, as put forward by the respondent in its letter dated 11 September 2020 (point 7.11) and during the oral proceedings, the formation of solvates, let alone their properties such as crystallinity and hygroscopicity, is highly unpredictable. This is evident, for example, from D10 (page 945, paragraph bridging both columns; page 946, left column, second paragraph; figure 6), which suggests searching for solvates at an early stage of drug development because they display a wide and largely unpredictable variety of properties and therefore their sudden appearance at a later stage usually slows down the drug-approval process and makes planning difficult. In this context, the board acknowledges that D4 demonstrates that four structurally very different and unrelated APIs can be transformed into crystalline PG solvates. As regards hygroscopicity, however, D4 lacks experimental data showing that an API PG solvate is less hygroscopic than the API itself. D4 (page 44, last paragraph) only sets out the following (emphases added):

> "*Dynamic moisture sorption studies of* ***several embodiments of the present invention*** *have been discussed in PCT/US03/XXXXX filed on December 24, 2003, entitled "Pharmaceutical Compositions With Improved Dissolution" (Attorney Docket No. TPI-1700CXC2 PCT) by Tawa et al, which is hereby incorporated by reference, in its entirety. Dynamic moisture sorption studies can be used to illustrate important characteristics of the solvates of the present invention,* ***such as decreased hygroscopicity or increased form stability.***"

According to the appellant, moisture sorption studies were commonly used to examine the hygroscopicity of a compound. After all, the respondent had used the same

method in D12. It could therefore be inferred from the above paragraph that the API PG solvates from D4 also had to exhibit a lower hygroscopicity than the corresponding APIs themselves.

This argument cannot be accepted. The above paragraph refers to "*several embodiments of the present invention*" and not, for example, to all embodiments. It also indicates that sorption studies may be used to illustrate properties other than hygroscopicity. Therefore, it cannot be inferred from this paragraph alone that a lower hygroscopicity is achieved with such a high number of structurally very different and unrelated APIs that this would have given the skilled person a reasonable expectation of success.

Furthermore, the examples in D4 cast legitimate doubt on whether the effect of a lower hygroscopicity is actually achieved as universally as suggested. In Example 1, celecoxib sodium PG solvate is prepared. Then in Example 7, this PG solvate is allowed to bind water from the environment, eventually resulting in celecoxib sodium PG trihydrate (i.e. a mixed PG/water solvate of celecoxib sodium). **This shows that celecoxib sodium PG solvate, i.e. a PG solvate according to the teaching of D4, is still hygroscopic.**

According to the appellant, this did not allow the conclusion to be drawn that a lower hygroscopicity would not have been achieved. In order to draw such a conclusion celecoxib sodium PG solvate would have had to be compared with its reference compound celecoxib sodium (D4: page 14, last paragraph). This argument fails to convince because D4 does in fact allow an indirect comparison between celecoxib sodium PG solvate and celecoxib sodium in terms of their hygroscopicity.

D4 provides a classification scheme for the degree of hygroscopicity ranging from class 1 (non-hygroscopic) to class 4 (very hygroscopic). According to this classification scheme compounds are very hygroscopic if they absorb moisture at relative humidities as low as 40 to 50% (D4: page 14, paragraph 2). Based on this scheme, celecoxib sodium PG solvate is very hygroscopic because it begins to absorb moisture even at relative humidities between 31 and 40% (D4: page 43, lines 6 to 7 below "Example 7"). With celecoxib sodium PG solvate belonging to the worst hygroscopicity class, its hygroscopicity cannot be lower than that of its reference compound, celecoxib sodium, at least when judged according to D4's own classification scheme.

Based on the above, the skilled person would have considered the effect suggested by D4, namely the universal decrease in hygroscopicity, to be a mere allegation. Given the generally recognised high unpredictability of solvate properties (see above), the skilled person would not have had a reasonable expectation of obtaining a less hygroscopic form of dapagliflozin.

5.5.5 In view of the foregoing, the present case is also clearly different from the case underlying decision T 777/08, on which the appellant relied. In that decision, as in the present case, the starting point for the assessment of inventive step was the amorphous form of an API. The objective technical problem was considered that of providing a form having improved filterability and drying characteristics. The board concluded (page 12, paragraph 3; emphases added):

> "*Thus, in view of his general knowledge, as reflected in this excerpt from document (28), the*

skilled person, starting from the amorphous form of a pharmaceutically active compound as closest prior art, would have a ***clear expectation that a crystalline form thereof would provide a solution to the problem as defined under point 5.1 above.*** *Although this might not be true of every crystalline form obtained (cf. document (28), page 527, left-hand column, second and third sentences), it was nevertheless obvious to try this avenue* ***with a reasonable expectation of success*** *without involving any inventive ingenuity.*"

Hence, in this case, the skilled person would have had a reasonable expectation that providing a crystalline form of the API would have solved the objective technical problem. The present case is different in that, although a solution to the objective technical problem may have been suggested by D4, the skilled person would not have had a reasonable expectation that the solution offered by D4 would have actually solved this problem.

5.5.6 In summary, the subject-matter of claim 1 involves an inventive step over amorphous dapagliflozin as disclosed in D1 in combination with D4 because the skilled person, considering the teaching of D4, would not have had a reasonable expectation of obtaining a form of dapagliflozin which is less hygroscopic than amorphous dapagliflozin.

6. The crystalline complex of dapagliflozin with L-phenylalanine as the starting point

6.1 The subject-matter of claim 1 differs from the crystalline complex of dapagliflozin with L-

phenylalanine in that it comprises (*S*)-PG and water instead of L-phenylalanine.

6.2 The appellant argued that the distinguishing feature was not linked to a technical effect and that therefore the objective technical problem had to be considered that of providing an alternative crystalline form of dapagliflozin. In the appellant's favour it is assumed that this is correct.

6.3 The appellant argued, and the board fully shares this view, that the skilled person, faced with the objective technical problem of providing an alternative crystalline form of dapagliflozin, would not have used the crystalline complex of dapagliflozin and L-phenylalanine as such in crystallisation attempts according to D4 but would have started from amorphous dapagliflozin as disclosed in D1. This is simply because D4 only ever uses the APIs themselves (or their alkali metal salts) for the preparation of the corresponding API PG solvates, but never uses compounds which would be comparable to a complex of an API with another organic compound, such as the complex of dapagliflozin with L-phenylalanine. In view of this, it is highly questionable whether the skilled person, starting from the crystalline complex of dapagliflozin with L-phenylalanine, would have considered D4 at all.

The appellant nevertheless pointed to D4 and argued that the complex should be regarded as a composition and that the transition from the complex of D1 to the SC-3 form corresponded to the situation in which one component (L-phenylalanine) of a composition (the complex) was merely replaced by another (PG/water). With regard to the objective technical problem of providing an alternative crystalline form of

dapagliflozin, such a replacement could not involve an inventive step because D4 disclosed that APIs could be converted into a crystalline form by forming their PG solvates.

The board cannot agree with this. The appellant's argument directed at the replacement of L-phenylalanine by PG/water does not take into account that first L-phenylalanine has to be removed from the complex, that afterwards only dapagliflozin remains and that it is then this dapagliflozin which has to be used in a crystallisation. Ultimately, this argument disguises that the starting point, i.e. the substance actually used in the crystallisation, and with that the assessment of inventive step along the lines of the problem solution approach, changes during the (mental) replacement, namely from the crystalline complex of dapagliflozin with L-phenylalanine to dapagliflozin itself. Following the appellant’s argumentation, the skilled person would thus ultimately not have subjected the crystalline complex of dapagliflozin with L-phenylalanine to crystallisation, but the form of (pure) dapagliflozin which is actually disclosed in the closest prior art D1, namely amorphous dapagliflozin. However, starting from amorphous dapagliflozin, an inventive step is to be acknowledged, as already concluded above.

7. In the written proceedings (letter of 20 December 2017, point 3.3), the appellant also referred in a general way to D5 to D7 as an alternative to D4; however, it did so without citing any passages of D5, D6 or D7 in support of the objections raised. Moreover, the appellant did not refer to any of D5 to D7 during the oral proceedings either. Thus, due to the

unsubstantiated nature of the objections based on D5 to D7, they cannot be taken into account.

8. It follows that the subject-matter of claim 1 involves an inventive step and that the main request is allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated