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Datasheet for the decision of 27 October 2021

Case Number: T 1732/18 - 3.3.01

Application Number: 06706291.9

Publication Number: 1845961

IPC: A61K31/00, A61K31/5377, A61P7/02, A61P9/10

Language of the proceedings: EN

Title of invention:
TREATMENT OF THROMBOEMBOLIC DISORDERS WITH RIVAROXABAN

Patent Proprietor:
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Relevant legal provisions:
EPC Art. 100(c), 123(2), 54, 105, 113(1), 100(b), 56
EPC R. 79
RPBA 2020 Art. 13(2)

Keyword:
Amendments - added subject-matter (no)
Novelty - (yes)
Admittance of evidence filed in Appeal
Admittance of submissions filed at a late stage
Sufficiency of disclosure (yes)
Inventive step - (yes)

Decisions cited:
G 0005/83, G 0002/08, T 2506/12, T 2034/19

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1732/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 27 October 2021

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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted on 30 April 2018 revoking European patent No. 1845961 pursuant to Article 101(3)(b) EPC.

Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	P. de Heij

Summary of Facts and Submissions

I. European patent No. 1 845 961 (patent in suit) originates from European patent application No. 06706291.9. The application was filed with a set of eight claims. Claims 1 and 3-6 read as follows:

"1. A method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor no more than once daily for at least five consecutive days in an oral dosage form to a patient in need thereof, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

3. The use of an oral dosage form of a direct factor Xa inhibitor for the manufacture of a medicament for the treatment of a thromboembolic disorder administered once daily for at least five consecutive days, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

4. The method or use as claimed in any of Claims 1 to 3, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.

5. The method or use as claimed in any of Claims 1 to 4, wherein the oral dosage form is a rapid-release tablet.

6. The method or use as claimed in any of Claims 1 to 5, wherein the direct factor Xa inhibitor is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide."

II. The patent in suit was granted with two claims, which read as follows:

"1. The use of a rapid-release tablet of the compound 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide for the manufacture of a medicament for the treatment of a thromboembolic disorder administered no more than once daily for at least five consecutive days, wherein said compound has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

2. The use as claimed in Claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke."

III. Other names for the compound mentioned in claim 1 are BAY 59-7939 and rivaroxaban.

IV. Thirteen oppositions were filed, opposing the patent in suit under Article 100(a), (b) and (c) EPC 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.

V. The patent proprietor requested that the oppositions be rejected (main request) and also filed auxiliary claim requests 1 to 27 (enclosed with a submission dated 16 November 2016) and auxiliary claim requests 28 and 29 (both filed during oral proceedings before the opposition division).

VI. The documents cited in the course of the opposition proceedings included the following:

D1: US 2003/0153610 A1

D2: Blood 102(11): American Society of Hematology, Forty-fifth annual meeting program and abstracts, Part 1, Abstract no. 3004 (2003)

D3: Blood 102(11) Part 1, Abstract no. 3010 (2003)

D4: M.E. Aulton (ed.), Pharmaceutics: The Science of Dosage Form Design, 2nd edn., Churchill Livingstone (2002), pages 410-411

D6: Current Topics in Medicinal Chemistry, 1(2), 151-159 (2001)

D8: Janssen Pharmaceuticals, Inc.: Xarelto® Dosing and Transition Management (April 2015)

D9: Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 10th edn. (2001), Chapter 1

D11: Pathophysiol Haemost Thromb 33 (Suppl 2), p. 98, Abstract no. PO080 (2003)

D12: Pathophysiol Haemost Thromb 33 (Suppl 2), p. 98, Abstract no. PO081 (2003)

D14: Rowland, Tozer: Clinical Pharmacokinetics: Concepts and Applications, 83-105 (1995)

D15: Pathophysiol Haemost Thromb 33 (Suppl 2), p. 97, Abstract no. PO078 (2003)

D16: Journal of Thrombosis and Haemostasis 3, 514-521 (first published online on 26 January 2005)

D17: Blood 102(11) Part 1, Abstract no. 3003 (2003)

D23: MMP 31(11), 412-416 (2008)

D77: Annu. Rev. Med. 56, 63-77 (2005), first published online on 13 August 2004

D91: Circulation 114, 2374-2381 (2006)

D103: Seminars in Thrombosis and Hemostasis 33(5), 515-523 (2007)

D106: J Clin Pharmacol 47, 1398-1407 (2007)

D108: Clin Appl Thromb/Hemostasis 22(5), 412-422 (2016)

D110: Declaration of Dr. Misselwitz (15 January 2018)

D110d: Blood 102(11), Suppl. Abstract no. 41 (2003)

D121: Summary of Data on File in the Proceedings - Doses of rivaroxaban applied once-daily in clinical trials

VII. The decision under appeal is the opposition division's decision revoking the patent in suit, announced on 7 February 2018 and posted on 30 April 2018.

VIII. According to the decision under appeal:

(a) The subject-matter of claim 1 as granted did not extend beyond the content of the application as filed (Articles 100(c) and 123(2) EPC), met the requirement of sufficiency of disclosure (Article 100(b) EPC) and was novel relative to the disclosure of, *inter alia*, documents D1, D2 and D11 (Articles 100(a), 52(1) and 54 EPC).

(b) However, the subject-matter of claim 1 as granted did not involve an inventive step (Articles 100(a), 52(1) and 56 EPC).

The multi-dose phase I clinical trial described in documents D2 and D11 represented the closest prior art. The technical problem to be solved was to provide a safe and effective oral dosage regimen of rivaroxaban for the prophylactic and therapeutic treatment of thromboembolic disorders. In view of the teaching of documents D15 and D17 regarding the sustained effect of single oral doses of rivaroxaban, the person skilled in the art would not have needed inventive skill to establish the dosage regimen of claim 1 (i.e. once-daily administration of a rapid-release tablet of

rivaroxaban for at least five consecutive days) to solve this technical problem.

(c) The various limitations added in the amended claims of auxiliary requests 1 to 27 could not overcome the objection of lack of inventive step. Auxiliary requests 28 and 29 were not admitted into the proceedings.

IX. The patent proprietor (appellant) filed an appeal against this decision.

X. Opponent 1 withdrew its opposition, thus terminating its participation in the appeal proceedings.

XI. In preparation for oral proceedings, the board issued a communication pursuant to Article 15(1) RPBA (dated 17 March 2021).

XII. Two further parties ("respondent 14" and "respondent 15" below) filed notices of intervention to join the oppositions against the patent in suit (Article 105(1)a) and Rule 89 EPC).

XIII. The appellant submitted replies to both notices of intervention.

XIV. With a further submission dated 24 September 2021, the appellant replied to the board's communication under Article 15(1) RPBA.

XV. In the course of the appeal proceedings, the parties filed further documents as evidence.

(a) The appellant submitted:

- documents D2a, D3a, D11a, D12a, D15a, D17a, D42a, D63a, D78c, D80c, D110c[a], D110d[a], D122, D122a-D122f, D123, D123a-D123f, D124, D124a, D124b, D125,

D126, D127, D128a-D128c and D129a-D129g (with the statement setting out the grounds of appeal)

- documents D143, D143a and D144 (by letter dated 26 February 2020)
- documents D153, D153a, D153b, D154-D160, D160a and D160b (with the reply to the notice of intervention of respondent 15)

In both its replies to the notices of intervention (see point XIII. above), the appellant also stated that it was relying by reference on, and thereby effectively refiling, all its appeal submissions, including all documents and requests referred to therein.

Documents D2a, D3a, D11a, D12a, D15a, D17a, D42a, 110c[a] and 110d[a] are enlarged copies, with line numbering and sentence numbering, of documents filed during the proceedings before the opposition division.

(b) The opponents (respondents), with their respective replies to the statement setting out the grounds of appeal, submitted documents D130-D142 and D142a-D142g (as renumbered). With its letter of 28 September 2020, respondent 11 submitted a further document (identical to D122c filed by the appellant) as "D145".

With its notice of intervention, respondent 15 submitted, *inter alia*, documents D149-D152.

XVI. The following document filed in appeal has remained relevant for this decision:

D122: Expert Declaration of Prof. Dr. med. Sylvia Haas (7 September 2018)

XVII. Oral proceedings before the board took place on 26-27 October 2021, in the absence of respondent 9, which had advised the board in writing that it would not be attending (Article 15(3) RPBA and Rule 115(2) EPC).

XVIII. The respondents' arguments relevant to this decision may be summarised as follows.

Added subject-matter (Articles 100(c) and 123(2) EPC)

Claim 3 of the application as filed did not provide an adequate basis for the subject-matter of claim 1 as granted. Original claim 3 specified "once daily" dosing of the medicament. However, in claim 1 as granted, this feature had been modified to "no more than once daily" dosing. Since this also encompassed a dosing frequency of less than once daily, the claimed scope extended beyond the disclosure of original claim 3 and the application as filed.

Contrary to the appellant's assertion, the expression "no more than once daily" was not synonymous to "once daily" in the context provided in the patent in suit, which also included the administration of two or more dosage forms simultaneously or consecutively within a short time period (paragraph [0033]).

Novelty (Article 100(a), 52(1) and 54 EPC)

The subject-matter of claim 1 as granted lacked novelty relative to the disclosure of documents D1 and D2/D11.

Document D1, in claims 1 and 10 and paragraphs [0355], [0368] and [0372], disclosed the features of claim 1 as granted. The skilled person would infer that the treatment according to D1 could involve once-daily

dosing for five consecutive days and that the dosage form was a rapid-release tablet.

The treatment of healthy male subjects disclosed in documents D2 and D11 included prophylactic treatment covered by claim 1 as any individual was at some risk of suffering from a thromboembolic event. According to D2/D11, the maximum serum concentration (C_{max}) of rivaroxaban was reached after 2.5-4 hours. This was consistent with a rapid-release dosage form. Moreover, the term "rapid-release tablet" was a relative term which was therefore unclear. It should be interpreted as including any oral dosage form that was not specifically identified as a slow-release form.

Admittance of the appellant's documents filed in appeal

Most of the documents that the appellant had filed (e.g. D159 and D160) or re-filed in response to the interventions did not address any new point raised in the interventions. Respondent 14 had not even relied, in its statement of grounds, on new arguments or evidence going beyond the scope of the decision under appeal. Respondent 15 had not presented a fresh case either, relying mainly on documents and objections already presented in the appeal proceedings. The appellant should not be permitted to misuse its right to file "observations" in reply to an intervention within a specified period (Rule 79(1)EPC) by filing unrelated material which might otherwise not have been admitted. There was an implicit understanding that such observations must be relevant.

As a matter of general principle, if the filing of an intervention had the effect of opening up a time slot for patentees during which they could file absolutely anything, this might give rise to straw man

interventions initiated by patentees who wished to take advantage of such an opportunity.

The appellant's documents should also be rejected under the revised Rules of Procedure of the Boards of Appeal (OJ EPO 2019, A63) on submissions filed at a late stage of the proceedings.

Admittance of the appellant's submission of 24 September 2021

The submission in question had come outside the time limit for replying to the interventions and months after the board had issued its communication under Article 15(1) RPBA. The appellant had not provided adequate justification within the meaning of Article 13 RPBA for filing it at this late stage of the proceedings. The entire case law discussion presented in this submission was new. Also, the appellant should have commented at an earlier time on the issue of patient convenience, discussed by respondents 2, 3 and 4 in their replies to the grounds of appeal.

Sufficiency of disclosure (Article 100(b) EPC)

The claimed invention was insufficiently disclosed on account of the following concerns:

(a) There was uncertain scope of the terms "thromboembolic disorder" and "rapid release tablet".

(b) There was a lack of guidance for carrying out the invention:

(b.1) with regard to specific instructions for preparing rapid-release tablets;

(b.2) across the full scope of rivaroxaban doses and dosage frequencies covered by claim 1;

(b.3) with regard to the plasma concentration half-life parameter. According to claim 1, it was mandatory to ensure that the plasma concentration half-life of rivaroxaban was ten hours or less in each patient undergoing the treatment. Since the patent in suit and the underlying application did not provide any guidance as to how this could be achieved and did not indicate a method for measuring this parameter *in vivo*, the skilled person was not enabled to verify whether they were working within the scope of the claim.

(c) The experimental data in the application as filed only related to prophylaxis of venous thromboembolism (VTE). This could not render the treatment benefit plausible across a more general scope of thromboembolic disorders and patient populations, e.g. inflammatory diseases, rheumatic diseases of the musculoskeletal system or Alzheimer's disease as set out in paragraph [0024] of the patent in suit.

Inventive step (Articles 100(a), 52(1) and 56 EPC)

The disclosure of abstracts D2/D11, referring to the pharmaceutically active compound as "BAY 59-7939", was the closest prior art. Contrary to the appellant's allegation, D2/D11 disclosed rivaroxaban, as the chemical identity of "BAY 59-7939" had been known and the compound had been available at the effective date of the patent. Reference was made to documents D16 and D1.

Some of the respondents agreed with the objective technical problem as formulated by the opposition division, others argued that the aspects of efficacy and safety should not be taken into account in the formulation of the technical problem.

Starting from the disclosure of abstracts D2/D11, the person skilled in the art seeking to provide an oral dosage regimen of rivaroxaban for the prophylactic and therapeutic treatment of thromboembolic disorders would have consulted further documents providing information on rivaroxaban.

Documents D17 and D15 (both abstracts reporting on another phase I clinical study of rivaroxaban) reported a sustained effect on thrombin generation for up to 24 hours. This was a clear pointer to once-daily dosing.

The subject-matter of claim 1 as granted also lacked an inventive step based on the teaching of D2/D11 in light of the common general knowledge. The dosage regimen defined in claim 1 was merely the straightforward result of routine phase II dose-finding studies.

XIX. The appellant's arguments relevant to this decision may be summarised as follows.

Added subject-matter (Articles 100(c) and 123(2) EPC)

The feature "no more than once daily for at least five consecutive days" in claim 1 as granted defined a dosage regimen of once-daily administration. Contrary to the respondents' view, it did not encompass less frequent dosing since it was impossible to administer something not every day but for five consecutive days.

This technical feature was supported by claims 3, 5 and 6 of the application as originally filed.

Novelty (Article 100(a), 52(1) and 54 EPC)

None of documents D1, D2 and D11 relied on by the respondents prejudiced the novelty of claim 1 as granted.

There was no passage in D1 that specifically disclosed the once-daily administration of a rapid-release tablet of rivaroxaban for at least five consecutive days.

As to the objections based on either D2 or D11, neither document even disclosed tablets. Their disclosure was, moreover, limited to the use of rivaroxaban in healthy volunteers without an increased blood coagulation risk (an exclusion factor for participants in a study for testing a new anticoagulant). While claim 1 encompassed the prophylactic treatment of thromboembolic disorders, the skilled person was aware that prophylaxis for thromboembolism necessarily involved only patients at a heightened risk for thromboembolism above that of a healthy subject, and this was how the claim must be construed. Conditions that called for prophylaxis with anticoagulants had pathophysiological manifestations different from the physiological situation in healthy individuals.

Thus, documents D2 and D11 did not disclose the treatment of a thromboembolic disorder and did not provide data observed with prophylactic or therapeutic treatment. Phase I studies such as the one described did not permit any conclusion to be drawn as to the clinical efficacy of a dosage regimen in treating patients.

Admittance of the appellant's documents filed in appeal

The appellant had responded to both notices of intervention within the respective time limits set by the board, by relying on and effectively refiling all

its appeal submissions, including all documents referred to in them. Documents timely filed in response to an intervention automatically formed part of the proceedings without requiring a separate decision on admittance. Reference was made to decisions T 2034/19, Reasons 2.1 and T 1665/16, Reasons 2.2-2.5 and 3.2.

Filing interventions had been the interveners' decision, which carried its own risks. Only assumed infringers as defined in Article 105(1) EPC were entitled to file interventions, so that no danger of straw man interventions could arise.

Admittance of the appellant's submission of 24 September 2021

The submission of 24 September 2021 responded to the board's preliminary opinion and addressed the issues of admittance of documents and inventive step. It did not constitute a change of case but merely summarised and highlighted the appellant's views on certain points, especially where the appellant disagreed with points made by the board, e.g. concerning the formulation of the objective technical problem. There was also nothing unusual in citing supporting case law. The appellant had provided its comments in writing several weeks before the date of the oral proceedings to facilitate the preparation of the case for both the respondents and the board. This was a matter of convenience and procedural fairness.

Sufficiency of disclosure (Article 100(b) EPC)

Some of the respondents' objections related to lack of clarity (Article 84 EPC) rather than insufficiency of disclosure.

The feature "rapid-release tablet" was a term of art and as such was clear and enabling. Specifying a dose

in claim 1 was not necessary for an enabling disclosure since the skilled person would know the claim to be limited to practical doses. In accordance with the established case law of the EPO, medical use claims and dosage regimen claims were granted without there being a general necessity to specify a dose range. As to dosing frequency, the features "no more than once daily" and "once daily" were used synonymously in the patent and excluded "less than once daily" dosing.

As the half-life parameter merely served to characterise the class of drug compounds under consideration in the application as filed, it was redundant in claim 1 as granted, which had been restricted to one specific compound (rivaroxaban). The half-lives known for rivaroxaban in humans at the effective date of the patent had all been reported to be well below ten hours.

It was common practice in the field of anticoagulant development to perform the proof-of-concept studies in postoperative VTE prophylaxis, and this had also been done in the study reported in example 1 of the patent in suit. In the field of anticoagulants, both prophylaxis and treatment had the same underlying mechanism. Other known anticoagulants were already known and approved for treating the entire range of thromboembolic disorders. Based on the phase II data in the patent and the compound's known activity, the benefit of rivaroxaban in both prophylactic and therapeutic treatment across the entire class of thromboembolic disorders was already credible.

The phase II data also met at least the threshold of plausibility that safe and effective treatment could be achieved by once-daily administration. A person of ordinary skill would be capable of determining appropriate doses that were safe and effective.

The respondents had failed to provide any evidence that rivaroxaban would not work in the claimed dosage regimen. Post-published evidence confirmed that the claimed dosage regimen was safe and effective across a wide range of thromboembolic disorders and for all dosages tested and had since been approved by health authorities in over 130 countries. The appellant's rivaroxaban medicament Xarelto® had subsequently become a successful blockbuster drug.

Inventive step (Articles 100(a), 52(1) and 56 EPC)

The abstracts D2/D11 disclosed neither the use of tablets nor the clinical efficacy of any particular dosing scheme. Moreover, the active direct factor Xa inhibitor was mentioned in D2/D11 only under the name "BAY 59-7939". The chemical identity of "BAY 59-7939" had not been known publicly at the relevant date.

Starting from the technical teaching of abstracts D2 and D11, the objective technical problem was thus to provide a safe and effective dosage regimen of an oral direct factor Xa inhibitor for the prophylactic and therapeutic treatment of a thromboembolic disorder.

Even assuming that the chemical identity of the active agent had been known, the suitability of the dosage regimen involving once-daily administration of rapid-release tablets of rivaroxaban (as demonstrated by the phase II data included in the patent) was surprising and inventive.

Considering the short plasma concentration half-life of rivaroxaban known from D2/D11 or D3/D12 (namely three to six hours) and the further teaching of these abstracts, the person skilled in the art would have expected that twice-daily or thrice-daily dosing, or

else the use of a sustained-release formulation, would be required for maintained efficacy and safety.

The decision under appeal applied too low a standard for the skilled person's reasonable expectation of success, especially since human testing in a clinically unexplored field was involved. Due to ethical and safety concerns, the skilled person would have adopted a very cautious attitude regarding the set-up of first-time dose-ranging clinical studies of a novel anticoagulant in patients. A major concern would have been that fluctuations in drug concentration might result in either excessive bleeding (due to overdosing) or thromboembolism (due to underdosing).

A correct analysis of the data reported in abstracts D15/D17 did not teach towards a once-daily dosage regimen, either.

The parties' requests

I. The appellant requested

- that the decision under appeal be set aside and that the oppositions be rejected;
- in the alternative, that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of one of auxiliary requests 1 to 27, all filed with the appellant's response to the oppositions dated 16 November 2016;
- that all documents filed together with the statement setting out the grounds of appeal and documents D143 to D144, as well as the documents filed in response to the interventions, be admitted into the proceedings.

II. Respondents 2, 3 and 4 requested

- that the appeal be dismissed;
- that documents D143 and D144 be not admitted into the proceedings.

III. Respondents 5 and 6 both requested that the appeal be dismissed.

IV. Respondent 7 requested

- that the appeal be dismissed
- that none of the documents filed by the appellant be admitted into the proceedings.

V. Respondent 8 requested that the appeal be dismissed.

VI. Respondent 9 did not state any request in the course of the appeal proceedings.

VII. Respondent 10 requested

- that the appeal be dismissed;
- that documents D122, D122a-D122f, D123, D123a-D123f, D124, D124a, D124b, D126, D127, D128a-D128c and D129a-D129g be not admitted into the proceedings;
- that documents D137 and D138 (filed as D130 and D131 with the respondent's reply to the statement setting out the grounds of appeal) be admitted into the proceedings.

VIII. Respondent 11 requested

- that the appeal be dismissed;
- that documents D122-D129, D143, D143a and D144 and the appellant's submission dated 24 September 2021 be not admitted into the proceedings;

- that, if D143, D143a and D144 were admitted, document D145, filed by letter dated 28 September 2020, be admitted into the proceedings as well.

IX. Respondent 12 requested

- that the appeal be dismissed;
- that documents D122-D129g, D143 and D144 be not admitted into the proceedings;
- that documents D142 and D142a-D142g (filed as D130 and D130a-D130g with the respondent's reply to the statement setting out the grounds of appeal) be admitted into the proceedings if the appellant's expert opinions (D122-D124) were admitted.

X. Respondent 13 requested

- that the appeal be dismissed;
- that the documents submitted with the appellant's statement of grounds (with the exception of the enlarged copies of previously filed documents) be not admitted into the proceedings;
- that the documents filed with the appellant's letter dated 3 September 2021 (i.e. the reply to the intervention of respondent 15) be not admitted into the proceedings.

XI. Respondent 14 requested that the appeal be dismissed.

XII. Respondent 15 requested

- that the appeal be dismissed;
- that documents D159 and D160 and the appellant's submission dated 24 September 2021, including Annexes I and II, be not admitted into the proceedings.

Reasons for the Decision

1. Admissibility of the appeal and the interventions

1.1 The appeal complies with Articles 106 to 108 EPC and Rule 99 EPC; it is admissible.

1.2 The interventions meet the requirements of Article 105 EPC. Their admissibility was not disputed. Pursuant to Article 105(2) EPC, an admissible intervention shall be treated as an opposition.

2. Patent in suit

2.1 The patent in suit (see paragraph [0001]) relates to the field of blood coagulation, in particular to a medicament and dosage regimen for treating thromboembolic disorders by administering a direct factor Xa inhibitor.

2.2 Factor Xa plays an important part in blood coagulation. The activated serine protease Xa cleaves prothrombin to thrombin. The resulting thrombin cleaves fibrinogen to the coagulant fibrin. Thrombin is also a potent effector of platelet aggregation (see the patent in suit, paragraph [0002]).

2.3 According to claim 1 as granted, the envisaged treatment is once-daily administration (see point 3.1 below), for at least five consecutive days, of a rapid-release tablet of the direct factor Xa inhibitor rivaroxaban.

2.4 This dosage regimen is backed up by data from a clinical phase II dose guiding study with 642 patients undergoing elective primary total hip replacement (see the patent in suit, paragraphs [0035] to [0045]). The

objective of the study was the assessment of safety, tolerability and efficacy of rivaroxaban at different oral doses (od and bid) compared with subcutaneously administered enoxaparin in the prevention of venous thromboembolism (VTE).

3. Claim construction

3.1 Dosage regimen

3.1.1 According to claim 1 as granted, the medicament is to be administered for at least five consecutive days. This can only mean that the medicament is to be administered on consecutive days, and therefore at least once daily. Since the claim also requires that the medicament is to be administered no more than once daily, the dosage regimen defined in claim 1 is once-daily administration.

3.1.2 Once-daily administration as conventionally understood includes the administration, once a day, either of just one dosage form or of two or more dosage forms simultaneously or consecutively within a short time period. This is also how the term is understood in the application as filed (see page 10, lines 18 to 20) and the patent in suit (see paragraph [0033]).

3.2 Plasma concentration half-life

3.2.1 It was a subject of dispute whether the claim feature *"wherein said compound has a plasma concentration half life of 10 hours or less when orally administered to a human patient"* is redundant or has a delimiting effect.

3.2.2 In claim 1 of the application as filed, the definition of the drug compound had a broader scope ("a direct factor Xa inhibitor, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient").

The application states that rivaroxaban is a preferred embodiment of such compounds (see page 3, lines 19 to 30 and claim 6 as filed). While claim 1 as granted is restricted to the preferred embodiment rivaroxaban, it still recites the feature in question relating to plasma concentration half-life.

3.2.3 The respondents argued that this feature must be regarded as limiting since it was not inherent to the compound and the half-life requirement would not inevitably be met by all patients, in particular not by elderly patients (see D8, page 2: "After procedure"; D23: page 413, column 1, paragraph 2 and D108: page 413, column 2, lines 2-7; all reporting that the half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years and 11 to 13 hours in the elderly). This mattered all the more because the thromboembolic disorders to be treated were especially relevant in the elderly.

3.2.4 The appellant submitted that the half-life parameter merely served to characterise the class of drug compounds under consideration. Thus, it was redundant in granted claim 1, which had been restricted to one specific compound (rivaroxaban). The only half-lives known for rivaroxaban in humans at the effective date of the patent had been reported to be well below ten hours.

3.2.5 For a skilled person considering the wording of claim 1, the question of what would be required to comply with the claim feature defining a plasma concentration half-life of ten hours or less would indeed arise. In these circumstances, it would be logical to consult the description to establish the context in which this feature occurs.

3.2.6 According to paragraph [0001] of the patent in suit, the active compounds envisaged for treating thromboembolic disorders are direct factor Xa inhibitors which have "a plasma concentration half-life indicative of a bid or tid administration interval, e.g. of 10 hours or less", but, nevertheless, these compounds are to be administered once daily.

Thus, it is apparent to the reader that the patent uses the half-life parameter to describe a group of drug compounds envisaged for the invention.

It is also mentioned that the plasma concentration half-life of rivaroxaban was found to be four to six hours in the participants of a multiple-dose escalation study (see paragraphs [0014] and [0017] of the patent specification, referencing document D2). According to the context given in the patent, rivaroxaban therefore meets the half-life criterion.

Based on its presentation in the patent in suit, it cannot be inferred that the half-life parameter is supposed to be an absolute criterion (i.e. that the half-life is required to be ten hours or less in all humans or in all patients with thromboembolic disorder under any circumstance). Nor can it be inferred that the plasma concentration half-life has any relevance for the implementation of the treatment in individual patients.

3.2.7 Since claim 1 is restricted to rivaroxaban, characterised in the description as having a half-life of four to six hours, and no other intended meaning of the feature is apparent from the context given in the patent, the feature *"wherein said compound has a plasma concentration half life of 10 hours or less when orally administered to a human patient"* is redundant.

4. Added subject-matter (Articles 100(c) and 123(2) EPC)

4.1 Claim 1 as granted finds support within the meaning of Articles 100(c) and 123(2) EPC in claim 3 of the application as filed, combined with dependent claims 5 and 6 and/or the passage on page 10, lines 10 to 12, which states that rapid-release tablets containing rivaroxaban as the active ingredient are "very particularly preferred".

4.2 The disorders listed in dependent claim 2 as granted are identical to those in claim 4 of the application as filed.

4.3 As set out in point 3.1 above, the term "administered no more than once daily for at least five consecutive days" has the same meaning as "administered once daily for at least five consecutive days". Thus, the addition of the words "no more than" in granted claim 1 does not give rise to a difference in scope in comparison with claim 3 as originally filed.

4.4 As far as "once daily" administration includes the administration of two or more dosage forms simultaneously or consecutively within a short time period, the board fails to see why the wording "no more than once daily" would exclude such administration (as argued by respondent 13). The meaning of "once daily" has not changed.

4.5 In conclusion, the subject-matter of the claims as granted does not extend beyond the content of the application as filed.

5. Novelty (Article 100(a), 52(1) and 54 EPC)

Swiss-type claim format

5.1 Claim 1 as granted relates to a specific medical use and is drafted in the "Swiss-type" format, i.e. it is directed to the use of a composition (namely, a rapid-release tablet of rivaroxaban) for the manufacture of a medicament for a specified therapeutic application.

5.2 The novelty of the subject-matter of such a claim can be derived not only from the novelty of the composition or of the method of manufacture but also from the novelty of the therapeutic application, which is regarded as a functional technical feature, as instituted by decision G5/83 of the Enlarged Board of Appeal (OJ EPO 1985, 64, Order 2, Reasons 21 and 23; see also Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, I.C.7.2.1).

5.3 This "special approach to the derivation of novelty" (see G5/83, Reasons 21) applies in this case, since the application for the patent in suit was pending at the time of the publication of Enlarged Board of Appeal decision G2/08, which abolished the Swiss-type format but had no retroactive effect (OJ EPO 2010, 456, Order 3, Reasons 7.1.4).

Technical features of claim 1

5.4 Since claim 1 does not define any specific manufacturing step, novelty can only be derived from the technical features defining the composition and/or from those defining the therapeutic application.

5.5 The therapeutic application is defined in claim 1 as the "treatment of a thromboembolic disorder administered no more than once daily for at least five consecutive days". It was common ground that this

covers prophylactic and therapeutic treatment (see also the patent in suit: paragraph [0022]). It is implicit in this feature that the treatment has a clinical benefit, in particular that it is effective. Since a treatment without acceptable safety cannot realistically be considered as having a clinical benefit, the aspects of both efficacy and safety have to be taken into account to determine whether the treatment defined in claim 1 is disclosed in the prior-art citations relied on by the respondents (see also decision T 2506/12, Reasons: 2.8).

Novelty in relation to D1

5.6 Document D1 discloses compounds of a "general formula (I)" and envisages their use as anticoagulants, for the prophylaxis and/or therapy of thromboembolic disorders (D1: claims 1 and 10). Rivaroxaban is a preferred compound (D1: claim 7, paragraph [0145]). According to D1 (paragraph [0367]), all customary administration forms are suitable, including tablets.

5.7 While some of the relevant features are thus disclosed in different passages of the document, the respondents failed to identify direct and unambiguous specific disclosure in D1 of all the mandatory technical features of claim 1 of the patent in suit in combination (i.e. rapid-release tablets of rivaroxaban, administered no more than once daily for at least five consecutive days and showing a clinical benefit in a thromboembolic disorder).

5.8 The further passages of D1 relied on by the respondents either do not add any information (paragraph [0355] is about "compounds of the general formula (a)" *[sic]* and the treatment of "disorders" in general) or merely state that it may be advisable to divide large amounts

of the medicament into several administrations over the course of one day (paragraphs [0368] and [0372]). This does nothing to remedy the lack of specific disclosure of the required combination of features.

Novelty in relation to D2 and D11

5.9 The content of documents D2 and D11 is largely identical. Both relate to the same phase I clinical study of rivaroxaban carried out with healthy male volunteers.

Neither document discloses tablets (let alone rapid-release tablets) or a clinical benefit of a once-daily dosage regimen of rapid-release rivaroxaban in the therapy or prophylaxis of thromboembolic disorders.

Accordingly, the subject-matter of claim 1 differs from the disclosure of D2 and D11 in features defining the composition and in features defining the therapeutic application.

5.9.1 The mere assumption that tablets may well have been used in the study of D2/D11 does not meet the standard of direct and unambiguous disclosure in the prior art.

5.9.2 The clinical study described in D2/D11 was a preliminary phase I study carried out with healthy subjects. It was not designed to test the efficacy and safety of a specific dosage regimen in subjects requiring prophylactic or therapeutic anticoagulant treatment.

The board concurs with the appellant that the group of candidates eligible for prophylactic treatment with anticoagulants does not include healthy subjects. There has to be a reason, i.e. some risk factor for thromboembolism, to justify prophylactic treatment with a medicament which may potentially cause major bleeding as a severe adverse effect. Hence, claim 1 of the

patent in suit, even where it relates to prophylactic treatment, does not encompass the treatment of healthy subjects.

Clinical efficacy is only determined in phase II and phase III studies. A phase I study limited to the initial testing of a range of doses on healthy subjects to obtain certain base parameters cannot establish the clinical efficacy of a dosage regimen for treating patients with pathology.

Also, the established absence of bleeding complications in healthy subjects treated with the drug (as reported in D2/D11) is not sufficient by itself to justify the conclusion that the same treatment is safe for patients with pathology. As credibly set out by the appellant, susceptibility to bleeding or potential causes of bleeding are exclusion criteria for a phase I anticoagulant trial (see the statement setting out the grounds of appeal, page 41, point (119); D110: page 14, second paragraph and D122: point 55). As a consequence, the absence of bleeding in the subjects of a phase I trial would be expected but would not necessarily be indicative of clinical safety in patients. On the other hand, if bleeding nevertheless occurred, this would indicate a serious safety problem.

Conclusion on novelty

5.10 For these reasons, the subject-matter of claim 1 as granted is novel relative to the disclosure of documents D1, D2 and D11. The same conclusion applies to dependent claim 2.

6. Admittance of the appellant's documents

6.1 The documents submitted with the appellant's timely replies to the interventions form part of the proceedings and do not require separate admission

(see T 2034/19, Reasons 2.1; Article 105(2) and Rule 79(1)EPC).

6.2 This includes the documents that were re-filed (see point XV.(a) above) as there is no legal basis for not admitting them under the procedural circumstances in which they were re-filed.

6.3 Article 13 RPBA is not applicable since a first reply to the grounds for opposition of an intervener cannot be considered an amendment to the appellant's case at a late stage of the proceedings.

6.4 As the board has no discretion in this matter, the respondents' request for non-admittance must be refused.

7. Admittance of the appellant's submission of 24 September 2021 (Article 13(2) RPBA)

7.1 As is made clear in the document's title and first paragraph, the appellant's letter of 24 September 2021 was filed in reply to the board's preliminary opinion under Article 15(1) RPBA (see points XI. and XIV. above). The board had not set a time limit for replying to the preliminary opinion. The time limits set for replying to the interventions are not relevant in this context. The criteria under Article 13(2) RPBA apply.

7.1.1 In the first part of the letter, the appellant observed that the procedural situation with regard to the admittance of evidence had changed due to the interventions filed by respondent 14 and respondent 15, so that no separate decision on admittance of the appellant's documents would be required. This is an explanatory remark relating to already completed procedural acts of the appellant, which had re-filed all its previous appeal submissions in reply to the

interventions (see point XV.(a) and section 6. above). As the appellant's reply to the interventions and the re-filing occurred after the summons to oral proceedings, the observation could not have been part of the appellant's case as presented before the summons.

7.1.2 In the main part of the text, the appellant summarised and supplemented some of its known arguments regarding inventive step (without introducing new arguments). This includes an analysis of recent case law. Citing case law in support of an argument is not, as a rule, considered an amendment to a party's case. Annexes I and II of the submission provide overview tables relating to the issues discussed in the main letter.

7.1.3 In its comments on inventive step, the appellant also explained why it disagreed with certain points made in the board's preliminary opinion. This included the board's formulation of the objective technical problem with a requirement that the desired oral dosage regimen be, *inter alia*, convenient (see point 6.6 of the board's communication of 17 March 2021 and section II of the appellant's submission).

While it is correct that respondents 2, 3 and 4 had mentioned patient convenience as a general desirable goal in their written submissions, they had not included it in their formulation of the objective technical problem (see these respondents' identical replies to the grounds of appeal, points (74), (111) and (23)). The appellant had addressed the respondents' point in point (29) of its submission of 26 February 2020. Its comments in response to the board's preliminary opinion concerned the different question of whether it was appropriate to include

"convenient" in the formulation of the objective technical problem.

7.2 The board considered that the appellant's observations in the submission of 24 September 2021 were justified in the particular circumstances, did not amount to a change of case and/or responded to points raised by the board in its preliminary opinion.

7.3 The board therefore concluded that it had no reason for not taking the submission of 24 September 2021 (including Annexes I and II) into account under Article 13(2) RPBA.

8. Sufficiency of disclosure (Article 100(b) EPC)

8.1 The respondents' objections regarding insufficiency of disclosure cannot succeed for the following reasons.

8.2 Objections regarding the scope of the terms used in claim 1

8.2.1 The respondents' objections concerning the skilled person's (lack of) understanding of the terms "rapid-release tablet" and "thromboembolic disorder" come down to an alleged lack of clarity (Article 84 EPC) rather than insufficiency of disclosure since, at most, the boundaries of these terms might be in doubt.
As both terms appear in claim 1 as granted, this ground for objection cannot be dealt with in opposition appeal proceedings (see Enlarged Board of Appeal decision G3/14, OJ EPO 2015, A102).

8.2.2 Both terms are, in any case, readily understood.
The widely used and accepted term "thromboembolic disorder" in claim 1 is understood, without any need for consulting the description, as any condition that promotes or increases the risk of intravascular thrombus formation, which may lead to thromboembolic

events (as a piece of a thrombus can detach as an embolus, which can travel through the circulation and lodge somewhere else as an embolism). "Rapid-release tablet" (also referred to as "immediate-release tablet") is a well-known term of art.

8.3 Objections regarding lack of guidance

8.3.1 Preparation of rapid-release tablets

Indeed, rapid-release (or immediate-release) tablets are one of the most common dosage forms in the field of pharmacy (see also D4: page 410, right column). There is no reason to doubt that a person of ordinary skill in the art would be able to prepare rapid-release tablets on the basis of common general knowledge and routine measures. Specific instructions in the application/patent are not required.

8.3.2 Dosage frequency

As set out above (see point 3.1), claim 1 requires that the tablets be administered once daily. Hence, it is not necessary that the patent and the underlying application provide data in support of dosage regimens that involve less frequent dosing.

8.3.3 Dosage range

The respondents' arguments that claim 1 ought to indicate a dosage range and that efficacy may be lacking at low doses cannot succeed either.

The dosage regimen in claim 1 is characterised by once-daily administration (implicitly of an adequate dose, see also point 8.4.1 below) of rivaroxaban in rapid-release form. While claim 1 does not specify a dosage range, the person skilled in the art would be well aware that there must be, in practice, a lower dosage limit to ensure efficacy and an upper limit to ensure safety, and that these can be determined by

appropriate clinical studies within the ordinary scope of ability of a skilled person. Hypothetical "literal" embodiments involving doses clearly outside the scope of practical application would not be regarded as being covered by the claims. The description of the patent in suit also provides some reference points with regard to dosing (see paragraph [0032] and example 1).

This situation is different from the situation examined in decision T 1038/14 (cited by respondent 14).

The medical use concerned involved twice-weekly dosing of the drug in question. It had not been rendered credible that the treatment could be effective without an induction period involving more frequent (daily) applications. However, this induction period was not mentioned as a mandatory technical feature in the claim under consideration. As set out in the board's reasoning in T 1038/14, the person skilled in the art reading this claim would not simply assume that the claim was implicitly restricted to embodiments involving an induction period. Since a patent was presumed to describe and claim a new invention, the reader would not be in a position to infer that features or steps known from the prior art or common general knowledge were supposed to be mandatory in spite of their not being mentioned in the claim. The invention might simply not require these steps or features to be put into practice.

The conclusions drawn in case T 1038/14 on the basis of a different situation are not pertinent to the current case. Firstly, it is implicit that only safe and effective doses can provide clinical treatment. Secondly, the respondents did not provide evidence to doubt that the favourable dose range can be determined by usual means without undue burden.

8.3.4 Plasma concentration half-life

As established in section 3.2 above, the treatment defined in claim 1 does not include any mandatory step of verifying the plasma concentration half-life of rivaroxaban in the individual patient being treated and/or adjusting this parameter to keep within certain limits. Hence, there is no basis for an objection of insufficient disclosure in this regard.

8.4 Objections regarding lack of support for the therapeutic indication

8.4.1 Since claim 1 concerns a further medical use, attaining the claimed treatment benefit is a functional technical feature of the claim. To meet the requirement of sufficiency of disclosure, the suitability of the treatment for the claimed therapeutic indication must therefore be disclosed unless this was already known to the person skilled in the art.

8.4.2 The application as filed contains experimental evidence on this account in example 1 (see pages 11 to 14). Example 1 reports on a phase II study carried out to test the safety and efficacy of different dosage regimens of rivaroxaban, including the once-daily oral administration of 30 mg in the form of rapid-release tablets, in the prevention of venous thromboembolism in patients undergoing total hip replacement. The application reports that the efficacy and safety of this treatment were found to be in (approximately) the same range as standard anticoagulant therapy with enoxaparin (low-molecular-weight heparin) (see page 13, Table 1-1 and lines 1 to 11, and page 14, Table 1-2 and lines 1 to 5). This evidence and the conclusions expressed in the application are presumed credible in the absence of evidence to the contrary.

8.4.3 The respondents did not provide any experimental counter-evidence obtained with rivaroxaban that might have called the results of example 1 into question or might have shown that the treatment according to claim 1 could not be carried out in any particular embodiment.

8.4.4 They argued, however, that the safety results (in terms of post-operative major bleeding events) as shown in Table 1-2 of the patent in suit for 30 mg od rivaroxaban were inferior to those reported for enoxaparin and not better than the results known for razaxaban, the only other direct factor Xa inhibitor which had entered a phase II trial and been tested in patients (D110d: for prevention of deep vein thrombosis in knee replacement surgery). In the case of razaxaban, the three highest dose arms had had to be discontinued due to major bleeding. This called into question the alleged safety of the od dosage regimen of rivaroxaban.

- In particular, example 1 in the application as filed reported an incidence rate of 4.5% of "any major bleeding event" for 30 mg od rivaroxaban, as opposed to 0.0% for 40 mg od enoxaparin.
- D110d is a scientific abstract summarising a dose-response study of razaxaban. According to D110d, the three highest doses of razaxaban (50 mg bid, 75 mg bid and 100 mg bid) had been stopped before the intended per-group sample size of 150 patients was reached due to increased reports of bleeding, mainly at the surgical site. The incidence rate of "major bleeding" in the case of razaxaban 50 mg bid had been 4.1%.

8.4.5 The respondents' objection regarding insufficient evidence of safety in the application as filed does not succeed for the following reasons.

The application as filed also mentions that for low-molecular-weight heparin in similar studies, major bleeding rates of 1.5% to 5.3% had been observed (see page 14, lines 1 to 2 under Table 1-2). The statement on page 14 that the occurrence of major bleeding was low (4 patients in 88, see Table 1-2) and approximately in the range of standard therapy therefore appears justified.

As further explained in the application as filed (page 13, lines 8 to 11), there were neither fatal bleeds or bleeds in critical organs, nor clinically significant bleeds that could not be treated. In contrast to the case of razaxaban reported in D110d, there is no suggestion in the application as filed that any of the rivaroxaban study arms had to be discontinued because of safety concerns. There is thus no basis for the respondents' assumption that major bleeding observed in the rivaroxaban study must have had the same severity as major bleeding observed in the (unrelated) study on razaxaban. A mere comparison of incidence rates (4.5% vs 4.1%) is not conclusive if the severity of the effects observed and categorised as major bleeding was different.

8.4.6 The board is also satisfied that the prevention of post-operative VTE addressed in example 1 may be regarded as representative for the prophylactic and therapeutic treatment of thromboembolic disorders in general. The term "thromboembolic disorders" (see point 8.2.2 above) does not encompass inflammatory diseases, rheumatic diseases of the musculoskeletal system or Alzheimer's disease (mentioned in paragraph [0024] of the patent). The description cannot

be used to extend the clear scope of the claim. While thromboembolic disorders may occur in the context of these diseases, the treatment of these diseases as such, including coagulation-independent manifestations, is not claimed.

As outlined in the application as filed:

- the activated serine protease factor Xa cleaves prothrombin to thrombin and plays a central role in blood coagulation (see page 1, second paragraph);
- factor Xa inhibitors were known to be under consideration as anticoagulants for the treatment and prophylaxis of thromboembolic disorders (page 2, lines 20 to 29; see also the review article D6);
- rivaroxaban was known as an orally active direct inhibitor of factor Xa (page 3, line 27 to page 4, line 9 citing document D16).

The formation of a thrombus involves factor Xa. The basis for prophylaxis and therapy is the same, namely the anticoagulant effect of the drug. Based on its activity as a factor Xa inhibitor, i.e. its anticoagulant action, and the favourable study results reported for the prevention of VTE, rivaroxaban would thus be expected to have efficacy in the treatment or prevention also of other thromboembolic disorders.

Document D23 (page 413, left column, paragraph on clinical studies) confirms that the prevention of post-operative VTE is an essential indication for anticoagulants. For this reason, and in analogy to other anticoagulants (e.g. *inter alia*, low-molecular-weight heparins), rivaroxaban was first tested for this indication.

8.4.7 In conclusion, the board considers that the information provided in the application as filed renders the medical indication of claim 1 of the main request credible.

8.4.8 As a consequence, post-published evidence is not required but may also be considered. According to this evidence, as summarised in the appellant's document D121, subsequent phase II and phase III studies demonstrated the clinical efficacy and safety of the claimed dosage regimen at various od doses in both the prophylactic and therapeutic treatment of thromboembolic disorders, and several of these applications, falling within the ambit of claim 1, subsequently received regulatory approval.

8.5 For these reasons, the ground for opposition under Article 100(b) EPC does not prejudice maintenance of the patent as granted.

9. Inventive step (Articles 100(a), 52(1) and 56 EPC)

9.1 The technical background and content of the patent in suit are summarised in section 2. above.

Starting point in the prior art

9.2 At the priority date, the entirety of published clinical data on rivaroxaban was phase I data. It was common ground that the conference abstracts D2 and D11 represented the closest prior art.

9.3 The content of D2 and D11 is largely identical. Both relate to the same clinical study, namely the appellant's own placebo-controlled phase I clinical trial of rivaroxaban (BAY 59-7939) in healthy male subjects. This was a multiple-dose escalation study investigating the pharmacodynamics, safety and pharmacokinetics of rivaroxaban, in development for the

prevention and treatment of thromboembolic diseases. The oral doses given were 5 mg once daily, twice daily or three times daily; or 10 mg, 20 mg or 30 mg twice daily for five days.

Distinguishing technical features and alleged technical effects

9.4 Both D2 and D11 mention the investigated drug compound only by its internal project code name "BAY 59-7939". The appellant's argument that D2/D11 do not provide enabling disclosure of the active compound does not succeed since the person skilled in the art would have found no difficulty in looking up the chemical identity and preparation of "BAY 59-7939" in the appellant's further publications on this compound. As this was a recent development, only a limited number of publications would have had to be viewed. D16 (entitled: *"In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939 - an oral direct factor Xa inhibitor"*) indicates the chemical name and structure of "BAY 59-7939" (see D16: page 515, left column, first paragraph and Figure 1). D1 is the basic patent application disclosing its synthesis (see D1: claim 7 and example 44). Thus, the specific choice of the factor Xa inhibitor is not a technical feature distinguishing the claimed subject-matter from the disclosure of D2/D11.

9.5 As already determined in the context of novelty assessment (see point 5.9 above), D2/D11 neither disclose the use of tablets nor do they establish the clinical benefit of any specific dosage regimen of rivaroxaban in the therapy or prophylaxis of thromboembolic disorders. The release properties of the dosage form and the dosing frequency are functionally linked and together constitute the dosage regimen.

9.6 Thus, the features distinguishing the subject-matter of claim 1 from the disclosure of D2/D11 are the use of tablets and the medical use achieved with a specified dosage regimen (namely, once-daily dosing of rapid-release rivaroxaban for at least five consecutive days).

9.7 Tablets are a conventional dosage form. The appellant did not base its reasoning in favour of inventive step on the choice of tablets over other dosage forms (e.g. capsules).

9.8 The proposed dosage regimen involving once-daily administration of rapid-release rivaroxaban has the alleged benefits of providing safe and effective treatment as well as patient convenience (patent in suit: paragraphs [0009] and [0012] and example 1).

Objective technical problem and solution

9.9 The objective technical problem may thus be defined as providing a safe, effective and convenient oral dosage regimen of "BAY 59-7939" (i.e. rivaroxaban) for the prophylactic and therapeutic treatment of thromboembolic disorders.

9.10 The views of the parties diverged on the question of which of the above-named technical effects should be included in the formulation of the objective technical problem.

9.11 Some respondents contested that efficacy and safety should form part of the technical problem:

- According to respondents 7 and 10, claim 1 did not indicate a limiting dosage range that ensured the safety and efficacy of the treatment across the scope claimed.

- According to respondent 6, example 1 of the patent in suit did not credibly demonstrate the safety of the treatment in light of the disclosure of D110d (relating to a phase II study of razaxaban).

9.12 As mentioned above, the medical indication "for the treatment of a thromboembolic disorder" in claim 1 implies that the treatment provided by the medicament and dosage regimen fulfils its purpose, i.e. that it is safe and effective. Embodiments that do not achieve this are not encompassed by the claim. The respondents' concerns under point 9.11 are thus an issue under sufficiency of disclosure rather than inventive step, and are dealt with in points 8.3.3 and 8.4 above.

9.13 According to the appellant, it was not justified to include patient convenience in the formulation of the objective technical problem. Since no patient had been known to have taken rivaroxaban in any dosage regimen, there was no baseline patient convenience measure at the priority date, and it would have been too early to have patient convenience as a goal at the priority date of the patent.

9.14 The board takes the view that it is appropriate to include patient convenience in the formulation of the objective technical problem since this is an evident benefit obtained by the claimed subject-matter. As acknowledged in the patent in suit (see paragraph [0009]), a once-daily dosage regimen is favourable in terms of the generally desirable goal of patient convenience and the resulting improved compliance. The technical problem as defined in point 9.9 above does not translate into a requirement that patient convenience be improved over an implied existing dosage regimen or that the aspect of convenience be prioritised over efficacy and safety. Mentioning

convenience in the objective technical problem is not a pointer to the solution, either, since different measures contributing to convenience might have been considered.

9.15 According to respondent 13, the objective technical problem should in addition to convenience include the requirement that a sustained-release form be avoided, as this was a further advantage mentioned by the appellant in its statement setting out the grounds of appeal.

9.16 This suggestion would, however, introduce a pointer to the solution (the subject-matter of claim 1) by implying that an immediate-release form should be used.

9.17 For these reasons, the board considers the objective technical problem defined in point 9.9 above to be correct.

9.18 In view of the known clinical data, the board also considers that the objective technical problem is credibly solved by the subject-matter as defined in claim 1 (see the comments made in section 8 above in the context of sufficiency of disclosure).

Obviousness of the solution

9.19 Based on D2/D11 stating that rivaroxaban was a direct factor Xa inhibitor and in development for the prevention and treatment of thromboembolic diseases, the person skilled in the art would have had a general expectation that this drug could provide clinical efficacy for this indication. D2/D11 also reports preliminary favourable results regarding safety in healthy subjects. Thus, there was agreement among the parties that the skilled person would have made the transition from phase I to phase II clinical testing.

9.20 The issue to be decided under obviousness is whether the skilled person would have had an incentive and reasonable expectation of clinical success regarding the specific regimen defined in claim 1, i.e. once-daily dosing of rapid-release rivaroxaban for at least five consecutive days, in patients, i.e. subjects at heightened risk for thromboembolism.

No pointer in D2/D11

9.21 The respondents argued that the disclosure of D2/D11 was consistent with rapid-release dosing. Abstracts D2/D11 also taught that pharmacodynamic effects were still present after 12 hours.

While half-life was usually a guiding factor for determining dosing frequency, the importance of using pharmacodynamic data obtained in phase I trials was also generally recognised. After the phase I study described in D2/D11, the skilled person would not have ruled out once-daily dosing (in any case a desirable goal in terms of patient convenience and compliance) as a viable regimen since no discouraging results had been observed.

In addition, it was known from the pre-published review article D6 that short-term direct inhibition of factor Xa could lead to a sustained downstream biological action and that the therapeutic window of direct factor Xa inhibitors was expected to be relatively large in comparison to other anticoagulants (see D6: page 153, left column, last paragraph and page 154, left column, second paragraph).

9.22 The board considers that the disclosure of D2/D11 by itself, or in light of common general knowledge, would not have provided motivation to the person skilled in the art to pursue clinical testing of a once-daily

regimen of rapid-release rivaroxaban in patients, for the following reasons.

9.22.1 The abstracts D2/D11 relate to a phase I study in healthy volunteers. This was a multiple dose escalation study following up on a phase I single dose escalation study with healthy volunteers (in turn described in abstracts D3 and D12, both relating to the same single dose study).

At the effective date of the patent in suit, it had not been shown that rivaroxaban was safe and effective in patients, i.e. subjects requiring therapeutic or prophylactic anticoagulant treatment (see also point 5.9.2 above). Neither had this been shown for the class of direct-acting oral factor Xa inhibitors in general.

Solving the objective technical problem thus involved providing a dosage regimen for rivaroxaban's first medical use in patients. The current case differs in this aspect from the typical situation in other "dosage regimen cases", where development is based on established therapeutic uses of the drugs concerned.

9.22.2 Due to ethical and safety concerns, the person skilled in the art would have adopted a cautious attitude regarding the set-up of first-time dose-ranging clinical studies of a novel anticoagulant in patients since the risk of both bleeding and thrombosis was expected to be high.

Participants in phase I anticoagulant studies are selected to exclude susceptibilities to and potential causes of bleeding. The fact that no bleeding complications had been observed with rivaroxaban in healthy volunteers did not permit drawing the conclusion that the drug would be safe in patients with pathology.

It was known, for instance, that the phase II trial for the direct factor Xa inhibitor razaxaban had revealed serious safety concerns despite positive phase I results (see D110d and D77: page 69, first paragraph).

Before the publication of phase II data, nothing was known about the therapeutic window of rivaroxaban. The therapeutic window of anticoagulants can be narrow, since the same mechanism is responsible for the therapeutic effect (anticoagulation) and the potentially lethal side effect of bleeding. There would have been legitimate concerns that fluctuations in drug concentration might result in either excessive bleeding (due to overdosing) or thromboembolism (due to underdosing).

9.22.3 The skilled person would, therefore, have pursued an approach that minimises such fluctuations. To avoid over- or underdosing, they would have considered the half-life of the drug, as this was, in common general knowledge, the fundamental factor in determining dosing frequency (see also paragraph [0010] of the patent in suit citing D14; D14: page 89, final paragraph; and D9, page 26, paragraph bridging left and right columns).

On this basis, the skilled person would have wanted to select a dosage form and frequency that compensated for rivaroxaban's short half-life (four to six hours according to D2/D11 or three to four hours according to D3/D12).

Considering the short plasma concentration half-life of rivaroxaban known from D2/D11 and D3/D12, the person skilled in the art would have expected that twice- or thrice-daily dosing, or else the use of a sustained-release formulation (with the added advantage

of less frequent dosing, i.e. better convenience), would be required for maintained efficacy and safety.

9.22.4 In summary, the serious concerns about safety in the case of a new anticoagulant did not warrant a "try-and-see" attitude for the dosage regimen, and the known, relatively short, half-life of rivaroxaban would not have supported an expectation of success with regard to once-daily dosing of rapid-release rivaroxaban.

9.22.5 The study design (see point 9.3 above) also suggests that the phase I dose escalation study described in D2/D11 was performed in anticipation of a bid dosage regimen in subsequent phase II studies, as the vast majority of doses tested were bid and the only od dose included was the initially tested lowest starting dose (5 mg). In dose escalation studies, the doses are tested in order of increasing strength. The skilled person would have been aware that the study design followed the usual practice of starting with a very low dose as a safety precaution or subtherapeutic control regimen and would not have regarded the inclusion of a low od dose as an indication that this regimen was expected by the authors of the phase I study to have clinical relevance as a therapeutic dose.

9.22.6 As far as the relevance of pharmacodynamic data is concerned, it was not known at the priority date which level of a pharmacodynamic effect in which assay would be required to achieve both clinical efficacy (in preventing thrombosis) and safety (in avoiding bleeding) as these clinical correlations can only be established in trials on patients. At most, the pharmacodynamic effect of factor Xa inhibition, being the direct and selective action of rivaroxaban, might have been taken into consideration.

9.22.7 The statements in D2 and D11 that relevant changes in the pharmacodynamic parameters were still present after 12 hours or (in D11: sentences 12 and 13) that factor Xa inhibition effects were maintained for 8 to 12 hours at the 5 mg od dose, and "-12 hours" at the 10 mg bid, 20 mg bid and 30 mg bid doses cannot change the conclusions based on general safety considerations and half-life.

This is because it is not possible to infer from these statements that the effects observed would be maintained for longer than 8 to 12 hours and would also suffice to maintain the required level of anticoagulation in a patient at risk of thromboembolism over 24 hours.

9.22.8 Document D6 is a review article (published four years before the priority date of the patent) based on preclinical data of early drug candidates in the class of direct factor Xa inhibitors, not including rivaroxaban. The remarks in document D6 cited by the respondents relate to direct factor Xa inhibitors in general and do not include any specific quantitative data for rivaroxaban. On this general and rather speculative basis, the person skilled in the art could not have formed a reasonable expectation that rivaroxaban would show long-sustained efficacy and have a therapeutic window sufficiently broad to enable once-daily administration of a rapid-release form.

No pointer in D15/D17

9.23 The respondents also argued that the disclosure of the complementary documents D15/D17 (especially the statement that a sustained effect of BAY 59-7939 on thrombin generation for up to 24 hours had been observed) would have provided the skilled person seeking to solve the objective technical problem with

an expectation of success regarding once-daily dosing of rapid-release rivaroxaban.

9.24 The board arrives at a different conclusion for the following reasons:

9.24.1 Like D2 and D11, documents D15 and D17 are conference abstracts. Both relate to a further phase I study, in this case a single-dose study of rivaroxaban (BAY 59-7939) that examined thrombin generation in healthy subjects. This effect was investigated in a placebo-controlled, randomised crossover study in which twelve healthy volunteers received a single 5 mg or 30 mg dose of rivaroxaban. Several assays relating to thrombin generation were carried out, including endogenous thrombin potential (ETP), platelet-induced thrombin generation time (PITT) and platelet-induced clotting time (PICT). Both D15 and D17 state that a single 30 mg dose exerted a sustained effect "on thrombin generation" (D15: sentence 10) or "in some assays of thrombin generation" (D17: sentence 9) for up to 24 hours. The results observed in the individual assays are shown in D17 (for 2 and 12 hours post dose).

9.24.2 According to the study design of D15 and D17, these parameter values were determined in healthy subjects. No information is provided on their potential correlation with clinical efficacy and safety in patients requiring anticoagulant treatment (whose system may be in a hypercoagulable state different from that of healthy subjects) or on relevant threshold values or ranges of these parameters.

9.24.3 The respondents did not provide any evidence of known correlations or threshold values which would have permitted the person skilled in the art to conclude from the study results reported in D15/D17 on the clinical efficacy and safety of rivaroxaban doses in

patients, let alone decide on a dosage regimen including frequency of administration. The skilled person had no reason to assume that the data and statements in D15/D17 were incorrect. However, owing to a lack of an established correlation of the assay parameters with clinically relevant effects (thrombosis and bleeding), it would not have been possible to make any predictions regarding dosing frequency on this basis.

9.24.4 The respondents also relied in their reasoning on several post-published documents (D91, D103, D106 and D108) for interpretation of D15/D17. D106 is the full paper relating to the study of D15/D17 (published four years after the abstracts).

All of these post-published documents contain statements made by their authors with hindsight, after the clinical success of rivaroxaban had been proven. In this context, it appeared plausible that the thrombin generation data from the study of D15/D17 was consistent with the general concept of once-daily administration.

As these documents (and the larger context they were based on) were not available to the person skilled in the art before the priority date, it is not permissible to use them to interpret the statements and data provided in the abstracts D15/D17.

9.24.5 For these reasons, the skilled person could not have derived a teaching or expectation of success from the data reported in D15/D17 that would have provided them with the specific motivation to explore once-daily dosing of a rapid-release form of rivaroxaban in subsequent phase II studies in patients.

Phase II testing would not necessarily have led to the invention

9.25 The respondents argued, in one approach, that in the course of phase II testing, routine assessment for determining the therapeutic window would have revealed that once-daily dosing was feasible.

9.26 This approach does not succeed because:

- The relevant state of the art for the assessment of inventive step is the state of the art publicly available at the effective date of the patent rather than the inventors' own subsequent research results.
- Once the decision to continue with phase II studies had been taken, there was no pre-determined path which would inevitably have led the skilled person to the dosage regimen defined in claim 1.

9.26.1 As set out above (see points 9.22, 9.24), it would not have been obvious, based on the publicly available phase I data, to include an od regimen of rapid-release rivaroxaban.

9.26.2 Also, the skilled person setting up a phase II clinical trial of a new anticoagulant was not in a routine "try-and-see" situation. Without a reasonable expectation of success with regard to clinical efficacy and safety, the mere wish for patient convenience would not have been sufficient as an incentive for testing an od regimen of a rapid-release form of the drug.

9.26.3 The information leading to the claimed subject-matter would thus have had to be acquired by the skilled person's own subsequent research.

9.26.4 Even after finding an unexpectedly wide therapeutic window in a study exclusively testing bid or tid regimens, or sustained-release regimens included for patient convenience, the skilled person would not inevitably have taken the decision to switch the dosing frequency. They might just as well have continued clinical development with one of the tested bid, tid or sustained-release regimens that looked most promising in terms of safety and efficacy.

9.27 For these reasons, the subject-matter of claim 1 of the main request involves an inventive step within the meaning of Article 56 EPC. The same conclusion applies to the dependent claim.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The oppositions are rejected.

3. The patent is maintained as granted.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated