Internal distribution code:

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

Datasheet for the decision of 19 January 2023

Case Number: T 0215/20 - 3.3.02

Application Number: 15181545.3

Publication Number: 3045466

IPC: C07H7/04, C07H15/207, A61K31/7034, A61K45/06, A61P3/10

Language of the proceedings: EN

Title of invention:

(2S,3R,4S,5S,6R)-2-[4-CHLORO-3-(4-ETHOXY-BENZYL)-PHENYL]-6-HYDROXYMETHYL-2-METHOXY-TETRAHYDRO-PYRAN-3,4,5-TRIOL PROPYLENE GLYCOL SOLVATE AS SGT2 INHIBITOR FOR THE TREATMENT OF DIABETES

Patent Proprietor:

AstraZeneca AB

Opponent:

Generics (U.K.) Limited

Relevant legal provisions:

EPC Art. 56

Keyword:

Inventive step

Decisions cited:
T 0777/08

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 0215/20 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 19 January 2023

Appellant: (Opponent)	Generics (U.K.) Limited Building 4, Trident Place Mosquito Way Hatfield Herts AL 10 9UL (GB)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 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:	**Decision of the Opposition Division of the European Patent Office posted on 25 November 2019 rejecting the opposition filed against European patent No. 3045466 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	A. Lenzen
	M. Blasi

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the opponent (appellant) against the opposition division's decision (decision under appeal) to reject the opposition against European patent No. 3 045 466 (patent).

II. Before the opposition division, the appellant had requested revocation of the patent in its entirety, relying on the grounds for opposition under Article 100(a) EPC (lack of inventive step) and Article 100(b) EPC. On appeal, the appellant only invoked the former ground.

III. The following documents, filed before the opposition division, are relevant for the present decision:

D1 WO 2004/063209 A2
D4 WO 2004/060347 A2
D12 Declaration of Li Tao (5 pages)

IV. With the reply to the statement of grounds of appeal, the patent proprietor (respondent) continued to pursue the granted patent as the main request. It also filed, *inter alia*, the sets of claims of auxiliary request 1 and the following documents:

D13 A. Braem et al., Top. Med. Chem., 12, 2014, 73-94
D14 D. Brage et al., Chem. Comm., 2005, 3635-3645

V. The oral proceedings before the board took place as a videoconference on 19 January 2023 in the presence of both parties. The respondent made auxiliary request 1, filed with the reply to the statement of grounds of

appeal, its main request. At the end of the oral proceedings, the chair announced the order of the present decision.

VI. Summaries of the appellant's arguments are contained in the reasons for the decision.

VII. The respondent's arguments relevant to the present decision can be summarised as follows.

D1 was the closest prior art. Amorphous dapagliflozin, as disclosed in example 20 of D1, was a suitable starting point for the assessment of inventive step. The fact that a moisture adsorption/desorption isotherm was shown in D12 for form SC-3 but not for amorphous dapagliflozin did not prevent a proper comparison of both forms. The appellant's argument that the amorphous forms of D1 and D12 were different was merely an allegation. Thus, it had to be concluded from D12 that form SC-3 referred to in claim 1 of the main request was more stable, i.e. less hygroscopic, than amorphous dapagliflozin. This effect was achieved over the entire breadth of claim 1 because, first, the appellant had provided no evidence to support its contention that claim 1 encompassed more crystalline forms than used in D12 and, second, because the higher stability of form SC-3 was also achieved when it was contained in a composition as shown by D13. Hence, the objective technical problem was to provide a pharmaceutical composition comprising a crystalline form of dapagliflozin which was more stable, i.e. less hygroscopic. The teaching of D4 was so broad and so general that the skilled person would not have considered it to be as generally applicable as suggested. This was because the formation of crystalline forms and their properties were highly

unpredictable. Furthermore, a comparison of examples 1 and 7 of D4 strongly indicated that a reduced hygroscopicity was in fact not achieved.

The crystalline complex of dapagliflozin/L-phenylalanine was not disclosed in an enabling manner in example 13 of D1. Even if it had been disclosed in an enabling manner, the skilled person would not have started from this complex when attempting to prepare a PG solvate of dapagliflozin according to the teaching of D4. The combination with D4 was based on hindsight. To obtain the solvate of claim 1, the skilled person would have had to resort to amorphous dapagliflozin over which an inventive step was to be acknowledged.

Thus, the subject-matter of claim 1, and by the same token of its dependent claims, involved an inventive step.

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

The appellant requested that the patent be revoked in its entirety and that D14 not be admitted into the proceedings.

The respondent requested that the patent be maintained in amended form based on the set of claims of the main request, filed as auxiliary request 1 with the reply to the statement of grounds of appeal.

Reasons for the Decision

Admittance of D14

1. D14 was filed by the respondent with the reply to the statement of grounds of appeal as evidence of common general knowledge. D14 showed that the formation of crystalline forms and their properties were highly unpredictable.

At the oral proceedings before the board, the appellant did in fact accept as common general knowledge what D14 was submitted as evidence for. Nevertheless, it maintained its request not to admit D14 into the proceedings because it could not be ruled out that the appellant also relied on other aspects of D14.

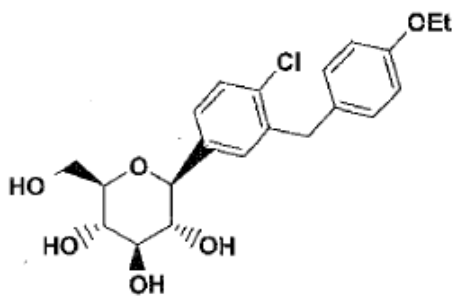
Since the appellant did not rely on such other aspects, it was not necessary to decide on the admittance of D14.

Main request - Inventive step - Article 56 EPC

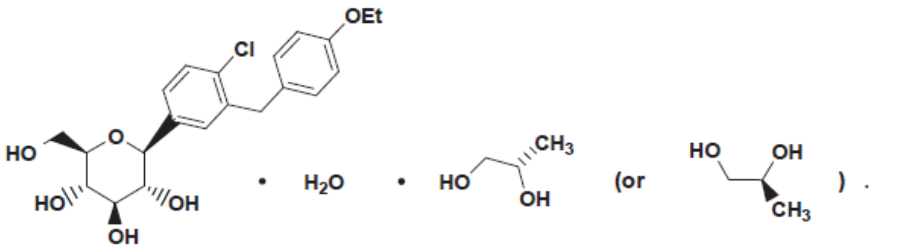
2. Claim 1 of the main request reads as follows:

> "*A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a crystalline structure of a compound of formula I*

I



in the form of its propylene glycol solvate for use in treating a disorder selected from diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, dyslipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis or hypertension, or for use in increasing high density lipoprotein levels in a mammal,
wherein the crystalline structure is an (S)-propylene glycol ((S)-PG) solvate of the structure (form SC-3) Ia



Compound Ia "

The compound of formula I above, 1-C-(6-chloro-4'-ethoxydiphenylmethane-3-yl)-β-D-glucopyranose, is commonly known as dapagliflozin. Thus, claim 1 is directed to second medical uses of a crystalline solvate of dapagliflozin with water and (S)-propylene glycol which comprises these three constituents in equimolar amounts (1:1:1 molar ratio). In accordance with claim 1, this crystalline solvate is referred to as form SC-3 below. Furthermore, the following abbreviations are used:

PG	for	propylene glycol
API	for	active pharmaceutical ingredient

3. D1 (page 1, lines 5 to 13 and page 35, lines 13 to 20) relates to a process of producing 1-C-(substituted diphenylmethane-3-yl)-β-D-glucopyranose compounds, such as dapagliflozin in particular. It also pertains to crystalline complexes of these C-aryl glucoside compounds formed with an amino acid complex forming agent such as L-phenylalanine. The 1-C-(substituted diphenylmethane-3-yl)-β-D-glucopyranose compounds of D1 are stated to be useful in the treatment of diabetes (page 20, lines 10 to 26), i.e. one of the conditions mentioned in claim 1 of the main request.

Against this background, it was common ground between the parties that D1 constitutes the closest prior art. The board saw no reason to deviate from this unanimous view.

4. 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). The parties disagreed on whether this disclosure was enabling. In the following, it is accepted in the appellant's favour that example 13 of D1 does in fact disclose a crystalline complex of dapagliflozin with L-phenylalanine in an enabling manner.

5. 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.

Amorphous dapagliflozin as the starting point

6. It was common ground between the parties that the subject-matter of claim 1 differs from amorphous dapagliflozin in that, *inter alia*, dapagliflozin is present as form SC-3, i.e. a crystalline solvate of dapagliflozin with water and (S)-PG comprising these three compounds in equimolar amounts (1:1:1 molar ratio) instead of its amorphous form.

7. D12 is a summary of the respondent's efforts made in the course of developing a pharmaceutically acceptable form of dapagliflozin. Points 8 and 19 of this declaration relate to amorphous dapagliflozin and form SC-3 of claim 1, respectively. These points read as follows:

> "8. *[...] After the solvent(s) were removed from the gel, an amorphous glassy foam was generally formed. 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.*"
>
> "*19. [...] SC-3 (dapagliflozin + 1 (S)-propylene glycol + 1 H_2O) is physically stable under ambient temperature and humidity. Results from moisture sorption-desorption studies indicate that SC-3 is non-hygroscopic at 25 °C (Fig. 2).*"

In figure 2 under point 19, D12 also shows the moisture adsorption/desorption isotherm for form SC-3.

8. The above two statements are clear, and nothing was apparent that could have called their accuracy into question. While it is true that D12 shows a moisture adsorption/desorption isotherm for form SC-3 but not for amorphous dapagliflozin, as argued by the appellant, both points 8 and 19 nevertheless allow a direct comparison to be made between both forms. It can be concluded that form SC-3 has a higher stability, i.e. a lower hygroscopicity, than amorphous dapagliflozin.

9. The appellant did not agree with this conclusion. It argued that D12 could not show any effect relative to the amorphous dapagliflozin of D1. While both D1 and D12 referred to amorphous dapagliflozin, detailed instructions for its preparation were only disclosed in D1. Therefore, it was possible that both amorphous forms were in fact not the same. It was quite conceivable that dapagliflozin showed polyamorphism, i.e. that several amorphous forms existed. This was supported by the fact that D12 described the amorphous form as a "*glassy foam*", whereas D1 spoke of a "*glassy off white solid*" without mentioning a foamy appearance.

However, 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. A supposedly different macroscopic appearance ("solid" vs "foam") does also not allow any conclusion to be drawn

about the arrangement of the molecules in the solid form and thus whether the amorphous form used in D12 must necessarily be different from that disclosed in D1.

10. Thus, in line with the respondent's position, the objective technical problem can be considered that of providing a pharmaceutical composition comprising a crystalline form of dapagliflozin which is more stable, i.e. less hygroscopic.

11. The appellant disagreed with this objective technical problem. According to it, an effect, if any, could not be acknowledged over the entire breadth of claim 1 of the main request, and the objective technical problem had to be formulated less ambitiously, namely as that of providing a pharmaceutical composition comprising a crystalline form of dapagliflozin.

11.1 The appellant argued that form SC-3 of D12 had a specific crystal structure. While claim 1 of the main request specified the molar ratios of dapagliflozin, (S)-PG and water, its subject-matter was not limited in terms of crystal structure. This meant that claim 1 actually encompassed further solid forms which had the same molar ratio but a different crystal structure from form SC-3 of D12. However, nothing had been shown in terms of hygroscopicity for such further solid forms.

The board agrees with the appellant that form SC-3 of D12 not only comprises the three constituents in a molar ratio of 1:1:1 but also has a specific crystal structure. However, the mere fact that the subject-matter of claim 1 of the main request is limited only by the molar ratio of the constituents does not allow the conclusion that there must necessarily be other

solid forms with the same molar ratio besides the form actually used in D12. The appellant, who bears the burden of proof, did not demonstrate that such a further solid form exists.

11.2 The appellant further submitted that claim 1 of the main request related to a pharmaceutical composition. It could not simply be assumed that form SC-3 was more stable when contained in such a composition.

However, the board fails to see why form SC-3 should not retain its higher stability in terms of a lower hygroscopicity compared to amorphous dapagliflozin in a pharmaceutical composition. From the fact that form SC-3 was chosen for the pharmaceutical development of the drug ultimately on the market (D13: page 88, last paragraph), precisely the opposite conclusion must be drawn.

12. As regards obviousness, the appellant pointed to D4.

12.1 D4 relates to PG solvates of APIs and states, quite generally, (on page 4, paragraph 4; page 3, paragraphs 2 and 3) that:

(a) the formation of PG solvates makes it possible to obtain crystalline compounds from APIs which are difficult to crystallise
(b) API PG solvates are more stable and less hygroscopic than the corresponding APIs

12.2 The appellant argued that the skilled person would have turned to D4 because it 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. Consequently, the subject-matter of

claim 1 did not involve an inventive step over a combination of D1 and D4.

12.3 The appellant's 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 solve the objective technical problem. However, this is not the case, as set out in the following.

12.4 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 T-1095 (page 267, entry 4), i.e. a compound which is structurally similar to dapagliflozin. In view of points 12.1 (a) and (b) 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 the compound dapagliflozin which is less hygroscopic than amorphous dapagliflozin. The reason is that, as agreed by both parties at the oral proceedings, the formation of crystalline forms and their properties such as hygroscopicity is highly unpredictable. So while the board acknowledges that D4 demonstrates that four structurally very different and unrelated APIs can be transformed into crystalline PG solvates, D4 lacks experimental data showing that an API PG solvate is less hygroscopic than the API itself.

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. 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 properties of crystalline forms (see above), the skilled person would not have had a reasonable expectation of obtaining a less hygroscopic form of dapagliflozin.

13. In view of the foregoing, the current case is also different from the case underlying decision T 777/08, on which the appellant relied.

13.1 In that decision, as in the current 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 deciding board concluded (OJ EPO 2011, 633, point 5.2 of the Reasons, third-last paragraph; 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.*"

13.2 Hence, in this case, the deciding board held that 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 current case is different in that, first, the effect relied on for inventive step is different (filterability and drying characteristics in T 777/08 vs hygroscopicity in the case at hand) and, second, 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 solved this problem.

14. 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.

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

15. It was common ground between the parties that the subject-matter of claim 1 differs from the crystalline dapagliflozin/L-phenylalanine complex of D1, *inter alia*, in that the dapagliflozin component comprises (S)-PG and water (at a dapagliflozin:(S)-PG:water molar ratio of 1:1:1) instead of L-phenylalanine.

16. According to the appellant, this distinguishing feature was not linked to a technical effect. The objective technical problem, therefore, had to be considered that of providing a pharmaceutical composition comprising an

alternative crystalline form of dapagliflozin, and its solution was obvious in view of D4.

17. The board does not agree with this for the following reasons.

17.1 The appellant conceded, and the board 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 dapagliflozin/L-phenylalanine complex as such in crystallisation attempts according to D4. The skilled person would have turned to amorphous dapagliflozin as disclosed in D1. This is simply because D4 only uses the APIs themselves (or their alkali metal salts) for the preparation of the corresponding API PG solvates; not compounds which would be comparable to a complex of an API with another organic compound, such as the crystalline complex of dapagliflozin with L-phenylalanine. This conclusion is tantamount to stating either that the crystalline dapagliflozin/L-phenylalanine complex of D1 when combining it with D4 would have turned out to be not suitable for this combination to solve the objective technical problem, or that the skilled person, when starting from this crystalline complex of D1, would not have taken into account the teaching of D4.

17.2 In so far as the appellant concedes that the skilled person in starting from the crystalline dapagliflozin/ L-phenylalanine complex of D1 would have used the amorphous dapagliflozin of D1 to prepare form SC-3 according to claim 1, it concedes that its objection of inventive step in fact does not start from the crystalline complex but from amorphous dapagliflozin. When starting from the amorphous dapagliflozin

disclosed in D1, an inventive step has to be acknowledged as set out above.

The need to resort to amorphous dapagliflozin means that the crystalline dapagliflozin/L-phenylalanine complex as the starting point requires at least one further step to arrive at the claimed solution than if starting from amorphous dapagliflozin, namely the isolation of amorphous dapagliflozin from the crystalline complex. In other words, the crystalline complex must be more remote from the claimed subject-matter than amorphous dapagliflozin, over which an inventive step is to be acknowledged (see above). Therefore, an inventive step must, *a fortiori*, be acknowledged if the crystalline complex is taken as a more remote starting point.

Conclusion

18. Thus, the subject-matter of claim 1 involves an inventive step within the meaning of Article 56 EPC. The reasoning above applies, *mutatis mutandis*, also to the subject-matter of dependent claims 2 to 5. The appellant did not raise any objection against these dependent claims. The set of claims of 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 in amended form with the following claims and a description to be adapted

thereto: claims 1 to 5 of the main request, filed as auxiliary request 1 with the reply to the statement of grounds of appeal.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated