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Datasheet for the decision of 12 December 2019

Case Number: T 0184/16 - 3.3.02

Application Number: 04771314.4

Publication Number: 1651658

IPC: C07H19/06

Language of the proceedings: EN

Title of invention:
NOVEL COMPOUNDS HAVING INHIBITORY ACTIVITY AGAINST SODIUM-DEPENDANT TRANSPORTER

Patent Proprietor:
Mitsubishi Tanabe Pharma Corporation

Opponent:
Galenicum Health S.L.

Headword:

Relevant legal provisions:
EPC Art. 56, 100(a), 83, 100(b)
EPC R. 106

Keyword:
Inventive step
Sufficiency of disclosure
Objection under Rule 106 EPC

Decisions cited:
G 0003/14, T 0068/85, T 1329/04, T 0433/05, T 1599/06, T 0279/07, T 0491/08, T 0108/09, T 1760/11, T 0919/15, T 0488/16, T 1868/16, R 0002/08, R 0004/08, R 0009/08, R 0008/09, R 0013/09, R 0014/11, R 0018/12

Catchword:
Plausibility - (points 2.1 to 2.8, 7.2 and 11)

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Case Number: T 0184/16 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 12 December 2019

Appellant: (Opponent)	Galenicum Health S.L. Avenida Diagonal 123 floor 11 08005 Barcelona (ES)
Representative:	Galenicum Health S.L. Avenida Diagonal 123, Floor 11 08005 Barcelona (ES)
Respondent: (Patent Proprietor)	Mitsubishi Tanabe Pharma Corporation 3-2-10, Dosho-machi, Chuo-ku, Osaka-shi Osaka 541-8505 (JP)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 7 December 2015 concerning maintenance of the European Patent No. 1651658 in amended form.**

Composition of the Board:

Chairman	M. O. Müller
Members:	S. Bertrand
	L. Bühler

Summary of Facts and Submissions

I. European patent No.°1 651 658 was opposed under Article 100(a) (lack of inventive step), (b) and (c) EPC.

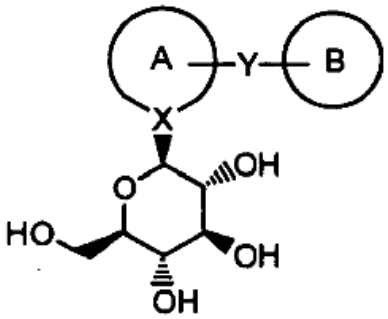
II. The appeal by the opponent (hereinafter "appellant") lies from the interlocutory decision of the opposition division that, in the amended form according to the auxiliary request then on file, the European patent met the requirements of the EPC.

III. The following documents are referred to in the present decision:

D1	GB 2 359 554 A
D2	US 2003/0114390 A1
D4	Comparative examples filed with the EPO by the patentee on 18 April 2011
D7	WO 01/27128 A1

IV. The auxiliary request that the opposition division found to be allowable corresponds to the claim request on which the present decision is based. It contains seventeen claims. Independent claims 1, 9 and 12 recite the following:

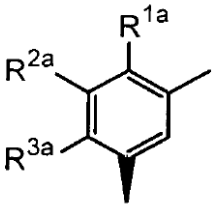
"*1. A compound of formula (I):*



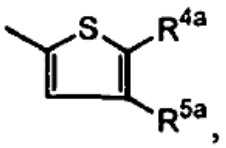
(I)

wherein:

Ring A is



wherein R^{1a} is a halogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxyalkyl group; R^{2a} and R^{3a} are hydrogen atoms; Ring B is



wherein R^{4a} is a phenyl group substituted by a halogen atom, a cyano group, a C_{1-6} alkyl group, a halo-C_{1-6} alkyl group, a C_{1-6} alkoxy group, a halo-C_{1-6} alkoxy group, and a mono- or di-C_{1-6} alkylamino group; or a heterocyclyl group substituted by a halogen atom, a cyano group, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group; R^{5a} is a hydrogen atom;

X is a carbon atom; and
Y is -CH_2-
or a pharmaceutically acceptable salt thereof."

"*9. A pharmaceutical composition, which comprises a compound as set forth in any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, and a pharmaceutically acceptable carrier or diluent*."

"*12. A compound as set forth in any of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in treating or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension.*"

V. With regard to this auxiliary request, the opposition division came *inter alia* to the following conclusions:

- The invention as defined in the auxiliary request was sufficiently disclosed within the meaning of Article 83 EPC.

- The post-published document D4 was further evidence of a technical effect and to be considered in formulating the objective technical problem.

- The subject-matter of the claims according to the auxiliary request involved an inventive step in view of D1 or D2 as the closest prior art.

VI. In its statement setting out the grounds of appeal, the appellant contested the reasoning of the opposition division and submitted that the subject-matter of the claims according to the auxiliary request filed at first instance was insufficiently disclosed and did not involve an inventive step.

VII. The patent proprietor (hereinafter "respondent") filed a response to the statement of grounds of appeal and provided counter-arguments regarding sufficiency of disclosure and inventive step.

VIII. Subsequently, the board issued a communication in preparation for the oral proceedings scheduled according to the requests of the parties.

IX. Third-party observations were submitted by letter dated 9 December 2019.

X. Oral proceedings before the board were held on 12 December 2019.

XI. The appellant's arguments, where relevant to the present decision, may be summarised as follows.

Sufficiency of disclosure had to be denied for the following reasons:

- The skilled person would need inventive skill in order to manufacture most of the claimed compounds, because the examples in the patent never referred to compounds with large substituents, such as bromine or iodine as halogen atoms.

- No salts could be produced in the case of some of the claimed compounds (claim 1).

- The skilled person would not know how to synthesise the prodrug referred to in claim 9 of the request on file. The application did not contain any examples of prodrugs or the synthesis thereof. The synthesis of such compounds was difficult. The term "prodrug" was a broad term. Reference was made to T 279/07 and T 68/85.

- In the absence of tests for determining sodium-dependent glucose transporter (SGLT) inhibition in the patent application, and given the fact that no common general knowledge had been cited and that D1 and D2 were not mentioned in the patent application as filed, the skilled person would not know which test to use. Reference was made *inter alia* to T 108/09.

- There was no example in the patent application showing that the claimed compounds were suitable for the use according to claim 12. The patent application contained no evidence to establish sufficiency of disclosure as required by T 491/08. It was thus not plausible that the claimed compounds were suitable for the claimed use. In view of this lack of plausibility, the post-published evidence D4 should not be taken into account.

- It was questionable whether the compounds having large groups as substituents would be suitable for the claimed uses. In post-published document D4, only 51 compounds were tested *in vitro* and only 29 of these compounds were tested *in vivo*, and none of the tested compounds had a bromine or iodine substituent.

- D4 provided technical data showing SGLT2 inhibition only. No effect regarding SGLT1 inhibition was provided in that document.

- The compounds of formula (I) represented a different family of compounds from the compounds disclosed in D7. The essential structural similarity between the compounds of formula (I) and the compounds of D7 as required by T 1329/04 was missing.

Inventive step had to be denied for the following reasons:

- There was no evidence in the patent application as filed that the claimed compounds would show any SGLT inhibitory effect. Said effect was thus not plausible. In view of this lack of plausibility, the post-published evidence D4 should not be taken into account.

- T 1329/04 supported the argument that D4 should not be considered in evaluating the effect provided by the claimed compounds.

- If D4 were not considered, the patent merely provided new compounds with no clear effect.

- Even if D4 was considered, it provided technical data showing SGLT2 inhibition only. No effect regarding SGLT1 inhibition was provided in that document. Furthermore, D4 provided a comparison with example 26 of D2 only, and not with the preferred embodiments (C-aryl glucosides substituted by a chlorine atom or a methyl group at the para position of the phenyl ring attached to the glucose moiety) disclosed in claim 9 of D2,

which represented the closest prior art from the point of view of structure.

- The objective technical problem was therefore to provide alternative SGLT2 inhibitors in view of D2 as the closest prior art.

- The compounds of formula (I) were obvious alternatives.

The appellant also raised objections under Rule 106 EPC:

- If the decision on sufficiency acknowledged plausibility on the basis that the compounds of the invention belonged to the same family as the prior art, but in respect of inventive step the compounds were considered a new family, then the right to be heard would have been violated.

- If the decision on inventive step did not take into account the arguments on plausibility, then the right to be heard would have been violated.

XII. The respondent's arguments, where relevant to the present decision, may be summarised as follows.

Sufficiency of disclosure had to be acknowledged for the following reasons:

- The pharmacodynamic target, the SGLT, had been established at the priority date of the patent in suit. It was shown in D7 that the aryl C-glucosides disclosed therein had a direct effect on the same metabolic mechanism as in the patent in suit, namely inhibition of SGLT, which was the basis for the use defined in claim 12. It was thus plausible that the claimed structure resulted in SGLT2

inhibition. The post-published evidence D4 could thus be taken into account. D4 proved that the claimed compounds were suitable as SGLT2 inhibitors. The fact that SGLT1 inhibition contributed to the therapeutic effects of claim 12 as well and was not tested in D4 was not relevant: it was enough to show the SGLT2 inhibition. The use as defined in claim 12 was thus sufficiently disclosed. The situation in the present case was different from that in T 1329/04.

- The mere fact that a claim was broad was not in itself a ground for considering that the application did not comply with the requirement under Article 83 EPC that it be sufficiently disclosed. The burden of proof that a skilled person using their common general knowledge would be unable to carry out the invention was on the appellant. The appellant had not substantiated its allegation with verifiable facts.

- As set out on pages 2 and 3 of the application as filed, the pharmacodynamic target, the SGLT, had already been well established at the priority date of the patent in suit. The present situation was comparable to that in T 108/09, where it had been concluded that the evaluation of sufficiency of disclosure had to take account of the entire information to be found in the patent, including the claims, description and figures. In the case in hand, page 3 of the A1 publication (corresponding to paragraphs [0007] to [0008] of the patent as granted) referred *inter alia* to D7 as disclosing aryl C-glucosides with a related structure as SGLT inhibitors. In this context, D7 provided an *in*

vitro assay for SGLT inhibitory activity on page 52.

- The patent provided substantial general guidance, which made it possible, *per se* and also in combination with the general background knowledge of a person skilled in the art, to obtain the compounds of the invention, including those with alternative large substituents. The compounds themselves were quite simple molecules. Coupling and protection/deprotection reactions, and the introduction of various substituents, were well within the abilities of the person skilled in the art.

- At least the compounds of the present invention having amino substituents might exist in the form of a pharmaceutically acceptable salt. In accordance with established principles, a patent should be interpreted by a mind willing to understand, not a mind desirous of misunderstanding, so the fact that not every single compound of the invention might exist in the form of a salt did not mean that the subject-matter was insufficiently disclosed.

- A suitable prodrug for a carbohydrate derivative was well within the common knowledge of a person skilled in the art. The A publication gave a clear definition of the term "prodrug" and its synthesis on page 12, lines 24 to 32. T 279/07 had considered the question of whether the term "prodrug" in a claim directed to structurally remote steroid derivatives rendered the claimed subject-matter unclear, contrary to the requirements of Article 84 EPC, which was not a ground for opposition.

Inventive step had to be acknowledged for the following reasons:

- The compounds of the present invention shared the following structural characteristic features: ring A, an optionally substituted phenyl or naphthyl ring, and ring B, a thiophene ring which is substituted by a substituted phenyl. This represented a three-ring system which was essential to the invention.

- The facts in the case of T 1329/04 and the present case were completely different, so the principles of T 1329/04 were not applicable to the present case. The post-published evidence D4 was to be accepted and taken into account in evaluating whether the claimed compounds involved an inventive step, despite the lack of experimental evidence for the effect in the application, because it was plausible that the problem had been solved at the priority date.

- D4 established that the compounds claimed exhibited increased activity as SGLT2 inhibitors by comparison with example 26 of D2. The compound of this example possessed a three-ring system in the same way as that of formula (I) according to claim 1. For this reason, of the compounds disclosed in D2, it came closest to the structure shown by formula (I) in claim 1.

- The appellant had not in any way provided verifiable facts to support its allegation that not all compounds covered by the claims worked. The burden of proof was on the appellant.

- The objective technical problem underlying the invention was the provision of an SGLT2 inhibitor having improved activity.

- The claimed subject-matter involved an inventive step.

XIII. The parties' final requests were the following:

The appellant requested that the decision under appeal be set aside and that European patent No. 1 651 658 be revoked.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The present decision is based on the claim request filed on 19 August 2015 and found to be allowable by the opposition division.

Sufficiency of disclosure

2. Claim 1 relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof (IV, *supra*). Claim 12 relates to a compound *inter alia* of claim 1 for use in treating or delaying the progression or onset of "*diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension*" (IV, *supra*).

Claim 12 is thus a medical use claim relating to a compound of formula (I) for obtaining a certain therapeutic effect, namely the treatment or delay of the progression or onset of the above diseases.

These diseases are all directly or indirectly linked to diabetes. The mechanism underlying the treatment of these diseases, and thus obtaining the claimed therapeutic effect, is based on the inhibition of the sodium-dependent glucose transporter (hereinafter "SGLT"), and in particular of SGLT2. More specifically, as set out in D7, SGLT2 appears to be the major transporter responsible for renal glucose reabsorption (page 2, lines 5-13). Inhibition of SGLT2 therefore reduces plasma glucose levels in diabetic patients (page 3, lines 19-21). The link between the therapeutic effect to be obtained according to claim 12 and SGLT2 inhibition was not contested by the appellant.

2.1 The appellant argued that there was no evidence in the application as filed to show that the claimed compounds were suitable for SGLT2 inhibition. For this reason, it was not plausible in the application as filed that the claimed therapeutic effect could be obtained using the claimed compounds. Therefore, the post-published evidence D4 filed by the respondent to show that various compounds falling under formula (I) of claim 12 resulted in SGLT2 inhibition should not be taken into account. As a consequence, sufficiency of disclosure had to be denied.

2.2 The board acknowledges that according to, for example, T 488/16 (point 4.2), T 1329/04 (point 12) and T 433/05 (point 28), a precondition for taking into account post-published evidence to demonstrate a certain effect is that it was already plausible at the filing date

that said effect was obtained. This approach is based on the concept that in a first-to-file system the (earlier) filing date of the application, rather than the date at which the invention was made determines which of several persons who have independently invented something has the right to a European patent (cf. Article 60(2) EPC). Consequently, in such a system it is particularly important that the application makes it possible to conclude that the invention had been made, i.e. that a claimed effect is indeed obtained and thus the problem the application aims to solve is indeed solved, and not merely put forward at the filing date of the application (T 1329/04, point 10).

2.3 The plausibility of a technical effect (or property) relied on in the application as filed must be judged on the basis of the disclosure in the application as filed, taking into account the common general knowledge available on the filing date of that application as well as prior art (common general knowledge: see for example T 1599/06, point 6 and T 1868/16, point 4.2; prior art: see for example T 108/09, points 2.3.1, 2.3.2 and 2.4.5 and T 491/08, point 6).

2.4 Plausibility has been acknowledged, and post-published evidence has been taken into account, for example in cases where there had been no "*prima facie* serious doubts" about plausibility:

In T 108/09, in acknowledging plausibility the board contrasted the case underlying that decision with that in T 1329/04. More specifically, in T 108/09 (point 2.4.5) the board stated that

> *"As regards whether it is permissible to submit post-published evidence (document (10)) for demonstrating that alleged effects are indeed*

obtained, the board notes that the present case is different from the situation described in decision T 1329/04, which had been cited by the appellant-opponent in this context. In decision T 1329/04, there had been ***prima facie serious doubts*** *that the polypeptide denominated GDF-9 belonged to the TGF-ß superfamily and thus solved the problem of the invention." (emphasis added)*

In T 1760/11 too (point 10.5.1), the board contrasted the case before it with that in T 1329/04 and stated that in contrast to that decision, "*the board can see* ***no reason a priori*** *for the skilled person to regard it [i.e. the obtainment of the claimed effect] as being implausible*" (insertion in squared brackets by the board).

Lastly, several decisions have acknowledged plausibility on the ground that there was no **indication in the common general knowledge** of any lack of plausibility (see for example T 919/15, point 5.6) (emphasis added by the board).

2.5 In the present case, the application as filed does not contain any experimental evidence as regards the disputed plausibility, i.e. the plausibility of the claimed compounds being SGLT2 inhibitors.

It is thus necessary to determine whether plausibility can nevertheless be acknowledged in view of the common general knowledge and the prior art.

2.6 The board has no indication, nor has the appellant argued that there exists any, that there is *prima facie* any serious doubt that the claimed therapeutic effect can be obtained. Furthermore, there is no *a priori* reason or any indication in the common general

knowledge that the claimed therapeutic effect cannot be obtained.

2.7 On the contrary, on page 3, line 1, the application as filed cites WO 01/27128, which is D7 in the proceedings in this case. D7 (claim 1) refers to aryl C-glucosides, i.e. compounds with the same core structure as the compounds referred to in claim 12. D7 (claim 16) considers these aryl C-glucosides to be SGLT2 inhibitors. Furthermore, D7 (page 5, line 18, to page 8, line 15) cites thirteen different patent documents and scientific articles, all disclosing O-aryl glucosides as SGLT2 inhibitors.

In view of the above, the board considers it plausible that the therapeutic effect defined in claim 12 is indeed obtained.

2.8 The appellant argued that the compounds defined in claim 12 represented a new family of compounds, different from the compounds disclosed in D7. The essential structural similarity between the compounds as defined in claim 12 and the compounds of D7 as required by T 1329/04 was missing. The reference to D7 in the description did not make the suitability of the claimed compounds for the claimed uses plausible.

The board does not agree. The present case differs from T 1329/04 (points 11-12), in which plausibility was not accepted.

In the case underlying T 1329/04, claim 1 was directed to a polynucleotide sequence encoding a polypeptide denoted as GDF-9. The problem to be solved was isolating a further member of the TGF-beta superfamily. However, GDF-9 lacked the most striking structural feature which served to establish whether or not a

polypeptide belonged to the TGF-beta superfamily, namely the presence of seven cysteine residues, and furthermore had only 34% sequence homology with known members of the TGF-beta superfamily. Those seven cysteine residues played a fundamental role in the tertiary structure of the protein, which was in turn to a very large extent responsible for its functional activity. The board held that accordingly, any change in the pattern of the seven cysteine residues would be expected to have significant repercussions for the function of a TGF-beta family member. The board therefore considered that any compound which did not exhibit those residues could not clearly and unambiguously be considered a member of the TGF-beta superfamily unless further evidence was available to that effect. *P*lausibility was therefore denied and post-published evidence not taken into account.

In the present case, however, the core structure of the claimed compounds of formula (I) conforms to that of the C-aryl glucoside family identified in D7. The situation in the present case is thus different from that in T 1329/04.

2.9 In view of this, the post-published evidence D4 can be taken into consideration to support the disclosure in the patent application.

D4 provides activity data of certain compounds as defined in claim 12. Human SGLT2 inhibition was tested *in vitro* and the 50% inhibitory concentration (IC_{50}) was calculated for fifty-one compounds according to claim 12 and set out in table 1 of D4. Twenty-nine compounds according to claim 1 were tested *in vivo* (in rats) to evaluate the urinary glucose amount ranges as shown by A (A ≥ 2000 mg) and B (2000 mg > B ≥ 1500 mg)

in table 2. Each of the compounds tested in tables 1 and 2 exhibits SGLT2 inhibition, as evidenced by the IC_{50} values in table 1 (1.1 nM to 10 nM) or the daily amount of glucose extracted in urine in table 2 (from 1500 mg to more than 2000 mg).

D4 thus supports the view that the compounds of formula (I) exhibit SGLT2 inhibition.

2.10 The appellant submitted that the description of the application referred to two targets, SGLT1 (glucose transporter found in the small intestine) and SGLT2 (glucose transporter found in the kidney) (page 1, lines 7-9 of the application as filed). However, D4 evidenced activity against SGLT2 only. No evidence had been provided to show activity against SGLT1.

The board acknowledges that D4 indeed provides data for SGLT2 inhibition only. However, as set out above, the claimed therapeutic effect is obtained by SGLT2 inhibition alone. The fact that SGLT1 inhibition may contribute to this effect as well and was not tested in D4 is not relevant.

2.11 The appellant also argued that changing the substituents of the compounds defined in claim 12 would inhibit the activity of the compounds.

It is true that the activity of the compounds as defined in claim 12 is influenced by their substituents. This is shown by D4, where the compounds with different substituents all have different levels of activity as expressed by the SGLT2 inhibition value. However, D4 shows that all the compounds tested therein exhibit activity against SGLT2 (see point 2.9 above). There is no evidence in D4 that some of the compounds

as defined in clam 12 are inefficient as SGLT2 inhibitors.

2.12 Lastly, the appellant argued that it was questionable whether the compounds defined in claim 12 would be suitable for obtaining the claimed therapeutic effect if they had large groups as substituents. In D4, only fifty-one compounds had been tested *in vitro*, and only twenty-nine of these compounds had been tested *in vivo*. None of the tested compounds had a large halogen atom, such as a bromine or iodine atom, as R^{1a}.

The board does not agree. Each party bears the burden of proof for its assertions (Case Law, 9th edition 2019, III.G.5.1.1). Therefore it is for the appellant to show that the compounds defined in claim 12 with large substituents are not suitable for the claimed use. In the absence of any such evidence, the board cannot conclude that compounds with large substituents are not suitable to obtain the therapeutic effect defined in claim 12.

2.13 For all these reasons, the appellant's objection of insufficiency of disclosure regarding SGLT2 inhibition must fail.

3. The appellant presented a number of further insufficiency objections, which are dealt with below.

3.1 The appellant objected to the absence in the patent application of tests for determining SGLT inhibition, with the result that the skilled person would not know which test to use. This would confront the skilled person with an undue burden, such that the claimed invention was insufficiently disclosed.

As set out above, the application as filed refers *inter alia* to D7. D7 discloses *in vitro* tests for SGLT2 inhibitors (pages 52-53). Therefore, the skilled person would have at their disposal at least one experimental protocol in order to test the SGLT2 inhibitory activity of the compounds defined in claim 12. Furthermore, the target SGLT has been known before the priority date of the patent (paragraph [0004] of the patent), with the result that it represents common general knowledge. Based on this common general knowledge, the skilled person would know which tests could be used to provide evidence of the SGLT2 inhibitory activity of the compounds as defined in claim 12. Consequently, the fact that no test method is identified in the application as filed does not result in an undue burden for the skilled person.

3.2 The appellant submitted that the skilled person would need inventive skill in order to manufacture most of the compounds defined in claims 1 and 12 because the examples of the patent never referred to compounds with large substituents, such as bromine or iodine as halogen atoms.

The board does not find this argument convincing. In the tables on pages 23-34 and on pages 46-49 the patent discloses various compounds according to the invention. Some of the compounds comprise for example a chlorine atom as a substituent (see, for example, example 25). The skilled person, based on their common general knowledge, would know how to introduce a bromine or iodine atom instead of a chlorine atom by selecting the corresponding equivalent reactant and using the method disclosed in any of reference examples 1-4 of the patent (paragraphs [0145], [0147] and [0151]).

Consequently, the board is convinced that the patent provides guidance that, *per se* and also in combination with common general knowledge, enables the skilled person to obtain the compounds of the invention, even if they have alternative large substituents such as a bromine or iodine atom.

In view of this and in the absence of any serious doubts substantiated by verifiable facts, it is concluded that the synthesis of compounds of formula (I) with large substituents does not represent an undue burden.

3.3 The appellant submitted that salts of the compounds of formula (I) referred to in claim 1 were insufficiently disclosed. More specifically, claim 1 covered compounds for which no salts could be produced.

The board is not convinced. The wording "or a pharmaceutically acceptable salt thereof" in claim 1 would be understood by the skilled person as meaning that claim 1 covers the alternative of such a salt only if it can be made. This finding corresponds to the established case law that *"the skilled person should try, with synthetical propensity, i.e. building up rather than tearing down, to arrive at an interpretation of the claim which is technically sensible and takes into account the whole disclosure of the patent*" (Case Law, 2019, II.A.6.1). At most, it is unclear which compounds can be transferred to their salts and thus which salts are covered by claim 1. The appellant's objection thus represents an objection of lack of clarity (Article 84 EPC) rather than an objection of insufficiency of disclosure (Article 83 EPC).

Since the supposed lack of clarity exists in the granted claims (claim 1), compliance with the requirements of Article 84 EPC cannot be examined (G 3/14, OJ EPO 2015, A102, Order).

3.4 The appellant also considered the invention defined in claim 9 to be insufficiently disclosed. This claim refers to a prodrug of the compound defined in claim 1, and the appellant asserted that the skilled person would not know how to synthesise this prodrug.

As pointed out by the respondent (XII, *supra*), the application as filed (WO 2005/012326 A1) gives a clear definition of the term "prodrug" and its synthesis on page 12, lines 24 to 32: "*an ester or carbonate, which is formed by reacting one or more hydroxy groups of the compound of the formula I with an acylating agent substituted by an alkyl, an alkoxy or an aryl by a conventional method to produce acetate, pivalate, methylcarbonate, benzoate, etc. Further, the prodrug includes also an ester or amide, which is similarly formed by reacting one or more hydroxy groups of the compound of the formula I with an α-amino acid or a β-amino acid, etc. using a condensing agent by a conventional method*".

Sufficiency of disclosure must be assessed on the basis of the application as a whole and not of the claims alone (Case Law, 2019, II.C.3.1). As an example, reference can be made to T 68/85. In that decision (point 8.1), it was concluded that adequacy of disclosure may under no circumstances be judged solely on the basis of the claims and that an objection under Article 83 EPC is to be judged on the basis of the European patent application as a whole. Since in the present case the description of the patent gives a

clear definition of the term "prodrug", the skilled person would know how to synthesise the prodrug referred to in claim 9. The invention defined in claim 9 is thus sufficiently disclosed.

T 279/07 (point 2.1), which the appellant cited in this regard, is not relevant in that it does not refer to sufficiency of disclosure. In that decision, a "prodrug" of a steroid derivative was considered unclear (Article 84 EPC). The appellant's submission with respect to the term "prodrug" therefore actually represents an objection of lack of clarity (Article 84 EPC). The supposed lack of clarity exists in the granted claims (claim 11), so the objection of lack of clarity is to be disregarded (G 3/14, OJ EPO 2015, A102, Order).

4. As the appellant's objections are not convincing, the invention underlying claims 1, 9 and 12 must be considered sufficiently disclosed.

Inventive step

5. The closest prior art

Both parties referred to D2 as the closest prior art.

Like the patent, D2 aims to provide a C-aryl glucoside and use thereof as an SGLT2 inhibitor (abstract and paragraph [0001] of D2). The board therefore agrees that D2 is a suitable starting point for the assessment of inventive step.

6. Distinguishing features

As acknowledged by both parties, the subject-matter of claim 1 differs from the compounds of D2 in that a 2-substituted thiophene ring is present as ring B in formula (I).

7. Formulation of the technical problem

7.1 The respondent defined the problem to be solved in view of D2 as the provision of improved SGLT2 inhibition. The respondent in this respect relied on the experimental evidence available in D4.

7.2 The appellant argued that there was a "new family" of inhibitors and that there was thus no information available in the application as filed and in the common general knowledge that would make the inhibitory property of the "new family" plausible for all compounds claimed. Post-published evidence D4 should thus not be taken into account when deciding whether the problem referred to by the respondent was solved.

However, as set out above when discussing sufficiency of disclosure, the board considers it plausible that the claimed compounds result in SGLT2 inhibition. Therefore, post-published evidence D4 can be taken into account. D4 (2.9, *supra*) provides a comparison of the *in vitro* and *in vivo* activity data of a compound according to D2 and compounds of formula (I) according to claim 1. In table 1 of D4 example 26 of D2 exhibits an SGLT2 IC_{50} of 84 nM. The fifty-one compounds of formula (I) show an SGLT2 IC_{50} ranging from 1.1 nM (example 156 on page 6) to 10 nM (example 136 on page 5). The fifty-one compounds of formula (I) have thus a lower SGLT2 IC_{50}, implying higher SGLT2 inhibition than example 26 of D2. In table 2 the

urinary glucose amount for example 26 of D2 is 754 mg while the urinary glucose amount for the twenty-nine compounds of formula (I) ranges from 1500 mg to more than 2000 mg (depicted by A and B in Table 2, see the definition of A and B under paragraph (2) on page 10). The twenty-nine compounds of formula (I) enable a higher daily amount of glucose extracted in urine per individual implying a higher SGLT2 inhibitory activity when compared to example 26 of D2.

D4 thus shows that the compounds of formula (I) tested in D4 exhibit an improved inhibitory activity when compared to example 26 of D2.

Therefore, the objective technical problem is the provision of improved SGLT2 inhibition.

7.3 The appellant argued that example 26 of D2 did not constitute the compound closest to the compounds of formula (I). Instead, the compounds of claim 9 of D2 should have been used for comparative purposes.

As argued by the respondent (XII, *supra*), the compounds of formula (I) are characterised by the presence of two rings, A and B. Ring A is a substituted phenyl ring. Ring B is a thiophene ring substituted by a phenyl or heterocyclyl group. The combination of ring A and ring B according to formula (I) represents a three-ring system. The C-aryl glucoside compound of example 26 of D2 is substituted with a first phenyl group, which itself is substituted with a phenylbenzyl group (see table 1 of D2). This compound also encompasses a three-ring system. It thus represents a suitable embodiment of D2 with which the compounds of formula (I) can be compared. The compounds of claim 9 of D2 referred to by the appellant, i.e. the C-aryl glucosides substituted

by a chlorine atom or a methyl group at the para position of the first phenyl ring (last three compounds of the left-hand column and the first two compounds of the right-hand column on page 39 of D2), do not possess the three-ring system which is essential to the invention in the patent. Furthermore, contrary to the appellant's argument, they do not represent the most preferred embodiments of D2, but at best represent only some of the several equally preferred embodiments referred to in claim 9 of D2. More specifically, besides the para-substituted C-aryl glucosides, this claim discloses other C-aryl glucosides with no substituents at that position (see for example the first seven compounds of claim 9 of D2). The appellant's argument is thus not convincing.

7.4 Finally, the appellant argued that no effect regarding SGLT1 inhibition was provided in D4. However, this argument is not relevant. In the problem-solution approach, the question to be answered after having identified the closest prior art is how the objective technical problem can be formulated in view of the effect achieved by the distinguishing feature. In the present case, the effect achieved by the distinguishing feature (improved SGLT2 inhibition) has been identified and the objective technical problem formulated accordingly (7.1 above). The fact that SGLT1 inhibition was not evidenced is irrelevant, since this effect is not part of the technical effect underlying the objective technical problem.

8. Obviousness of the solution

The non-obviousness of the solution was not contested by the appellant, and the board is satisfied that none of the cited prior-art documents teach introducing a 2-

substituted thiophene in place of the phenyl-ring substituents R3 and R4 in the structure of the formula shown in claim 1 of D2 in order to improve SGLT2 inhibition activity.

9. Based on the above considerations, the board comes to the conclusion that, in view of the cited prior art, it would not have been obvious to the skilled person to modify the C-aryl glucosides disclosed in D2 so as to arrive at the compounds of formula (I) as defined in claim 1.

10. Therefore, the subject-matter of claim 1, and by the same token all of the remaining claims of the main and sole request, involves an inventive step pursuant to Article 56 EPC.

The board therefore comes to the conclusion that the main request, i.e. the claim request filed on 19 August 2015 and found to be allowable by the opposition division, and the description adapted thereto, are allowable.

11. As set out above (points 2.1 to 2.8 and 7.2), the board has acknowledged plausibility, i.e. it considers it plausible in view of the prior art that the claimed compounds have SGLT2 inhibitory properties. It is to be noted that this is not in contradiction of the finding that the claimed subject-matter is non-obvious in view of the prior art. The criteria for plausibility and obviousness are different. On the one hand, as set out above, for plausibility of a claimed effect to be acknowledged, it is enough if there are no *prima facie* serious doubts that the effect can be obtained and conversely no *a priori* reason and indication in the common general knowledge that the effect cannot be obtained. On the other hand, obviousness is decided in

the framework of the problem-solution approach, where generally an important consideration is whether the claimed solution is suggested and thus made obvious by the prior art.

Objections under Rule 106 EPC

12. During the oral proceedings, the appellant filed two written objections under Rule 106 EPC in which it made explicit reference to a fundamental violation of Article 113 EPC. These objections were as follows:

"*In the case of the decision on sufficiency acknowledged plausibility on the basis that the compounds of the invention belong to the same family of the prior art, but for inventive step the compounds are considered a new family, then the right to be heard would have been violated.*"

"*In case that the decision on inventive step did not take into account the arguments on plausibility, then the right to be heard would have been violated.*"

12.1 At the point in time when these objections were made, i.e. during the oral proceedings, they were conditional. More specifically, they were made under the condition that a certain event occurred in the future, namely that a reasoning is put forward in the written decision that would violate the appellant's right to be heard. The objection, thus, pertained to alleged procedural defects that had not yet arisen in the proceedings. Moreover, it related to possible reasons for findings on substantive issues on which the parties had been heard but with which the appellant as the loosing party obviously disagreed.

12.2 As the Enlarged Board has consistently held, the requirement pursuant to Rule 106 EPC to raise an objection should enable the board confronted with the objection to react immediately and appropriately by either removing the cause of the objection or, as provided in Rule 106 EPC, by dismissing it (R 4/08, point 2.1 of the reasons; R 14/11, points 2.5 and 2.6 with further references). Since in the present case the cause for the objections had yet to occur, the objections were misplaced and the board had no other option than to dismiss them during the oral proceedings.

Apart from that, the first objection relates to the requirements of sufficiency and inventive step and thus concerns substantive law. However, as set out in R 2/08 (point 5), R 9/08 (point 6.3), R 8/09 (point 2.7), R 13/09 (point 2.2), under no circumstances can a petition for review be a means to review the correct application of substantive law. Accordingly, as set out in R 18/12 (point 19), an objection under Rule 106 EPC made during the oral proceedings must be drafted such that the board is able to discern that the objection is directed at a procedural defect within the meaning of Rule 106 EPC and not to an allegedly wrong assessment of substantive issues by the board, or, as in the present case, to an alleged disagreement with the case law, which is outside the legal scope of review.

12.3 Therefore the appellant's objections under Rule 106 EPC were dismissed.

Third party observations under Article 115 EPC

13. Third-party observations were filed with telefax on 9 December 2019, i.e. three days before the oral proceedings which took place on 12 December 2019. None

of the parties referred to these observations during the written or oral proceedings and the board did not see any reasons to take them into account.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated