Internal distribution code:

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

Datasheet for the decision of 9 February 2024

Case Number: T 1437/21 - 3.3.07

Application Number: 14715578.2

Publication Number: 2981271

IPC: A61K31/7048, A61P3/10, A61P13/12

Language of the proceedings: EN

Title of invention:
THERAPEUTIC USES OF EMPAGLIFLOZIN

Patent Proprietor:
Boehringer Ingelheim International GmbH

Opponents:
KRKA, d.d., Novo mesto
EGIS Gyógyszergyár Zártkörüen Müködö Részvénytársaság
Teva Pharmaceutical Industries Ltd.
Stada-Arzneimittel Aktiengesellschaft
Generics (U.K.) Limited
ZAKLADY FARMACEUTYCZNE POLPHARMA S.A.
Gillard, Richard Edward

Headword:
Empagliflozin/BOEHRINGER INGELHEIM

Relevant legal provisions:
EPC Art. 83, 54, 56

Keyword:
Amendments - allowable (yes)
Sufficiency of disclosure - (yes)
Novelty (yes) - second (or further) medical use
Inventive step (yes) - no reasonable expectation of success

Decisions cited:
T 2963/19, T 2506/12, T 0239/16, T 1123/16

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 1437/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 9 February 2024

Appellant: (Patent Proprietor)	Boehringer Ingelheim International GmbH Binger Strasse 173 55216 Ingelheim am Rhein (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Opponent 1)	KRKA, d.d., Novo mesto Smarjeska cesta 6 8501 Novo Mesto (SI)
Representative:	Kutzenberger Wolff & Partner Waidmarkt 11 50676 Köln (DE)
Respondent: (Opponent 3)	EGIS Gyógyszergyár Zártkörüen Müködö Részvénytársaság Keresztúri út 30-38 1106 Budapest (HU)
Representative:	Stolmár & Partner Patentanwälte PartG mbB Blumenstraße 17 80331 München (DE)
Respondent: (Opponent 4)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)

Respondent: (Opponent 5)	Stada-Arzneimittel Aktiengesellschaft Stadastrasse 2-18 61118 Bad Vilbel (DE)
Representative:	Kernebeck, Thomas Kernebeck Patentanwalts GmbH Stiftstraße 2 60313 Frankfurt am Main (DE)
Respondent: (Opponent 6)	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: (Opponent 7)	ZAKLADY FARMACEUTYCZNE POLPHARMA S.A. ul. Pelplinska 19 83-200 Starogard Gdanski (PL)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Opponent 8)	Gillard, Richard Edward Elkington and Fife LLP Thavies Inn House 3-4 Holborn Circus London EC1N 2HA (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 25 June 2021 revoking European patent No. 2981271 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	S. Ruhwinkel

Summary of Facts and Submissions

I. European patent 2 981 271 ("the patent") was granted on the basis of eleven claims.

The independent claim 1 as granted defined:

"Empagliflozin for use in a method for treating prediabetes, type 1 or type 2 diabetes mellitus in a patient or for improving glycemic control in a patient with prediabetes, type 1 or type 2 diabetes mellitus comprising administering empagliflozin to the patient, wherein the patient has moderate renal impairment or stage 3 chronic kidney disease (CKD) or wherein the patient's estimated glomerular filtration rate (eGFR) is ≥30 ml/min/1.73 m2 and <60 ml/min/1.73 m2."

II. Eight oppositions had been filed against the grant of European patent 2 981 271 on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed. Opponent 2 withdrew its opposition during the first instance proceedings.

III. The appeal was filed by the patent proprietor against the decision of the opposition division to revoke the patent.

The decision was based on the patent as granted (main request) and auxiliary requests 1-12 filed on 12 November 2020 with reversed ranking of auxiliary requests 4 and 5 as requested during the oral proceedings held on 19 May 2021.

In its decision the opposition division cited *inter alia* the following documents:

D1: ClinicalTrials.gov archive, History of Changes for Study: NCT01164501, January 8, 2013
D5: MMWR Weekly, March 2, 2007 / 56(08); 161-165
D8: Curr Diab Rep (2012), 12:230-238
D10: Clinical Study Synopsis for Public Disclosure, Boehringer Ingelheim BI Trial No. 1245.12, Synopsis, 11 January 2011
D22: Press release from Boehringer Ingelheim of 7 January 2011: "Boehringer Ingelheim and Eli Lilly and Company announce positive top-line pivotal Phase Ill data results for empagliflozin"
D29: Press release from Eli Lilly and Company of 7 January 2011: "Boehringer Ingelheim and Eli Lilly and Company announce positive top-line pivotal Phase Ill data results"
D32: Diabetes Obes Metab.(2013 May), 15(5):463-73
D37: GlobalData: "Pharmacokinetics, Pharmacodynamics Safety and Tolerability of BI 10773 in Type II Diabetes Patients with Different Degrees of renal Impairment", last reviewed 27 July 2017
D43: Diabetes Obes Metab. (2012), 14(1), 83-90
D46: Curr Opin Nephrol Hypertens (2013 Jan), 22(1), 113-119
D53: Lancet Diabetes Endocrinol (2014), 2, 369-384
D58: Kidney International (2014), 85, 962-971 (published online 25 September 2013)
D63: Diabetes 2012, 61, A273, 1062-P
D64: Nefrologia (2010), 30(6), 618-625
D69: Lancet Diabetes Endocrinol (2013 Aug), 1, 140-151
D70: Expert Opin. lnvestig. Drugs (1 March 2013), 22(4), 463-486

D77: MDedge-Endocrinology: "PDA panel rejects new empagliflozin indication for type 1 diabetes", 13 November 2019

The opposition division arrived at the following conclusions:

(a) The press releases of documents D22/D29 reported the successful completion of a clinical study involving the use of the sodium glucose transporter-2 (SGLT-2) empagliflozin in the treatment of type 2 diabetes mellitus (T2DM) patients with mild, moderate and severe renal impairment (Study 1245.36). The subject-matter of claim 1 of the patent as granted therefore lacked novelty.

(b) Auxiliary requests 1-3, 5 and 7-10 did not introduce any distinguishing feature with respect to the prior art and did therefore not meet the requirement of novelty.

(c) Auxiliary requests 4, 6 and 11-12 introduced the feature that the treatment involved the oral administration of a daily amount of 10 mg empagliflozin. This feature distinguished the claimed subject-matter from the prior art, but did not support an inventive step in view of documents D22/D29 as closest prior art.

IV. With the statement of grounds of appeal the patent proprietor upheld its requests on which the decision under appeal was based.

V. In its communication pursuant to Article 15(1) RPBA the Board expressed *inter alia* the preliminary opinion that

- the patent as granted complied with the requirement of sufficiency of disclosure

- the subject-matter of the patent as granted was new over the disclosure in documents D22/D29

- the crucial issue to be decided was whether the skilled person would in view of the prior art have reasonably expected that empagliflozin would show significant efficacy in the treatment of diabetes in patients with moderate renal impairment.

VI. Oral proceedings were held on 9 February 2024.

VII. The arguments of the patent proprietor relevant to the present decision are summarized as follows:

(a) Sufficiency

No serious doubts as to the sufficiency of the disclosure of the claimed invention had been substantiated.

Prediabetes, type 1 diabetes mellitus (T1DM) and T2DM all involved high blood glucose levels. The mechanism of action of SGLT2 inhibitors such as empagliflozin involved the increase of urinary glucose excretion (UGE). It was therefore reasonable to conclude that empagliflozin was suitable for the treatment of prediabetes and T1DM on the basis of its demonstrated efficacy in treatment of T2DM.

The patent further provided sufficient guidance regarding the effective dosing of empagliflozin.

(b) Novelty

The press releases of documents D22/D29 announced results of a study involving the administration of empagliflozin to patients with "mild, moderate or severe renal impairment". In line with the description of the same study in document D1, the press releases thereby presented a generic description of a group of patients with renal impairment ranging from mild to severe (eGFR between 15-90 ml/min/1.73m^2). The effective treatment from administration of 25 mg empagliflozin reported in documents D22/D29 therefore only concerned this patient population as a whole.

The suggestion that documents D22/D29 disclosed effective treatment in each of the subgroups of patients defined by the mentioned levels of renal impairment was based on an incorrect reading of these press releases and was, as a matter of fact, contradicted by the lack of efficacy in patients with severe renal impairment reported in the post-published document D53.

The inference from positive comments in documents D22/D29 on the reported results and from the reported efficacy of 10 mg empagliflozin in patients with mild renal impairment that the 25 mg dose must have been effective at least also in the patients with moderate renal impairment was purely speculative and could not be based on any "Data on file" referred to in documents D22/D29.

(c) Inventive step

The experimental results in the patent demonstrated the significant effectiveness of the treatment of patients with moderate renal impairment in terms of lowering HbA1c and fasting plasma glucose (FPG). The remarkable effect of empagliflozin in patients with moderate renal impairment was further supported by the results reported in the patent regarding the change in UGE from a single dose of empagliflozin.

Starting from documents D22/D29, which failed to specifically report results of treatment for patients with moderate renal impairment, the objective technical problem was the provision of an effective treatment of diabetic patients with moderate renal impairment.

The mere inclusion of patients with moderate renal impairment in the Phase III clinical trial involving treatment of diabetic patients with renal impairment reported in documents D22/D29 did *per se* not provide the skilled person with a reasonable expectation of success for the treatment of diabetes in the patients with moderate renal impairment. This was already evident from the further inclusion of patients with severe renal impairment for which any efficacy of treatment could hardly have been expected.

Speculations based on the positive comments regarding the results in documents D22/D29 and the reported effect of the lower 10 mg dose in patients with mild renal impairment did not provide a reasonable expectation of efficacy of treatment of patients with moderate renal impairment with a dose of 25 mg empagliflozin. There was furthermore no basis for the assumption that the patient population in the trial of

documents D22/D29 reflected the general prevalence of moderate renal impairment amongst patients with renal impairment described in document D5. Documents D10 and D37 reporting a Phase I clinical trial involving the administration of empagliflozin to diabetic patients with renal impairment were not available at the relevant date and should therefore not be taken into account.

The prior art regarding the known effects of other SGLT-2 inhibitors in diabetic patients with moderate renal impairment did not provide any reasonable expectation of the efficacy of empagliflozin in the treatment of diabetic patients with moderate renal impairment either and actually dissuaded from such expectation.

The review articles of documents D64 and D8 indicated that the efficacy of SGLT-2 inhibitors in treatment of diabetic patients depended on their renal function. Document D8 observed in this context that treatment with dapagliflozin or ipragliflozin did not result in a clinically significant decrease in FPG and HbA1c in patients with moderate renal impairment. The efficacy of canagliflozin in patients with moderate renal impairment reported in document D32 was in view of the explanations in the review article of document D46 likely associated with its residual SGLT-1 inhibitory activity, which was absent in the the highly selective SGLT-2 inhibitor empagliflozin. Document D63 reported the effects of a single dose of luseogliflozin on UGE, postprandial plasma glucose (PPG) and FPG in patients with renal impairement, but such effects from a single dose did not reveal actual therapeutic efficacy in the treatment of diabetes. The reduced benefit from SGLT-2 inhibitors for diabetic patients with moderate renal

impairment mentioned in the review of these studies in document D70 did not suggest that at least some efficacy in the treatment of diabetes in these patients was to be expected from SGLT-2 inhibitors in general.

VIII. The arguments of the opponents relevant to the present decision are summarised as follows:

(a) Sufficiency

The patent only provided experimental data for T2DM patients. Taking account of the FDA's rejection to recognize the indication of empagliflozin for type 1 diabetes reported in document D77 the patent thereby failed to sufficiently disclose the suitability of empagliflozin for treatment of prediabetes and type 1 diabetes mellitus (T1DM) as defined in the claims as granted.

Moreover, the patent only described examples of treatment involving a 25 mg dose of empagliflozin and did thereby not credibly disclose the efficacy of a 10 mg dose.

(b) Novelty

Documents D22/D29, which were press releases from Boehringer Ingelheim and Eli Lilly and Company, reported the effective treatment of T2DM in patients having mild, moderate and severe renal impairment by daily administration of 25 mg of empagliflozin in a Phase III clinical trial.

The skilled person would conclude from the specific mention of the various levels of renal impairment in these reports that within each of the subgroups of

patients defined by the mentioned levels of renal impairment, including the subgroup of patients having moderate renal impairment, the primary efficacy end point defined as a significant change in HbA1c from baseline compared to placebo was indeed reached.

This conclusion was in particular justified with respect to patients with moderate renal impairment in view of the positive comments on the results from the trial expressed in the press releases. Having regard to the efficacy of 10 mg empagliflozin in patients with mild renal impairment, which had been separately reported in the press releases, the skilled person would in view of these positive comments understand that the efficacy of the 25 mg dose must have extended beyond the patients with mild impairment and that efficacy of treatment had at least also been observed in the patients with moderate renal impairment. Such understanding would be in line with the references to "Data on file" regarding the results and the consideration that press releases from public companies need to be correct and precise in view of their potential influence on the stock exchange rate of the companies.

The disclosure of efficacy in documents D22/D29 was not affected by the less detailed information in the earlier announcement of the trial in document D1 nor by the more detailed information in document D53, which anyway confirmed the efficacy in patients with moderate renal impairment and only suggested an issue with treatment of patients with severe kidney disease.

(c) Inventive step

In as far as the subject-matter of claim 1 as granted was to be considered new in view of documents D22/D29, because the primary efficacy end point was reported as met for the general group of patients with renal impairment and not specifically for patients with moderate renal impairment, the difference of the claimed subject-matter could only concern the actual efficacy in the treatment of the patients having moderate renal impairment. Starting from documents D22/D29 the objective technical problem should then be seen in the provision of effective treatment in patients with moderate renal impairment.

The disclosure of treatment of diabetic patients with moderate renal impairment with the SGLT-2 inhibitor empagliflozin in the Phase III clinical trial in documents D22/D29 already provided by itself the skilled person with an expectation of success of this treatment. This conclusion was in line with the considerations in T2506/12, T239/16 and T1123/16. The prior art did not dissuade from such expectation and, as indicated by documents D10 and D37, no relevant safety concerns from such treatment had arisen.

Documents D22/D29 specifically confirmed this expectation by the mentioned positive comments on the results from the trial and by reporting the efficacy of the lower 10 mg dose of empagliflozin in patients with mild renal impairment, which in view of the only progressive decrease in efficacy of SGLT-2 inhibitors with decreasing renal function at least justified the reasonable expectation that the higher dose of 25 mg would show efficacy in patients with moderate renal impairment, which only represented the next level to

mild renal impairment. The expectation of successful treatment of patients with moderate renal impairment was further justified on the basis of the efficacy of treatment in the group of diabetic patients with mild, moderate and severe renal impairment reported in documents D22/D29 in view of the prevalence of moderate renal impairment amongst patients with renal impairment as described in document D5.

The expectation of efficacy of the defined treatment in patients with moderate renal impairment also derived from the common general knowledge expressed in the available review articles concerning the efficacy of SGLT-2 inhibitors. The earlier reviews in documents D64 and D8 indicated that the efficacy of SGLT-2 inhibitors depends on renal function with a progressively decrease in the glucose-lowering ability of the drug as the glomerular filtration rate (GFR) decreases. The more recent review article in document D70 suggested on the basis of results from studies on the efficacy of SGLT-2 inhibitors in patients with renal impairment that patients with moderate renal impairment still benefit from treatment with SGLT-2 inhibitors, be it less than patients with normal renal function or only mild renal impairment. As confirmed in document D32, the expectation of a reduced benefit was still significant for diabetic patients with moderate renal impairment in view of the limited options for treatment of such patients.

The skilled person further expected the treatment of diabetic patients with moderate renal impairment with empagliflozin to be effective in view of the clinical efficacy from SGLT-2 inhibition by canagliflozin in such patients as described in document D32 as well as the efficacy of the SGLT-2 inhibitors ipragliflozin and

luseogliflozin in such patients as described in documents D61, D62 and D63. The effect of luseogliflozin, which was like empagliflozin a highly selective SGLT-2 inhibitor, confirmed that the efficacy reported for canagliflozin should not be attributed to its residual SGLT-1 inhibiting activity. Document D32 further indicated that the lack of significant efficacy in terms of glycemic control in patients with moderate renal impairment reported for dapagliflozin may have been due to the design of the study reported from. This was confirmed in document D58, which acknowledged that the relevant study was not powered to determine the significance of the efficacy of dapagliflozin.

IX. The patent proprietor (appellant) requested that the decision under appeal be set aside and that the patent be maintained as granted.

X. The opponents (respondents) requested that the appeal be dismissed.

Reasons for the Decision

Main request (patent as granted)

1. Basis for the claimed subject-matter in the application as filed

In the grounds of appeal the patent proprietor indicated the basis for the claimed subject-matter in the original application. During the appeal proceedings the opponents did not further contest that the subject-matter of the claims as granted had been disclosed in the application as originally filed.

2. Sufficiency

In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that the main request fulfills the requirement of sufficiency of disclosure. According to the preliminary opinion it was reasonable to conclude the suitability of empagliflozin in the treatment of prediabetes and T1DM on the basis of its demonstrated efficacy in treatment of T2DM in view of the mechanism of action of empagliflozin. The assessment of sufficiency of disclosure of the utility of a medicament as a requirement for patentability was to be distinguished from the assessment of a medicament for market authorisation by an agency such as the FDA as reported in document D77. The patent further provided sufficient guidance regarding effective dosing of the empagliflozin and no serious doubts had been substantiated by the opponents in this respect.

No substantive arguments regarding the requirement of sufficiency of disclosure were subsequently presented by the opponents.

The Board has therefore confirmed its preliminary opinion and concluded that the patent as granted meets the requirement of sufficiency of disclosure of the claimed invention.

3. Novelty

3.1 Claim 1 as granted (see point I above) defines empagliflozin for a specific use in therapeutic treatment in the format of Article 54(5) EPC. Accordingly, the therapeutic efficacy of empagliflozin in the defined treatment represents a functional feature of the defined subject-matter.

3.2 Documents D22/D29, which are press releases from Boehringer Ingelheim and Eli Lilly and Company with essentially identical technical content, announced results for four completed Phase III clinical trials involving empagliflozin for treatment of T2DM patients as follows:

> "In all four studies, the primary efficacy endpoint defined as significant change in HbA1c from baseline compared to placebo, was met with empagliflozin (10 and 25 mg) taken once daily.
>
> These four pivotal studies from the empagliflozin programme are:
> [...]
> - Study 1245.36 (n=741) evaluated 25 mg dose of empagliflozin in Type 2 Diabetes patients with mild, moderate or severe renal impairment, and 10 mg dose in those with mild renal impairment versus placebo for 52 weeks.[1]"

The reference "1" in the reported results relates in document D22 to "www.clinicaltrials.gov Data on file, Boehringer Ingelheim Pharma GmbH&Co KG" and in document D29 simply to "Data on file, Boehringer Ingelheim Pharma GmbH&Co KG"

3.3 The Board considers that in accordance with the precise wording of the press releases in documents D22/D29 the announced efficacy of treatment with the 25 mg dose of empagliflozin in Study 1245.36 may well be understood as relating to the patient population having mild, moderate or severe renal impairment as a whole. Therefore, from these press releases the skilled person cannot directely and unambiguously derive the

information that the treatment is effective in each of the subgroups of patients defined by the mentioned levels of renal impairment.

In this context the Board observes that documents D22/D29 only present the total number of participants in Study 1245.36 ("n=741") and do not provide, neither explicitly nor by reference to the unspecified "Data on file", specific information regarding the number of participating patients with moderate renal impairment. Without this information the positive comments on the results from the trial expressed in the press releases of documents D22/D29 ("encouraged by the efficacy and safety results", "pleased with these results for these Phase III clinical trials for empagliflozin") and the reported efficacy of 10 mg empagliflozin in patients with mild renal impairment do not provide any basis for the skilled reader to conclude that as a matter of fact the 25 mg dose must also have been effective in the patients with moderate renal impairment.

The Board further observes that the precise reading of documents D22/D29 as press releases from public companies reveals the announcement of the positive result of the trial with respect to the group of diabetic patients with mild, moderate or severe renal impairment as a whole to be correct in spite of the actual lack of glucose-lowering efficacy of the 25 mg dose of empagliflozin in patients with severe renal impairment as subsequently reported in document D53 (see D53, page 379, left column; see also page 382, right column).

3.4 The skilled person could therefore not directly and unambiguously derive from the reported results in document D22/D29 that the treatment of the diabetic

patients with moderate renal impairment had been successful in terms of the primary efficacy end point of a significant change in HbA1c from baseline compared to placebo and that empagliflozin was thus effective in treatment of these patients as defined in claim 1 as granted.

Accordingly, the Board concludes that the subject-matter of claim 1 as granted is new over the prior art.

4. Inventive step

4.1 Closest prior art

It was not in dispute that the content of the press releases in documents D22/D29 represented the closest prior art.

As explained in section 3 above, the difference between the subject-matter of claim 1 as granted and the disclosure in documents D22/D29 concerns the efficacy in treatment of the defined forms of diabetes in patients with moderate renal impairment.

4.2 Objective technical problem

The efficacy of empagliflozin in the treatment of diabetic patients with moderate renal impairment in terms of lowering HbA1c and FPG is apparent from the experimental results in Figures 1 and 7 of the patent and confirmed *inter alia* in document D53.

The results reported in Figure 2 of the patent further indicate a prominent increase in UGE from a single dose of empagliflozin in patients with moderate renal renal impairment to a similar extent as in patients with mild

renal impairment in spite of the baseline level of UGE in patients with moderate renal impairment being reduced to a similar extent as in patients with severe renal impairment, in wich empagliflozin caused only a minor change in UGE and showed no efficacy in terms of lowering HbA1c. The results in Figure 2 of the patent thereby underline the distinctive status of diabetic patients with moderate renal impairment and confirm the efficacy of empagliflozin in the treatment of these patients.

The objective technical problem in view of documents D22/D29 as closest prior art may therefore be formulated as the provision of effective treatment for diabetic patients with moderate renal impairment.

4.3 Assessment of the solution

4.3.1 The prior disclosure that an investigational product for use in the treatment of a particular condition is undergoing clinical trials may in accordance with established jurisprudence preclude that a subsequently claimed invention involving this product for use in the treatment of that specific condition is considered to involve an inventive step, even where the results of the trial have not been made available to the public (see T 2506/12, reasons 3.10 and 3.15; T 239/16, reasons 6.5 and 6.6; T 1123/16, reasons 11; T 2963/19, reasons 4.3.1).

However, as explained in T 2963/19, the approval of a clinical study depends on the assessment of the foreseeable risks to the participants in relation to the anticipated benefit in terms of the relevance of the findings. The approval of a clinical trial does therefore not, by way of a heuristic, imply an expected

positive outcome of the treatment. Furthermore, as underlined in point 4.3.1 of T 2963/19 by reference to the "Communication from the Commission 2010/c 82/01", the authorisation of a clinical trial does not represent a scientific advice on the development programme of the investigational product tested. The considerations in T 2506/12, T 239/16 and T 1123/16 regarding the expectation of success in view of the disclosure of clinical trials are, as in T 2963/19, evidently linked to the further circumstances of the cases decided therein, in particular the nature of the investigational product and of the condition to be treated and the absence of information suggestive of failure of the trial.

The crucial issue in the assessment of inventive step starting from the teaching in documents D22/D29, in particular the reported results from Study 1245.36, thus remains whether in view of the available information in the prior art, including the information in documents D22/D29, the skilled person had a reasonable expectation that empagliflozin would be effective in treatment of diabetic patients having moderate renal impairment.

4.3.2 As indicated in the review articles D8 (see page 235, left column) and D70 (see page 473, right column), the mechanism of action of empagliflozin by SGLT-2 inhibition mentioned in documents D22/D29 evidently depends on the GFR of the kidneys, which by definition is reduced in patients with renal impairment. As pointed out by the patent proprietor and confirmed in the post-published document D53 (see page 382, right column) efficacy of treatment was as a matter of fact not expected in patients with severe renal impairment. The Board therefore considers that the mere inclusion

of diabetic patients with renal impairment beyond the stage of mild renal impairment in the Phase III clinical trial described in documents D22/D29 could not by itself have provided the skilled person with a reasonable expectation of success of the treatment in these patients with moderate or severe renal impairment.

4.3.3 As observed in section 3.3 above, documents D22/D29 do not provide any specific information on the number of patients in Study 1245.36 having moderate renal impairment. In view of this lack of information the opponents' justification of an expectation of effective treatment of diabetic patients with moderate renal impairment from the reported efficacy in the group of patients with renal impairment as a whole relying on the prevalence of moderate renal impairment within the general population of patients with renal impairment as described in document D5 and the positive comments on the results in documents D22/D29 remains purely speculative and is therefore not considered convincing.

The skilled person would furthermore not have expected the efficacy of the 25 mg dose of empagliflozin in patients with moderate renal impairment on the basis of the efficacy of the 10 mg dose in patients with mild renal impairment reported in documents D22/D29 due to the distinctive status of patients with moderate renal impairment which directly affects the mechanism of action of empaglifolozin. Precisely because the efficacy of SGLT-2 inhibitors was known to decrease progressively with decreasing renal function (see D8, page 235, left column), the skilled person could not reasonably expect that any significant efficacy of empagliflozin as still observed according to documents D22/D29 within the group of patients with mild renal

impairment would even be retained in the distinctive group of patients with moderate renal impairment.

Documents D10 and D37, which indicate that the Phase III trial of documents D22/D29 followed the successful conclusion of a Phase I clinical trial involving the administration of empagliflozin to diabetic patients with renal impairment, were not available at the relevant earliest priority date for the patent and do therefore not affect the assessment of inventive step. In this context the Board notes that in view of the mechanism of action of empagliflozin, which requires proper functioning of the kidneys (see 4.3.2 above), the availability of the information regarding the safety of empagliflozin in patients with renal impairment would not affect the skilled person's expectation regarding the efficacy of treatment in diabetic patients with moderate renal impairment.

4.3.4 The opponents further referred to the known effects of other SGLT-2 inhibitors in diabetic patients to argue that the skilled person would expect similar efficacy from empagliflozin. The opponents relied in particular on the effects of ipragliflozin as described in documents D61 and D62, canagliflozin as described in document D32 and luseogliflozin as described in document D63. In this context the opponents dismissed the significance of the lack of efficacy in patients with moderate renal impairement reported in the prior art for dapagliflozin.

Documents D61 (see page 1261, Table 1) and D62 (see Table in the abstract) indicate that a single dose of the SGLT-2 inhibitor ipragliflozin increases the UGE in diabetic patients with moderate renal impairment. However, these documents do not demonstrate that

ipragliflozin actually lowers glucose/HbA1c in these patients, which document D61 acknowledges as ultimately determining the clinical utility of the drug (see D61, page 1264, middle column). By contrast, the review in document D8 (see page 235, left column) reports that ipragliflozin did not provide for a clinically significant decrease in FPG and HbA1c in patients with moderate renal impairment.

Document D63 also reports only the effects of a single dose of luseogliflozin in diabetic patients with renal impairement, including specifically patients with moderate renal impairment. Whilst document D63 indicates that such a single dose significantly increases the UGE and decreases the PPG and FPG in patients with moderate renal impairment, document D63 does not report clinically significant efficacy from administration of luseogliflozin in the treatment of diabetes in these patients, for instance by demonstration of a significant effect on the HbA1c. In fact, document D63 itself acknowledges that a long-term clinical trial to assess the efficacy of luseogliflozin in T2DM patients with moderate renal impairment was still in progress.

The review in document D8 reported that the SGLT-2 inhibitor dapagliflozin had, similar to ipragliflozin, failed to significantly decrease FPG and HbA1c in patients with moderate renal impairment (see D8, page 235, left column). This lack of observed significant clinical efficacy of dapagliflozin in patients with moderate renal impairment in terms of a reduction of HbA1c is also reported in the review article of document D70 (see D70, page 474, sentence bridging the columns). Whilst at the earliest priority date the skilled person may, like the authors of document D32

(see D32, penultimate paragraph under "Discussion"), have considered the possibility that the lack of an observed significant clinical efficacy in the study with dapagliflozin could have been due to the design of the study, as later acknowledged in document D58 (see D58, page 968, bridging sentence between the columns), this possibility does not distract from the fact that at the relevant date for the patent the reported efficacy of dapagliflozin in patients with moderate renal impairment was qualified as insignificant in the review articles of documents D8 and D70.

Canagliflozin thus remains the only SGLT-2 inhibitor for which the cited prior art actually indicated efficacy in treatment of diabetic patients with moderate renal impairment (see document D32, Abstract under "Conclusion").

However, as mentioned in the review in document D70, canagliflozin was known as a SGLT-2 inhibitor with only moderate selectivity for SGLT-2 with respect to SGLT-1, whereas empagliflozin was known to be highly selective for SGLT-2 (see D70, page 466, right column). At the same time the skilled person was from the review in document D46 also aware that the reduction in glucose reabsorption in patients treated with SGLT-2 inhibitors may partly be compensated by SGLT-1 and that the lack of a complete blockade by SGLT-2 inhibitors explains the interest in dual SGLT-1/SGLT-2 inhibitors (see D46, page 114, left column and page 115, left column). The skilled person's expectation with regard to the efficacy of empagliflozin on the basis of the known effects of other SGLT-2 inhibitors in patients with moderate renal impairment was therefore affected by the difference in selectivity for SGLT-2 between canagliflozin and empagliflozin.

Accordingly, the skilled person would from the known effects of other SGLT-2 inhibitors in patients with moderate renal impairment not have derived a reasonable expectation of efficacy of empagliflozin in the treatment of diabetes this group of patients because

- ipragliflozin and dapagliflozin had been reported to lack clinically significant efficacy in the treatment of diabetic patients with moderate renal impairment

- the clinical efficacy of luseogliflozin in the treatment of diabetic patients with moderate renal impairment remained to be demonstrated

- the SGLT-1 inhibitory effect of the only moderately selective SGLT-2 inhibitory canagliflozin possibly contributed to its efficacy in the treatment of diabetic patients, whereas empagliflozin was highly selective for SGLT-2.

4.3.5 The review article in document D70 suggested on the basis of the reported known effects of SGLT-2 inhibitors in patients with renal impairment that SGLT-2 inhibitors will confer less benefit for patients with moderate renal impairment than for patients with normal renal function or only mild renal impairment (see page 474, right column). Contrary to the opponents' argument the skilled person would not understand document D70 as suggesting that patients with moderate renal impairment will benefit at least to some extent from SGLT-2 inhibitors, be it less than the other mentioned patients, because such understanding is contradicted by the report in document D70 (see page 474, right column) that the SGLT-2 inhibitor

dapagliflozin provides no significant difference in reduction of HbA1c with respect to placebo. In the light of the reported known effects of SGLT-2 inhibitors the skilled person would rather understand the "less benefit" of the suggestion in document D70 as including "no benefit" in case of a SGLT-2 inhibitor such as dapagliflozin and "some benefit" in the case of a SGLT-2 inhibitor such as canagliflozin.

The Board therefore considers that from the mentioned suggestion in document D70 the skilled person would not have derived any reasonable expectation of efficacy of empagliflozin in the treatment of diabetic patients with moderate renal impairment either.

4.3.6 In the absence of a reasonable expectation of significant efficacy of empagliflozin in the treatment of diabetic patients with moderate renal impairment the Board concludes that the subject-matter of claim 1 as granted was not obvious to the skilled person in view of the prior art and thus involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated