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Datasheet for the decision of 29 June 2026

Case Number: T 0251/25 - 3.3.04

Application Number: 14715274.8

Publication Number: 2981255

IPC: A61K31/155, A61K31/522, A61K31/7048, A61P9/10, A61P3/10, A61K45/06

Language of the proceedings: EN

Title of invention:
Therapeutic uses of empagliflozin

Patent Proprietor:
Boehringer Ingelheim International GmbH

Opponents:
TEVA PHARMACEUTICAL INDUSTRIES, LTD.
ZAKLADY FARMACEUTYCZNE POLPHARMA S.A.
SANDOZ AG
Zentiva k.s.
STADA Arzneimittel AG
Sanovel Ilaç San. ve Tic. A.S
Adalvo Ltd.
Aera A/S
HGF Limited
Generics (U.K.) Limited
Dr Reddy's Laboratories (UK) Limited

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Relevant legal provisions:
EPC Art. 83

Keyword:
Sufficiency of disclosure - (no)

Decisions cited:
G 0001/03, G 0002/08, G 0002/21, R 0025/22, R 0014/23, T 0019/90, T 0241/95, T 0158/96, T 0609/02, T 0063/06, T 1558/11, T 0294/20, T 0853/22, T 0583/23

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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

Case Number: T 0251/25 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 29 June 2026

Appellant: (Opponent 1)	TEVA PHARMACEUTICAL INDUSTRIES, LTD. 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	von Kauffmann, Carl Global IP Group - Teva Field House, Station Approach Harlow CM20 2FB (GB)
Appellant: (Opponent 2)	ZAKLADY FARMACEUTYCZNE POLPHARMA S.A. ul. Pelplinska 19 83-200 Starogard Gdanski (PL)
Appellant: (Opponent 3)	SANDOZ AG Centralbahnstrasse 4 4051 Basel (CH)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Appellant: (Opponent 4)	Zentiva k.s. U Kabelovny 130 Dolni Mecholupy 102 37 Praha 10 (CZ)
Representative:	Reddie & Grose LLP The White Chapel Building 10 Whitechapel High Street London E1 8QS (GB)
Appellant: (Opponent 5)	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel (DE)

Representative:
Kernebeck, Thomas
Kernebeck Patentanwalts GmbH
Stiftstraße 2
60313 Frankfurt am Main (DE)

Appellant:
(Opponent 6)
Sanovel IIaç San. ve Tic. A.S
Balabandere Cad. IIaç Sanayi Yolu
34460 Istanbul (TR)

Representative:
Kraus & Lederer PartGmbB
Thomas-Wimmer-Ring 15
80539 München (DE)

Appellant:
(Opponent 8)
Aera A/S
Niels Hemmingsens Gade 10, 5th floor
1153 Copenhagen K (DK)

Representative:
Bardehle Pagenberg S.L.
Avenida Diagonal 598, 3°, 1ª
08021 Barcelona (ES)

Appellant:
(Opponent 9)
HGF Limited
1 City Walk
Leeds Yorkshire LS11 9DX (GB)

Representative:
HGF
HGF Limited
4th Floor, 1 City Square
Leeds LS1 2ES (GB)

Appellant:
(Opponent 10)
Generics (U.K.) Limited
Building 4, Trident Place
Mosquito Way
Hatfield
Hertfordshire AL10 9UL (GB)

Representative:
Ter Meer Steinmeister & Partner
Patentanwälte mbB
Nymphenburger Straße 4
80335 München (DE)

Respondent:
(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)

Party as of right: (Opponent 7)	Adalvo Ltd. Malta Life Science Park, Building 1 Level 4, Sir Temi Zammit Buildings, San Gwann Industrial Estate, San Gwann, SGN 3000 (MT)
Representative:	Slavík, Jiri Artistu 3183/14 193 00 Praha-Horní Pocernice (CZ)
Party as of right: (Opponent 11)	Dr Reddy's Laboratories (UK) Limited 410 Cambridge Science Park Milton Road Cambridge CB4 0PE (GB)
Representative:	Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted/ electronically transmitted on 30 January 2025 concerning maintenance of the European Patent No. 2981255 in amended form.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	R. Hauss
	A. Bacchin

Summary of Facts and Submissions

I. European patent No. 2 981 255 (patent in suit) was granted with a set of 12 claims.

II. Ten oppositions were filed against the patent in suit on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed (Article 100(a), (b) and (c) EPC).

III. In the proceedings before the opposition division, the patent proprietor requested as its main request that the oppositions be rejected and the patent be maintained as granted. It furthermore submitted 16 amended claim requests as auxiliary requests.

IV. Claim 1 of auxiliary request 1 is identical to claim 1 as granted and reads as follows:

> *"1. Empagliflozin for use in a method for preventing, reducing the risk of or delaying the occurrence of a cardiovascular event in a patient with type 2 or type 1 diabetes mellitus or with pre-diabetes comprising administering empagliflozin, optionally in combination with one or more other therapeutic substances, to the patient wherein said cardiovascular event is selected from cardiovascular death and heart failure requiring hospitalization."*

The same cardioprotective therapeutic indications for empagliflozin are recited in independent claim 2.

V. The documents cited in the proceedings before the opposition division and in the appeal proceedings included the following:

D23: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), "Guidance for Industry, Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to treat Type 2 Diabetes" (December 2008)

D24: European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), CPMP/EWP/1080/00 Rev. 1, "Guideline on clinical investigation of medicinal products in the treatment and prevention of diabetes mellitus" (14 May 2012)

D38: Clinical Diabetes 26(2), 77-82 (2008)

D40: European Heart Journal, 33, 1049-1057 (2012)

D79: J Am Coll Cardiol 60(16), 1455-1469 (2012)

D80: European Heart Journal 26(1), 65-69 (2005)

D81: AJP-Heart Circ Physiol 301: H2181-H2190 (2011)

D82: Blood 112(11), 5470 (2008), 2 pages

D83: Circulation 113, 664-670 (2006)

D84: Circulation 121, 505-511 (2010)

D85: J Am Coll Cardiol 55(13), 1318-1327 (2010)

VI. The decision under appeal is the opposition division's interlocutory decision rejecting the patent proprietor's main request and finding that the patent as amended in the form of auxiliary request 1 met the requirements of the EPC.

The following reasons were given on sufficiency of disclosure (Article 83 EPC). The suitability of empagliflozin for the claimed cardioprotective therapeutic indications was rendered credible by the

experimental data shown in the application as filed, in particular in Examples 1 and 8, and in light of the technical background provided in D79. The opponents' further objection that the claimed subject-matter could not be carried out across the entire scope claimed had not been adequately substantiated so as to meet the required standard of serious doubt substantiated by verifiable facts.

VII. Opponents 1, 2, 3, 4, 5, 6, 8, 9 and 10 (the appellants) all filed appeals against this decision.

VIII. The non-appealing opponent 7 is party to the appeal proceedings as of right (Article 107 EPC).

IX. The patent proprietor (respondent) replied to the appeals, requesting as its main request that the appeals be dismissed or, in the alternative, that the patent be maintained on the basis of the claims of one of auxiliary requests 2 to 16 filed with the department of first instance.

X. The board issued a summons to oral proceedings.

XI. A further party filed a notice of intervention to join the oppositions against the patent in suit (Article 105(1)a) EPC). The intervention was based on the grounds for opposition under Article 100(a) (lack of novelty and inventive step), (b) and (c) EPC. The intervener also requested that the appeal proceedings be accelerated in view of pending national proceedings for revocation and infringement of the patent in suit, for which oral proceedings were scheduled before the Chancery Division High Court of Justice of England and Wales (claim No. HP-2024-000037) for October 2026.

XII. The intervener was designated as opponent 11.

XIII. For ease of reading, the appellants and the intervener are referred to below as the opponents where no distinction is necessary.

XIV. The respondent advised the board that it concurred with the intervener in requesting that the appeal proceedings be accelerated.

XV. The board decided to grant the request for acceleration (Article 10(3) RPBA) and rescheduled the oral proceedings, originally set for 30 November to 2 December 2026, to take place on 29 June to 1 July 2026.

XVI. With its reply to the notice of intervention, the respondent submitted further amended sets of claims as auxiliary requests 17 and 18.

XVII. Opponents 6 and 7 advised the board that they would not be attending the oral proceedings.

XVIII. In the course of the appeal proceedings, the parties submitted new evidence (documents D95 to D134).

With their respective statements setting out the grounds of appeal, opponents 2 and 3 presented documents D95 to D97, opponent 6 presented documents D98 and D99 (filed as D95 and D96), opponent 8 presented documents D100 to D102 (filed as D95 to D97) and opponent 9 presented documents D103 and D104. With its reply, the respondent presented documents D105 to D108.

With the notice of intervention, opponent 11 presented new documents D109 to D127. It also relied in its reasoning on documents D95 and D97 to D102. With its

reply to the intervention, the respondent presented documents D128 to D132. The following documents are pertinent to the board's reasoning below:

D95: Curr Cardiol Rep 14, 59-69 (2012)

D97: Diabetes Care 34 (Supplement 2), S101-S106 (2011)

D100: Diabetes Vasc Dis Res 5, 310-318 (2008)

D101: Diabetes Vasc Dis Res 8(3), 195-201 (2011)

D102: Diabetes Research and Clinical Practice 86, 44-50 (2009)

D108: International Journal of Molecular Medicine 32, 158-164 (2013)

D110: European Journal of Pharmacology 660, 476-484 (2011)

D112: European Journal of Pharmacology 685, 116-125 (2012)

D113: Cell Biochem Funct 26, 478-485 (2008)

D114: Metabolism Clinical and Experimental 56, 1396-1401 (2007)

D115: N Engl J Med 357(1), 28-38 (2007)

D116: N Engl J Med 356(24), 2457-2471 (2007)

D128: Arterioscler Thromb Vasc Biol 27, 2627-2633 (2007)

D129: Circ J 73, 673-680 (2009)

XIX. In a communication under Article 15(1) RPBA issued in preparation for oral proceedings, the board noted that the intervention was admissible (which had not been contested) and advised the parties of its preliminary opinion on substantive issues, including on claim construction. With regard to the parties' various requests that certain documents not be admitted, the board found that documents cited in the notice of intervention and those cited in the respondent's timely reply to it were part of the appeal proceedings and did

not require separate admittance (see section 2 of the board's communication dated 22 May 2026). Only the admittance of D96 and D105 to D108 remained to be decided, if required, under the provisions of Article 12(4) and (6) RPBA.

XX. With a further submission, opponent 1 presented documents D133 and D134:

D133: K. A. Hicks et al., on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative, "Standardized Definitions for End Point Events in Cardiovascular Trials", Draft, 37 pages (20 October 2010)

D134: Circulation 119, 1977-2016 (2009)

XXI. Oral proceedings were held on 29 June 2026, in the absence of opponents 6 and 7, who had been duly summoned (Article 15(3) RPBA and Rule 115(2) EPC). The board decided, after hearing opponent 1 and the respondent, that D133 and D134 were not to be admitted. The debate focused on sufficiency of disclosure with regard to the main request (i.e. former auxiliary request 1 deemed allowable by the opposition division) and auxiliary request 17. The respondent withdrew auxiliary requests 2 to 16 and 18 (i.e. all other auxiliary requests on file). At the end of the oral proceedings, the board announced its decision to set the decision under appeal aside and revoke the patent.

XXII. Auxiliary request 17 has three claims. Claim 1 is the only independent claim. It is identical to claim 1 of the main request (see point IV. above) except that it limits the cardiovascular event to cardiovascular death ("wherein said cardiovascular event is cardiovascular death").

XXIII. The opponents' pertinent arguments may be summarised as follows.

Admittance of D133 and D134

Opponent 1 had submitted documents D133 and D134 in direct response to the board's communication under Article 15(1) RPBA, which had identified claim construction as a matter of particular significance but had not commented on the meaning of the terms "cardiovascular death" and "heart failure requiring hospitalisation". This was an exceptional circumstance under Article 13(2) RPBA. D133 and D134 were filed as evidence of the skilled person's understanding of these two expressions.

Sufficiency of disclosure - main request

The arguments presented included the following.

The claimed therapeutic efficacy of empagliflozin in preventing, reducing the risk of or delaying the occurrence of cardiovascular death or heart failure requiring hospitalisation in diabetic patients was not rendered credible in the application as filed and in light of the skilled person's common general knowledge at the time.

The experimental data provided in Examples 1 and 8 of the application as filed, which the respondent relied on for sufficiency of disclosure, was inadequate because there was no clear and established link between the parameters observed in these examples and a cardioprotective benefit, let alone between those parameters and the still more specific therapeutic indications recited in claim 1 of the main request.

Reference was made to decisions G 2/21, T 609/02 (Reasons 9), T 801/06 and T 158/96 (Reasons 3.5.2).

The data in Examples 1 and 8 could be referred to as data relating to cardiovascular biomarkers. This data concerned oxidative stress, vessel wall thickness and collagen content, endothelial dysfunction, and arterial stiffness. The application as filed contained no statement linking the observed parameters or biomarkers directly and unambiguously to the cardioprotective therapeutic indications specified in claim 1.

A distinction had to be made between informative and causative biomarkers. According to common general knowledge, the tested parameters might have been known as prognostic markers associated with a general cardiovascular risk, as argued by the respondent. However, it could not have been derived from any of the documents cited by the respondent that they were also causative and that a method of treatment targeting these biomarkers could provide a cardioprotective therapeutic benefit, especially a specific benefit as claimed. Correlation did not equal causation. There was not necessarily a direct and unambiguous link between interventions with positive effects on cardiovascular safety biomarkers and cardiovascular outcomes, especially considering that cardiovascular outcomes were late manifestations of a complex pathogenic process.

Furthermore, most of the documents cited by the respondent in support of the asserted relevance of the parameters tested in Examples 1 and 8 were original research articles that could not be regarded as representing common general knowledge at the relevant date.

Thus, the respondent as the patent proprietor had not discharged its initial burden to render the claimed technical effects credible.

Moreover, it was known that the antidiabetic active rosiglitazone, which, like empagliflozin, had previously been found to have a positive impact on parameters reflecting oxidative stress, endothelial function and arterial stiffness, nevertheless did not reduce the risk of heart failure or cardiovascular death. The available data from multiple studies suggested instead that the administration of rosiglitazone had a negative impact on cardiovascular safety. Hence, there was no direct link between the parameters observed in Examples 1 and 8 and the therapeutic indications in claim 1.

Reference was made to, among others, documents D95, D97, D100 to D102, D110 and D112 to D116.

In response to the failure of rosiglitazone and the resulting major concerns about the cardiovascular safety of new antidiabetic drugs, regulatory agencies had introduced new guidance for industry from 2008 onwards that required clinical data on cardiovascular safety for the approval of such drugs (see D23, D24, D97). Guidelines issued by regulatory agencies had to be regarded as evidence of the skilled person's common general knowledge.

These were facts substantiating a serious doubt that the parameters observed in Examples 1 and 8 were directly linked to a cardioprotective effect on a general level, let alone at the more specific level defined in claim 1 in relation to cardiovascular death and heart failure requiring hospitalisation.

In light of this information, it was not possible to infer favourable outcomes in the claimed therapeutic indications only based on the data presented in Examples 1 and 8, without confirmatory evidence obtained in a clinical setting.

The respondent's sweeping argument that clinical studies were never required for establishing sufficiency of disclosure was not correct. In fact, what evidence was required depended on the specific circumstances of each case.

Admittance of auxiliary request 17

The amendment in claim 1 of auxiliary request 17 could not have been occasioned by any new development since the arguments presented in the notice of intervention were not new. Auxiliary request 17 should, therefore, have been filed at an earlier stage of the proceedings.

Sufficiency of disclosure - auxiliary request 17

With auxiliary request 17, the respondent now relied upon a distinction between the therapeutic indications relating to cardiovascular death and to heart failure. This constituted an unexpected change of the respondent's appeal case. The respondent's arguments in relation to auxiliary request 17 were not evident from its written submissions in the reply to the notice of intervention. Any further substantiation was late filed and should not be admitted under Article 13(2) RPBA.

If the respondent's arguments were nevertheless to be taken into account, they could not overcome the objection of insufficient disclosure. It remained a fact that regulatory agencies required clinical studies on cardiovascular safety in diabetic patients and that these guidelines were still in place at the effective date of the patent. This weighed against taking surrogate biomarker data as a reliable basis for inferring the cardiovascular safety of empagliflozin, let alone the claimed cardioprotective effect.

The data in D115 and D116 could not be interpreted as showing that rosiglitazone did not increase the risk of cardiovascular death, and in any case it did not show a reduced risk. The interim analysis of a rosiglitazone study presented in D115 had limited statistical power to detect treatment differences. D116 did show a negative trend for cardiovascular death in the rosiglitazone group which was still cause for concern, even if of borderline statistical significance due to the low number of events in total. The nature of the endpoint should also be taken into account. It was not correct to look at the single endpoint of "cardiovascular death" (as favoured by the respondent); all cardiovascular risks and events contributed to the risk of cardiovascular death.

XXIV. The respondent's pertinent arguments may be summarised as follows.

Admittance of D133 and D134

Opponent 1 had presented documents D133 and D134 at a very late stage of the proceedings, namely less than three weeks before the oral proceedings, without cogent reasons justifying an exceptional circumstance within the meaning of Article 13(2) RPBA and without indicating in sufficient detail in which context these documents were intended to be used. There had been no time for the respondent to react in writing.
The admittance of both documents should, therefore, be rejected under Article 13(2) RPBA.

Sufficiency of disclosure - main request

The parameters observed in Examples 1 and 8 related to oxidative stress, endothelial dysfunction and arterial stiffness. These phenomena were well-established

predictors for cardiovascular events. Reference was made to documents D79 to D85 and D129.

The results according to Example 1 established that empagliflozin treatment of STZ rats (a known animal model of diabetic cardiomyopathy) prevented the development of endothelial dysfunction and oxidative stress.

The results in Example 8, a study in patients with type 1 diabetes, showed that empagliflozin reduced arterial stiffness.

The beneficial effects of empagliflozin on cardiac tissue, vessel walls and arterial stiffness reduced the risk for atherosclerosis, which was a major cause of cardiovascular death and heart failure requiring hospitalisation (see, for instance, D38, page 79, right-hand column).

Since the therapeutic benefit of empagliflozin was credible on this basis, post-published evidence could also be taken into account, including favourable results from a cardiovascular outcome study of empagliflozin and prescribing information confirming the regulatory approval of empagliflozin tablets for a therapeutic indication as defined in claim 1.

The reasons given in D116 (see page 2468, left-hand column) for the adverse cardiovascular outcomes observed with rosiglitazone were not directly relevant to empagliflozin, which belonged to a different class of compounds.

On a general note, failure in clinical safety could not be excluded for any drug until a clinical study was performed. However, in accordance with the established case law of the EPO, evidence from clinical studies was not required for the assessment of sufficiency of disclosure. A requirement that clinical studies be

conducted to rule out adverse effects would not be appropriate in such a context.

Admittance of auxiliary request 17

The amendment focusing on cardiovascular death in claim 1 of auxiliary request 17 was not arbitrary but made in response to the notice of intervention, in particular to the filing of documents D115 and D116 and the intervener's associated arguments, which related predominantly to heart failure requiring hospitalisation. It was also evident from the amendment to claim 1 that auxiliary request 17 had been filed to render any argument relating to heart failure requiring hospitalisation irrelevant. On this basis, auxiliary request 17 was suitable for overcoming the board's finding of insufficiency.

Sufficiency - auxiliary request 17

The amendment to claim 1 of auxiliary request 17 that deleted the therapeutic indication relating to heart failure requiring hospitalisation was suitable for overcoming any concerns in relation to sufficiency of disclosure. Since claim 1 was now restricted to the therapeutic indication of preventing, reducing the risk of or delaying the occurrence of cardiovascular death, the objection based on safety concerns no longer applied.

The opponents' arguments based on the unfavourable data reported in D115 and D116 for the cardiovascular safety of rosiglitazone did not apply to the outcome of cardiovascular death. Failure of rosiglitazone had only been shown in the case of heart failure, not in the case of cardiovascular death (D115: Table 2 and D116: Table 5).

Based on the data in D116, it could not be concluded that rosiglitazone failed with regard to cardiovascular death. Table 5 in D116 showed the odds ratio associated with rosiglitazone for subgroups defined according to the comparator drug. The odds ratio of 1.64 cited by the opponents was a composite driven by the comparison with insulin, whereas the odds ratio versus placebo was lower and also not significant.

Thus, no verifiable facts had been provided by the opponents that could substantiate serious doubt with regard to the suitability of empagliflozin for the remaining therapeutic indication, namely preventing, reducing the risk of or delaying the occurrence of cardiovascular death.

XXV. The parties' requests were as follows. Only the requests still relevant to the board's decision are mentioned.

(a) All appellants (opponents 1 to 6 and 8 to 10) requested that the decision under appeal be set aside and that the patent be revoked in its entirety. In addition:

- appellant-opponent 1 requested that documents D133 and D134 be admitted
- appellant-opponent 8 requested that auxiliary request 17 and D106 to D108 not be admitted

(b) The intervener-opponent 11 requested that the patent be revoked in its entirety.

(c) The respondent (patent proprietor) requested as its main request that the appeals be dismissed, the intervener's request for revocation be refused and the patent be maintained as amended in the opposition proceedings, i.e. in the version according to former auxiliary request 1

or, in the alternative, that the patent be maintained in amended form on the basis of the claims of auxiliary request 17 filed with the reply to the notice of intervention.

The respondent furthermore requested that documents D105 to D108 be admitted and that D133 and D134 not be admitted.

(d) Opponent 7 (party as of right pursuant to Article 107, second sentence, EPC) neither lodged an appeal nor filed any request or substantive submission during the appeal proceedings.

Reasons for the Decision

1. Admissibility of the intervention and acceleration of the proceedings (Article 105 EPC and Article 10(3) RPBA)

1.1 With the notice of intervention of 30 January 2026, the intervener submitted evidence showing that national infringement proceedings against it had been initiated by the respondent before the Chancery Division High Court of Justice of England and Wales, with claim No. HP-2024-000037 dated 6 November 2025 (Annex 1), which was served to the intervener on 10 November 2025 (Annex 2).

1.2 Thus, the intervention was filed within three months, in accordance with Rule 89(1) EPC, and meets the requirements of Article 105(1)(a) EPC (see point XI. above). The intervener is a third party, i.e. a legal person distinct from the appellants. The opposition fee was paid, and the notice of intervention contains

a reasoned statement, so the requirements of Rule 89(2) EPC are also fulfilled.

1.3 The intervention is admissible. The intervener (opponent 11) is a party to the appeal proceedings as of right (Articles 105(1) and 107 EPC).

1.4 Following the intervention and the concurring requests by the intervener and the respondent, the board decided to accelerate the appeal proceedings in accordance with Article 10(3) RPBA (see points XI. to XV. above).

2. Oral proceedings, absence of opponents 6 and 7

2.1 In conformity with Article 15(3) RPBA and Rule 115(2) EPC, the oral proceedings before the board took place in the absence of opponents 6 and 7.

2.2 Both had been duly summoned and had advised the board in advance that they would not be attending the oral proceedings (see point XVII. above).

2.3 Opponent 6 was treated as relying only on its written case (Article 15(3) RPBA).

2.4 Opponent 7 did not present any requests or arguments in writing (see point XXV.(d) above); thus, it chose not to avail itself of the opportunity to present its comments on the grounds and evidence in the appeal case (Article 113(1) EPC).

3. Claim construction

3.1 Claim 1 of the main request relates to a further therapeutic use and is drafted as a purpose-limited product claim in the format according to Article 54(5) EPC (for the wording of claim 1, see point IV. above).

3.2 Attaining the claimed therapeutic benefit is regarded as a functional technical feature of such claims. As a consequence, such a feature may establish novelty (as stated in Article 54(5) EPC) and inventive step (see Case Law of the Boards of Appeal of the European Patent Office, 11th edn. 2025, I.C.7.2.1; G 2/08, OJ 2010, 456, Reasons 5.10.9).

3.3 As a functional technical claim feature, therapeutic efficacy also has to be taken into account in the assessment of sufficiency of disclosure (see G 1/03, OJ EPO 2004, 413, Reasons 2.5.2; G 2/21, OJ EPO 2023, A85, Reasons 77).

3.4 The stated therapeutic purpose in claim 1 is preventing, reducing the risk of or delaying the occurrence of cardiovascular death or heart failure requiring hospitalisation. The patients have type 1 or 2 diabetes or pre-diabetes, but the claim does not require that empagliflozin be used for treating these conditions.

3.5 In line with point 3.2 above, the stated therapeutic purpose is a limiting feature.

3.6 According to claim 1, empagliflozin is the pharmacologically active compound that provides the claimed therapeutic effect. The optional other therapeutic substances are not required to have the same effect.

3.7 The terms "preventing", "reducing the risk of" and "delaying" are understood by the skilled person in a technically sensible way as indicating that, in a population of patients, these results will be attained on a statistical level.

3.8 There exists no fundamental distinction between reducing the risk of a cardiovascular event, delaying it and preventing it that could be decisive for the case in hand. If the risk is reduced for a population of patients, this means that the cardiovascular event in question will be delayed or prevented for a certain proportion of them. Prevention includes prevention for a certain time (in other words, delay).

4. Admittance of documents D133 and D134 (Article 13(2) RPBA)

4.1 Documents D133 and D134 concern the definition of the terms "cardiovascular death" and "heart failure requiring hospitalization". They were provided by opponent 1 less than three weeks before the oral proceedings before the board allegedly as evidence of the skilled person's understanding of these terms.

4.2 As the terms in question were present in claims 1 and 2 as granted, evidence regarding their definition should have been presented at an earlier time if the opponent's reasoning was to be based on a particular definition.

4.3 The fact that claim construction is mentioned as a relevant aspect of the case in section 3 of the board's communication under Article 15(1) RPBA cannot have surprised the opponent since claim construction is the basis for any examination of the claims, and as a question of law it is always incumbent on the board (see e.g. R 14/23, Reasons 7, R 25/22, Reasons 12, T 583/23, Reasons 1.2). Furthermore, it emerged from the parties' written submissions that certain points relating to this issue were in dispute.

4.4 Cardiovascular death and heart failure requiring hospitalisation are parameters known to have been used as endpoints in clinical studies. The fact that the board did not find it necessary to comment on the definition of these terms in its communication under Article 15(1) RPBA does not imply an invitation to the parties to put forward such definitions or constitute an exceptional circumstance under Article 13(2) RPBA that could have justified the filing of new evidence.

4.5 For these reasons, the board did not admit D133 and D134 (Article 13(2) RPBA).

5. Sufficiency of disclosure - main request (Article 83 EPC)

Applicable principles

5.1 As mentioned in section 3. on claim construction, claim 1 defines a therapeutic application and is drafted in the format provided in Article 54(5) EPC. The therapeutic efficacy of the claimed compound is a technical effect which is, at the same time, a feature of the claim. Since it is a technical effect expressed in the claim, therapeutic efficacy has to be taken into account in the assessment of sufficiency of disclosure (see point 3.3 above).

5.2 For the requirement of sufficiency to be met, the claimed therapeutic efficacy has to be credible at the effective date of the patent (see G 1/03, OJ EPO 2004, 413, Reasons 2.5.3), i.e. on the basis of the information provided in the patent application together with the common general knowledge then available to the person skilled in the art. Whether this criterion is met is assessed according to the circumstances of each case.

5.3 Mere assertion unsupported by evidence is not enough. If the required credibility cannot be derived from common general knowledge, the application as filed must provide appropriate experimental data or at least indicate a credible evidence-based technical concept or mode of action.

This may, for example, be information demonstrating that the claimed active compound or composition has a direct effect on a mechanism specifically involved in the targeted pathology (see T 609/02, Reasons 9), this mechanism being either demonstrated in the application or known from prior art cross-referenced in the application or from common general knowledge.

Thus, showing a pharmaceutical effect *in vitro* (or determining biomarkers *in vivo*) may be enough if, for the skilled person, this observed effect directly and unambiguously reflects the therapeutic application in question or, as it has also been put, if there is a clear and accepted relationship between the physiological activity or activities shown and the targeted pathology (see T 609/2, Reasons 9; T 241/95, Reasons 4.1.2; T 158/96, Reasons 3.5.2).

5.4 A claimed therapeutic application may be substantiated by any kind of evidence (principle of free evaluation of evidence, see G 2/21, Reasons 34) as long as this evidence renders it credible that the claimed compound or composition is suitable for the claimed therapeutic purpose (i.e. that it has therapeutic efficacy).
It is thus not mandatory that clinical data (i.e. data from clinical studies) be provided where the required credibility can be established on a different basis. However, where the required credibility cannot be established on a different basis, clinical data may be required.

Nothing else is said in T 609/02 (see Reasons 9), which states that evidence from clinical studies is "not always" necessary:

> "The boards of appeal have accepted that for a sufficient disclosure of a therapeutic application, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported."

Thus, the respondent's view that data from clinical studies is generally not required in support of sufficiency of disclosure cannot be followed.

5.5 Post-filed evidence may only be used for corroboration to back up the findings in the patent application but not as the sole element substantiating the claimed therapeutic application (see also the statement in G 2/21, Reasons 77, according to which "*the proof of a claimed therapeutic effect has to be provided in the application as filed, in particular if, in the absence of experimental data in the application as filed, it would not be credible to the skilled person that the therapeutic effect is achieved*").

5.6 As set out by the board in case T 294/20 (Reasons 5 and 6), these principles, established by the leading decision T 609/02, still apply and were indeed confirmed in G2/21.

5.7 The parties were also in disagreement as regards the burden of proof concerning sufficiency of disclosure.

In principle, each party bears the burden of proof for the facts it alleges. In opposition proceedings where the ground for opposition under Article 100(b) EPC is invoked, it is the opponent who initially bears the burden to prove that the patent does not disclose the

invention in a manner sufficiently clear and complete for it to be carried out by a skilled person. For the objection to be successful, the opponent has to show that there are serious doubts substantiated by verifiable facts (see T 19/90, Reasons 3.3).

It is recalled that the invention as claimed pertains to a further medical use where attaining the therapeutic effect is a functional claim feature (see points 3.2 and 3.3 above).

In this context the board interprets the statement in G 2/21, Reasons 77 (see point 5.6 above) as meaning that if there is no conclusive experimental data in the application as filed, a different proof of the claimed therapeutic effect has to be provided by the applicant (the later patent proprietor) in the application as filed, e.g. by way of a theoretical or mechanistic explanation or by relying on common general knowledge (see also T 853/22, Reasons 23).

The type and quality of this disclosure in the patent application determines what type and quality of submissions is required from an opponent. Depending on the circumstances, an opponent may discharge its burden of establishing insufficiency merely by submitting convincing arguments alone (see e.g. T 63/06, Reasons 3.3.2 and T 1558/11, Reasons 2.7.1).

For the sake of completeness, the board notes that Decisions T 409/91 and T 694/92 cited in the Guidelines for examination (F-III,1), and relied upon by the respondent (see reply to the statement of grounds of appeal, pages 11 and 12), do not support the relevant sentence in the Guidelines that "an objection of lack of sufficiency presupposes that there are serious doubts substantiated by verifiable facts" and are actually concerned with the problematic of broad claims (Article 84 EPC) in the context of the assessment of

sufficiency. In addition, T 409/91 pertains to the evaluation of sufficiency by an examining division, where the repartition of the burden of proof is obviously different than in opposition cases.

Assessment of sufficiency in relation to the case in hand

5.8 As set out above (see point XXIII.), the opponents essentially argued that the application as filed, together with the skilled person's common general knowledge then available, did not disclose the invention in a manner sufficiently clear and complete for it to be carried out by the skilled person. The central issue was the suitability of empagliflozin for the claimed therapeutic indications. In particular, it was questioned whether the experimental data shown in the patent application, specifically in Examples 1 and 8, taking into account the general technical background then available (as provided *inter alia* in document D79) was sufficient to render the claimed therapeutic indications credible. Furthermore, the opponents disputed that the claimed subject-matter could be put into practice across the entire scope claimed, particularly with regard to the definition of the patient group and the optional feature relating to combination therapy.

5.9 Cardiovascular disease is a known complication of diabetes (see also D38: page 80, left-hand column, second full paragraph). Empagliflozin is an SGLT2 inhibitor and antidiabetic agent. According to the patent in suit and the application as filed, it is also suitable for preventing, reducing the risk of or delaying the occurrence of cardiovascular events.

5.10 According to the respondent, the claimed therapeutic effect is based on the activity of empagliflozin to

reduce oxidative stress, endothelial dysfunction and arterial stiffness. This is presumed to result in the claimed effect of preventing, delaying or reducing the risk of a cardiovascular event that is either cardiovascular death or heart failure requiring hospitalisation.

5.11 The underlying premise is thus that oxidative stress, endothelial dysfunction and arterial stiffness can serve as physiological targets for drugs for the purpose of improving cardiovascular outcomes and specifically those recited in claim 1.

5.12 In addition to other objections, the opponents called into question that this cardioprotective mechanism was rendered credible in the application as filed.

5.13 Examples 1 and 8

5.13.1 Examples 1 and 8 report parametric data presumed to reflect oxidative stress, endothelial dysfunction and arterial stiffness. As suggested by opponent 11 (see the notice of intervention, section 2, point 32), the data in Examples 1 and 8 may be referred to as data relating to cardiovascular biomarkers.

5.13.2 Example 1 presents the results of several studies conducted with empagliflozin in a rat model of diabetic cardiomyopathy (streptozotocin (STZ)-treated rats).

5.13.3 Example 8 presents the results of a study observing the effect of empagliflozin on arterial stiffness in normotensive human subjects with type 1 diabetes mellitus.

5.13.4 Irrespective of the opponents' further criticisms, for instance in relation to the methodology used in the examples and the statistical significance of the resulting data, it will be assumed in the following, in

the respondent's favour, that Example 1 demonstrates, in a valid animal model of diabetes, that empagliflozin treatment counteracts the development of endothelial dysfunction and oxidative stress, and that Example 8 demonstrates that empagliflozin reduces arterial stiffness in normotensive human patients with type 1 diabetes mellitus. Example 1 also reports that aortic wall thickness and collagen content (presumably associated with arterial stiffness) was slightly increased in diabetic rats and was normalised by empagliflozin treatment.

5.13.5 Thus, the assumption is that the examples show that the administration of empagliflozin reduces oxidative stress, endothelial dysfunction and arterial stiffness in the claimed patient population.

5.14 Mechanistic link

5.14.1 Examples 1 and 8 provide data on cardiovascular biomarkers only (i.e. measurable parameters such as NADPH oxidase activity in the cardiac tissue, endothelium-dependent vasorelaxation, aortic wall thickness or pulsed wave velocity). Nothing can be inferred from the examples themselves about how these biomarkers are linked to the claimed therapeutic application (see point 5.11 above) or about the potential impact of reducing oxidative stress, endothelial dysfunction and/or arterial stiffness on cardiovascular outcomes, in particular the severe outcomes of heart failure requiring hospitalisation and cardiovascular death.

5.14.2 The application as filed sets out (see page 25, line 26 to page 26, line 7 of the description; corresponding to paragraph [0087] of the patent in suit) that endothelial dysfunction is associated with proinflammatory, pro-oxidative and prothrombotic

changes within the arterial wall and with increased vessel wall thickness and collagen content, that it is thought to be a key event in the development and progression of atherosclerosis and arterial stiffness, and that it precedes clinically obvious vascular complications. It is of prognostic significance in detecting vascular disease and predicting adverse vascular events. The same passage also mentions that there is supporting evidence that oxidative stress does not only contribute to endothelial dysfunction or damage but also to vascular disease.

5.14.3 On this basis, it might be hypothesised that a treatment that counteracts endothelial dysfunction, oxidative stress and arterial stiffness may contribute to cardiovascular safety. A further passage in the application as filed speculates, albeit more generally, that treating oxidative and/or vascular stress, preferably independently of glycemic status, may prevent or delay the onset of long-term diabetic complications, particularly those associated with or induced by oxidative stress, or treat such complications (see page 28, lines 6 to 12, corresponding to paragraph [0097] of the patent in suit).

5.14.4 However, no evidence for this postulated mechanistic link, such as experimental data or a reference to supporting scientific literature, is provided in the application as filed.

5.14.5 Thus, the application itself provides no evidence for the premise that endothelial dysfunction, oxidative stress and arterial stiffness (i.e. the medical states reflected by the parameters observed in Examples 1 and 8) are not only of prognostic value but that targeting them by way of a therapeutic intervention has

a direct impact on cardiovascular outcomes by lowering the risk for cardiovascular death and heart failure requiring hospitalisation. Cardiovascular events are late complications resulting from a complex pathogenic process that is influenced by diverse risk factors. As pointed out by the opponents, it is thus not a foregone conclusion that an improvement in certain cardiovascular biomarkers relevant for endothelial dysfunction, oxidative stress and arterial stiffness reflects a reversal of damage (such as atherosclerotic lesions) that will translate into an improved cardiovascular prognosis within the meaning of claim 1.

5.14.6 Since the direct link between the experimental data and the claimed therapeutic indication is not found in the application as filed, the question to be answered is whether it was part of the common general knowledge.

Among documents D79 to D85, D100 to D102, D110, D112, D113, D114, D128 and D129 relied on by the respondent, only D79 and D81, as review articles, are of a nature that may be considered representative of the skilled person's common general knowledge at the relevant date.

D79 notes the association of endothelial dysfunction, oxidative stress and arterial stiffness with negative cardiovascular outcomes and also with heart failure pathogenesis and attributes a prognostic value for heart failure to these conditions. Endothelial dysfunction and arterial stiffness are also mentioned as possible future therapeutic targets. However, this is discussed in theory only. It cannot be conclusively derived from D79 that endothelial dysfunction, oxidative stress or arterial stiffness is amenable to targeted therapeutic intervention in a way that would improve cardiovascular outcomes as defined in claim 1 (see D79: page 1455, Abstract and right-hand column, last paragraph; Figure 1; paragraph bridging pages 1457

and 1458; paragraph bridging pages 1459 and 1460; page 1461, left-hand column, first paragraph and right-hand column, second paragraph; page 1464, Conclusions).

D81 observes that oxidative stress is associated with and involved in the pathophysiology of heart failure (see D81: Abstract; paragraph bridging pages H2182 and H2183). According to D81, a better understanding of such mechanisms may enable the development of new strategies against heart failure. The authors speculate that regulating oxidative stress may contribute to establishing effective treatment strategies and state that this approach should become a target for future investigation (see Abstract and last paragraph on page H2187).

In brief, in both documents the connection remains speculative and is not backed up by pertinent data.

5.14.7 As mentioned above, the remaining documents D80, D82 to D85, D100 to D102, D110, D112, D113, D114, D128 and D129 are not part of the common general knowledge and, for this reason alone, cannot be used to complement the content of the application as filed to establish sufficiency of disclosure.

D80, D82 to D85, D100 to D102, D110, D112, D113, D114, D128 and D129 are original research articles, a type of document not usually considered to represent common general knowledge. While D85 bears the subtitle "a systematic review and meta-analysis", it is not actually a review article as it concerns itself with a calculation method for predicting cardiovascular events, based on a meta-analysis of studies on arterial stiffness.

Moreover, the statements in these documents relied on by the respondent would not, in any case, conclusively substantiate the required causative mechanistic link

between the amelioration of endothelial dysfunction, oxidative stress or arterial stiffness and the therapeutic indications in claim 1 (see the respondent's statement replying to the statements setting out the grounds of appeal, point 4.3.1, page 18, last paragraph, page 19, penultimate paragraph to page 21, first paragraph, and the statement replying to the notice of intervention, point 3.2, pages 5 to 7). Statements to the effect that these conditions are involved in cardiovascular pathologies and have a prognostic value for cardiovascular outcomes are not sufficient for this purpose. The same is true for unsupported statements that interventions improving endothelial dysfunction, oxidative stress and/or arterial stiffness (or the values of associated biomarkers) may provide cardiovascular benefits.

5.14.8 The respondent also submitted that D108, which was published around the priority date, provided evidence that STZ-treated rats were an established model for diabetic cardiomyopathy and LV remodelling. In the respondent's view, this, in turn, meant that this animal model was indicative for cardiovascular mortality and heart failure (D108: page 158, last two paragraphs).

5.14.9 This argument is not convincing. The cited passage of D108 merely states that it was found that endothelial dysfunction is one of several factors "greatly involved in the development of cardiac dysfunction". This does not go beyond what is said in D79. No statement or evidence is found in D108 to the effect that interventions leading to an improvement in the biomarkers in question will lower the risk for the cardiovascular events defined in claim 1. Since D108 does not disclose the required mechanistic link, it was not necessary to determine whether D108 should be

admitted (see point XXV.(a) above), whether it was published before the priority date or whether its statements regarding the mouse model should be considered common general knowledge.

5.14.10 Thus, the missing mechanistic link appears to have been part of the common general knowledge as an unconfirmed hypothesis only that was based on the known association of endothelial dysfunction, oxidative stress and arterial stiffness with cardiovascular pathology and risks. Without supporting evidence, these speculative considerations cannot close the gap in relation to the link between the experimental data and the claimed therapeutic application.

5.15 Moreover, the evidence provided by the opponents in connection with rosiglitazone and the guidance issued by regulatory agencies on requirements for the approval of new antidiabetic drugs substantiates further doubt in relation to this missing link (see points 5.16 and 5.17 below).

5.16 Rosiglitazone

5.16.1 Rosiglitazone is a compound that was approved as an antidiabetic agent for type 2 diabetes mellitus.

5.16.2 The opponents cited, among others, documents D110, D112 to D114 and D100 to D102 as experimental evidence that rosiglitazone, like empagliflozin, favourably affects the same medical states and associated biomarkers that were studied in Examples 1 and 8 of the application as filed.

Endothelial function

- D110 reports on experiments in STZ rats and concludes that treatment with rosiglitazone restored, i.e. normalised, endothelial function

(specifically, the endothelium-dependent relaxation induced by acetylcholine in the aorta and corpus cavernosum tissues), which had been impaired in the diabetic group (see Abstract and Figure 2B).

This corresponds to the similar results on endothelial-dependent vasorelaxation found for empagliflozin in the application as filed (see Example 1 and Figure 2A).

- D101 relates to a study that aimed to assess the effect of rosiglitazone on endothelial function (assessed by flow-mediated dilation) in patients with advanced type 2 diabetes mellitus chronically treated with insulin. The finding was that low-dose treatment with rosiglitazone for six months significantly improved endothelial function (see Abstract and page 198: Discussion).

Oxidative stress

- According to Example 1 of the application as filed, Figure 10 shows that NADPH oxidase activity in the cardiac tissue, an important source of superoxide, is diminished with empagliflozin treatment.

  Corresponding results in rats are described in D112 for rosiglitazone treatment. This is relevant in relation to oxidative stress (see D112: Abstract and page 117 left-hand column, lines 5 to 24; page 123, last paragraph; page 124: Conclusions).

- D113 relates to a study investigating the effect of rosiglitazone on the lipid profile and oxidative status of STZ rats. Among other parameters, malondialdehyde and 3-nitrotyrosine levels in the left ventricular muscle were measured and found to be increased in diabetic rats, this being held to be indicative of oxidative/nitrosative stress.

These levels decreased upon treatment with rosiglitazone (see D113: Abstract; page 479, left-hand column, second paragraph; paragraph bridging columns on page 483).

- D100 relates to a randomised cross-over study in 12 metformin-treated patients with type 2 diabetes which found that rosiglitazone treatment lowered oxidative stress, as reflected by significantly reduced plasma malondialdehyde levels (see D100: Abstract; page 311, last paragraph; page 312, last full paragraph).

Arterial stiffness

- D114 relates to a clinical study which investigated the effect of rosiglitazone on arterial stiffness in type 2 diabetic patients. D114 reports that treatment with rosiglitazone significantly decreased pulse wave velocity, which reflects reduced arterial stiffness (see D114: Abstract; page 1397: right-hand column, first and second paragraphs).

  Corresponding results are presented in Example 8 of the application as filed for empagliflozin treatment in type 1 diabetic patients.

- D102 relates to a clinical study conducted in drug-naïve type 2 diabetic patients to evaluate the long-term effect of rosiglitazone monotherapy with medical nutrition treatment on arterial stiffness (among other parameters). The results suggested that rosiglitazone has favourable effects on arterial stiffness compared with metformin monotherapy (see D102: Abstract; Table 2; page 49 left-hand column, last paragraph).

5.16.3 In summary, these studies report that rosiglitazone, like empagliflozin, has a favourable effect on endothelial function, oxidative stress and arterial stiffness.

5.16.4 In addition, D95 reports that rosiglitazone was approved by the FDA based on its glucose-lowering capacity but also on a perceived potential for cardiovascular benefit evidenced by improvements in surrogate markers of endothelial function (see D95: page 60, left-hand column, first paragraph).

5.16.5 Based on further pertinent clinical data, rosiglitazone was nevertheless found to increase cardiovascular risks rather than provide cardioprotection.

As reported in D95 (see the passage bridging pages 60 and 61), prior to 2007, the approval of antihyperglycemic drugs was based on their ability to lower plasma glucose or HbA_{1c}, both surrogate markers primarily for microvascular diabetic complications. Effects on weight, lipid profile, C-reactive protein, adipose metabolism, and other atheroscloerotic surrogates were measured because of the increased prevalence, morbidity and mortality of cardiovascular disease in diabetic patients but did not form a central component of the approval process. This was consistent with the approach used for other drug classes (e.g. antihypertensive agents or lipid-lowering agents), whose approval required evidence of an improvement in surrogate markers for cardiovascular events (blood pressure and cholesterol levels, respectively) but did not require long-term cardiovascular outcome studies.

A meta-analysis published in 2007 demonstrated an increased risk of myocardial infarction with rosiglitazone, which led to general uncertainty about

its cardiovascular safety (see D95: page 60, left-hand column, second paragraph and reference [15] of D95, on file as D116 in these appeal proceedings).

According to the meta-analysis of 42 clinical trials presented in D116, the odds ratio for myocardial infarction in the rosiglitazone group, as compared with the control group, was 1.43 (95% confidence interval, 1.03 to 1.98; p = 0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% confidence interval, 0.98 to 2.74; p = 0.06)(see D116: Abstract/ Results). Thus, rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance (see D116: Abstract/Conclusions and Table 3). The authors also concluded that the estimates for the odds ratio for myocardial infarction and death from cardiovascular causes appeared consistently elevated for rosiglitazone in comparison with placebo or other commonly prescribed antidiabetic therapies (see D116: page 2467, right-hand column, first full paragraph and Table 5).

5.16.6 In conclusion, rosiglitazone showed favourable effects on the same biomarkers as empagliflozin, but data obtained in clinical studies of rosiglitazone point to a negative impact on cardiovascular safety rather than a cardioprotective effect within the meaning of current claim 1.

5.16.7 This evidence weighs against there being a direct and unequivocal relationship between the effects observed in Examples 1 and 8 and therapeutic efficacy within the meaning of claim 1.

5.17 Guidance issued by regulatory agencies

5.17.1 Due to the concerns raised by D116 about the cardiovascular safety of rosiglitazone, in combination with observations in relation to other antidiabetic drugs that suggested that reliance solely on surrogate markers of cardiovascular disease could be misleading, both the FDA and EMA (i.e. the US and European regulatory agencies) issued guidelines (see D23 and D24) that raised the threshold for the approval of new antidiabetic drugs by requiring direct clinical evidence of cardiovascular safety (see D40: page 1052, second paragraph; D95: page 60, right-hand column, last full paragraph to page 61, left-hand column, second paragraph; D97: S102, right-hand column to S104, middle column; D23; D24). While the version of the EMA guideline on file (D24) dates from 2012, D95 confirms that the EMA issued similar guidance in 2010 (see D95: page 61, second paragraph and reference [24] of D95).

5.17.2 In the pharmaceutical field, guidance issued by regulatory agencies would have been part of the skilled person's common general knowledge.

5.17.3 It was thus part of the skilled person's common general knowledge that the cardiovascular safety of new antidiabetic drugs could not be confirmed by reliance on surrogate biomarkers alone (see also D97; page S102, right-hand column, lines 8 to 10). It would, moreover, have been inferred from this that any additional cardioprotective benefit (such as those defined in claim 1) could not be conclusively shown by a positive effect on such biomarkers.

5.18 The respondent presented the following counter-arguments.

(a) The known concerns about the cardiovascular safety of rosiglitazone (D116) preceded the publication of D100 to D102, D110, D112 and D113, documents which confirmed that endothelial dysfunction, oxidative stress and arterial stiffness, as studied in Examples 1 and 8, were specifically involved in diabetic cardiovascular disease and that interventions favourably affecting these conditions (as measurable by the associated biomarkers) were still believed to reduce cardiovascular risk.

(b) The results reported in D115 and D116 with regard to cardiovascular death were not statistically significant. The result in D116 was driven by comparison with the group receiving insulin, whereas the correct comparator was the placebo group.

(c) Data obtained with rosiglitazone was not relevant for empagliflozin.

5.19 These arguments do not succeed for the following reasons.

(a) As set out in point 5.14.7 above, the documents relied on by the respondent according to point 5.18(a) neither represent common general knowledge nor provide conclusive evidence of the missing causative mechanistic link (see points 5.14.4, 5.14.5 and 5.14.6 above).

(b) The results for rosiglitazone reported in D116 (see point 5.16.5 above and D116: Table 5 and Abstract) are statistically significant with regard to the observed increase in the risk of myocardial

infarction as compared with placebo or with other antidiabetic agents. This was not contested by the respondent.

D115 relates to an interim analysis of a further study with insufficient statistical power (as acknowledged in D115: Abstract, Results), so its data is inconclusive and does not call the results presented in D116 into question.

D116 also attests "borderline" statistical significance to the results on cardiovascular death and furthermore points out that the observed adverse effects during rosiglitazone treatment were in fact not unique to any specific comparator regimen (see D116: last line on parge 2459 and page 2467, left-hand column, first and third paragraphs).

In any case, even if statistical significance was not established for the data for cardiovascular death, the absence of statistical significance cannot be taken to establish the missing causative mechanistic link with regard to cardioprotection. Reference is also made in this regard to the board's pertinent reasoning in points 7.3 to 7.6 below.

(c) While it is acknowledged that empagliflozin and rosiglitazone differ structurally and belong to different drug classes (SGLT2 inhibitors and PPAR agonists, respectively), no evidence is on file that sheds any light on why the results for cardiovascular safety observed with rosiglitazone were unfavourable despite favourable results in relation to endothelial dysfunction, oxidative stress and arterial stiffness. The possible reasons cited by the respondent and mentioned in D116

(page 2467, right-hand column to page 2469, left-hand column), D101 (page 199, right-hand column) or D128 (passage bridging pages 2631 and 2632) are not supported by any evidence. No direct experimental comparison of empagliflozin with rosiglitazone has been provided either. Consequently, it cannot be verified that the lack of a correlation with the therapeutic indications as defined in claim 1 is specific to rosiglitazone and has no relevance for empagliflozin (as argued by the respondent).

5.20 The respondent also submitted that the opponents' arguments in connection with rosiglitazone and the requirement for cardiovascular safety studies should be disregarded because it was, in its opinion, not appropriate that clinical safety should play a role in the assessment of sufficiency of disclosure of a therapeutic application. The relevant requirement was that therapeutic efficacy was rendered credible. Clinical safety could only be verified by clinical studies, which according to the established case law of the EPO were not required for this purpose.

5.21 The board does not share the respondent's view that clinical safety is generally to be disregarded in the assessment of sufficiency of disclosure of a therapeutic application or that clinical data is never required (for the latter aspect, see point 5.4 above). What information will be relevant depends on the individual circumstances of each case.

However, the respondent's argument is in any case misplaced and therefore must fail since the opponents' point was not that the clinical safety of empagliflozin, in terms of adverse effects unrelated to its clinical efficacy in the therapeutic indication, had not been confirmed. In the case in hand,

cardiovascular safety is not an aspect separate from therapeutic efficacy because the therapeutic indication itself as defined in claim 1 is cardioprotection. The opponents thus relied on the facts in connection with rosiglitazone as evidence that the alleged direct mechanistic link between the tested cardiovascular parameters and the claimed therapeutic indication does not exist.

5.22 Since the claimed therapeutic efficacy was not rendered credible initially (i.e. based on the content of the application as filed and common general knowledge at the relevant date), the respondent cannot rely on post-filed evidence as this would go beyond corroborating an established finding (see point 5.5 above).

5.23 For these reasons, the subject-matter defined in claim 1 of the main request is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

6. Admittance - auxiliary request 17

The board found that auxiliary request 17, filed with the respondent's timely reply to the notice of intervention, was part of the appeal proceedings. In view of the outcome of the appeal case in the opponents' favour, no detailed reasoning on this issue is required.

7. Sufficiency of disclosure - auxiliary request 17 (Article 83 EPC)

7.1 In claim 1 of auxiliary request 17, the therapeutic indication relating to heart failure requiring hospitalisation has been deleted.

7.2 However, the finding of insufficiency set out above (see section 5.) was based in essence on the lack of evidence for the postulated direct mechanistic link between the experimental data in Examples 1 and 8 on specific parameters and efficacy for the claimed therapeutic indications.

7.3 The focus of auxiliary request 17 on cardiovascular death does not overcome this objection. Statistical non-significance of the results reported in D115 and D116 for rosiglitazone in relation to cardiovascular death cannot in any case be interpreted as evidence of a cardioprotective therapeutic effect as defined in claim 1 of auxiliary request 17 (see also point 5.19(a) above). As a consequence, the required direct mechanistic link is still missing.

7.4 It was not in dispute that the guidelines for the approval of new antidiabetic drugs requiring cardiovascular safety studies, introduced by regulatory agencies from 2008 onwards, were applicable at the effective date of the patent. It was thus not deemed acceptable to rely on surrogate biomarkers to confirm cardiovascular safety. In combination with the analysis set out in point 5.12 above, this suggests that it does not suffice, either, to rely on such biomarkers, in particular the parameters studied in Examples 1 and 8, for evidence of a cardioprotective effect of antidiabetic drugs (see point 5.17.3).

7.5 Moreover, the application as filed refers to vascular complications, vascular disease and vascular adverse events in general (see also point 5.14.2 above). There is no statement that endothelial dysfunction, oxidative stress and arterial stiffness and the corresponding data in Examples 1 and 8 should be relevant specifically for cardiovascular death (or

heart failure requiring hospitalisation). Accordingly, the examples cannot be viewed differently because the reference to heart failure requiring hospitalisation has been deleted from claim 1. Their evidentiary value does not change.

7.6 Thus, notwithstanding the respondent's arguments as presented at the oral proceedings before the board, the same conclusion, based on essentially the same reasoning, applies as for claim 1 of the main request (see section 5.).

7.7 For these reasons, the subject-matter of claim 1 of auxiliary request 17 does not meet the requirement of sufficiency of disclosure (Article 83 EPC).

8. Admittance of evidence filed by the respondent (D105 to D108)

8.1 No decision on the admittance of documents D105 to D108 was required for the following reasons.

8.1.1 D105 and D107 concern issues that played no role for the board's reasoning set out above.

8.1.2 D106 was not deemed relevant. It was mentioned by the respondent as evidence that the meta-analysis reporting unfavourable cardiovascular clinical outcomes with regard to rosiglitazone (D116) was published in 2007. This was already known from other documents on file, in particular D116 itself (see point 5.16.5 above). Furthermore, D106 and the statements in it do not change the facts reported in D116.

8.1.3 The circumstances relating to D108 are addressed above (see points 5.14.8 and 5.14.9).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated