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November 16, 2016		160529EP-EING	0211 90490-0	Dr. Arwed Burrichter Dr. Ralph Minderop Dr. Natalie Kirchhofer

Opposition proceedings concerning European Patent 1 845 961 (06 706 291.9)

Title of the Patent:	**Treatment of thromboembolic disorders with rivaroxaban**
Patent Proprietor:	**Bayer Intellectual Property GmbH / DE**

For and on behalf of the Patentee, Bayer Intellectual Property GmbH, we herewith submit

PATENTEE'S RESPONSE TO THE NOTICES OF OPPOSITIONS

filed by:

Opponent O1:	**Breuer, Markus**
Opponent O2:	**Actavis Group PTC ehf**
Opponent O3:	**Zaklady Farmaceutyczne Polpharma S.A.**
Opponent O4:	**Teva Pharmaceutical Industries Ltd.**
Opponent O5:	**STADA Arzneimittel AG**
Opponent O6:	**Generics [UK] Limited**
Opponent O7:	**Abdi Ibrahim Ilac Sanayi ve Ticaret A.S.**
Opponent O8:	**Wittkopp, Alexander**
Opponent O9:	**Galenicum Health S.L.**
Opponent O10:	**ABG Patentes, S.L.**
Opponent O11:	**Stolmár, Matthias**
Opponent O12:	**Hexal AG**
Opponent O13:	**Kraus & Weisert Patentanwälte PartGmbB.**

This submission is structured as follows:

TABLE OF CONTENTS

A REQUESTS

(1) It is requested as **Main Request** to **reject the oppositions** and maintain the patent as granted.

(2) As an auxiliary measure, it is requested to maintain the patent in amended form on the basis of one of **Auxiliary Requests 1 to 27** enclosed herein (see section H below).

(3) Should the Opposition Division not be minded to grant the Main Request, **Oral Proceedings** are requested.

B DOCUMENTS

(4) A consolidated list of documents submitted by the opponents with a **cross-reference table** to opponents' numbering is attached as **Annex A**.

(5) Patentee submits documents **D1a, D9a-D9e, D25a,** and **D46** to **D87.**

A **complete list** of the **documents D1 to D87** on file is attached as **Annex B** and given in the following:

#	Reference
D1	US 2003/153610 A1
D1a	WO 2001/47919 A1
D2	Kubitza, D et al., "Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct factor Xa inhibitor in healthy male subjects." *Blood*, vol. 102, no. 11, 2003, Part 1, Abstract no. 3004.
D3	Kubitza, D et al., "Single dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct factor Xa inhibitor in healthy male subjects." *Blood*, vol. 102, no. 11, 2003, Part 1, Abstract no. 3010.
D4	Aulton, ME. *Pharmaceutics: The science of dosage form design.* 2nd ed., Churchill Livingstone, 2002.
D5	Lieberman, HA, Lachman, L, and Schwartz, JB. *PHARMACEUTICAL DOSAGE FORMS Tablets Volumes.* 2nd ed., Marcel Dekker, Inc., 1989.
D6	Leadley Jr, RJ. "Coagulation factor Xa inhibition: biological background and rationale." *Current Topics in Medicinal Chemistry*, vol. 1, no. 2, 2001, pp. 151-159.
D7	Foster, RW. *Basic Pharmacology.* 2nd ed., Butterworths, University of Manchester, 1986, p. 255.
D8	"Xarelto® Dosing and transition management." Janssen Pharmaceuticals, Inc., April 2015.
D9	*Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS.* 10th ed., The McGraw-Hill Companies, Inc., 2001, Chapter 1, pp. 1-29.

#	Reference
D9a	*Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS*. 7th ed., Macmillan Publishing Company, 1985, Chapter 1, pp. 3-34.
D9b	*Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS*. 10th ed., The McGraw-Hill Companies, Inc., 2001, Appendix II, pp. 1917-1924.
D9c	*Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS*. 10th ed., The McGraw-Hill Companies, Inc., 2001, 10th ed. 2001, Chapter 55, pp. 1519-1531.
D9d	*Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS*. 10th ed., The McGraw-Hill Companies, Inc., 2001, Chapter 3, pp. 48-56.
D9e	*Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS*. 7th ed., Macmillan Publishing Company, 1985, Chapter 58, pp. 1338-1352
D10	"Rote Liste® 2004", Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Aufendorf, 2004, entries #20 001 and #20 002.
D11	Kubitza, D et al. "Multiple dose escalation study investigating BAY 59-7939 - an oral, direct factor Xa inhibitor - in healthy male subjects." *Pathophysiol Haemost Thromb*, vol. 33 (Suppl. 2), 2003, p. 98, Abstract no. PO080
D12	Kubitza, D et al., "Single dose escalation study of BAY 59-7939 - an oral, direct factor Xa inhibitor - in healthy male subjects." *Pathophysiol Haemost Thromb*, vol. 33 (suppl. 2), 2003, p. 98, Abstract no. PO081
D13	Fareed, J et al. "Pharmacodynamic and pharmacokinetic properties of enoxaparin." *Clin Pharmacokinet*, vol. 42, no.12, 2003, pp. 1043-1057.
D14	Rowland, M and Tozer, TN. *Clinical Pharmacokinetics: concepts and applications*. Williams and Wilkins, 2005, pp. 83-105.
D15	Harder, S et al. "Effects of BAY 59-7939, an innovative, oral, direct actor Xa inhibitor, on thrombin generation in healthy volunteers." *Pathophysiol Haemost Thromb*, vol. 33 (suppl. 2), 2003, p. 97, Abstract PO078
D16	Perzborn, E et al. "In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939—an oral, direct Factor Xa inhibitor." *Journal of Thrombosis and Haemostasis*, vol. 3, 2005, pp. 514-521.
D16a	Confirmation of online publication date of D16
D17	Harder, S et al. "Effects of BAY 59-7939, an oral, direct factor Xa inhibitor, on thrombin generation in healthy volunteers." *Blood*, vol. 102, no. 11, 2003, Abstract no. 3003.
D18	Ritschel, WA and Bauer-Brandl, A. *Die Tablette: Handbuch der Entwicklung, Herstellung und Qualitätssicherung* 2nd ed., Editio Canto Verlag Aulendorf, 2002, p. 1.
D19	Kearon, C. "Duration of venous thromboembolism prophylaxis after surgery." *CHEST*, vol. 124, no. 6 (Supplement), 2003, pp. 386S-392S.
D20	Derendorf, H, Granmatté, T, and Schäfer, HG. "Pharmakokinetik: Einführung in die Theorie und Relevanz für die Arzneimitteltherapie". 2nd ed., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2002.
D21	Weinz, C et al. "Metabolism and distribution of [^{14}C]BAY 59-7939 - an oral, direct factor Xa inhibitor - in rat, dog and human." *Drug Metabolism Reviews*, vol. 36 (Suppl), 2004, Abstract no. 196.
D22	Vrijens, B and Heidbuchel, H. "Non-vitamin K antagonist oral anticoagulants: considerations on once-vs. twice-daily regimens and their potential impact on medication adherence." *Europace*, vol. 17, no. 4, 2015, pp. 514-523.

#	Reference
D23	Oberpichler-Schwenk, H. "Rivaroxaban - der erste orale Faktor-Xa-Hemmer." *Medizinische Monatsschrift für Pharmazeuten*, vol. 31, no. 11, 2008, pp. 412-416.
D24	*European Pharmacopeia.* 5th ed., published 15 June 2004, Section 2.9.3 Dissolution Test for Solid Dosage Forms, pp. 228-230.
D25	Birkett, DJ. "Pharmacokinetics made easy", Chapter 11 "Designing dose regimens." *Aust Prescr*, vol. 19, no. 3, 1996.
D25a	Birkett, DJ. *Pharmacokinetics Made Easy*. The McGraw-Hill Companies, Inc., 2002, pp. 20-23.
D26	US 2007/0026065 A1
D27	Roehrig, S et al. "Discovery of the novel antithrombotic agent BAY 59-7939, an orally active, direct Factor Xa inhibitor." *Alfred Burger Award Symposium - Recent Advances towards Novel Cardiovascular Therapies, 228th ACS Meeting, 22-26 August 2004*, 2004, Abstract No. 156.
D28	UK High Court Judgment in *Hospira UK Limited v. Genentech Inc.*, [2014] EWHC 1094 (Pat), April 10, 2014.
D29	Internet printout from www.clinicaltrialsregister.eu, EudraCT Number 2004-002171-16 dated December 29, 2015
D30	Rowland, M and Tozer, TN. *Clinical Pharmacokinetics: concepts and applications.* 3rd ed., 1995, Chapter 1, pp. 1-7.
D31	Patrono, C et al. "Platelet-active drugs: the relationships among dose, effectiveness, and side effects." *CHEST*, vol. 119, no. 1 (suppl), 2001, pp. 39S-63S.
D32	Mueck, W et al. "Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban." *Clin Pharmacokinet*, vol. 53, no. 1, 2014, pp. 1-16.
D33	Internet printout from https://clinicaltrials.gov, "Dose-ranging study of once-daily regimen of BAY 59- 7939 in the prevention of VTE in patients undergoing elective total hip replacement (ODIXaHIP-OD) dated January 11, 2016
D34	Abstract of article by Charbonnier, BA et al. "Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis." *Thromb and Haemost*, vol. 79, no. 5, 1998, pp. 897-901.
D35	Turpie, AGG et al. "BAY 59-7939: an oral, direct Factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study." *Journal of Thrombosis and Haemostasis*, vol. 3, no. 11, 2005, pp. 2479-2486.
D36	Kubitza, D et al. "Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor." *Clinical Pharmacology & Therapeutics*, vol. 78, no. 4, 2005, pp. 412-421.
D37	Griffin JP and O'Grady J. *The Textbook of Pharmaceutical Medicine*. 4th ed., BMJ Books, 2002, pp. 225-226 & 238-239.
D38	US Pharmacopeia (USP29), Chapter 1088: "In vitro and in vivo evaluation of dosage forms"
D39	Harron, D et al. "Bopindolol: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy." *Drugs*, vol. 41, no. 1, 1991, pp. 130-149.
D40	Center for Drug Evaluation and Research, "Clinical Pharmacology and Biopharmaceutics Review(s).", Application No. 0224060rig1s000, Addenum to April 6, 2009 Review, NDA 22-406, Submission Date December 30, 2010.

#	Reference
D41	Internet printout from www.clevelandclinicmeded.com dated November 27, 2015, *Pharmacotherapy Update*, vol. VI, no. 1, January/February 2003, "Enoxaparin Clinical Pearl."
D42	Fareed, J et al. "Studies on the mechanism of action of BAY 59-7939 — an oral, direct Factor Xa inhibitor." *Pathophysiol Haemost Thromb*, vol. 33 (suppl2), 2003, PO077.
D43	Lieberman, HA and Lachman, L. *Pharmaceutical dosage forms*. Volume 1-Tablets, Marcel Dekker Inc., 1980, pp. 172-181.
D44	Mattsson, S. "Pharmaceutical binders and their function in directly compressed tablets: Mechanistic studies on the effect of dry binders on mechanical strength, pore structure and disintegration of tablets." *Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy 238*, Acta Universitatis Upsaliensis, Uppsala, 2000.
D45	Rasenack, N and Müller, BW. "Crystal habit and tableting behavior." *International Journal of Pharmaceutics*, vol. 244, no. 1, 2002, pp. 45-57.
D46	*Bayer Annual Report 2015*, 2015, p. 70 and p. 156.
D47	"Fast Facts – About XARELTO® (rivaroxaban)." Janssen Pharmaceuticals, Inc., November 2011.
D48a	Summary of Product Characteristics for "Xarelto 10 mg film-coated tablets." European Medicines Agency, last updated July 1, 2015.
D48b	Summary of Product Characteristics for "Xarelto 20 mg film-coated tablets." European Medicines Agency, last updated May 20, 2016.
D49	"Highlights of Prescribing Information" and "Full Prescribing Information" for XARELTO® (rivaroxaban)." Janssen Pharmaceuticals, Inc., revised May 2016.
D50	Krauspe, R. "Der erste orale Faktor-Xa-Inhibitor Rivaroxaban (Xarelto®) zur Thromboseprophylaxe - eine neue Dimension." PZ Innovationspreis 2009, September 26, 2009, Düsseldorf, Germany.
D51	"Thrombosen verhindern - eine Tablette kann Leben retten: Kurzbeschreibung der Institute und Unternehmen zu ihren nominierten Projekten Nominierte 2009." Deutscher Zukunftspreis, 2009.
D52	"Xarelto®: Eine neue Dimension der Thromboseprophylaxe." version DE/2, Bayer Schering Pharma AG, May 2009.
D53	"Bayer's Xarelto® Recognised with 2010 International Prix Galien Award.", Bayer, October 7, 2010.
D54	*Bayer Annual Report 2009*, 2009, p. 38.
D55	"Deutscher Zukunftspreis 2009 für Frank Misselwitz, Dagmar Kubitza und Elisabeth Perzborn." Pressemitteilung des Bundespräsidialamtes, December 2, 2009.
D56	European Patent Office. "Communication pursuant to Article 94(3) EPC." July 26, 2010.
D57	Overview Table showing Opponents statements re half life being inherent property.
D58	Overview Table showing Opponents statements re rapid-release tablet is common and therefore well-defined.
D59	"CHMP Assessment Report for Xarelto." European Medicines Ageny, Evaluation of Medicines for Human Use, Doc. Ref.: EMEA/543519/2008, 2008.
D60	WO 2005/060940 A2

#	Reference
D61	Search Results from Thomson Innovation regarding PCT-application recited in para [0031] of Opposed Patent
D62	Fülgraff, G and Palm D. *Pharmakotherapie: Klinische Pharmakologie*. 11th ed., Urban & Fischer Verlag München, 2001, pp. 114-123.
D63	Schmutzler, R and Novotny, U. *Antikoagulation in Klinik und Praxis*. ComMed Basel, Verlagsagentur, 1999, Chapter 4, pp. 76-93.
D64	Dugina, TN et al. "Receptors of the PAR family as a link between blood coagulation and inflammation." *Biochemistry*, vol. 67, no. 1, 2002, pp. 65-74.
D65	"Points to consider on clinical investigation of medicinal products for prophylaxis of intra- and post-operative venous thromboembolic risk." The European Agency for the Evaluation of Medicinal Products, Committee For Proprietary Medicinal Products, CPMP/EWP/707/98, London, June 29, 2000.
D66	European Patent Office. "Annex to Communication under Rule 71(3) EPC." November 13, 2014.
D67	Jaehde et al. *Lehrbuch der Klinischen Pharmazie*. 2nd ed., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2003, Chapter 9, pp. 129-139.
D68	*Pschyrembel Klinisches Wörterbuch*. 258th ed., Walter de Grunyter & Co., 1997, p. 714.
D69	"Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67)." November 28, 2012.
D70	"EU Clinical Trials Register goes live." European Medicines Agency - Science, medicines, health, March 22, 2011.
D71	Raffaella, C and Novak, A. "Publication of Study 'EurdraCT Number 2004-002171-16/Sweden'." European Medicines Agency Service Desk.
D72	Patel, MR et al. "Rivaroxaban versus warfarin in nonvalvular atrial fibrillation." *N Engl J Med*, vol. 365, no. 10, 2011, pp. 883-891.
D73	*Bayer Annual Report 2011*, 2011, pp. 110-111.
D74	The EINSTEIN Investigators. "Oral rivaroxaban for symptomatic venous thromboembolism." *N Engl J Med*, vol. 363, no. 26, 2010, pp. 2499-510.
D75	The EINSTEIN-PE Investigators. "Oral rivaroxaban for the treatment of symptomatic pulmonary embolism." *N Engl J Med*, vol. 366, no. 14, 2012, pp. 1287-1297.
D76	Prins, MH et al. "Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies." *Thromb J*, vol. 11, 2013, pp. 1-10.
D77	Linkins, LA and Weitz JI. "New Anticoagulant Therapy." *Annu Rev Med*, vol. 56, 2005, pp. 63-77.
D78a	Aktories et al. *Allgemeine und spezielle Pharmakologie und Toxikologie*. 9th ed., Elsevier GmbH, München, 2005, pp. 72-74.
D78b	Aktories et al. *Allgemeine und spezielle Pharmakologie und Toxikologie*. 9th ed., Elsevier GmbH, München, 2005, pp. 82-84.
D79	Hauptmann, J and Stürzebecher J. "State of the art article: Synthetic inhibitors of thrombin and factor Xa: From Bench to bedside." *Thrombosis Research*, vol. 93, 1999, pp. 203-241.

#	Reference
D80a	Mutschler, E et al. *Mutschler Arzneimittelwirkungen*. 8th ed., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2001, pp. 48-51.
D80b	Mutschler, E et al. Mutschler Arzneimittelwirkungen. 8th ed., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2001, p. 497.
D81	Schwarz, JA. *Leitfaden Klinische Prüfungen von Arzneimitteln und Medizinprodukten*. 3rd ed., Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Aulendorf, 2005, pp. 63-65.
D82	Page, C et al. *Integrated pharmacology*. 2nd ed., Mosby International Ltd, 2002, pp. 210-211.
D83	Summary of Product Characteristics for "Eliquis 2.5 mg film-coated tablets." European Medicines Agency, last updated January 22, 2016.
D84	Meier, J et al. *Biopharmazie: Theorie und Praxis der Pharmakokinetik*. Georg Thieme Verlag Stuttgart, 1981, Chapter 11.2.2, pp. 322-325.
D85	Stapff, M. *Arzneimittelstudien*. 2nd ed., W. Zuckschwerdt Verlag GmbH, 2001, Chapter C5, pp. 48-49.
D86	Bisio, A et al. "Structural features of low-molecular-weight heparins affecting their affinity to antithrombin." *Thromb Haemost*, vol. 102, 2009, pp. 865-873.
D87	Harenberg, J et al. "Update of the recommendations on biosimilar low-molecular-weight heparins from the Scientific Subcommittee on Control of Anticoagulation of the International Society on Thrombosis and Haemostasis." *Journal of Thrombosis and Haemostasis*, vol. 11, no. 7, 2013, pp. 1421-1425.

Annex A	Cross-reference table with list of opponents' documents D1-D45
Annex B	Complete list of documents D1-D87 on file
Annex C	Feature Analysis of granted claims

(6) Of the documents cited by the opponents, documents **D1, D2,** and **D3** were considered during examination. **D1** (as **D1a**), **D2, D9** (as 1985 edition, see **D9a**), **D14, D16, D25** (as 2000 edition) and **D27** are cited in the Opposed Patent.

(7) Documents **D2** and **D11, D3** and **D12,** as well as **D15** and **D17** contain almost identical disclosures in their respective pairs and will be discussed hereinafter together as "**D2/D11**", "**D3/D12**" and "**D15/D17**".

(8) Documents **D8, D22, D23, D26, D28, D29, D32, D35, D36**, and **D40** cited by the opponents were published after the priority date of the patent and do not form prior art under Art. 54(2) or (3) EPC.

C INTRODUCTORY COMMENTS

(9) As set out in detail herein below, the subject matter of **EP 1 845 961 B1** (hereinafter: "the Opposed Patent") fulfills the requirements of the European Patent Convention. The opponents' allegations to the contrary are not founded, properly substantiated, or in line with the case law of the Technical Boards of Appeal of the European Patent Office (EPO). Consequently, the oppositions should be rejected.

C.1 Development of the claimed compound (rivaroxaban) and its once-daily dosage regimen were a milestone achievement in medicine

(10) The opponents have cited a very large number of documents and put forth a variety of arguments and assertions, but the fact remains that the claimed dosage regimen for treating thromboembolic disorders is nowhere disclosed in or suggested by any piece of prior art.

(11) The INN for *5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide*, the compound recited in claim 1 of the Opposed Patent, is rivaroxaban (also referred to as BAY 59-7939 in the prior art). Rivaroxaban was first synthesized and identified by Bayer, and was subsequently jointly developed with Janssen Research & Development, LLC. It is marketed under the brand name **Xarelto®** by Bayer and in the US by Janssen Pharmaceuticals, Inc. (see **D46**, Bayer Annual Report 2015, p. 70, 2nd and 5th para.).

(12) The dosage regimen recited in claim 1 of the Opposed Patent is characterized by the once-daily administration of rivaroxaban in the form of a rapid-release tablet for at least five consecutive days. To date, Xarelto® has been approved in the claimed dosage regimen in more than 130 countries worldwide and has been successfully launched in more than 80 countries, including Australia, Canada, China, Japan, the US, and within the European Union (see **D46**, p. 70, 2nd and 3rd para. and **D47**, "Fast Facts – About XARELTO®", p. 1, left col., penultimate bullet point). Rivaroxaban has been approved for more indications in the area of venous and arterial thromboembolism than any of the other non-vitamin-K-dependent oral anticoagulants (see **D46**, p. 70, 2nd para.).

(13) The European Medicines Agency (EMA) has authorized rivaroxaban as an antithrombotic agent given once daily as a rapid-release tablet for the following indications (see the SmPCs for rivaroxaban 10 mg and 20 mg, attached as **D48a** and **D48b**, respectively):

1. Prevention of **venous thromboembolism** (VTE) in adult patients undergoing elective hip or knee replacement surgery (**D48a**, section 4.1).

2. Prevention of **stroke and systemic embolism** in adult patients with non-valvular atrial fibrillation (SPAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack (**D48b**, section 4.1, 1st para.).

3. Treatment of **deep vein thrombosis** (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (**D48b**, section 4.1, 2nd para.).

(14) Similarly, the US FDA has authorized rivaroxaban 10 mg, 15 mg, and 20 mg for the following indications in the claimed once-daily dosage regimen (see **D49**, the FDA's "Highlights of Prescribing Information" for Xarelto®, p. 1, sections "INDICATIONS AND USAGE" and "DOSAGE AND ADMINISTRATION"):

1. To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

2. For the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and for the reduction in the risk of recurrence of DVT and of PE.

3. For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

(15) In addition to the currently approved indications, the use of rivaroxaban in the claimed dosage regimen is also being investigated in a broad range of other thromboembolic disorders. The extensive program of clinical trials evaluating rivaroxaban in the authorized indications as well as other potential indications makes it the most studied and published oral factor Xa inhibitor in the world (**D47**, p. 1, left col., 2nd diamond-shaped bullet point).

(16) More than 20 million Xarelto®-prescriptions have been written in the US alone to treat or help reduce the risk of DVT and PE blood clots and strokes. In fact, Xarelto® is now the most prescribed blood thinner in its class in the US (*https://www.**xarelto-us**.com*). With worldwide annual sales of **2.252 billion EUR in 2015**, Xarelto® has **blockbuster status** (see **D46**, p. 156, Table 3.13.3).

(17) Thromboembolic disorders are the most frequent cause of morbidity and mortality in most industrialized countries (Opposed Patent, para. [0004]). In Europe, more people die of venous thromboembolism than of breast cancer, prostate cancer, AIDS, and car accidents together. Without thrombosis prophylaxis, up to 60% of patients having undergone hip- or knee

replacement surgery develop a thrombosis (see **D50**, Statement of Prof. Dr. med. Krause, p. 2, 1st para. and Opposed Patent, table in para. [0018]). Left untreated, blood clots can detach from existing thrombi and travel via the circulation to the lung causing pulmonary embolism. Here, blood clots in the lung block oxygen supply, which can cause acute right heart failure and death, or chronically lead to right heart failure and chronic thromboembolic pulmonary hypertension (CTEPH). Pulmonary embolism is the most frequent cause of avoidable death in hospitalized patients (see **D50**, p. 3, final para.).

(18) Being the first oral direct factor Xa inhibitor to gain regulatory approval (see, e.g., **D23**, title and abstract), **Xarelto® satisfied a long-standing yet unmet medical need** (see, e.g., **D16**, p. 514, right col., end of 1st para. or **D51**, p. 1, 1st para.). The standard-of-care anticoagulants available at the effective filing date of the Opposed Patent had severe drawbacks (see Opposed Patent, para. [0005]-[0007]). Heparins, on the one hand, are administered via injection, which is painful and requires the presence of a healthcare provider to either administer an injection or train the patient in self-administration. Orally administered Vitamin K antagonists (VKAs) such as warfarin, on the other hand, lack predictable pharmacokinetic and pharmacodynamic properties. They therefore require coagulation monitoring and cannot simply be administered at a standardized and fixed dose. Two particular benefits of rivaroxaban compared to these prior art anticoagulants are its patient-friendly, **once-daily** oral administration and the lack of need for coagulation monitoring (see, e.g., **D52**, *"Xarelto®: eine neue Dimension der Thromboseprophylaxe"*, p. 1, 2nd and 3rd bullet point).

(19) Accordingly, the approval of rivaroxaban in the claimed dosage regimen was perceived by the medical community to be a **milestone achievement in medicine**. This perception and the outstanding technical contribution of the invention to the field are evidenced by the prestigious prizes and awards the inventors of the Opposed Patent have received. Importantly, these include:

- The **2010 "Prix Galien International"** award in the category **"Best Pharmaceutical Agent"**. The Prix Galien Award recognizes outstanding achievements in improving health through the development of innovative therapies, and is regarded as the equivalent of the Nobel Prize in biopharmaceutical research (see **D53**, p. 1, 1st para.).

- The **2009 "German Future Prize"** (*Deutscher Zukunftspreis,* see **D54**, p. 38, as well as **D55** and **D51**), one of the most prestigious innovation awards in Germany, awarded by the German Federal President. Xarelto®'s combination of *"potency, selectivity and oral bioavilability"* is termed a *"breakthrough"* in the corresponding documentation **D51** (see *id.*, p. 1, 3rd para. from the bottom, *"Durchbruch"*).

- The **2009 "Pharmazeutische Zeitung Innovation Prize"** (*PZ Innovationspreis*, see **D50**, award lecture by Prof. Krauspe characterizing therapy with Xarelto® in the title as "new dimension") awarded by the journal *Pharmazeutische Zeitung* for leap innovations (*"Sprunginnovationen"*) by an independent jury consisting i.a. of Prof. Dinnendahl, Chairman of the Drug Commission of German Pharmacists (*"Arzneimittelkommission der Deutschen Apotheker"*) and Prof. Schulz, director of the German Drug Testing Institute (*"Deutsches Arzneimittelprüfungsinstitut"*).

(20) The Patentee's surprising finding and subsequent development of rivaroxaban's **once-daily dosage regimen** is one of the key factors that has contributed to its huge success. In the words of the former President of the Federal Republic of Germany, Dr. Horst Köhler (see **D54**), and its Office's press release regarding the *Deutscher Zukunftspreis* 2009 see **D55**):

> *„Rivaroxaban hat in Studien nicht nur eine höhere Wirksamkeit gezeigt als die bisherige Standardtherapie – bei vergleichbarem Sicherheitsprofil –,* ***der Wirkstoff ermöglicht auch eine einfachere Anwendung: Die Patienten können ihn einmal täglich als Tablette einnehmen,*** *während konventionelle Präparate für die Kurzeitanwendung gespritzt werden müssen. Auch eine regelmäßige Kontrolle des Blutbildes, zum Bespiel während der oralen Langzeit-Standardtherapie, sowie eine Anpassung der Dosis an Alter, Körpergewicht und Geschlecht des Patienten sind bei einer Behandlung mit Rivaroxaban nicht erforderlich."*
> (**D55**, 5th para., emphasis added)

> *"The development of this drug* [Xarelto®] *was very expensive, and projects like this require a great deal of patience and stamina. That's why I'm particularly pleased that major corporations such as Bayer have long-term innovation strategies".*
> (**D54**, p. 38, left col. 2nd para., explanation in square brackets added)

C.2 Patentability of second medical use and dosage regimen claims as an important driver of innovation

(21) The European Patent Convention and the jurisprudence of the Technical Boards of Appeal of the EPO expressly allow for the patenting of novel and inventive second medical uses and dosage regimens (see, e.g., **G 2/08**). This also is necessary to provide the required incentive for originator companies like the Patentee to invest in the clinical development of novel and improved dosage regimens, which, as all clinical development and pharmaceutical innovation, is incredibly expensive and fraught with failure.

(22) Patent-mediated exclusivity compensates originator companies for the many years it takes to develop, test, and obtain approval for a new drug and dosage regimen, the high costs incurred, and the risks that the innovator company must bear regarding whether the pharmaceutical research program will prove successful at all. Encouraging pharmaceutical industry innovation today by awarding strong second medical use patents is key to helping as many patients tomorrow by improving therapies, in particular making them more effective and convenient.

(23) In assessing the present case, it is important for the Opposition Division to bear in mind the following considerations, which are unique to pharmaceutical innovations but which the opponents seem to ignore:

a) Clinical development is **inherently uncertain** and fraught with failure. Even if a compound or dosage regimen proves successful and promising in one stage of development, it cannot be predicted whether or not it will also pass even the next development stage, much less be successful in late-stage clinical development. In fact, the vast majority of drug development programs are discontinued during clinical development without ever producing an approved drug. It must be remembered that the entirety of these drug candidates had begun as very promising candidates. Patentee acknowledges that early *in vitro*, pre-clinical and phase I clinical testing are necessary and have an important value in drug development. However, as such, they are only a necessary but not a sufficient prerequisite for determining whether or not a drug in a particular dosage regimen – and specifically the particular dosage regimen claimed in the Opposed Patent – is medically effective when treating patients.

b) Due to the seemingly linear nature of drug development (from the first biochemical results to the preclinical, clinical phase I, clinical phase II, and clinical phase III results) inventions made during clinical development of a drug are particularly **prone to inadmissible ex post facto analysis.** In hindsight, the single piece of the puzzle that one had had in hand early on seems to fit perfectly into the bigger picture. Conversely, the bigger picture remains obscure when only a single piece of the puzzle, or even a combination of a few unrelated pieces, is known. For this reason, care must be taken, not to fall victim to **hindsight bias.** This bias is characterized by the inclination to perceive an invention as having been predictable after the invention has been made, despite there having been little or no objective basis for predicting it. Psychologically, for example, physicians recalling clinical trials they oversaw are often prone to a hindsight bias, believing they "knew all along" that the drug would work in the indication and dosage regimen tested.

c) The skilled person working in clinical drug development **does not adopt a "try and see approach"** and does not take any substantive risks. Patient safety and treatment ethics always take precedent over any "obvious to try" considerations. In addition, clinical development is too expensive to allow testing of all possible alternatives simply to "try and see". Thus, in the field of pharmaceutical drug development, even if only few alternatives exist, the skilled person only tests them if he or she has a high expectation of success, i.e. a clear indication that the dosage regimen to be tested will be safe and efficacious in treating the disease at hand.

(24) The case law of the Technical Boards of Appeal of the EPO regarding second medical use and dosage regimen patents has consistently taken these considerations into account. See, for example, the discussion of **G 2/08** and **T 715/03** in sections F.2 and F.4.2.2 below and of **T 293/07** and **T 847/07** in section G.7.7 below.

C.3 The Opposed Patent

(25) The Opposed Patent is based on international application no. PCT/EP2006/000431, filed January 19, 2006 and published on August 3, 2006 as **WO 2006/079474 A1** (the originally filed application will be referred to hereinafter as "**WO'474**").

(26) The Opposed Patent claims the **priority** of EP05001893, filed January 31, 2005. The patent specification of EP05001893 and WO'474 are identical. Accordingly, none of the opponents have contested the validity of the priority claim. The **effective filing date** of the Opposed Patent therefore is **January 31, 2005**.

(27) The invention is as defined in the claims of the Opposed Patent and is directed to a particular dosage regimen of rivaroxaban, namely in the form of a rapid-release tablet administered once daily for at least 5 consecutive days for the treatment of a thromboembolic disorder.

(28) The skilled person understands the term "**dose**" to refer to a specified ***amount* of medication** taken at one time. In contrast, the terms "**dosaging**" or "**dosage regimen**" imply **duration** and are used by the skilled person to refer to the ***frequency* of administration**. Accordingly, a "dosage regimen" is understood by the skilled person (and used herein accordingly) to refer to a treatment plan for administering a drug over a period of time.

(29) **Claim 1** can be dissected into the following features:

1. The **use** of

1.1 a **rapid-release tablet**

1.2 of the compound *5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide* [compound (I), **Rivaroxaban**]

1.3 for the manufacture of a medicament for the **treatment of a thromboembolic disorder**

1.4 administered **no more than once daily** for at least **five consecutive days**,

1.5 wherein said compound has a **plasma concentration half life of 10 hours or less** when orally administered to a human patient.

Claim 2 is the only further claim. It is dependent on claim 1 and recites the following features:

2. The use as claimed in Claim **1**,

2.1 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.

A copy of this feature analysis is attached as **Annex C**.

(30) The invention is based on the surprising finding that a direct factor Xa inhibitor (see feature 1.2, rivaroxaban) with a plasma concentration half life of 10 hours or less (see feature 1.5), which would normally be indicative of a twice-daily (bid) or thrice-daily (tid) administration (see para. [0001] of the Opposed Patent) can be administered once daily (see feature 1.4) in the form of a rapid-release tablet (see feature 1.1) to therapeutically or prophylactically treat a thromboembolic disorder (see feature 1.3 and para. [0022] of the Opposed Patent).

(31) The skilled person at the priority date of the Opposed Patent knew from phase I studies in healthy individuals that rivaroxaban had a half life of 4-6 hours (see para. [0017] of the Opposed Patent referring to **D2**). Furthermore, it belonged to the common general knowledge of the skilled person that when a drug is dosed in no more than a therapeutically-active amount, which is desired to minimize side effects, the drug must be administered approximately every half life (see para. [0010] of the Opposed Patent referring to **D14**). This was believed to be necessary for continuously ensuring therapeutically effective plasma concentrations and for avoiding hazardous plasma concentration fluctuations (see sections G.7.1 and G.7.2 below). **Conventional wisdom** would have led the skilled person to believe that therapeutic efficacy of a drug with a half life of 4-6 hours required more frequent dosaging, such as bid or tid dosaging.

(32) Surprisingly, the clinical data underlying the Opposed Patent demonstrated that the claimed once-daily dosage regimen is comparable in safety and efficacy to standard therapy and at the same time is as safe and effective as the corresponding twice daily (bid) administration (see the Opposed Patent, para. [0012], [0018]-[0020], as well as [0044] and [0046] under "Summary").

(33) Regarding the remaining written description of the Opposed Patent, reference is made to the patent specification itself, which – for brevity – will not be further summarized here. The

clinical data included in the Opposed Patent (see *id.*, para. [0018]-[0020] and Example 1 in para. [0035]-[0046]) is discussed in detail in section G.6.1 below.

C.4 Claim construction

(34) **Features 1.4 and 1.5** of claim 1 are in dispute and need to be construed (see sections E.3.3 and E.3.2, respectively, below).

(35) **Feature 1.4** of claim 1, properly grounded by the context of the remaining claim features, the specification of the Opposed Patent, and the skilled person's common general knowledge, is understood by the skilled person to refer to a **once-daily (i.e. one-a-day) administration** for at least five consecutive days, which does not allow for *"less than once-daily"* administration (see section E.3.3 below). The expression *"no more than once daily"* must be construed in the context of the remaining wording of feature 1.4, i.e. *"for at least five **consecutive** days"*. It is impossible to administer something *not every day* but *for five consecutive days*. The term ***"consecutive"*** can only be interpreted by the skilled person as an administration occurring on each of the days. Less frequent drug administration than once daily is not permitted under this explicitly required feature, which is in line with the Opposed Patent containing no indication whatsoever that administering rivaroxaban less than once daily would be a possibility. This claim construction is also supported by synonymous usage of the expressions *"once daily"* and *"no more than once daily"* in the specification of the Opposed Patent, which repeatedly describes the 'the present invention' as being a *"once daily"* administration (see para. [0001], [0012], [0013] of the Opposed Patent). Contrary to the unsupported assertions of some of the opponents, the claimed subject matter exclusively concerns an administration occurring no less and no more than once daily.

(36) **Feature 1.5** of claim 1 is understood by the skilled person to be an **inherent feature** which is **automatically fulfilled as soon as rivaroxaban is employed** (see section E.3.2 below). First of all, para. [0001], [0012], and [0013] of the Opposed Patent make clear that in the context of 'the present invention', the *"half life of 10 hours or less"* is a feature inherent to, directly related to, and defining **the broader term factor Xa inhibitor** (and not, for example, a patient group as suggested by O2 and O3 in their identical submissions). Second, whereas the invention according to the specification is said to include in the broader class of factor Xa inhibitors only those having a *"half life of 10 hours or less"*, the granted claims are limited to a specific factor Xa inhibitor, rivaroxaban, which in para. [0017] of the Opposed Patent is already defined as having a half life of 4-6 hours, i.e. as fulfilling feature 1.5 automatically. Thus, when properly construed in the context of the patent specification and feature 1.2 of claim 1 already requiring a particular compound having a particular half life, feature 1.5 is

understood by the skilled person to be in principle a redundant feature that is automatically fulfilled as soon as feature 1.2 is fulfilled. This also corresponds to the opinion of the vast majority of opponents (see section E.3.2 below).

D NO ADDED SUBJECT MATTER (ART. 100(c), 123(2) EPC)

(37) The claimed subject matter of the Opposed Patent does not extend beyond the content of the application as originally filed (hereinafter: "**WO'474**").

D.1 Summary of opponents' added matter arguments

(38) All opponents except O7, O10 and O12 raised objections under 100(c) EPC. Their objections are two-fold and will be addressed in turn below.

1. First, O2, O3, O4, O5, O6, O9, O11, and O13 argue that the feature "***no more than once daily***" in claim 1 would add matter because it would not have been originally disclosed in combination with the *Swiss-type* medical use embodiments. Our rebuttal arguments are presented in sections D.2.1 to D.2.3 below.

2. Second, O1, O8, and O11 argue that there would be no original disclosure for the combination of the feature "*half life of 10 hours*" with the feature "*compound (I)*", i.e. rivaroxaban, in granted claim 1. Our rebuttal arguments are presented in section D.3 below.

D.2 The feature "no more than once daily" in claim 1 complies with Art. 123(2) EPC

(39) Opponents' Art. 123(2) EPC objections regarding the feature "*no more than once daily*" in claim 1 can be summarized as follows:

a) Granted claim 1 contains the subject matter of **originally filed claims 3, 5, and 6** (*Swiss-type* use claims) with the additional feature that rivaroxaban is administered "*no more than* once daily". Opponents O2, O3, O4, O5, O6, O9, O11, and O13 argue that this combination was not originally disclosed. O2, O3, O9, O11, O13 take the position that neither **original claim 1** nor the text on **p. 3, l. 19-22** of the description as originally filed can serve as basis for granted claim 1 because the former two relate to "**method of treatment**" embodiments, whereas the latter is a "***Swiss-type* use**" claim. O9 additionally argues that *Swiss-type* use claims would be narrower than method of treatment claims and therefore directed to different subject matter. Patentee disagrees for the reasons set out in section D.2.1 below.

b) O9 argues that "*once daily*" and "*no more than once daily*" are **used separately** in WO'474. Thus, the application intended to distinguish the scope of the method of treatment and the *Swiss-type* use subject matter. It would not be permissible to mix and combine these subject matters. Based on a similar argument, O13 takes the position that granted claim 1 contains an **intermediate generalization**. Patentee disagrees for the reasons set out in section D.2.2 below.

(40) As will be explained in more detail in sections D.2.1 and D.2.2 below, the subject matter of granted claim 1 is supported independently by (1) **originally filed claims 1, 5 and 6**, because these were merely re-worded into the allowable (*Swiss-type*) medical use format, and (2) **originally filed claims 3, 5, and 6**, because, clearly, the application as filed (and also the Opposed Patent) use the terms *"once daily"* and *"no more than once daily"* synonymously (see also section E.3.3 below).

D.2.1 Support for the feature "no more than once daily" in granted claim 1

(41) Opponents O2, O3, O4, O5, O6, O9, O11, and O13 assert that there is no support for the feature *"no more than once daily"* in the context of granted claim 1. Patentee disagrees. Granted claim 1 is fully supported by originally filed claims 1, 3, 5, and 6 read in conjunction with p. 1, l. 1 to 5 and p. 3, l. 15 to 26 of WO'474.

(42) It is correct that originally filed claim 1 uses the term *"no more than once daily"* and is directed to a method of treating a thromboembolic disorder, whereas originally filed claim 3 is worded as *Swiss-type* use claim and uses the term *"once daily"* without reciting *"no more than"*. The wording of originally filed claims 1 and 3 is repeated on p. 3, l. 19 to 26 of WO'474.

(43) It is important to note, however, that WO'474 uses *"once daily"* and *"no more than once daily"* **synonymously** in the context of the overarching invention (see section D.2.2 below). The teaching of WO'474 was generally directed to a *"once-daily oral administration of a direct factor Xa inhibitor with a plasma concentration half life of 10 hours or less"*. See p. 1, l. 1 to 5, p. 3, l. 15 to 18, and p. 4, l. 20 to 23 of WO'474. Accordingly, there is a clear teaching to administer the factor Xa inhibitors of the invention *"once daily"*. This general and overarching teaching is independent from and applies to all of the different medical use, *Swiss-type*, and method of treatment wordings recited in WO'474, which were meant to be equivalent. The synonymously used *"no more than once daily"* only further contrasts the inventive dosage regimen from more than once-daily dosage regimens.

(44) The skilled person will appreciate that WO'474, the originally filed PCT application, was written in a style to accommodate support for both US-style method of treatment claims and European-style *Swiss-type* use claims, the latter still being allowed at the time of application (i.e. prior to **G 2/08**). However, the circumstance that WO'474 includes support for a US-style method of treatment claim and support for a *Swiss-type* use claim does **not** allow the conclusion that both passages of disclosure in WO'474 refer to different inventions or different embodiments of an invention.

(45) The opposite is the case: Originally filed claims 1 and 3 are understood by the skilled person to be directed to exactly the same concept. The term "no more than" as used in the US-style method of treatment claim (original claim 1) was only used to clearly define the "once-daily" administration also for the US patent examination proceedings. Thus, it was used as a precautionary measure to meet possible claim construction issues in US patent practice; it is not an indication for a different embodiment as compared to the wording of the *Swiss-type* medical use claim.

(46) In this regard it should also be taken into account that in cases of Euro-PCT applications that have their origin in the US and only include method of treatment claims, the Examining Divisions of the EPO request and accept the rewording of such US-style method of treatment claims into the allowable *Swiss-type* medical use language or, as is now the case, an EPC 2000-style second medical use claim under Art. 54(5) EPC. Accordingly, it is an accepted and well-established principle at the EPO that the subject matter of a method of treatment claim and of a *Swiss-type* medical use claim generally describe the same embodiment. This is the reason why an originally filed US-style method of treatment claim can be reworded into a format that adheres to EPO practice without violating Art. 123(2) EPC.

(47) Consequently, granted claim 1 can also be regarded as the result of rewording originally filed claim 1 of WO'474 into a *Swiss-type* medical use claim. Accordingly, the subject matter of **granted claim 1 is fully supported by claims 1, 5, and 6 as originally filed.**

D.2.2 "Once daily" and "no more than once daily" are used synonymously in the application as filed; no intermediate generalization present

(48) The skilled person reading WO'474 would have immediately recognized that WO'474 uses *"once daily"* and *"no more than once daily"* **synonymously**. For a detailed discussion of these terms in the context of the granted patent, see also section E.3.3 below. Its reasoning applies *vice versa* to the skilled person's understanding of these terms in the context of the originally filed application. As explained in section E.3.3, the skilled person's understanding of *"no more than once daily"* as used in the Opposed Patent (and the originally filed application) **does not include *"less than once-daily"*** administration.

(49) When summarizing the invention, the application as originally filed only used the wording *"once daily"* (see WO'474, p. 3, l. 15-18):

> *"Surprisingly, it has now been found in patients at frequent medication that **once daily oral administration** of a direct factor Xa inhibitor ... demonstrated efficacy when compared to standard therapy and at the same time was as effective as after twice daily (bid) administration."* (emphasis added)

Similarly, the introductory paragraph of WO'474 on p. 1, l. 2-5 also only recites *"once daily"* when summarizing the invention.

(50) Thus, while originally filed claim 1 and the repetition of its wording on p. 3, l. 23-26 use *"no more than once daily"*, the remaining general description of the invention and originally filed claim 3 use *"once daily"*. This indicates to the skilled person that *"no more than once daily"* is simply another way of putting *"once daily"*, i.e. in the sense of *"exactly once daily"*. Because of the synonymous usage of *"once daily"* and *"no more than once daily"* in WO'474, the subject matter of granted claim 1 is not only supported by claims 1, 5, and 6, but is also **fully supported by a combination of claims 3, 5, and 6 as originally filed.**

(51) Against this background, O13's allegation that the feature *"no more than"* would have been taken out of its initial context (originally filed method of treatment claim 1) and inadmissibly included in the *Swiss-type* use claim, thereby resulting in a "singling out" or an "**intermediate generalization**", is unwarranted. As explained above and in more detail in section E.3.3 below, the skilled person reading the disclosure of the Opposed Patent clearly understands the features *"no more than once daily"* and *"once daily"* to be **synonymous**. Therefore, *"no more than"* does not add anything to the claimed subject matter, nor can it be regarded as inextricably linked to other features of any particular embodiment. Thus, granted claim 1 is not the result of an intermediate generalization. Instead, it fully complies with Art. 123(2) EPC.

D.2.3 The Examining Division's suggestion

(52) The addition of *"no more than"* to the wording of originally filed claims 3, 5, and 6 must also be considered within the context of the **Examining Division's suggestion** during examination proceedings.

(53) In its communication pursuant to Art. 94(3) EPC of July 26, 2010 (see **D56**), the Examining Division raised a clarity objection under Art. 84 EPC regarding the feature *"once daily"* in originally filed claims 3 to 6 (see *id.*, point 4, para. bridging p. 2-3). Based on the usage of both *"once daily"* and *"no more than once daily"* in the application text, the Examining Division felt that the term *"once daily"* may be misconstrued to include dosages administered *"more than"* once daily. The Examining Division then explicitly suggested that:

> *"in order to meet the requirements of Art. 84 and to avoid further objections under Art. 54 EPC it is suggested to reformulate present claim 3 by including the feature "**no more than** once daily for at least five consecutive days"* (see *id.*, p. 3, 1st para.).

(54) To overcome this purported clarity objection, the suggestion was followed and *"once daily"* was clarified in good faith to *"no more than once daily"*. This was a mere clarification and did not change the meaning of the claim, as *"more than once daily"* is not, and was never intended to be, encompassed by the term *"once daily"*.

(55) Performing this clarification was also in full compliance with Art. 123(2) EPC, because, as explained in section D.2.2 above, and in more detail in section E.3.3 below, WO'474 uses *"once daily"* and *"no more than once daily"* synonymously. Thus, granted claim 1 does not contain added matter and the opponents' corresponding attacks are unjustified.

D.3 Combination of features "half life of 10 hours" and "compound (I)" in claim 1 complies with Art. 123(2) EPC

(56) O1, O8, and O11 argue that there would be no original disclosure for the combination of the feature "half life of 10 hours" with the feature "compound (I)", i.e. rivaroxaban, in granted claim 1. In particular, O1, O8, and O11 argue that:

a) the feature "plasma concentration half life of 10 hours or less" would only have been disclosed in combination with the generic term "factor Xa inhibitor", but not with the specific compound rivaroxaban;

and O1 and O11 further argue that:

b) the half life of rivaroxaban is disclosed in the patent to be 4 to 6 hours, which would not be equal to 10 hours or less.

(57) In contrast to opponents' view, the combination of rivaroxaban and the feature *"plasma concentration half life of 10 hours or less"* has **literal support** in the application as originally filed. See, for example, originally filed independent claims 1 and 3 and dependent claim 6, which refers back to both claims 1 and 3 of WO'474. In light of this direct support in the application as originally filed, the granted claims fully comply with Art. 123(2) EPC.

(58) Finally, as will be explained in section E.3.2 below, the skilled person recognizes feature 1.5 as a **redundant feature** because the **half life is a property inherent to a given compound**. This understanding is also confirmed by almost all opponents in their respective grounds of opposition (an overview of the opponents' respective statements is attached as **D57**). As an inherent feature, it is already included in the recitation of rivaroxaban in feature 1.2 of claim 1, which the specification of the Opposed Patent defines as having a plasma concentration half life of 4-6 hours (see *id.*, para. [0017]). In light of this redundancy, feature 1.5 does not add matter.

E SUFFICIENCY OF DISCLOSURE AND ENABLEMENT (ART. 100(b), 83 EPC)

(59) The Opposed Patent discloses the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

E.1 Summary of opponents' insufficiency arguments

(60) All opponents except O13 argue against sufficiency of disclosure. Opponents' assertions can be summarized as suggesting that the Opposed Patent has either failed to disclose information required for the skilled person to carry out the invention or has failed to provide sufficient information to determine the success of the invention.

(61) Specifically, opponents make the following assertions:

- O6, O7, and O11 consider the feature ***"rapid-release tablet"*** too unclear for the skilled person to carry out the invention. O6 and O11 claim that no **method for manufacturing** a rapid-release tablet was disclosed and O11 concludes therefrom that the feature would therefore amount to a **result to be achieved** (see section E.3.1 below).
- O2, O3, and O5 consider the feature *"plasma concentration half life of 10 hours or less"* to **implicitly define a patient group** (see section E.3.2.1 below).
- O2, O3, and O6 assert that a **measurement method** for monitoring blood plasma concentrations and determining the half life of rivaroxaban would be required (see section E.3.2.2 below).
- O1 and O9 assert a lack of enablement across the entire ***"range of plasma concentration half lives"***. Similarly O8 objects that there would be no teaching on ***"influencing or adjusting*** *the half life"* in the Opposed Patent (see section E.3.2.3 below).
- O1, O4, O8, and O12 argue it is not credible that the desired therapeutic effect is also achieved with dosing rivaroxaban ***"less than once daily"*** (see section E.3.3 below).
- O9, O10, and O12 consider the claimed subject matter not enabled over the **entire breath** of rivaroxaban **dose amounts** encompassed by claim 1 (see section E.3.4.1 below).
- O1, O4, O5, O6, and O8 consider the claimed subject matter not enabled over the **entire breath** of prophylactic and therapeutic **indications** encompassed by claim 1 (see section E.3.4.2 below).

- O5 and O8 consider the claimed subject matter not enabled over the **entire breath** of **patient groups** encompassed by claim 1 (see section E.3.4.3 below).
- O1, O5, and O8 additionally criticize in their insufficiency arguments particular aspects of the **clinical trial data of Example 1** of the Opposed Patent (see section E.3.5 below).

(62) None of the opponents' objections are justified or lead to an insufficiency under Art. 83 EPC. As explained in general in section E.2 below, the Opposed Patent discloses the claimed dosage regimen in a manner sufficiently clear and complete for it to be carried out by the skilled person. Indeed, it has been successfully carried out by the skilled person for the better part of a decade and patients are benefitting from it every day. Opponents' specific objections will be addressed in detail in section E.3 below.

E.2 The Opposed Patent fulfills the requirements of Art. 100(b) and 83 EPC

(63) Art. 100(b) and 83 EPC require the European patent to disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, wherein 'the invention' refers to the subject matter defined by the claims of the patent.

(64) Granted claim 1 itself already gives the skilled person clear and simple instructions on how to carry out the invention:

a) A known compound ("rivaroxaban", feature 1.2) must be

b) formulated in a specific oral dosage form ("a rapid-release tablet", feature 1.1)

c) and administered in a defined dosage regimen ("no more than once daily for at least five consecutive days", feature 1.4)

d) to a particular patient group (patients in need of "treatment of a thromboembolic disorder", feature 1.4).

(65) Feature 1.5 of claim 1 (*"wherein said compound has a plasma concentration half-life of 10 hours or less when orally administered to a human patient"*) is not relevant for carrying out the invention. Being an inherent (and in principle redundant) feature, it is automatically fulfilled as soon as rivaroxaban is employed in the claimed treatment. See section E.3.2 below.

(66) For a second medical use claim directed to a dosage regimen to be sufficiently enabled, the skilled person must be able to

1. prepare the compound in the dosage form claimed, and

2. the claimed dosage form and regimen must have proven effective in treating the claimed disorders.

Regarding **requirement (1)**, none of the opponents have contested that **rivaroxaban** can be readily obtained by the skilled person.

(67) Clearly, this is the case. At the effective filing date of the Opposed Patent, rivaroxaban was a **known compound**. The Opposed Patent in para. [0014] refers to **D1a** which in its Example 44 on p. 80-83 teaches the chemical synthesis of rivaroxaban and depicts its structure. There can be no doubt that the skilled person was able to obtain and to use rivaroxaban.

(68) O6's, O7's, and O11's objection to the term "**rapid-release tablet**" as being allegedly ill-defined is – if at all – a **clarity objection** under Art. 84 EPC, which, as recently again confirmed in **G 3/14**, cannot be dealt with in Opposition Proceedings. See section E.3.1.1 below.

(69) For a detailed rebuttal of opponents' individual objections to the term "*rapid-release tablet*", see section E.3.1.2-E.3.1.4 below. Importantly, O6's, O7's, and O11's objection to the term "**rapid-release tablet**" as being allegedly ill-defined is also directly contradicted by almost all other opponents in their novelty and inventive step arguments, where the opponents argue (1) that a rapid-release tablet would have been a common, if not the most common, oral dosage form, (2) that any tablet that is not a sustained- or retarded-release tablet would be a rapid-release tablet, or (3) suggest that the terms "*rapid-release tablet*" and "*tablet*" would be the same (see the overview attached as **D58**). To simplify matters for the present proceedings, we will adopt for the purpose of the present proceedings the understanding proposed by the majority of the opponents that any tablet that is not a sustained- or retarded-release tablet is a "*rapid-release tablet*" as recited in claim 1 of the Opposed Patent.

(70) Regarding **requirement (2)**, there can be no doubt that a once-daily administration of rivaroxaban is effective in the therapeutic and/or prophylactic treatment of thromboembolic disorders in general.

(71) Proof for this is provided by both the phase II clinical trial data contained in the Opposed Patent (for a detailed discussion, see inventive step section G.6.1 below) as well as the host of post-published data obtained in the numerous and extensive further clinical trials that investigate rivaroxaban for the treatment of a diverse **range of thromboembolic disorders**. Importantly, these additional clinical trials have already resulted, *inter alia*, in the marketing approval of rivaroxaban (tradename: Xarelto®) for the prophylaxis and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as for the prevention of stroke and

systemic embolism in patients with nonvalvular atrial fibrillation (for a detailed discussion, see section C.1 above and inventive step section G.6.2 below). As explained in these sections, Xarelto® has been approved in the claimed dosage regimen in more than 130 countries worldwide and is approved for more indications in the area of venous and arterial thromboembolism than any of the other non-vitamin-K-dependent oral anticoagulants (see **D46**, p. 70, 2nd para.).

(72) The available data also support a broad **range of doses**. Xarelto® is approved *inter alia* in the following doses: 10 mg, 15 mg, and 20 mg. Here clinical efficacy is proven by the underlying phase III clinical trials (for a detailed discussion, see inventive step sections G.6.2.1 to G.6.2.3 below). In addition, the phase II dose-ranging studies that led to the approval of Xarelto® also demonstrated clinical efficacy of further doses of rivaroxaban, e.g., 5 mg, 30 mg, and 40 mg once daily ("od") and up to 30 mg twice daily ("bid") (see **D59**, the EMA's 2008 Committee for Medicinal Products for Human Use Assessment Report, "CHMP AR 2008", p. 23-24, and section G.6.2.4 below)

(73) Thus, the data included in the Opposed Patent have meanwhile been confirmed and expanded to include a **range of doses** and **a range of different indications** in a vast number of clinical and post-marketing studies. In light of this wealth of evidence, opponents cannot dispute that the claimed dosage regime is effective across a broad spectrum of thromboembolic indications and dosages tested.

(74) All opponents merely set up hypothetical difficulties with the claims and assert that "*therefore*...." they would not comply with Art. 83 EPC. Speculation that certain theoretical embodiments or variants will not work is irrelevant if (1) the **Opposed Patent discloses at least one way** to carry out the invention and (2) the **suitability** of the compound for the claimed treatment **is plausible** across the scope of the claim[1].

(75) As shown above, there is ample evidence that the invention can be carried out. The skilled person certainly does not sit and contemplate or try to design hypothetical embodiments in which he might expect difficulties of the type put forward by the opponents (see sections E.3.1-E.3.4 below for a detailed discussion thereof). The fact remains that the claimed dosage regimen can be carried out by those skilled in the art, and indeed it is carried out in the field.

[1] For case law discussion, see especially, extensive case law on sufficiency including fundamental decisions **T 292/85**, headnotes 1 and 2; **T 81/87**, Reasons, point 4; **T 301/87**, Reasons, points 4.3-4.9; **T 19/90**, Reasons, points 3.3-3.9; and specifically for (second) medical use claims, decisions **T 433/05**, Reasons, points 28-29; **T 801/06**, Reasons, points 25-30; **T 1396/06**, Reasons, points 39-40; **T943/13**, Reasons, section 2; **T 1023/02**, Reasons, points 48-50; **T 2181/08**, Reasons, points 15-19; and **T 1616/09**, Reasons, section 6.2.

(76) According to the "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter II.C.8,

> *"The objection of lack of sufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts [...].Otherwise it is unlikely to succeed".* (emphasis added)

Importantly, the opponents have provided **no verifiable facts** and **no evidence of any failure to carry out the invention**. It is, however, established jurisprudence of the Technical Boards of Appeal of the EPO that, in order to establish insufficiency, the **burden of proof** is upon the opponent to establish, on the balance of probabilities, that a skilled reader of the patent, using his common general knowledge, would be unable to carry out the invention (see "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter II.C.8). In the present case, the **opponents have not discharged their burden of proof** for establishing a lack of sufficient disclosure. Already for this reasons, opponents' insufficiency arguments need to be dismissed.

E.3 The opponents' insufficiency arguments lack merit

(77) Patentee responds to the specific assertions put forward by the respective opponents as follows:

E.3.1 The feature "Rapid-release tablet" is clear and enabled

(78) O6, O7, and O11 consider the term "rapid-release tablet" **unclear**.

- O6 in its section 5.2 alleges that the reference to a **USP method** in **paragraph [0030]** of the Opposed Patent is insufficient to determine whether or not a tablet is a rapid-release tablet when compared with the requirements stated in **D24**, the *European* pharmacopoeia. As a consequence, the skilled person would not be able to determine whether he is *"working within the forbidden area of claim 1"* (see O6, p. 8, 5.2.4, l. 3-5). Similarly, O7 at p. 6-7 refers to **T 252/02** to conclude that the *"forbidden area of the claim is not clearly delimited"* (see O7, p. 6, 2nd para. from bottom, bold print).

- O6 in its section 5.3 and O11 in its section 4.3 object to the **reference** in **paragraph [0031]** of the Opposed Patent as allegedly being incorrect. Thus, no method for preparing a "rapid-release tablet" would be disclosed, which claim term would therefore only constitute an unallowable *"result to be achieved"* (O11, p. 6, l.1-2). O11 in this respect refers to **T 339/05**, **T 123/06** and **T 809/07**.

Patentee disagrees with all of these objections for the following reasons.

E.3.1.1 Clarity objections under Art. 84 EPC form no ground of opposition

(79) First, O6's, O7's and O11's objection to the term "rapid-release tablet" as being allegedly ill-defined is – if at all – a **clarity objection under Art. 84 EPC.** However, as recently again confirmed in **G 3/14**, such clarity objections cannot be dealt with in Opposition Proceedings.

(80) Similarly, O6's and O7's objection that the skilled person needs to be able to determine whether he is ***"working within the forbidden area of claim 1"*** is also a matter of **Art. 84 EPC**, not Art. 83 EPC. This has now been clearly set out in the Guidelines for Examination in the EPO, 2016, F-III.11, which cite more recent case law that has superseded **T 252/02** cited by O6:

> *"11. Sufficiency of disclosure and clarity*
>
> *An ambiguity in the claims may lead to an insufficiency objection. However, ambiguity also relates to the scope of the claims, i.e. Art. 84 (see F-IV, 4).* ***Normally****, therefore, an ambiguity in a claim* ***will lead to an objection under Art. 83 only if the whole scope of the claim is affected, in the sense that it is impossible to carry out at all the invention defined therein****. Otherwise an objection under Art. 84 is appropriate (see T 608/07).*
>
> *In particular (see T 593/09), where a claim contains an ill-defined ("unclear", "ambiguous") parameter (see also F-IV, 4.11) and where, as a consequence, the skilled person would* ***not know whether he was working within or outside of the scope of the claim****, this, by itself, is* ***not a reason to deny sufficiency of disclosure*** *as required by Art. 83. Nor is such a lack of clear definition necessarily a matter for objection under Art. 84 only. What is decisive for establishing insufficiency within the meaning of Art. 83 is whether the parameter, in the specific case,* ***is so ill-defined that the skilled person is not able, on the basis of the disclosure as a whole and using his common general knowledge, to identify (without undue burden) the technical measures necessary to solve the problem underlying the application at issue****.*
>
> *There is a delicate balance between Art. 83 and Art. 84, which has to be assessed on the merits of each individual case. Care has therefore to be taken in opposition that an* ***insufficiency objection is not merely a hidden objection under Art. 84****, especially in the case of* ***ambiguities in the claims*** *(T 608/07)."* (emphasis added)

(81) **T 252/02** cited by O7 at p. 6-7 is also particularly inapposite to the present case because its reasoning was context-specific to the patent and claim terms there at issue. **T 252/02** concerned a **so-called "parameter-invention"**, in which the success of the invention depended on the adherence to particular numerical threshold values recited in the claims for certain ill-defined parameters[2] (*"cup crush peak load value"* and *"cup crush energy value"*). By contrast, the Opposed Patent concerns no such "parameter-invention". The term *"rapid-*

[2] In the case underlying **T 252/02**, the claimed parameters read: *"wherein said laminate (12;13;15) has a cup crush peak load value of no more than 150 grams, a cup crush energy value of no more than 2250 g/mm, a hydrostatic head of at least 15 cm, and a porosity of at least 0.0236 m^3/s (50 scfm)."* (emphasis added)

release tablet" in granted claim 1 does not correspond to a numerical "parameter", the determination of which would be required for practicing the invention.

E.3.1.2 The majority of opponents assert that "rapid-release tablet" is a term of art, which as such is therefore clear and enabled

(82) O6's, O7's, and O11's objection to the term "**rapid-release tablet**" as being unclear and insufficiently disclosed is directly contradicted by almost all opponents in their novelty and inventive step arguments. Most opponents argue along the lines that (1) a rapid-release tablet would have been a common, if not the most common, oral dosage form, (2) that any tablet that is not a sustained- or retarded-release tablet would be a rapid-release tablet or (3) suggest that the terms "*rapid-release tablet*" and "*tablet*" would be the same (see the overview attached as **D58**, in particular O1, p. 13, 2nd para.; O2 and O3, p. 3, para. (17) and p. 7, section 6.4; O5, p. 9-10, bridging sentence.; O6, p. 4, para. 4.4.1; O7, p. 4, final para., p. 5, penultimate para.; O8, p. 9-10, bridging para.; O9, p. 3, final para., p. 10, 3rd para., p. 11, 3rd para.; O10, p. 6, 1st para.; O13, p. 8-9, bridging para.). As stated above, to simplify matters for the present proceedings, we will adopt for the purpose of the present proceedings the understanding proposed by the majority of the opponents that any tablet that is not a sustained- or retarded-release tablet is a "rapid-release tablet" as recited in claim 1 of the Opposed Patent.

(83) Importantly, opponents refer in this respect *inter alia* to the prior art **textbooks D4, D5, D18,** and **D43** and prior art documents **D44** and **D45**, all of which teach tablets and that these were the most common dosage form. **D4**, in its introductory para. to "TABLET TYPES Classification of tablets" (see **D4**, p. 410, right col.), confirms that rapid-(immediate-)release tablets were known:

> ***"TABLET TYPES***
> ***Classification of tablets***
> *Based on their drug-release characteristics, tablets can be classified into three types, immediate release, extended release and, delayed release. For* ***immediate-release tablets*** *the drug is intended to be* ***released rapidly*** *after administration, or the tablet is dissolved and administered as a solution.* ***This is the most common type of tablet*** *and includes disintegrating, chewable, effervescent, sublingual and buccal tablets."*
> (emphasis added)

Thus, even if one entertained the allegation that the exact boundaries of term "rapid-release tablet" were unclear, this would still not lead to a lack of enablement because numerous working embodiments of that term were at the skilled person's immediate disposal.

(84) Accordingly, also cases **T 339/05, T 123/06,** and **T 809/07** cited by O11 are inapposite, because the **well-defined** claim term "rapid-release tablet" is **a term of art** that does not

present a **"result to be achieved"**- or an **"invitation to perform a research program"**-situation as was underlying those cases (see, e.g., **T 123/06**, p. 8, end of 1st para.) . In addition, the claims at issue in **T 339/05** and **T 809/07** – like **T 252/02** discussed above – required particular numerical parameters to be fulfilled in order to practice the invention[3] and are therefore not applicable to the present case.

(85) Finally, the Opposed Patent at the end of para. [0029] distinguishes between *"tablets releasing the active compound rapidly **or** in a modified manner"* (emphasis added). From this it is clear to the skilled person that the Opposed Patent considers a tablet a rapid-release tablet if it is not specifically designed to release the active agent in a modified form. A host of such tablets was at the skilled person's immediate disposal and the opponents have not substantiated any concrete difficulties the skilled person would face in preparing such tablets.

E.3.1.3 Reference to the USP release method in para. [0030] of the Opposed Patent

(86) Regardless of the claim term "rapid-release tablet" being a well-defined term of art, the Opposed Patent in para. [0030]-[0031] also contains a clear statement of what it understands a "rapid-release tablet" to include. Para. [0030] of the Opposed Patent explains in this respect:

> *"rapid-release tablets are in particular those which, according to the USP release method using apparatus 2 (paddle), have a Q value (30 minutes) of 75 %."*
> (emphasis added)

The objections raised by O6 in its section 5.2 against the USP method described in para. [0030] of the Opposed Patent is immaterial to the question of sufficiency of disclosure, because (1) the granted claims do not specifically refer to this USP method, and (2) it is in any event within the competence of a person of ordinary skill in the art to prepare rapid-release tablets that comply with the USP release method (see sections E.3.1.2 above and E.3.1.4 below).

(87) The skilled person understands "USP" in the context of para. [0030] of the Opposed Patent to stand for "United States Pharmacopeia". Thus, O6's reference to **D24**, the *European* pharmacopoeia, is irrelevant. O11 has submitted an excerpt from the US Pharmacopeia (see **D38**), which will be referred to in the following. As explained on p. 2, 4th para. of **D38**, the

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[3] In the case underlying **T 339/05**, the claimed parameter read: *"characterised in that the said compound shows a crystallinity of less than 1% when a melt of the compound is cooled at a rate of 5°C/min to past its solidification path and is then heated at a rate of 20°C/min to above its melting temperature."*;
in the case underlying **T 809/07**, the claimed parameter read: *"dadurch gekennzeichnet, daß die Komponenten des Systems in Wasser mit einem Energieeintrag von weniger als 150 J/cm³, bezogen auf die Summe der Volumina der Komponenten und Wasser, eine wäßrige Dispersion mit einer Körnigkeit von <60 µm ergeben (bestimmt nach ISO 1524: 1983)"*.

Q value is a typical specification, which specifies the amount of active ingredient dissolved, expressed in percentage. Thus, the skilled person understands para. [0030] of the Opposed Patent to teach that a rapid-release tablet according to the patent is in particular one that releases 75% of the drug within 30 minutes when tested using apparatus 2 (paddle) described in the USP (see **D38**, USP section <711>, p. 2). This is perfectly in line with the skilled person's understanding, which was put forward by the majority of the opponents (see overview in **D58**), of a rapid-release tablet being a known tablet in which the release of the drug is not sustained or delayed.

(88) O6 in para. 5.2.3 and 5.2.4 merely puts forward **hypothetical difficulties** based on **D24**, the *European* Pharmacopoeia, according to which certain pieces of information would need to be prescribed. This information, however, is clear to the skilled person from para. [0030] of the Opposed Patent read in conjunction with his common general knowledge and **D38**, the USP referred to in para. [0030] of the Opposed Patent. Briefly, para. [0030] of the Opposed Patent already teaches the apparatus (paddle, apparatus 2), the time (30 minutes), and the quantity of active ingredients required to dissolve within a prescribed time (Q value: 75% after 30 minutes).

(89) **D38**, i.e., the USP itself, provides the remaining information:

Regarding the **temperature, composition, and volume** of the dissolution medium, **D38** at p. 1, 3rd and 4th para. from the bottom states:

> *"**Generally**, experiments are conducted at **37°**.*
>
> *The dissolution medium **preferably is deaerated water** or, if substantiated by the solubility characteristics of the drug or the formulation, a **buffered aqueous solution (typically pH 4 to 8)** or a **dilute acid (0.001 N to 0.1 N hydrochloric acid)** may be used. The **usual volume** of the medium is **500 to 1000 mL**".* (emphasis added)

Choosing 37°C and an acidic pH for the dissolution medium also makes perfect sense to the skilled person as this mimics the *in vivo* conditions in the stomach, the place where dissolution of a rapid-release tablet will primarily occur in the body.

Regarding the **rotation speed**, **D38** at p. 1, penultimate para. states in respect of the prescribed Apparatus 2 (paddle):

> *"The **most common operating speeds** are [...] **50 rpm** for Apparatus 2 (paddle) for solid-oral dosage forms [...]".*

Regarding the **sampling method**, **D38** in USP section <711>, p. 5, right col., 3rd para. from the bottom states:

> *"Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the Dissolution Medium and the top of the rotating basket or blade, not less than 1 cm from the vessel wall."*

The choice of the **method of analysis** as stated in the penultimate bullet point of para. 5.2.3 of O6, is not expected to influence the Q value. Being expressed as a ratio (% of the total amount of active ingredient), any differences in the analysis methods will be balanced out.

(90) In summary, O6's concerns regarding the reference to the USP method in para. [0030] of the Opposed Patent are unjustified. O6 only alleges hypothetical difficulties, without substantiating by means of verifiable facts or evidence that any of the choices in the measurement parameters discussed above would lead to an inability of the skilled person to carry out the invention as required by Art. 83 EPC.

E.3.1.4 Reference to preparation method of D60 in para. [0030] of the Opposed Patent

(91) As explained in section E.3.1.2 above, rapid-release tablets, including their preparation, were well-known and available to the skilled person. Regardless, the Opposed Patent in para. [0031] also provides a reference for the preparation of rapid-release tablets containing rivaroxaban as active ingredient:

> *"Very particularly preferred are rapid-release tablets containing **5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide*** [=rivaroxaban] *as active ingredient. Preparation of **such tablets** is for example described in **PCT/04/01289*** [=**D60**]." (emphasis and explanations in square brackets added)

The referred to PCT application PCT/04/012897, published as WO 2005/060940 A2 (**D60**) contains a detailed experimental section on how to prepare particularly well-suited rapid-release tablets of rivaroxaban.

(92) Patentee recognizes that – as noted by O6 and O11 – the reference to the PCT application **D60** in para. [0031] of the Opposed Patent contains a minor clerical error (cf. O6, para. 5.3.2 and 5.3.3, and O11, p. 3, penultimate para.): The final digit of the application number was inadvertently omitted; the correct number is PCT/04/012897. When trying to retrieve this reference, the skilled person would have immediately realized the clerical error, because there is no PCT application no. PCT/04/01289. Subsequently, the skilled person would have had no difficulty to unambiguously identify the correct reference: A simple search in a patent database program such as THOMSON INNOVATION® for patent applications with the country code WO (PCT-applications) filed in the year of 2004 and containing the chemical entity "1,3-oxazolidin-5-yl" as identified in para. [0031] of the Opposed Patent in its claims or description

(original search string: AY=(2004) AND CC=(WO) AND ALL=("1,3-oxazolidin-5-yl")) yields only 6 patent families (s. Annex **D61**):

#	**1. Publication No.** **2. Application No.** **3. Assignee/Applicant**	**Title** (emphasis added)
1	1. WO2005068456A1 2. WO2004EP14870A 3. Bayer HealthCare AG	**Production method**
2	1. WO2005060940A2 (=**D60**) 2. **WO2004EP12897A** 3. Bayer HealthCare AG	Method for the production of a **solid, orally applicable pharmaceutical composition**
3	1. WO2005009436A1 2. WO2004IB2461A 3. Pharmacia & Upjohn Company LLC	Dispersible formulation of an **anti-inflammatory agent**
4	1. WO2004089943A1 2. WO2004IB1135A 3. Pharmacia & Upjohn Company LLC	**Antimicrobial** [3.1.0] bicyclohexylphenyl-oxazolidinone derivatives and analogues
5	1. WO2004087697A1 2. WO2004IB943A 3. Pharmacia & Upjohn Company LLC	N-aryl-2-oxazolidinone-5-carboxamides derivatives with **antibacterial activity**
6	1. WO2005054234A2 2. WO2004IN276A 3. Deshpande Prasad Keshav	Substituted piperidino phenyloxazolidinones having **antimicriobial activity** with improved in vivo efficacy

Of these six hits, only two concern rivaroxaban, and only one contains in its application number the digits "1289": hit #2, the correct PCT application PCT/EP04/012897, published as WO 2005/060940 A2 (**D60**). It is also the only hit which has a title and a claim relating to the production of solid oral dosage forms such as tablets (see Annex **D61**, hit 1 concerns the synthesis of rivaroxaban, hits 3-4 are completely unrelated to rivaroxaban, being antimicrobial/anti-inflammatory compound patents). Thus, the reference to **D60** in para. [0031] of the Opposed Patent is sufficiently identified for the skilled person to recognize and resolve the error.

(93) **D60**, albeit being a post-published reference, must be taken into account when assessing the question of sufficiency of disclosure. First, it is established case law that references in the patent description may also enable the skilled person to carry out an invention (see the "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter II-C.3.2). Second, the EPO's requirements for cross-referencing to a document that had not yet been publicly available at the filing date of a patent are fulfilled in the present case (see the Guidelines for Examination in the EPO, 2016, H-IV.2.2.1 and the "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter II-C.3.2, both referring to **T 737/90**). Briefly, the EPO was the receiving Office both for the PCT application underlying the Opposed Patent as well as for PCT/04/012897 filed November 13, 2003. Thus, the latter was available to the EPO at the priority date of the

Opposed Patent. PCT/04/012897 was published as WO 2005/060940 A2 on July 7, 2005 (**D60**), i.e. before the publication date of the application underlying the Opposed Patent (August 3, 2006). In summary, the requirements set out in the Guidelines for Examination in the EPO, 2016, H-IV.2.2.1 are fulfilled. Para. [0031] of the Opposed Patent and its reference to **D60** are therefore to be taken into account when assessing the question of sufficiency of disclosure.

(94) In **D60**, starting on p. 7, the skilled person finds detailed instructions in the experimental section on how to prepare particularly well-suited rapid-release tablets of rivaroxaban. Consequently there is no basis for the opponents' conclusions that the term "rapid-release tablet" would lead to an insufficiency under Art. 83 EPC.

E.3.2 The feature "plasma concentration half life of 10 hours or less" is an intrinsic property of rivaroxaban and therefore a redundant feature

(95) In their identical submissions, O2 and O3 take the astonishing position that feature 1.5 of claim 1 of the Opposed Patent (*"the compound has a plasma concentration half-life of 10 hours or less when orally administered to a human patient"*) would **implicitly define a patient group**. In this respect, O2 and O3 refer to a post-published Xarelto® product information leaflet (**D8**), which states that in **elderly patients** (age >75 years, see **D59**, p. 54, 2nd para.) the half life of Xarelto® was found to be **11 to 13 hours** (**D8**, p. 2, left col., last 2 lines under "After procedure"). O5, albeit in a different context, also seems to suggest that the success of the claimed treatment would depend on the particular half life of rivaroxaban in the patient group studied. See O5 at p. 8, 2nd para. of its notice of opposition referring to **D23**, p. 413, left col., 2nd para., which also states the half life of rivaroxaban in the elderly to be in the range of 11 to 13 hours.

(96) O2 and O3 go on to conclude that in order for the skilled person to be aware that he is working within the scope of the claim he would have to **measure and monitor the blood plasma concentration** of each patient following administration. No measurement method for this would be disclosed. O6 in section 5.1 similarly objects to feature 1.5 on the circumstance that the Opposed Patent **does not describe a method for monitoring the blood plasma concentration** of rivaroxaban *in vivo*. In this regard, O2 (para. 71-72), O3 (para. 71-72), and O6 (section 5.1) rely on the skilled person having to be able to determine whether he was working within the scope of the claims and point to certain case law or to section F-III-2 of the 2015 Guidelines for Examination concerning enablement requirements for claims containing *"parameters"*.

(97) Patentee disagrees. As feature 1.5 of claim 1 must be regarded an **inherent property** of rivaroxaban, which **does not define a patient group**, no method for monitoring the blood

plasma concentration of rivaroxaban is required to carry out the invention or to determine whether one falls within the scope of the claims (see section E.3.2.1 below). Regardless, the skilled person of course knows how to monitor blood plasma concentrations of active pharmaceutical ingredients (see section E.3.2.2 below). The remaining objections of the opponents (O1, O8 and O9) regarding the feature plasma concentration half life are rebutted in section E.3.2.3 below.

E.3.2.1 Plasma concentration half life of 10 hours or less does not define a patient group

(98) The term *"wherein said compound has a plasma concentration half life of 10 hours or less when orally administered to a human patient"* in claim 1 of the Opposed Patent is not a definition of the patient group. In fact, this term is understood by the skilled person (and has always been used and regarded by the Applicant and the Examining Division) as a feature further characterizing the term "direct factor Xa inhibitor" recited in originally filed claims 1 and 3.

(99) Para. [0001] of the Opposed Patent in its summary of the invention indicates:

> *"... wherein **the factor Xa inhibitor has a plasma concentration half life** indicative of a bid or tid administration interval, e.g. of 10 hours or less".* (emphasis added)

Thus, already the very first sentence of the Opposed Patent makes clear that a half life of 10 hours or less is a feature directly related to and defining **the factor Xa inhibitor** (and not a patient group).

(100) This is confirmed again in para. [0012] of the Opposed Patent which states:

> *"Surprisingly, it has now been found in patients at frequent medication that once daily oral administration of **a direct factor Xa inhibitor with a plasma concentration half life time** of 10 hours or less...".* (emphasis added)

The term "with" in the above sentence signifies that the plasma concentration half life is a feature inherent to the factor Xa inhibitor described and does not define a group of patients.

(101) Similarly, also para. [0013] of the Opposed Patent teaches that *"the present invention"* (i.e. the claimed subject matter) relates to the use of a direct factor Xa inhibitor (i.e. rivaroxaban recited in feature 1.2 of granted claim 1) for the manufacture of a medicament, wherein said inhibitor **has** a plasma concentration half-life of 10 hours or less.

(102) The skilled person usually refers to the half life measured in healthy normal adults, especially because in the course of drug development this is the first half life that is obtained in phase I

studies. This is confirmed by the standard pharmacology textbook Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, the first chapter from its 1985 version being cited in para. [0009] and para. [0011] of the Opposed Patent and attached as **D9a** (the corresponding chapter from the 10th ed. of that textbook was submitted by the opponents as **D9**). Appendix II to the 10th ed. of that textbook, entitled *"Design and optimization of dosage regimens: pharmacokinetic data"* (attached as **D9b**), for example, states (emphasis and explanation in square brackets added):

> *"Unless otherwise indicated in footnotes, data reported in the table* [NB: table lists half life values i.a., see p. 1924] *are those* ***determined in healthy adults.*** *" (p. 1917, right col., final para.)*
>
> *"Unless otherwise specified, the values in Table A-II-I* [NB: table lists half life values i.a., see p. 1924] *represent* ***mean values for populations of normal adults"****.*
> *(p. 1921, right col., final para.)*

This confirms that unless otherwise stated, the skilled person understands half life values to correspond to those determined in healthy normal adults.

(103) Regarding the Opposed Patent, there can be no ambiguity regarding the meaning or measurement of rivaroxaban's "half life" in claim 1, because para. [0017] states exactly what the Opposed Patent defines rivaroxaban's half life to be (4-6 hours). It corresponds to the established jurisprudence of the Technical Boards of Appeal of the EPO that a patent, being a legal document, is its own dictionary (see, e.g., T 311/93, point 2.4 of the Reasons; T1321/04, point 2.2 of the Reasons; T1388/09, point 2.5.2 of the Reasons; and T 500/01, point 6 of the Reasons). In line with this, Art. 69(1) EPC stipulates that *"the description and drawings shall be used to interpret the claims"*. When grounded by the context of the claims, the patent specification, and the skilled person's common general knowledge, feature 1.5 is clearly understood as a feature inherent to rivaroxaban.

(104) Patentee's claim construction, which is technically sensible and takes into account the whole disclosure of the Opposed Patent (see in particular para. [0012], [0013] and [0017] read in conjunction), is also confirmed by O1, O2, O3, O4, O5, O8, O9, O10, O11, and O13, which at some point in their submissions all have conceded that feature 1.5 of claim 1, i.e. the *"half life of 10 hours or less"*, must be considered an inherent feature of feature 1.2, i.e. rivaroxaban.

See, e.g., O2 and O3 at para. (06):

> *"This feature of the claim cannot be seen to limit the scope of the invention in any way, as the plasma concentration half-life of any drug is an inherent physiochemical property resulting from the interaction of the chemical structure of the drug per se with human blood."*

For an overview table listing all of the opponents' respective statements, see attached **D57.**

(105) Whereas the feature *"plasma concentration half life of 10 hours or less"* was present already in the originally filed independent claims, these claims were directed to factor Xa inhibitors in general and only during prosecution were limited to rivaroxaban as a reaction to the Examining Division's Communication pursuant to Art. 94(3) EPC of July 26, 2010 (**D56**). After this claim amendment, the direct factor Xa inhibitor rivaroxaban was clearly defined in the claims by its IUPAC name, thereby obviating the need to additionally define the compound by its half life of 10 hours or less. In light of the half life definition given for rivaroxaban in para. [0017] of the Opposed Patent (4-6 hours), the limitation of the feature *"factor Xa inhibitor"* to rivaroxaban in claim 1 made the additional feature *"plasma concentration half life time of 10 hours or less"* **redundant.**

(106) In summary, the feature *"plasma concentration half-life of 10 hours or less"* was always and is used in the Opposed Patent as a feature to characterize the factor Xa inhibitor. After limiting the direct factor Xa inhibitor to rivaroxaban, which is defined in para. [0017] of the Opposed Patent to have a plasma concentration half life of 4-6 hours, the feature *"plasma concentration half-life of 10 hours or less"* became redundant. As also the majority of opponents have realized (see overview table in **D57**), feature 1.5 is an inherent feature which is automatically fulfilled as soon as rivaroxaban is employed.

(107) Finally, it is a general principle in claim construction (see "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter II-A-6.1) that

> *"The skilled person, when considering a claim, should rule out interpretations which are* ***illogical*** *or which* ***do not make technical sense****. He should try, with synthetical propensity, i.e. building up rather than tearing down, to arrive at an interpretation of the claim which is* ***technically sensible and takes into account the whole disclosure of the patent. The patent must be construed by a mind willing to understand, not a mind desirous of misunderstanding*** *(****T 190/99****; confirmed inter alia in* ***T 437/98, T 1084/00, T 920/00, T 552/00, T 500/01, T 1023/02, T 749/03, T 859/03, T 1241/03, T 1418/04, T 906/05, T 405/06, T 1537/05, T 1204/06, T 1771/06****)."* (emphasis added)

O2's, O3's, and O5's claim interpretation does not make technical sense, because it would require the skilled person to determine the individual half life, i.e. measure a time course of rivaroxaban blood concentration in each patient to be treated following a test administration, and calculate the half life (cf. O2/O3, para. 71).

(108) This claim interpretation is clearly hypothetical and far removed from the capabilities, economic considerations, and daily practice of the physician, who does not determine individual half lives in patients. The physician relies on the half life published in the medical literature. Thus, in the context of the Opposed Patent, the skilled person refers to para. [0017]

where the half life of rivaroxaban is defined as being 4-6 hours when measured in the healthy male subjects of **D2**.

(109) O2 and O3 in para. 67 to 71 of their submissions clearly have construed claim 1 with *"a mind desirous of misunderstanding"*. In fact they only seem to have chosen this claim construction in order to be able to make their argument in subsequent para. 72 that the invention cannot be carried out without undue burden.

(110) O2's and O3's claim construction is not only entirely disconnected from the meaning of the claim to a person of ordinary skill in the art, but also from the context of the patent specification. There is no indication whatsoever in the Opposed Patent—neither that patients have to be selected before therapy according to the half life of the compound in their body, nor that half life would need to be measured in patients to be treated. Quite to the contrary, the example of the Opposed Patent includes a broad and not further selected patient group with an age range of 30 to 92 years (see para. [0041] of the Opposed Patent), the main inclusion criteria only being "adult men and postmenopausal women undergoing elective primary total hip replacement" (see para. [0037] of the Opposed Patent).

(111) If one were to follow O2's and O3's anomalous claim construction, then rivaroxaban's half life being 11-13 hours in the elderly (age > 75 years, see **D59**, p. 54, 2nd para.) would result in only a part of the patent's example to be included in the claim scope. Clearly this could not have been intended and such an interpretation can only be reached by *"a mind desirous of misunderstanding"*. As shown by the data discussed in section E.3.4.3 below, the claimed dosage regimen is also specifically effective in the elderly. Thus, there is no lack of sufficiency regarding this patient group.

(112) In addition, it should be kept in mind that for sufficiency purposes, the effective filing date of the Opposed Patent is the relevant date. See, e.g., **T 671/05**, point 4.1, 2nd para. which concerned claims related to a fast disintegrating tablet. Here, the Board commented that

> *"The content of the whole patent, i.e. the claims and the description (including the examples), has to be investigated by the skilled person in the light of the knowledge of the technical field involved, without making use of inventive skills.* ***On this point it must to be remembered that, for the requirements of sufficiency of disclosure, the relevant date to be considered is that of the effective filing date of the application.***" (emphasis added)

Thus, the claims should be interpreted from the vantage point of the skilled person **at the effective filing date** of the Opposed Patent.

(113) At that time, however, rivaroxaban was known to be within the class of factor Xa inhibitors with a half life of 10 hours or less. The only half lives that were known for the

pharmacokinetics of rivaroxaban in humans were the ones determined in healthy subjects. Unanimously, these had been reported to be well below 10 h (see, e.g., **D2**, l. 16: "4-6 h", cited in para. [0017] of the Opposed Patent and **D3**, l. 15: "3-4 h"). Thus, from the vantage point of the skilled person at the effective filing date of the Opposed Patent, feature 1.5 of claim 1 could only have been understood to be an inherent property of rivaroxaban. O9 on p. 14 also concedes this in its discussion of **D17**:

> *"The terminal half life is not explicitly described in D8* [≙**D17**]*, but at the time of filing the application would have been considered inherent in the administration of an oral dosage form of Rivaroxaban to be 10 hours or less, since in D2* [≙**D2**] *(of the same date as D8* [≙**D17**]*) it is stated 'the terminal half life was 4-6 hours".* (emphasis and explanation in square brackets added)

(114) In summary, there is absolutely no reason to impart an anomalous meaning to feature 1.5, i.e. to regard the feature *"plasma concentration half-life of 10 hours or less"* as a feature that would implicitly define a patient group. As evidenced by the overview provided in **D57**, O2 and O3 are alone in their errant interpretation of that feature, with the vast majority of opponents naturally understanding it to be an inherent property of rivaroxaban. This alone, already speaks for itself.

(115) Furthermore, the group of patients is already defined in claim 1 of the Opposed Patent by the feature that they are in need of treatment of a thromboembolic disorder. Also against this background, the skilled person when reading the patent specification would not interpret the feature *"plasma concentration half-life of 10 hours or less"* of claim 1 as additionally defining the group of patients to be treated.

(116) Finally, since the person skilled in the art would not regard the feature *"plasma concentration half-life of 10 hours or less"* as a definition of the patient group, monitoring blood plasma concentration of rivaroxaban *in vivo* as alleged by O2 and O3is not at all required to carry out the invention. Rather, feature 1.5 is understood by the skilled person to be redundant in the sense that it is an inherent property of feature 1.2, i.e. that is automatically fulfilled as soon as rivaroxaban is used.

(117) As the "parameter" half life does not need to be determined when carrying out the invention, the reference to the Guidelines for Examination in the EPO and the case law cited by the opponents regarding sufficiency of disclosure of parameter inventions is not pertinent to the present case (see O2 and O3, para. (72), and O6, para. 5.1.3). Finally, even if one were to assume that the "parameter" half life would need to be determined to know whether one is falling within the scope of the claims, which is not the case, then this would still only raise issues under Art. 84 EPC, not Art. 83 EPC, as discussed in section E.3.1.1 above.

E.3.2.2 Methods for monitoring blood plasma concentrations and determining half life were known

(118) The patent specification and the host of post-published data discussed in more detail in section G.6.2 below leave no doubt that the invention can be carried out simply by administering rivaroxaban in the claimed dosage regimen. As explained in the preceding section, the skilled person does not need to monitor the blood plasma concentration or determine the half life of rivaroxaban in order to carry out the invention. It is already stated in para. [0017] of the Opposed Patent. Thus, the opponents' allegations that the Opposed Patent would need to disclose methods for monitoring the blood plasma concentration of rivaroxaban and determining its half life (cf. O2 and O3 at para. 71 and 72 and O6 in section 5.1) are irrelevant already for this reason.

(119) Regardless, methods for identification of rivaroxaban concentrations in blood plasma and the determination of its half life were of course available to the person skilled in the art at the priority date of the Opposed Patent. For example, WO 01/047919 A1 (**D1a**, cited in para. [0014] of the Opposed Patent), describes in its example 44 starting on p. 80 the synthesis as well as qualitative and quantitative analysis of rivaroxaban. **D1a** indicates on p. 83 the analytical methods used for identification of the compound. This passage informs the skilled person that, for example, a combination of High Performance Liquid Chromatography (HPLC) and Mass Spectrometry (MS) is an appropriate tool for determining the concentration of rivaroxaban.

(120) Regarding the calculation of the half life, the Opposed Patent in para. [0009] refers to p. 27 of the 7th edition (1985) of the standard pharmacology textbook Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, which in its penultimate para. defines the usually reported half life as the *"terminal log-linear rate of elimination"* (see **D9a**, p. 27, right col., penultimate para., last 4 lines). In general, the skilled person has no difficulties in determining plasma concentrations and calculating the half life of chemical compounds such as rivaroxaban. Methods employed to this end, such as HPLC and MS, were routine for the skilled person and formed part of his common general knowledge. The opponents have not substantiated why plasma concentration determination should not have been possible at the effective filing date of the Opposed Patent. Patentee submits that this clearly was the case.

E.3.2.3 O1's, O8's, and O9's objections regarding "ranges of plasma concentration half lives" and the necessity for "influencing or adjusting the half life" are nonsensical

(121) O1 at p. 10, final para. takes the astonishing position that, for its disclosure to be sufficient, the Opposed Patent

> *"would have to render credible that the plasma concentration in a human patient of the particular compound is distributed within the entire range from 10 hours or less."* (emphasis added)

Similarly, also O9 at p. 15-16 contends that the Opposed Patent, for its disclosure to be sufficient, would have to teach

> *"how to put the invention into effect across the full range of plasma concentration half lives of Rivaroxaban".* (O9, p. 15, 1st subtitle under point 8; emphasis added)

These arguments are nonsensical. Whatever O1 and O9 intended to put forward, it does not appear to be an Art. 83 EPC objection.

(122) As explained in section E.2 above, granted claim 1 itself already gives the skilled person clear and simple instructions on how to carry out the invention. Feature 1.5 of claim 1 reciting *"a plasma concentration half-life of 10 hours or less"* is not relevant for carrying out the invention. Being an inherent (and redundant) feature, it is automatically fulfilled as soon as rivaroxaban is employed in the claimed treatment. There is no room for a finding of insufficiency here.

(123) In support of this, almost all opponents have naturally conceded that feature 1.5, i.e. the plasma half life of 10 hours or less, is an inherent feature of rivaroxaban (see overview table **D57**). O1's and O9's hypothetical claim construction is entirely disconnected from the meaning of the claim to a person of ordinary skill in the art, especially when read in the context of the patent specification (see section E.3.2.1 above). There is no indication in the Opposed Patent that the interindividual variability in half life would play any role whatsoever in the ability of the skilled person to carry out the invention. There is also no indication that the invention would need to be put into effect across a *"range of plasma concentration half lives of Rivaroxaban"* (see O9, p. 15, 1st subtitle under point 8). Even if the latter were the case, the entire range would not need to be known or enabled in order for the skilled person to carry out the claimed dosage regimen.

(124) In summary, it is incomprehensible, how O1 and O9 arrive at the conclusion that the half life of rivaroxaban would need to be distributed within the entire range of 10 hours or less for the invention to be sufficiently disclosed. The opponents do not present any reason why their speculative allegations should lead to an insufficient disclosure under Art. 83 EPC. Application

respectfully discourages any weight be given to these unsupported allegations which have no relevance to Art. 83 EPC.

(125) O8 acknowledges at p. 4, penultimate sentence that the plasma half life of a pharmaceutical agent is an inherent feature of the agent itself. O8 in the subsequent sentence, however, contends that

> *"[t]he patent does not provide any teaching how this physiochemical property could be **influenced**, and, therefore, lacks enabling disclosure for those cases, in which the plasma half-life needs to be **adjusted**".* (emphasis and explanation in square brackets added)

(126) This argument is similarly nonsensical as the ones of O1 and O9 quoted above. It is incomprehensible, on which basis O8 believes that the half life would need to be *"influenced"* or what should constitute a *"case"*, in which half life *"needs to be adjusted"*.

(127) Moreover, O8 contradicts itself in the sentence directly prior to the aforementioned quote and in its introductory explanations on p. 2, 4th para., where O8 states that the half life is an inherent feature of a given agent. Finally, it is not clear how O8's position, even if it were assumed to be reasonable, could lead to a finding of insufficient disclosure under Art. 83 EPC.

E.3.2.4 Conclusion on feature "Plasma concentration half life of 10 hours or less"

(128) In conclusion, the Opposed Patent makes clear that the feature *"the compound has a plasma concentration half-life of 10 hours or less when orally administered to a human patient"* does not define a patient group, but is to be considered a product feature inherent to rivaroxaban. This also corresponds to the opinion of the vast majority of opponents.

(129) Moreover, as explained above, there was no need to indicate (known) analytical methods in the patent specification to monitor the blood plasma concentration of rivaroxaban in different patients in order to enable the skilled person to carry out the claimed subject matter.

E.3.3 The features "no more than once daily" and "once daily" are used synonymously in the Opposed Patent and exclude "less than once daily" dosaging

(130) O1, O4, O8, and O12 argue it is not credible that the desired therapeutic effect is also achieved with dosaging rivaroxaban "less than once daily", which they believe is encompassed by the wording of feature 1.4 of claim 1 ("administered no more than once daily for at least 5 consecutive days"). Thus, opponents argue that the claim would also cover non-working embodiments (e.g. administration every second day or only on day 1 and 4).

(131) If properly construed, however, claim 1 of the Opposed Patent does not encompass "less than once-daily" administration. Grounded by the claim's context ("*no more than once daily for at least five **consecutive** days*"), and also given the specification's repeated description of the "*present invention*" as being a "*once daily*" administration (see *id.*, para. [0001], [0012], [0013]), the skilled person understands the term "*no more than once daily*" in claim 1 to be synonymous with "*once daily*" (in the sense of meaning "*exactly once daily*"; see also section D.2.2 above).

(132) Whereas the granted claims, which define 'the present invention', recite an administration of "*no more than once daily for at least five consecutive days*", the 'present invention' is described throughout the Opposed Patent's specification exclusively in connection with a "*once daily*" dosage regimen:

> "*[0001] **The present invention** **relates to** the field of blood coagulation, more specifically it relates to a method of treating a thromboembolic disorder by administering a direct factor Xa inhibitor **once daily** in oral dosage form* [...]". (emphasis added)
>
> "*[0012] Surprisingly, **it has now been found** in patients at frequent medication that **once daily oral administration** of a direct factor Xa inhibitor with a plasma concentration half life time of 10 hours or less demonstrated efficacy when compared to standard therapy and at the same time was as effective as after twice daily (bid) administration.*"
>
> "*[0013] **The present invention** **relates to** 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* [...]". (emphasis added)

Clearly, the disclosure of the patent specification does not take into account an administration of less than once daily. It also has never been the intention of the Patentee or of the Examining Division to include "*no more than*" in order to cover a dosage regimen that allows for administration of less than once daily.

(133) In line with this, all examples in the Opposed Patent involve at least a once daily administration (see para. [0019]-[0020] and [0039] of the Opposed Patent). Similarly, the summaries on p. 6, l. 9 to 11 and 37 to 39 of the Opposed Patent conclude that the test results in Table 1-1 and 1-2 demonstrate the efficacy and safety, respectively, of "*the od* [once-daily] *administration*" of the invention.

(134) Thus, once grounded by the context of the specification, it is clear that "*once daily*" administration is used in the specification of the Opposed Patent to embody the same meaning as "*no more than once daily*" in the context of the claimed subject matter. The skilled

person reading the Opposed Patent understands that *"no more than once daily"* is simply another way of putting *"once daily"*, i.e. in the sense of *"exactly once daily"*.

(135) The **single definition provided in the Opposed Patent** also supports this view. The Opposed Patent in para. [0033] defines *"once daily"* as being *"well known by those skilled in the art"* and meaning *"administration of the drug once a day"*. If *"no more than once daily"* was to represent anything different than *"once daily"*, this would have been defined separately. It was not.

(136) The recitation of "no more than" in granted claim 1 must also be considered within the context of the **Examining Division's suggestion (D56)**. As outlined in section D.2.3 above, the Examining Division had felt that the term *"once daily"* in originally filed claim 3 might be misconstrued to include dosages administered *"more than"* once daily. Thus, it raised a corresponding objection under Art. 84 EPC and invited the Applicant to reformulate the claim by including the term *"no more than once daily for at least five consecutive days"* (see the Examining Division's communication pursuant to Art. 94(3) EPC of July 26, 2010, p. 3, 1st para., **D56**). The Applicant followed this suggestion in good faith to clarify that not *"more than"* but *exactly* once daily was meant to be claimed.

(137) Finally, opponents' claim construction entirely ignores that the feature *"no more than once daily"* is not recited in isolation in claim 1, but as part of the expression *"no more than once daily for at least five **consecutive** days"*. It is impossible to administer something *not every day* but *for five consecutive days*. The term ***"consecutive"*** can only be interpreted by the skilled person as an administration occurring on each of the days. Less frequent drug administration than once daily is not permitted under this explicitly required feature.

(138) Therefore, it is immediately clear not only to the skilled person, but even to the layman, that the claimed subject matter exclusively concerns an administration occurring no less and no more than once daily. This is evident from the repeated use of the term "once daily" to characterize 'the present invention' in the specification and by the inherent meaning of "consecutive" in feature 1.4 of claim 1 of the Opposed Patent.

(139) There is no indication in the Opposed Patent that administering rivaroxaban less than once daily is in any way desired or intended. Clearly, the overall teaching of the Opposed Patent is directed to a once-daily administration of rivaroxaban.

E.3.4 The patent's disclosure is enabled over the whole breadth of claim 1

E.3.4.1 Specifying a dose in claim 1 is not necessary for an enabling disclosure (O9, O10 and O12)

(140) O9 on p. 16, penultimate para. alleges that any dose and any variation over the claimed period of for at least five consecutive days is included in claim 1. O9 claims that the 30 mg once daily regimen of the example in the patent specification would not provide support for the entire range and that, in view of the preferred range of 5 mg to 30 mg, an effect would only have been shown for one end of the range. O9 concludes that the present claims are not enabled over the whole breadth of dose amounts covered. Similarly, also O10 (see *id.*, p. 21-22) and O12 (see *id.*, section 4.1) object to the fact that no dose amounts for rivaroxaban is recited in the claims.

(141) Importantly, O9 apparently agrees that the claimed invention is at least disclosed sufficiently clearly and completely for it to be carried out for the 30 mg Rivaroxaban once daily dosage regimen used in the Example of the Opposed Patent. Thus, at least one way to carry out the invention was uncontestably provided in the application as filed. The Technical Boards of Appeal of the EPO have in many cases considered this sufficient to satisfy the requirements of Art. 83 EPC (see the "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter II.C.4.2 and 6.1.2).

(142) Contrary to opponents' unsupported assertions, the claims of the Opposed Patent do not need to recite a specific quantitative dose range (i.e., in milligrams) for sufficiency of disclosure to be acknowledged. It is a general legal principle of the EPC that the protection conferred by a patent should correspond to the technical contribution to the art made by the disclosure of the invention. The claimed invention is based on the surprising finding that rivaroxaban can be efficacious with only once-daily dosaging for at least five days with a rapid-release oral dosage form (see, e.g., Opposed Patent, para. [0012]-[0013] and claim 1).

(143) The possibility of once-daily dosaging is a major contribution over the prior art and has contributed to the positive reception and huge success of rivaroxaban in the clinic (see section C.1 above). The claims of the Opposed Patent do not need to recite a specific quantitative dose (i.e., in milligrams) because the instant invention relates to the novel and surprising finding that rivaroxaban can be efficacious in a certain dosage regimen (i.e., using once-daily dosaging for at least five consecutive days in a rapid-release oral dosage form), independent of its efficacy in any given *dose amount*.

(144) Whereas it is generally correct that sufficiency of disclosure presupposes that the skilled person is able to obtain substantially all embodiments falling within the ambit of the claims, this is not the case for those embodiments falling under the literal wording of the claim but

which the skilled person would immediately exclude as being clearly outside the scope of practical application of the claimed subject matter. This general principle has in particular been applied for claims including an open ended range for a parameter where it was clear for a skilled person that the open-ended range was limited in practice. See the "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter II.C.7.1, 1st para.:

> *"Values of the parameter not obtainable in practice would not be regarded by the skilled person as being covered by the claims and thus could not justify an objection of insufficiency of disclosure (**T 1018/05**)"*

and the summary of the supporting case law in **T 1018/05**, point 2.3 of the Reasons.

(145) The phase II data contained in the Opposed Patent already fully support and make credible that the technical teaching of the invention can be achieved, i.e. that a once-daily dosage regimen of rivaroxaban administered for at least five consecutive days in a rapid-release oral dosage form is safe and effective in treating thromboembolic disorders. Thus, it is admissible to provide further confirmatory support of sufficiency of disclosure by way of **post-published evidence** (see the "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter II.C.5.8 and 6.2).

(146) As already discussed in section C.1 and alluded to in section E.2 above, Xarelto® is approved *inter alia* in the following doses: 10 mg, 15 mg, and 20 mg once daily. For these doses, clinical safety and efficacy was proven by the underlying phase III clinical trials (described in sections G.6.2.1 to G.6.2.3 below). The phase II dose-ranging studies that led to the approval of Xarelto® also demonstrated clinical efficacy of further doses of rivaroxaban, e.g., 5 mg, 30mg, and 40 mg once daily and up to 30 mg twice daily (see the EMA's CHMP AR 2008, **D59**, p. 23-24 and section G.6.2.4 below)

(147) Thus, the data included in the Opposed Patent have meanwhile been confirmed and expanded to include a range of doses and many different indications in a vast number of clinical and post-marketing studies. In light of this wealth of evidence, opponents cannot dispute that the claimed dosage regimen is effective across a broad spectrum of doses tested.

(148) Furthermore, it can be expected that, depending on factors such as possible combination therapy, the length of treatment, the condition, its severity, or the patient (sub)population to be treated, the technical teaching of the invention can also be achieved with lower and higher doses than were specifically tested in the clinical trials described above.

(149) Importantly, the Opposed Patent is not silent on doses, but instead provides a detailed teaching which doses can be considered appropriate for treating thromboembolic disorders with rivaroxaban. Para. [0032] of the Opposed Patent teaches that rivaroxaban can be applied

in doses of 1 to 100 mg (preferentially 2 to 50 mg and particularly preferred 5 to 30 mg). Thus, the Opposed Patent clearly teaches, which doses of rivaroxaban can be administered once daily to a patient in order to carry out the invention. Opponents' corresponding Art. 83 EPC objections are unjustified.

(150) Finally, **none of the opponents provided any evidence** of any failure to carry out the invention using other doses or raised serious doubts verifiable by facts to that end. The **burden of proof**, however, generally lies with an opponent to establish that an invention is insufficiently disclosed (see "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter II.C.8). O9 in particular does not provide any reasonable arguments why the Opposed Patent's disclosure is not sufficiently clear and complete for the invention to be carried out at doses other than 30 mg. O9 is also silent on possible obstacles that might complicate the success of the invention at other doses.

(151) O10 and O12 similarly fail to explain why a particular dose of rivaroxaban must be included in claim 1 regardless of para. [0032] of the Opposed Patent, which teaches specific, fully enabling dose ranges. Importantly, Art. 83 EPC requires the applicant to disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Art. 83 EPC does not require that such disclosure is included in the claims.

(152) O10, in its argument of insufficiency, refers to the bid regimens in Example 1 of the Opposed Patent to argue that since the VTE incidence rate increased to 17.4% for 30 mg bid in comparison with 10.2% for 20 mg bid, it would appear that 30 mg bid – corresponding to a 60 mg total daily dose – is less efficient. O10 then, however, commits an error in reasoning when concluding that this would result in reasonable doubts that all *once daily* doses of rivaroxaban are actually safe and effective to treat a thromboembolic disorder.

(153) O10's attempts to transfer alleged inconsistencies in the dose-efficacy relationships of the tested bid regimens (which were included merely for comparative purposes) to the enablement of the claimed od regimens is deprived of logic. The efficacy results observed with the 20 mg bid and 30 mg bid dosage regimens are irrelevant for the question of sufficient disclosure of the claimed od dosage regimens.

(154) Even if one were to follow O10's suggestion, this would not lead to a finding of insufficiency. Whereas the value of the primary efficacy endpoint for the 30 mg bid dosage (17.4 %, see Table 1-1 of the Opposed Patent) may theoretically not be perfectly in line with the corresponding values for the other bid dosages, it still shows a strong reduction when compared to untreated conditions (see *"placebo"* in para. [0018] of the Opposed Patent, 54.2 %). Thus, there can be no doubt that also the 30 mg bid dosage regimen showed clinical

efficacy. This entire comparison, however, is irrelevant as the claims do not encompass bid dosage regimens.

(155) O12 merely speculates that there would be "doubts" as to whether significantly lower doses than 30 mg once daily would be sufficient for the treatment of thromboembolic disorders. O12 fails, however, to provide any explanation or substantiation for these "doubts". Certainly, these unsubstantiated allegations have not discharged O12 of its onus of proof.

(156) In summary, O9, O10 and O12's insufficiency arguments lack merit. Specifying a dose in claim 1 is not necessary for an enabling disclosure.

E.3.4.2 It is credible that clinical efficacy is achieved for therapy and prophylaxis of "thromboembolic disorders" in general

(157) O1, O4, O5, O6, and O8 seem to generally object to the term *"thromboembolic disorders"* in claim 1 of the Opposed Patent as being too broad. They assert that Example 1 of the Opposed Patent only demonstrates prophylaxis of venous thromboembolism (VTE). Some opponents also criticize how the study reported in Example 1 was performed (see section E.3.5 below). In summary, opponents argue that there would be no enabling disclosure across all the *"myriad of diseases"* encompassed by claim 1 (see, e.g. O1, p. 9).

(158) The opponents' insufficiency arguments find no support in law or fact and should not be given any weight. First, the question of whether the technical effect is achieved over the entire scope of the claim is a question of inventive step, not sufficiency of disclosure. We refer to the respective section in our discussion of inventive step below (see section G.6.3).

(159) What the case law of the Boards of Appeal looks to when considering sufficiency is whether a skilled person trying to carry out the claimed subject matter is, given the disclosure of the patent, **proven by evidence** to be unable to do so. None of the opponents' arguments even remotely prove the inability of a skilled person with the patent to treat a thromboembolic disorder by administering rivaroxaban in the claimed dosage regimen. It is legally and factually untenable to say that (1) the Opposed Patent does not provide the skilled person with a sufficiently clear and complete disclosure for carrying out the claimed dosage regimen or (2) that it would not be "credible" that the claimed dosage regimen would work for the class of thromboembolic disorders.

(160) As Patentee has described in section C.1 and alluded to in section E.2 above, and as will be explained in more detail in section G.6.2 below, this very dosage regimen has been approved by the EMA, the FDA and a vast number of other regulatory authorities for primary examples of thromboembolic disorders (e.g., prophylaxis and therapy of venous thromboembolism

such as DVT and PE as well as prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation).

(161) The skilled person working in the field of thromboembolic disorders also typically chooses VTE, the disease studied in Example 1 of the Opposed Patent, as a representative disorder for clinical testing of a new anticoagulant. This is evidenced, e.g., by **D23** (cited by O5), which underscores the usefulness and habitualness of first studying new anticoagulants in the postoperative prophylaxis of VTE (see **D23**, p. 413, left col., *"Klinische Studien"*):

> *„Eine **wesentliche Indikation für Gerinnungshemmer** ist die **Prophylaxe postoperativer venöser Thromboembolien (VTE)**. Besonders hoch ist das VTE-Risiko bei orthopädischen Eingriffen. In Analogie zu anderen Gerinnungshemmern (z. B. niedermolekularen Heparinen, Fondaparinux, Thrombinhemmern) wurde Rivaroxaban **deshalb** zunächst für diese Indikation untersucht. Das **umfangreiche klinische Studienprogramm** umfasst aber auch Studien zur Therapie von Venenthrombosen sowie zur VTE-Prävention bei kardiologischen Erkrankungen (z. B. Vorhofflimmern)."* (emphasis added)

Thus, in the field of anticoagulant drug development it is common practice to perform the **proof-of-concept studies** in postoperative VTE-prophylaxis (Example 1 of the Opposed Patent) to evidence the treatment's suitability in this indication, but also for the class of thromboembolic disorders. O4's respective objection at p. 6, para. 2 of its Notice of Opposition is clearly unjustified.

(162) The data contained in the Opposed Patent already render credible rivaroxaban's therapeutic effect for the entire class of thromboembolic disorders as the formation of a thrombus involves factor Xa and thromboembolic disorders generally involve a common underlying disease contributor and pathophysiology: a hypercoagulation state. See, e.g., Fülgraff , „Pharmakotherapie", 11th ed. 2001 (**D62**), p. 116, left col., 2nd para. – right col., 1st para. which is quoted in full in margin note (242) in section F.4.2.1 below. See also para. [0003] of the Opposed Patent which refers to an *"uncontrolled activation of the coagulant system"* as one underlying disease mechanism for the class of thromboembolic disorders.

(163) Before the effective filing date of the Opposed Patent it was already established that anticoagulants provide effective treatment options for the entire range of thromboembolic disorders addressed by the Opposed Patent (see, e.g., chapter 4, "Therapie mit Antikoagulanzien – Thromboembolische Krankheiten" in the textbook "Antikoagulation in Klinik und Praxis", **D63**, sponsored by O12). According to **D63**, which is only a short manual, the clinically treated indications already included:

- prophylaxis of thromboembolic disorders (**D63**, chapter 4.1),
- venous thrombosis (**D63**, chapter 4.2),

- pulmonary embolism (**D63**, chapter 4.3),
- myocardial infarction, including angina pectoris (**D63**, chapter 4.4, final para.),
- stroke, including cardiogenic (thrombo)embolism, atrial fibrillation and arrhythmia (**D63**, chapter 4.5),
- (peripheral) arterial occlusion disorders, including an indication of atherosclerosis (**D63**, chapter 4.6),
- disseminated intravascular coagulation (DIC, **D63**, chapter 4.7),
- thromboembolism in tumor patients, including inhibition of tumor growth and development of metastasis (**D63**, chapter 4.8),
- hereditary and immune-mediated coagulopathies, including inflammatory diseases such as Lupus (**D63**, chapter 4.9), and
- thromboembolism in pregnancy, including risk factors such as prosthetic heart valves (**D63**, chapter 4.10).

(164) In addition to these clinically practiced indications, the plausibility of a success in treating with an anticoagulant such as rivaroxaban is also credible for the remaining indications listed as "thromboembolic disorders" in para. [0024] of the Opposed Patent. In particular, all of these diseases were known to be mechanistically or at least symptomatically linked to Factor Xa or downstream thrombin generation, both of which are inhibited by rivaroxaban. O5 objects to the inclusion of *"inhibition of tumor growth and development of metastasis"*, *"rheumatic diseases of the musculoskeletal system"*, *"Alzheimer's disease"*, *"diabetic retinopathy"*, and *"diabetic nephropathy "* (O5, p. 7, 3rd para.). However, as evidenced by the attached review of Dugina et al., 2002 (**D64**) and references cited therein, thrombin, which is directly downstream of factor Xa, had already been implicated in inflammation, tissue repair, artheroscleosis, carcinogenesis and many other clinically relevant processes (see **D64**, p. 65, introductory para.) that are thought to play a causative or symptomatic role in these diseases. Thus, due to factor Xa and/or thrombin's involvement in these processes, it is credible that by inhibiting factor Xa, rivaroxaban may be effective in the therapeutic or prophylactic treatment of the entire range of thromboembolic disorders listed in para. [0024] of the Opposed Patent.

(165) Also the review article **D6** cited by O2, O3, O6, and O11 emphasizes ***the suitability*** of factor Xa inhibitors for the entire class of thrombotic indications. See **D6**, p. 156, left col., final para.:

> *"If the mechanistic, safety, and efficacy advantages of fXa inhibition ring true, the **potential therapeutic uses for fXa inhibitors are virtually unlimited**. Any thrombotic indication that has an underlying pathology of fibrin deposition or thrombin-dependent platelet activation and aggregation would certainly benefit from fXa inhibition."* (emphasis added)

(166) In their insufficiency argumentation, O1-O5 and O8 cite **T 609/02**, which established that for second medical use claims, the method of treatment is a functional feature relevant to the question of sufficiency of disclosure. However, **T 609/02** clearly indicates that the inclusion of clinical data, let alone for all indications claimed, is not a requirement under Art. 83 EPC. See **T 609/02**, point 9 of the Reasons:

> *"*[U]*nder Article 83 EPC, unless this is already known to the skilled person at the priority date, the* ***application must disclose the suitability of the product to be manufactured for the claimed therapeutic application****. It is a well-known fact that proving the suitability of a given compound as an active ingredient in a pharmaceutical composition might require years and very high developmental costs which will only be borne by the industry if it has some form of protective rights. Nonetheless, variously formulated claims to pharmaceutical products have been granted under the EPC, all through the years. The patent system takes account of the intrinsic difficulties for a compound to be officially certified as a drug by not requiring an absolute proof that the compound is approved as a drug before it may be claimed as such.* ***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.*** [...] *It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se. Showing a pharmaceutical effect in vitro may be sufficient if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application* [...] *or, as decision T 158/96 also put it, if there is a "clear and accepted established relationship" between the shown physiological activities and the disease (loc. cit.).* ***Once this evidence is available from the patent application, then post-published (so-called) expert evidence (if any) may be taken into account,*** *but only to back-up the findings in the patent application in relation to the use of the ingredient as a pharmaceutical, and not to establish sufficiency of disclosure on their own."* (emphasis added)

(167) **T 601/05**, which cites **T 609/02** additionally established that the pharmaceutical usefulness (as required by **T 609/02**) may also be *prima facie* evident from the skilled person's common general knowledge. See *id.*, point 101 of the Reasons:

> *"A first thing to note with regard to these objections is that* ***generally examples are not a mandatory requirement in a patent.*** *Also,* ***the pharmaceutical usefulness of an agent may be prima facie evident in the light of common general knowledge.*** *It is stated in decision T 609/02, point 9, second sentence: "As a consequence, under Article 83 EPC,* ***unless this is already known to the skilled person at the priority date,*** *the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application"."* (emphasis added)

(168) At the effective filing date of the Opposed Patent, rivaroxaban was already known to be a highly selective and potent inhibitor of factor Xa (reviewed, e.g., in **D16**). Factor Xa, given its integrating and downstream position at the crossroads of intrinsic and extrinsic pathways of coagulation, was perceived as a very promising target for anticoagulation therapy in general

(reviewed, e.g., in **D6**). The data contained in the Opposed Patent for the first time provided evidence that the claimed once daily dosage regimen of rivaroxaban is safe and effective in the *prophylaxis* of VTE, a primary thromboembolic indication. These data were later confirmed in phase III clinical studies and expanded also to the *treatment* of VTE and to a series of other thromboembolic disorders (see section E.2 above and G.6.2 below). In addition to the currently approved indications, the use of rivaroxaban in the claimed dosage regimen is also being investigated in a broad range of other thromboembolic disorders.

(169) In light of the above, it is reasonable to extrapolate these successes in treating thromboembolic disorders to the entire class. This is especially the case as the opponents fail to bring forward any evidence that would come close to supporting the claim that a skilled person cannot carry out the claimed treatment for a particular thromboembolic disorder encompassed by the claims.

E.3.4.3 It is credible that the therapeutic effect can be achieved over all patient groups

(170) O5 and O8 regard it as not credible that the therapeutic effect of the claimed rivaroxaban dosage regimen applies to all patient groups (in particular the elderly, premenopausal women, and children). O5 objects that no age of the patients experiencing DVT and PE is indicated in Example 1 of the Opposed Patent and thus, a proof that occurrence of DVT and PE is not age-dependent was not provided. Post-published document **D23** would subsequently show that the plasma concentration half life of rivaroxaban seems to be age-dependent, being 5 to 9 h in young, healthy adults, and 11 to 13 h in the elderly.

(171) It is not clear how these presumptions of O5 could justify a finding of lack of enablement. As explained in section E.3.2.1 above, feature 1.5 of claim 1, which indicates the plasma half life of rivaroxaban, cannot be reasonably construed to define a patient group. As the half life does not need to be measured to carry out the invention, this feature cannot be relevant under Art. 83 EPC.

(172) The fact that rivaroxaban's half life was subsequently discovered to be 11 to 13 h in **the elderly** does not change the fact that therapy with rivaroxaban in the claimed dosage regimen is very effective in this patient group. The pivotal phase III clinical trials carried out for rivaroxaban demonstrate that the therapeutic effect can be achieved over all patient groups (subpopulations) studied. As required by the regulatory authorities, the clinical trials that led to the approval of rivaroxaban specifically studied possible age- or other subpopulation-related effects. None were found that would justify a different dosage regimen than claimed. The EMA's independent 2008 CHMP AR (**D59**) summarizes the results for efficacy and safety in the different subpopulations as follows:

p. 36, 2nd para:

> *"In the overall population of the 3 pivotal studies, rivaroxaban was generally more effective than enoxaparin in preventing total VTE (MITT analysis) in nearly **all subpopulations**. These subpopulations with an observed odds ration less than the upper 95% CI limit of the overall population estimate (0.44) were: **both genders**, white and Asian race, **all age groups**, bodyweight >50 to 110 kg, [...]".*

p. 46, 6th para.:

> *"Overall, considering the presented subgroup analyses of bleeding events in the three phase III trials and the relevant data available for the comparator, there is **no suggestion** of the need **to restrict the use of rivaroxaban according to gender, race, age or bodyweight**."*

p. 54, 2nd-3rd para.:

> *"Elderly (> 75 years) and fragile subjects tended to have a lower risk for bleeding events with rivaroxaban, but in both cases, the observations are based on overall low event rates and no dose adjustment was needed. At present no specific antidote is available for rivaroxaban.*
>
> *Overall from the presented subgroups analyses of bleeding events in the three phase III trials, **no evidence was found, to restrict the use of rivaroxaban 10 mg od** according to gender, **age** and bodyweight."*

(173) Accordingly, the regulatory approvals for rivaroxaban also do not foresee any special dosage regimen for specific subpopulations. In fact, rivaroxaban has been prescribed and administered in the claimed dosage regimen to thousands of elderly patients and has proven to be effective. There can be no doubt that the Opposed Patent sufficiently enables the skilled person to carry out the claimed dosage regimen also in this patient group.

(174) In addition, and contrary to the assertions of some of the opponents, the age of the patients involved in Example 1 of the Opposed Patent ranged from 30 to 92 years, and thus included the elderly (see section E.3.2.1 above and para. [0041] of the Opposed Patent).

(175) Rivaroxaban's observed half life in the elderly also stands in no contradiction to claim 1 of the Opposed Patent, which, if properly read in conjunction with the patent specification, refers to the half life of rivaroxaban as determined in **D2**, i.e. in healthy human males (see section E.3.2.1 above and para. [0017] of the Opposed Patent).

(176) O8's objection that Example 1 of the Opposed Patent would not include **pre-menopausal women and children**, and that "thus" the claimed treatment effect would not be credible for these patient groups is similarly unavailing (see O8, para. bridging p. 3-4).

(177) It is clear to the skilled person that the phase II study reported in Example 1 of the Opposed Patent was a proof-of-concept study. It was one of the first to test rivaroxaban, and the claimed dosage regimen, in patients. At this early stage of drug development, the final results of the required reproduction toxicity studies are not yet available. For women of childbearing potential (WOCBP), there is a high level of concern for the unintentional exposure of an embryo or fetus to a drug, particularly if its reproduction toxicity has not yet been fully clarified. In such cases, it is unethical to include WOCBP in clinical trials. For similar precautionary and ethical reasons, children are not included in early clinical trials.

(178) For these reasons, it is common practice to conduct phase II studies such as the one reported in Example 1 of the Opposed Patent in post-menopausal women and adult men. The pivotal phase III clinical trials that proved efficacy of rivaroxaban in the various currently approved indications included pre- and postmenopausal women (see sections G.6.2.1 to G.6.2.3 below and references cited therein). Regarding the pediatric population, O8 ignores that guideline recommendations for antithrombotic therapy in pediatric patients are generally based mainly on extrapolation from adult clinical trial data, owing to the limited number of clinical trials in pediatric populations. Whereas special clinical trials testing the claimed dosage regimen in children are currently under way, this seems irrelevant to the question of sufficiency of disclosure. O8 has not in the least substantiated why the adult clinical trial data for rivaroxaban should not be extrapolated to the pediatric population.

(179) In summary, none of O5 and O8's sufficiency arguments based on patient population are sound. The same is true for O2 and O3's related patient group-based arguments, which are discussed in section E.3.2.1 above.

E.3.5 Rebuttal of specific objections to Example 1 of the Opposed Patent

(180) Individual issues raised by O1, O5, and O8 with regard to the clinical trial data of Example 1 of the Opposed Patent will be rebutted in the following.

(181) O1 at p. 10, 2nd para. and O5 at p. 7, final para. object to the primary efficacy endpoint in Example 1 of the Opposed Patent being a composite endpoint (DVT, PE, and death). In lack of differentiation, this would not provide an unambiguous support for the individual thromboembolic disorders, DVT and PE. Opponents fail, however, to explain any benefit that would result from such differentiation or why this could lead to a lack of enablement under Art. 83 EPC.

(182) For the skilled person, the composite endpoint used in Example 1 of the Opposed Patent in fact is the primary efficacy endpoint of choice for this indication and study type. Exactly such

composite endpoints are part of the regulatory authorities' requirements. See, e.g., the EMA's official guidelines entitled *"Points to consider on clinical investigation of medicinal products for prophylaxis of intra- and post-operative venous thromboembolic risk"*, section 3.1 "Primary Efficacy Endpoint" (**D65**):

> **3.1 Primary Efficacy Endpoint**
>
> In therapeutic confirmatory studies designed to show superiority of a new agent to an existing agent, the primary endpoint should be a composite endpoint consisting of the following events: (i) proximal DVT's or any (proximal plus distal) DVT's (ii) symptomatic and well documented (i.e. perfusion/ventilation lung scan, spiral computer tomogram,and/or pulmonary angiography) non fatal PE (iii) death from all causes including PE (see section 5.2 Therapeutic confirmatory studies).

(183) Thus, the fact that the Opposed Patent does not list the individual components of the VTE composite endpoint has no impact on the significance of the reported finding that rivaroxaban in the claimed dosage regimen was demonstrated to be safe and effective in the prophylaxis of VTE. In case the Opposition Division is interested in the values for the individual components of the composite endpoint, it is referred to the EMA's 2008 CHMP Assessment Report, p. 33 (**D59**), bottom table, which provides a comprehensive compilation of all individual efficacy endpoints determined in the phase III RECORD 1 and RECORD 3 trials that led to the approval of rivaroxaban for VTE prevention (for a more detailed discussion of this data, see section G.6.2.1 below). Rivaroxaban reduced the number of incidences for all individual endpoints, similar to standard therapy with enoxaparin, a low molecular weight heparin ("LMWH") administered by subcutaneous injection.

(184) O1 on p. 10, 1st para. and O5 on p. 7, final para. seem to object to the fact that no "negative" or "placebo" control was included in the phase II clinical trial reported in example 1 of the Opposed Patent. As explained in para. [0018] of the Opposed Patent, 54.2 % of placebo-treated patients develop a deep vein thrombosis after total hip replacement surgery (see values stated for *"Placebo"* in the table in para. [0018] of the Opposed Patent). Similarly, **D36** at p. 412, right col. reports that after major orthopedic surgery, 50% to 80% of patients are at risk of venous thromboembolism, and within the same group of patients the risk of PE has been reported to be as high as 10% (see also **D63**, p. 79, l. 1-7).

(185) Prophylactic treatment with LMWH leads to a reduction of DVT prevalence from 54.2 % to **16.1 %** (see table in para. [0018] of the Opposed Patent). Therefore, prophylaxis with LMWH, such as enoxaparin, was the **standard of care** following total hip replacement surgery at the effective filing date of the Opposed Patent. In light of the high thrombosis risk, it would be unethical to deny enrolled study patients that standard of care in trials testing a new anticoagulant therapy. Ethics committees are in place to prevent such trial designs in practice.

Also the regulatory authorities ask that new anticoagulants are compared to the standard of care and not to placebo. Thus O5's objection clearly is improper.

(186) O5 fares no better with its objection that no direct comparison of the same daily dose administered od and bid was included in Example 1 of the Opposed Patent (see O5, sentence bridging p. 7-8). It is not at all apparent, and O5 provides no hint, as to how this should lead to a finding of lack of enablement. If at all, the issue of comparative data is only relevant when assessing inventive step (for a discussion of how the claimed once-daily regimen relates to comparative bid regimens, see sections G.6.1 and G.6.2.4 below).

(187) O8 proposes that the Opposed Patent did not make it credible that the desired therapeutic effect could be achieved for other treatment durations than the 7 to 9 days used in the clinical trial in Example 1 of the Opposed Patent.

(188) First, Patentee submits that a certain degree of generalization regarding the lower range endpoint (*"for at least five consecutive days"*) must be allowable to guarantee a sufficient scope of protection. In addition, whereas treatment duration is stated in para. [0036] of the Opposed Patent as *"7 to 9 days"*, the primary efficacy endpoint was evaluated already earlier, namely 5 to 9 days after surgery (see para. [0040], l. 16 of the Opposed Patent). The efficacy results reported in the Opposed Patent reflect this range of treatment durations. Thus, the lower range endpoint of *"at least five consecutive days"* is sufficiently supported by the data included in the Opposed Patent.

(189) Second, as evidenced by the table on p. 25 of the EMA CHMP AR 2008 (**D59**), the pivotal phase III clinical trials for VTE prevention involved treatment durations of 35 ± 4 days and 12 ± 2 days for the RECORD 1, 2 and RECORD 3 studies, respectively. Thus, safety and efficacy of the claimed therapy is also supported for more extended treatment durations.

(190) Finally, the skilled person knows that therapeutic and prophylactic treatment of thromboembolic disorders with anticoagulants usually lasts for durations of longer than 5 days. See, for example, **D63**, p. 81, penultimate para. prescribing a permanent treatment with oral anticoagulants over **6 months** after pulmonary embolism, or **D63**, p. 86, table, right col. prescribing **life-long** therapy with oral anticoagulants for patients with peripheral arterial occlusion disorder and an elevated risk of thromboembolism. Opponents also concede the possibility of long-term therapy in their discussion of inventive step. See, for example, O1 at p. 6, penult. para.:

> *"The skilled person is aware of the fact that **many thromboembolic disorders require** long-term treatment,* i.e. *treatment for **significantly more** than five days."* (emphasis added)

(191) As shown above, opponents' attempts to question the credibility of the data presented in Example 1 of the Opposed Patent are not in the least substantiated. Meanwhile, the results of the initial proof-of-concept study reported in Example 1 of the Opposed Patent have been thoroughly corroborated in further post-published phase II and III trials for rivaroxaban, as explained in sections C.1 and E.2 above and in more detail in section G.6.2 below.

E.4 Conclusion on Sufficiency of Disclosure

(192) In summary, the insufficiency arguments of the opponents have proven unconvincing. The Opposed Patent discloses the claimed dosage regimen in a manner sufficiently clear and complete for it to be carried out by the skilled person. Indeed, it is successfully carried out by the skilled person and patients are benefitting from it every day.

The correct conclusion is thus that the requirements for sufficiency of disclosure are fulfilled.

F NOVELTY (ART. 100(a), 54 EPC)

(193) The claimed subject matter of the Opposed Patent is novel over the documents cited by the opponents.

F.1 Summary of opponents' novelty arguments

(194) The opponents' novelty objections, if any, can be summarized as follows:

- O12 has not raised any novelty objections and therefore accepts that the claimed subject matter is novel.
- O4 asserts that the claimed subject matter would lack novelty over document **D1**.
- O1-O3, O5-O9, O11, and O13 assert that the claimed subject matter would lack novelty over document **D2**. O5 additionally raises novelty objections with regard to an almost identical document, **D11**. In addition O1, O8, O9, and O11 all inadmissibly combine **D2** and **D3** for arguing lack of novelty, O9 further combines **D2** and **D26**, and O11 further combines **D2** and **D36** in this respect.
- O10 asserts that the claimed subject matter would lack novelty over document **D29**.

(195) As will be demonstrated below, the opponents' arguments are neither founded, nor properly substantiated, nor in line with the case law of the Technical Boards of Appeal of the EPO.

(196) Of note, documents **D1, D2** (and thereby also the subject matter of the almost identical document **D11**), and **D3** were already considered by the Examining Division in its finding of novelty. The subject matter of the Opposed Patent is clearly novel over **D1** and **D2/D11** (see sections F.3 and F.4, respectively, below). It is impermissible to additionally consider a combination of these documents with **D3** (or **D26** or **D36**) for arguing lack of novelty. In the case of **D26** and **D36** this is particularly impermissible because they were published after the priority date of the Opposed Patent and therefore do not belong to the prior art.

(197) Similarly, document **D29** also does not belong to the prior art and therefore cannot be prejudicial to the novelty of the claimed subject matter (see section F.5 below).

F.2 General considerations regarding novelty of medical use claims

(198) The claims of the Opposed Patent are in the form of "*Swiss-type*" medical use claims (**G 5/83**) for which the notional novelty, and thus, non-obviousness, is not derived from the substance

or composition as such, but from its intended therapeutic use (Art. 54(5) EPC, see also **G 2/08**, point 5.10.9 of the Reasons and the "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter I.C.6.2).

(199) In its fundamental decision, **G 2/08,** the Enlarged Board of Appeal held that Art. 54(5) EPC also applies to cases where a **dosage regime** is the only feature claimed which is not comprised in the state of the art. As a consequence, all the technical features of the claimed therapeutic indication (*"treatment of a thromboembolic disorder"*) and of the dosage regimen (*"a rapid-release tablet [...] administered no more than once daily for at least five consecutive days"*) must be taken into account when considering whether or not the claimed subject matter is novel.

(200) According to the established case law of the Technical Boards of Appeal of the EPO (see, e.g., **T 715/03**, discussed in more detail in section F.4.2.2 below), if a prior art document discloses clinical investigations such as phase II or III studies (or states that these investigations are ongoing), but the document fails to disclose the final result of these studies, this document **cannot** be novelty-destroying for a claimed therapeutic treatment (see also "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter I.C.4.1, p. 103, 3rd para.).

(201) Applying these principles, the novelty of the presently claimed subject matter must be acknowledged, and indeed has been rightly acknowledged by the Examining Division of the EPO over the prior art cited.

F.3 Novelty over D1

(202) **D1** is generally directed to a new genus of oxazolidinone derivatives and their use in the field of blood coagulation. One of the species to that genus is rivaroxaban (see, e.g., claim 7 and example 44 of **D1**). **D1** is silent with regard to a once-daily administration of a rapid-release tablet for at least five consecutive days. Accordingly, the claimed subject matter is novel over document **D1**.

(203) O4 is the only opponent raising novelty objections based on **D1**. Since **D1** was already considered in the examination proceedings leading to the Opposed Patent, it can be assumed that all other opponents knew of **D1**, but rightly came to the conclusion that it does not anticipate the claimed subject matter. O4 attempts to support its novelty attack by combining aspects of different, separate embodiments with a series of alleged implicit disclosures in **D1**. O4 combines in this respect the disclosure in para. [0356], [0367], [0368], Example 44, and claim 7 of **D1**.

(204) Para. [0356] of **D1** suggests that the compounds of this document can be employed in medicaments for the prophylaxis and/or therapy of thromboembolic disorders. Example 44 and claim 7 of **D1** concern rivaroxaban.

(205) Regarding the claim feature ***"administered for at least five consecutive days"***, O4 simply contends that use of an anticoagulant in the prophylaxis of deep vein thrombosis would require that the drug is administered for more than 5 consecutive days without citing any evidence. **D1**, however, is silent regarding administration for at least five consecutive days. There also is no direct and unambiguous implicit disclosure to that effect. For this reason alone, the claimed subject matter is novel over **D1**.

(206) Para. [0368] of **D1** states that "[i]*n the case of administration of relatively large amounts, it may be advisable to divide these into several individual administrations over the course of the day*". O4 takes the astonishing position that this sentence would amount to an implicit disclosure of a **once-daily administration** based on the implication that the division into several doses per day would not necessarily be required. O4's assertion is based on a selective reading of **D1**. Also, it is contradicted by the established case law of the Technical Boards of Appeal of the EPO, which have laid out strict requirements on implicit disclosure for novelty purposes.

(207) According to the Guidelines for Examination in the EPO 2016, Chapter G VI-2 and the "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter I.C.4.3, a prior art document can destroy the novelty of a claimed subject matter only if the latter is **directly and unambiguously derivable** from that document, including any features implicit to a person skilled in the art. However, an alleged disclosure can only be considered "implicit" if it is immediately apparent to the skilled person that **nothing other than the alleged implicit feature** forms part of the subject matter disclosed (see, e.g, **T 95/97**). The limitation to subject matter "*derivable directly and unambiguously*" from the document is critical. According to the case law of the Technical Boards of Appeal of the EPO on assessing novelty, the teaching of a document, independent of its nature, is not to be interpreted as embracing equivalents not disclosed in that document (see also **T 167/84, T 517/90, T 536/95**). According to these standards, there is no implicit teaching or suggestion of a once-daily dosage regimen in **D1**.

(208) Para. [0366] to [0368] of **D1** present very general considerations on appropriate dosage forms for the large group of substituted oxazolidinone factor Xa inhibitors taught by **D1**. Along these lines, para. [0366] of **D1** lists possible administration routes. The next paragraph refers to customary formulations and indicates possible amounts of the factor Xa inhibitor compounds in such pharmaceutical formulations. According to the 1st sentence of para. [0368] of **D1** it is allowed, if appropriate, to depart from the amounts mentioned in the paragraphs before. And

further, with view to the loading of the drug compound in the pharmaceutical formulation, it is advised that in case of an administration of relatively large amounts, it may *"be advisable"* to divide these large amounts into several individual administrations over the course of the day.

(209) O4 interprets this latter statement of **D1** in an unallowable inversion of argument (*argumentum e contrario; Umkehrschluss)* to mean that generally the compounds of **D1** would be administrated once daily and only in case of relatively large amounts of the drug, several individual administrations over the course of the day would be required. The conclusions of O4 amount to mere speculation and are also factually incorrect.

(210) Para. [0368] of **D1** leaves open what *"relatively large amounts"* are. Moreover, it does not take into account any pharmacodynamic or pharmacokinetic parameter of a specific factor Xa compound, let alone rivaroxaban, but only considers the load of compound in the pharmaceutical formulation. In addition, para. [0368] of **D1** also leaves entirely open, whether or not in case of *"an administration of relatively small amounts"*, it may also *"be advisable"* to divide these amounts into several individual administrations over the course of the day. In fact, given the reported short half life of rivaroxaban, the skilled person would have presumed exactly this. As explained in more detail in inventive step section G.7 below, the skilled person would have refrained from choosing a once-daily dosage regimen for rivaroxaban based on the information that was publicly available prior to the present invention.

(211) In summary, para. [0368] of **D1** does **not** teach a once daily administration of rivaroxaban for the treatment of thromboembolic disorders.

(212) Finally, the claimed subject matter is clearly novel over **D1** because this document contains no disclosure of a ***"rapid-release tablet"***. According to para. [0367] of **D1** the compounds can be included into customary formulations, such as tablets, sugar-coated tablets, pills, etc. The skilled person is well aware that the generic term *"tablet"* comprises next to rapid-release also, for example, sustained-release tablets (see, e.g., **D4**, in its introductory para. to *"TABLET TYPES Classification of tablets"* on p. 410). Document **D1** is silent with regard to rapid-release tablets. According to the established practice of the EPO Examining and Opposition Divisions, the generic term *"tablet"* cannot anticipate the more specific claim feature *"rapid-release tablet"* (see Guidelines for Examination in the EPO 2016, Chapter G VI-5).

In conclusion, the subject matter of claim 1 of the Opposed Patent is novel over **D1**.

F.4 Novelty over D2 and D11

(213) O1-O3, O5-O9, O11, and O13 assert that the claimed subject matter would lack novelty over **D2**. O5 additionally raises novelty objections with regard to the almost identical document, **D11**. For brevity, the objections based on either **D2** or **D11** (hereinafter denoted "**D2/D11**") will be discussed together in the following.

(214) The claimed invention is novel over **D2/D11** for at least two reasons:

(1.) **D2/D11** does not disclose the use of a tablet as oral dosage form, let alone a rapid-release tablet.

(2.) **D2/D11** reports results obtained in a phase I trial, i.e. its disclosure is limited to administering rivaroxaban to healthy people. In contrast, claim 1 of the Opposed Patent is directed to the use of a particular rivaroxaban dosage regimen for the treatment of thromboembolic disorders, i.e. the treatment of ill people[4].

F.4.1 D2/D11 does not disclose the use of a tablet

(215) **D2/D11** describes a parallel-group, randomized, single-blind and placebo-controlled multiple-dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of rivaroxaban (BAY 59-7939) in healthy male subjects (see **D2/D11**, title and l. 2-3 of **D2** or l. 4-5 of **D11**).

(216) Regarding the dosage form(s) tested, **D2/D11** only states that *"64 subjects received multiple **oral doses** of BAY 59-7939"* (see **D2**, l. 3-4 and **D11**, l. 5-6, emphasis added). Contrary to O2's and O3's unsupported assertions [see O2/O3, para. (17)], it is not implicit that the "oral dose" received by the subjects in **D2** was a rapid-release tablet.

(217) Even if one were to side with O6 (which one should not, see section E.3.1 above) in considering the term *"rapid-release"* in claim 1 of the Opposed Patent a non-specific definition or unclear and thus unable to *"distinguish [the] invention from the prior art"* (see O6, para. 3.2.4-3.2.9) then claim 1 of the Opposed Patent still requires at least a tablet. O6's conclusion that the term *"rapid-release tablet"* should be interpreted as including *any* oral dosage form (O6, p. 3.2.6) clearly lacks merit.

[4] To the skilled person working in the field of drug development for anticoagulant therapy, the term "ill people" also includes people experiencing a strong thrombogenic stimulus (e.g., post-operatively) and who therefore are at risk of developing a thrombosis.

(218) The fact remains that **D2/D11** does not mention tablets; it is silent as to the type of oral dosage form used. The skilled person has many different types of customary oral dosage forms at his disposal. Tablets are just one example. Besides tablets, oral dosage forms are recognized by those skilled in the art to include, *inter alia*, liquid formulations (for example, solutions, suspensions or syrups), pastes, granules or powders, as well as capsules or sachets filled therewith (cf., e.g., Opposed Patent, para. [0029] and **D1**, para. [367]). According to the established practice of the EPO Examining and Opposition Divisions, the generic term *"oral dose"* cannot anticipate the more specific claim feature *"rapid-release tablet"* (see Guidelines for Examination in the EPO 2016, Chapter G VI-5). O13's argument that an oral dose would also be a rapid-release tablet therefore falls flat (O13, p. 5, 2nd para.).

(219) O5's unsupported argument that a dose of 5 mg could orally only be effectively administered in form of a tablet (see O5, p. 9, 2nd para.) is directly contradicted by **D3** which teaches that 5 mg doses of rivaroxaban were administered as oral solution (see **D3**, l. 4).

(220) O7 argues that the skilled reader would *"know however, from common general knowledge, that an oral dosage form would conveniently be a tablet"* (O7, p. 4, final para., emphasis added). Similarly, O8 argues that tablets would by far be the *"most common"* oral dosage form, and, therefore, in the absence of any mention of an alternative, standard tablets must have been used in **D2** (O8, p. 6, 1st para.). These arguments are unavailing. For the purpose of novelty, it is of no consequence which undisclosed embodiments the skilled person would consider *'convenient'* or *'common'*. What the case law looks at is whether or not there is a direct and unambiguous disclosure. The fact remains that there is none in **D2**.

In summary, opponents' arguments are insufficient to establish an implicit disclosure of *"rapid-release tablet"* in **D2/D11**.

(221) Opponents fare no better with their **attempts to read the oral dosage form used in D3 into the disclosure of D2/D11**. O1 and O9, for example, take the position that because **D2** and **D3** would be by the same authors and published in the same volume of the same journal, their disclosures would need to be read in conjunction (O1, p. 11, final para., O9, p. 6, 3rd para.). O8 and O11 similarly contend that **D2** and **D3** would need to be read in direct conjunction (O8, p. 6, final para.; O11, p. 6, final para).

(222) In considering novelty (as distinct from inventive step), however, it is not permissible to combine two separate items of prior art together (see Guidelines for Examination in the EPO 2016, Chapter G VI-1). **D2/D11** and **D3** are separate prior art documents. They report on entirely different clinical trials. Their publication in the same journal volume is irrelevant for them having to be considered as two separate disclosures for novelty purposes.

(223) Moreover, even within a single prior art document, which **D2/D11** and **D3** are clearly not, it is not permissible to combine separate items belonging to different embodiments described in one and the same document, unless such combination has specifically been suggested (see, e.g., **T 305/87**).

(224) As evidenced already by their respective titles, **D2/D11** and **D3** do not concern the same or even similar studies. According to **D2/D11**, 64 subjects received multiple doses of rivaroxaban over a time course of 5 days with food (see **D2**, l. 3-4). By contrast, according to **D3**, 103 subjects received a single dose (either as tablet or as oral solution) of rivaroxaban under fasting conditions (see **D3**, title and l. 3-4). There is nothing in **D3** to suggest that the oral dosage form used in **D2/D11** would have been a tablet, let alone a rapid-release tablet. Contrary to O9's assertion, it is not at all reasonable to infer from **D3** as to the nature of the oral dosage form used in **D2**.

(225) For the same reasons as explained for **D3** above, also the disclosure of **D26** and definitions for oral dosage forms contained therein cannot be read into the disclosure of **D2/D11** for novelty purposes (as attempted by O9, at p. 6, 4th para. of its Notice of Opposition).

(226) In summary, **D2/D11** neither explicitly nor implicitly discloses what kind of oral dosage form of rivaroxaban was used. In particular, **D2/D11** does not mention that a tablet was used.

For this reason alone, the claimed subject matter is novel over **D2/D11**.

F.4.2 D2/D11 does not disclose dosage regimens for the treatment of thromboembolic disorders

(227) **D2/D11** reports results obtained in a phase I trial, i.e. its disclosure is limited to administering rivaroxaban to healthy people. In contrast, claim 1 of the Opposed Patent is directed to the use of a particular rivaroxaban dosage regimen for the treatment of thromboembolic disorders, i.e. the treatment of ill people[5].

(228) This has also been confirmed by the Examining Division, which in item 2 of its explanations accompanying the Rule 71(3) EPC Communication dated November 13, 2014 (**D66**) correctly concluded that:

> *"2. [...] However, the study* [=**D2**] *focused on* ***safety issues*** *of rivaroxaban and was conducted on* ***healthy subjects****. The document* ***is silent about the efficacy of the dosage regimens tested in the treatment of thromboembolic disorders****. Strictly*

[5] To the skilled person working in the field of drug development for anticoagulant therapy, the term "ill people" also includes people experiencing a strong thrombogenic stimulus (e.g., post-operatively) and who therefore are at risk of developing a thrombosis.

> *speaking **none of the dosage regimen[s] tested**, including the dosage regimen of 5 mg od, **can be considered to represent a dosage regimen for the treatment of a thromboembolic disorder**.[...]"* (emphasis and explanations in square brackets added)
>
> *"3. [...] However, **none of documents of the prior art** [=**D1-D3**] **discloses a specific dosage regimen for the treatment of thromboembolic disorders** with rivaroxaban.[...]"* (emphasis and explanations in square brackets added)

(229) The art of developing a safe and efficacious dosage regimen for a drug involves many steps after a molecule is identified as having biological activity. In the initial step of **phase I** human trials, **healthy volunteers** are used to evaluate the safety, pharmacokinetic (PK), and pharmacodynamic (PD) properties of the drug. Dose escalation trials for anticoagulants, such as the one described in **D2/D11**, do not begin with ill patients that require an anticoagulant. These patients cannot be treated ethically with a drug that has not been shown to work or at a dosage so high that it may cause an unacceptable degree of bleeding. These patients also cannot be given a placebo in dosage trials for similar ethical reasons (see section E.3.5 above). Thus, patients requiring an anticoagulant cannot be the initial subjects for testing dosages of a new anticoagulant.

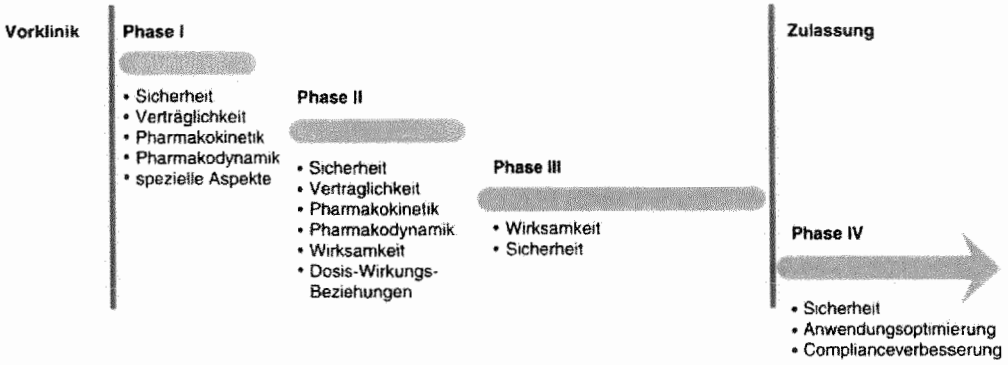
(230) Drugs are also not initially tested in ill patients because it is first required to test them in healthy volunteers with no known risk factors for disease, no internal wounds, or other pathophysiological circumstances that could render them susceptible to bleeding. Healthy male adults, the preferred study population for phase I dose escalation trials, are at the least risk of being harmed by an incorrect dose and are therefore the standard patient population for phase I trials, such as the one described in **D2/D11**.

(231) Thus, contrary to the opponents' assertions (see, e.g., O9, p. 6, 1st para.), **D2/D11** clearly does not teach administration of rivaroxaban to *patients*. Already the title of **D2/D11** explicitly states that **healthy male adults** were the subjects of these phase I trials.

(232) It also forms part of the skilled person's general knowledge that – by definition – healthy subjects, and not patients, are the first to be tested in phase I clinical trials. See, e.g., Jaehde et al., 2nd ed. 2003, „Lehrbuch der klinischen Pharmazie" (**D67**), at p. 133, left col., 2nd para. (emphasis added) and Fig. 9.1 on p. 130:

> *"Der **gesicherte Nachweis der Wirksamkeit** einer neuen Substanz **wird in keinem Fall im Rahmen von Phase-I-Studien am Probanden erbracht**. **Definitionsgemäß** werden **Probanden** in die Untersuchung einbezogen, die im Rahmen der Ein- und Ausschlussbedingungen der Studien als **gesund** gelten. Da aber das **Vorliegen entsprechender Krankheitssymptome** für die Bewertung der Wirksamkeit ausschlaggebend ist, **kann dies beim Gesunden nicht getestet werden**. Für einzelne pharmakodynamische Effekte (u. a. Blutdrucksenkung) kann auch beim Probanden evtl. eine entsprechende Wirkung beobachtet werden. Die **Aussagekraft dieser Befunde** für den Hypertoniker ist jedoch **fragwürdig**, weil die pathophysiologischen*

Mechanismen der Erkrankung und deren pharmakodynamische Beeinflussung sehr verschieden sein können."



Versuchs-teilnehmer	Probanden	Patienten	Patienten	Patienten
Anzahl	< 100	100 – 500	> 1000	verschieden

Abb. 9.1: Phasen der klinischen Entwicklung und deren Hauptziele.

Fig. 1 (reproduction of **D67,** p. 130, Fig. 9.1)

Note that Fig. 9.1 of **D67** speaks of "*patients*" ("*Patienten*") only in connection with phase II-IV trials. The healthy subjects of phase I are distinguished therefrom as "*subjects*" ("*Probanden*").

(233) The above-cited passage from the Jaehde textbook (**D67**) confirms that **clinical efficacy** and **related dosage-clinical efficacy relationships** are not determined in phase I studies. No conclusions on clinical efficacy of a dosage regimen in treating patients can be drawn from phase I studies, which involve healthy people only, not patients with a relevant disease. Phase I study results, accordingly, cannot determine clinical efficacy of a dosage regimen for treating patients. Therefore, and as explained in more detail in sections G.9.3.2-9.3.5 below, pharmacodynamic effects determined in healthy subjects during phase I studies, and specifically the results of the *in vitro* clotting assays[6] mentioned in **D2/D11**, are not predictive of the clinical efficacy of the claimed dosage regimen.

[6]The term "clotting assay" is used herein and understood by the skilled person to refer to the class of *in vitro* coagulation assays that measure the formation of a clot, either continuously over time or as "clotting time" (e.g., the time it takes to form a clot with a specified stability or density). The assays can differ in the matrix used (e.g., whole blood, platelet-poor plasma or platelet-rich plasma), in the initiation of coagulation (e.g., different compounds as trigger for clot generation), and the detection, which can be conducted by visual, optical, or electromechanical means. PT (Prothrombin Time), aPTT (activated Partial Thromboplastin Time) and HepTest are typical examples of such clotting assays.

(234) O9 asserts that the disclosure of **D2** would be *"more than a mere proposal for treatment"* (O9, p. 6, 1st para.). Ignoring **D2**'s title, which explicitly states *"healthy male subjects"*, O9 argues that rivaroxaban would nevertheless be administered to *"a patient"* (O9, p. 6, 1st para.). O9's line of argumentation is contrary to the skilled person's common understanding of phase I trial results and is based on a selective reading of document **D2** motivated by hindsight. The skilled person understands **D2** to not even contain a *"proposal for treatment"*. Rather, its disclosure is clearly limited to the initial testing of escalating doses to determine certain base PK and PD parameters **in healthy subjects**. Clearly, this does not amount to a *"proposal for treatment"* as suggested by O9.

(235) To confuse matters further, O9 relies on *"the absence of side effects"* (O9, p. 6, 1st para.) in the healthy male adults employed according to **D2** to conclude that at least one effect of rivaroxaban would have been shown in **D2**. O9 also states that *"efficacy"* would be inherent to the administration to humans (O9, p. 6, 1st para.). This anomalous interpretation of **D2** cannot be followed.

(236) The term **"efficacy"** may be used in early drug development to describe biochemical effects of a drug, e.g. binding to or inhibition of target molecules or impact on surrogate markers such as *in vitro*[7] blood coagulation assays.

(237) The **skilled person** addressed by the Opposed Patent and for the present case determined according to the established case law of the Technical Boards of Appeal of the EPO is:

> ***a physician and/or pharmacologist with several years of practical experience in the clinical development of drugs, in particular anticoagulants, for the treatment of thromboembolic disorders.***

(238) In this field of clinical drug development, however, the term "efficacy" is used synonymously with **"clinical efficacy"** or **"therapeutic efficacy"** and means the effect that a drug has on **clinical outcome**, which is measured by incidence of **clinical endpoints** (such as strokes, incidences of thrombosis or death) in controlled (phase II and phase III) clinical trials. "Efficacy", "clinical efficacy" and "medical efficacy" are used herein synonymously as just defined (i.e. meaning the proven effect on clinical outcome in patients). Thus, contrary to O9's assertion, the relevant skilled person's concept of efficacy does not apply to healthy human subjects. It can therefore also not be considered generally inherent to administrations of rivaroxaban in the context of phase I clinical studies, the subject of **D2/D11**.

[7] The term *"in vitro"* is used herein to include any experiments performed *"outside the body"*, i.e. in a test tube. It also includes experiments that by some would be referred to as *"ex vivo"*.

F.4.2.1 The claims of the Opposed Patent do not include administration to healthy people

(239) The Opposed Patent in para. [0022] defines the term *"treatment"* to also include *"prophylactic treatment of thromboembolic disorders"*. Several opponents (e.g., O6 at para. 3.2.3) have asserted that administering rivaroxaban to healthy subjects would therefore be encompassed by the claims of the Opposed Patent. It is not. The skilled person understands the term *"prophylactic treatment of thromboembolic disorders"* to refer not to the use of the compound in healthy people, but rather to the use of the invention in patients having a risk of a thromboembolic disease or condition.

(240) For example, the EMA has authorized prophylaxis with rivaroxaban for patients undergoing hip or knee replacements (see Xarelto® 10 mg SmPC, **D48a**). Surgical interventions activate the coagulation system, which, depending on the type of surgery, increases the risk of clot formation not only at the site of the surgical wound, but also elsewhere in the body. During surgery, the major leg veins that return the blood to the heart may be damaged. Hip and knee replacement surgeries are known to have a high risk of inducing this clot formation in the lower extremities.

(241) The EMA has also authorized prophylaxis with rivaroxaban for patients with non valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (See Xarelto® 20 mg SmPC, **D48b**). This cardiogenic condition is characterized by intermittent or persistent arrhythmia of the heart (see Opposed Patent, para. [0025]). It is associated with an increased risk of blood pooling and subsequent clot formation in the heart, and thus (cardiogenic) thromboembolisms.

(242) These indications are just two examples of the many possible prophylactic uses for rivaroxaban. Prophylaxis for thromboembolism necessarily involves a patient at a heightened risk for thromboembolism, i.e. above that of a normal healthy person. This **condition of having an increased coagulation risk** is termed ***"hypercoagulation"*** by those skilled in the art. Conditions that call for prophylaxis with anticoagulants have concrete pathophysiological manifestations (i.e., are different from the physiological situation in healthy individuals).

See, e.g., Pschyrembel, 258 ed. 1997 „Klinisches Wörterbuch", p. 714 (**D68**):

> ***„Hyperkoagulabilität*** *(↑; Koagul-*) f: (engl.) hypercoagulability; vermehrte Gerinnbarkeit des Bluts; führt zu Thrombose* od. Embolie*;* ***Urs.:*** ***1.*** *gesteigerte Aktivierung der Blutgerinnung* durch zerfallende Malignome, Verbrennung, postoperativ u. postpartal;* ***2.*** *Mangel an Hemmstoffen der Gerinnung (Antithrombin III, Heparin-Cofaktor-II, Protein C, Protein S);* ***3.*** *Mangel an Fibrinolyseinhibitoren*. Vgl. Verbrauchskoagulopathie."*

See also Fülgraff , „Pharmakotherapie" (**D62**), 11th ed. 2001, p. 116, left col., 2nd para. – right col., 1st para.:

> *„8.2* ***Hyperkoagulabilität***
> *8.2.1* ***Pathophysiologische Vorbemerkungen***
>
> *Das unter physiologischen Bedingungen gut aufeinander abgestimmte* ***Gleichgewicht*** *zwischen den zahlreichen Komponenten des hämostatischen Systems und ihren ebenso zahlreichen Kontrollmechanismen ist* ***bei*** **atherosklerotischen Veränderungen der Gefäßwand** ***gestört****. Eine pathologische Endothelzellfunktion mit Expression von Adhäsionsrezeptoren, Aktivierung der plasmatischen Gerinnungssysteme und Thrombozytenhyperreaktivität fördert die Entstehung von Thrombosen.* ***Pathophysiologische Grundlage ist eine endotheliale Dysfunktion*** *mit reduzierter Bildung von antithrombotischen, fibrinolytischen und vasodilatierenden Faktoren. Daraus resultiert eine* ***Verschiebung des Hämostasegleichgewichts in Richtung einer Hyperkoagulabilität.***
>
> *Ein erhöhtes Risiko* arterieller Thrombosen *besteht bei fortgeschrittenen Stadien der* **Atherosklerose,** ***bei*** **Lipidstoffwechselstörungen** ***und*** **Diabetes mellitus***. Im Vordergrund steht eine* Hyperreaktivität der Thrombozyten *mit Aktivierung der Thromboxansynthese, Freisetzung von Thrombozyteninhaltsstoffen (Serotonin, Wachstumsfaktoren) und Expression von Adhäsionsmolekülen (Selektine, Integrine), die eine Anlagerung der Thrombozyten an die Gefäßwand und Bildung von Thrombozytenaggregaten fördern. „Tissue factor" aktiviert die plasmatische Gerinnung, insbesondere im Bereich rupturierter atheromatöser Plaques. Wichtige Komplikationen akuter thrombembolischer arterieller Gefäßverschlüsse sind Myokardinfarkt und (ischämischer) Schlaganfall sowie die kritische Extremitätenischämie bei peripheren arteriellen Durchblutungsstörungen (vgl. Kap. 19).*
>
> Tiefe Venenthrombosen *sind mögliche Komplikationen größerer* ***operativer Eingriffe,*** *vorwiegend im Bereich der Hüfte und des kleinen Beckens, sowie stärkere Verletzungen mit länger dauernder Bettlägerigkeit oder Immobilisation von Extremitäten. Im Vordergrund steht hier eine* ***Aktivierung der plasmatischen Gerinnung im Zusammenhang mit der venösen Stase****, mit der Folge der Fibrinbildung, und nicht die Thrombozytenaktivierung. Lebensbedrohende Komplikation ist hier die Lungenembolie."* (emphasis added)

(243) Healthy volunteers, such as those used in the phase I study according to **D2/D11**, will not be undergoing hip or knee replacement and do not have atrial fibrillation or any of the risk factors mentioned above. By definition, these healthy volunteers cannot be considered as *"patients"*. They do not have an increased coagulation risk and are therefore not subject to a *"prophylactic treatment of thromboembolic disorders"* when enrolled in phase I trials for rivaroxaban. A claim construction that would include healthy volunteers is disconnected from the context of the Opposed Patent and the skilled person's general understanding of the term *"prophylactic treatment of thromboembolic disorders"*.

(244) The opponents' contention that healthy people would be within the patient population of claim 1 is also incorrect because the skilled person would not distort the normal hemostasis of a healthy person by administering an anticoagulant unnecessarily.

(245) The Opposed Patent in para. [0003] states that "*[m]aintenance of normal haemostasis — the balance between bleeding and thrombosis — is subject to complex regulatory mechanisms*." This understanding is also confirmed by standard textbooks in the field, see, e.g., Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, p. 1519, introductory abstract (**D9c**):

> *"The physiological systems that control blood fluidity are both complex and elegant. Blood must remain fluid within the vasculature and yet clot quickly when exposed to nonendothelial surfaces at sites of vascular injury. When intravascular thrombi do occur, a system of fibrinolysis is activated to restore fluidity. In the normal situation,* ***a delicate balance prevents both thrombosis and hemorrhage and allows physiological fibrinolysis without excess pathological fibrinogenolysis.*** *The drugs described in this chapter have very different mechanisms of action, but all are designed to achieve the same aim: namely, to alter the balance between procoagulant and anticoagulant reactions.* ***The efficacy and toxicity of these drugs are necessarily intertwined.*** *For example, the desired therapeutic effect of anticoagulation can be offset by the toxic effect of bleeding due to* ***overdosing of anticoagulant****. Similarly, overstimulation of fibrinolysis can lead to systemic destruction of fibrinogen and coagulation factors."* (emphasis added)

(246) Administration of an anticoagulant involves delicately balancing the increased need to prevent coagulation, such as clot formation in a patient, with the **increased risk of uncontrolled bleeding** from the anticoagulant. Along these lines, prophylactic treatment with anticoagulants can be described as *walking the tight rope between anticoagulation and bleeding*. Improper interference with the coagulation system can cause various thromboembolic disorders. (See Opposed Patent, para. [0003]-[0005]). The opponents' interpretation of the phrase "*prophylactic treatment of thromboembolic disorders*" to include the administration to healthy volunteers makes a leap in reasoning that ignores these concerns.

(247) Prophylactic treatment of thromboembolic disorders logically excludes treatment of healthy people having no increased risk for a given disease because such people are not patients in need of prophylactic treatment for that disease. The skilled person understands that treatment of a thromboembolic disorder – *even including prophylaxis* – is only for a person with increased risk of thromboembolism.

(248) Thus, **D2/D11** does not disclose a once-daily treatment of a thromboembolic disorder with rivaroxaban. Dealing merely with results from phase I safety and *in vitro* pharmacodynamics studies, **D2/D11** does not teach and cannot inform the skilled person about whether a particular dosage regimen would be medically effective. See also section G.9.3 below.

Such disclosure, however, would be required to anticipate a second medical use claim as demonstrated by the case law discussed in the next section below.

F.4.2.2 Case Law on clinical trial disclosures and novelty of second medical use claims

(249) The Examining Division's finding of novelty of the claimed subject matter over the phase I trial results reported in **D2/D11** is also in line with the established case law of the Technical Boards of Appeal of the EPO regarding clinical trial disclosures and novelty of second medical use claims.

(250) According to **T 715/03**, even if a prior art document discloses that advanced clinical investigations, such as phase II or III studies, are ongoing, but fails to disclose the final result of these studies, this document is not novelty-destroying for a claimed therapeutic treatment. The same rationale must apply to the current situation, where **D2/D11** only reports results from a phase I study, which was conducted in healthy volunteers. As such, it is entirely inconclusive regarding clinical efficacy of the claimed dosage regimen and cannot anticipate the claimed subject matter.

(251) In **T 715/03** the claims at issue were directed to a compound (ziprasidone) for the use in treating Tourette's syndrome (TS). There was a prior art disclosure that the known antipsychotic, ziprasidone, was *"in late phase III development"* (**T 715/03**, p. 11, 2nd para.) and was undergoing *"a phase II (clinical trial on efficacy and tolerability in TS patients) double blind (since it is placebo controlled) study which is unfinished and whose results are unknown"* (**T 715/03**, p. 12, 2nd para.). The Board held that this disclosure was not novelty-destroying for a second medical use claim directed to ziprasidone and the treatment of TS.

On p. 12, final para., **T 715/03** states:

> *"The fact that **phase II studies** are running also means that **phase I studies** are concluded. However, from this information the skilled person can only conclude that the results on safety and tolerability in humans, as well as the pharmacokinetics studies, were positive. However, there is **no information about a possible beneficial effect on TS patients**."* (emphasis added)

(252) If even the disclosure of phase II clinical trials in the claimed clinical indication (without knowledge of the results thereof) cannot anticipate a particular treatment regimen, then certainly the mere disclosure of results and dosages used in phase I trials with healthy volunteers (see **D2/D11**) cannot anticipate a claimed treatment regimen.

(253) In summary, the Examining Division correctly concluded that the claimed subject matter is novel over the disclosure of **D2/D11**.

F.4.2.3 The pharmacodynamic assay results reported in D2 are not predictive of the clinical efficacy of the claimed dosage regimen

(254) O1 and O8 assert that the pharmacodynamic parameters reported in **D2** would anticipate that rivaroxaban has the required therapeutic activity (O1, p. 11, 5th para; O8, p. 5, final para.). On this basis, O1 then concludes that rivaroxaban's use for the treatment of a thromboembolic disorder would have been made available to the public in **D2.** O1 and O8 have no basis for making these assertions.

(255) As already explained under point F.4.2 above, *clinical* efficacy is only determined in phase II and III studies. No conclusions on *clinical* efficacy can be drawn from the phase I study results of **D2/D11**, which indicate the safety and PK/PD effects in healthy people only. For more details, see the inventive step sections G.9.3.1-G.9.3.4 below.

(256) This understanding is also confirmed and codified in the official EU drug approval legislation. Directive 2001/83/EG (**D69**), which governs the manufacture, marketing authorization and distribution of medicinal products for human use in the EU, distinguishes in its Annex I (entitled *"Analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products"*) between:

- *"Reports of Human Pharmaco-dynamic Studies"* and
- *"Reports of Efficacy and Safety Studies"*

(see **D69**, section 5.1 on p. 145, last two italicized bullet points, emphasis added).

This confirms that the skilled person understands efficacy in the sense of *clinical* efficacy and not to be the same as or determined by human *pharmacodynamic* studies.

(257) Within its category *"Reports of Human Pharmaco-dynamic Studies"*, EU Directive 2001/83 (**D69**) distinguishes between:

- *"Healthy Subject Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Study Reports"* and
- *"Patient Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Studies Study Reports"*

(see **D69**, section 5.1 on p. 145, 3rd and 4th bullet point from the bottom, emphasis added).

It is important to note that **D2/D11** does not even relate to *"Patient Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Studies Study Reports"*, but merely summarizes phase I data, i.e results from *"Healthy Subject Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Study Reports"*.

(258) **D69** in its section 5.2.4 on p. 149 makes clear that whereas some pharmacodynamic actions may be found to be correlated to the efficacy of a drug, other pharmacodynamic actions may not be related to efficacy. Section 5.2.4 of EU Directive 2001/83 (**D69**, p. 149) expressly states that:

> *"The demonstration of **pharmaco-dynamic effects** in human beings shall **not** in itself be **sufficient** to justify conclusions regarding any particular potential therapeutic effect."* (emphasis added)

Thus, it is clear to the skilled person that pharmacodynamic effects, especially those observed in the early phase I trials with healthy volunteers, in no way establish clinical efficacy, let alone establish that a particular dosage regimen is efficacious, which can only be determined in phase II/III clinical studies.

(259) All anticoagulants will – at higher doses – increase the risk of bleeding. At the time phase I studies are performed, it has not been established whether a prolongation in a certain blood clotting assay *in vitro* with a given compound will be associated *in vivo* in a patient with (1) antithrombotic efficacy alone, (2) major bleeding, (3) both, or (4) none of these. Therefore, the dose-response relationships found using *in vitro* assays in phase I studies involving *healthy* volunteers cannot be used to predict the clinical efficacy of the claimed dosage regimen. For a more detailed discussion of this point, see inventive step sections G.7.4.2 and G.9.3 below.

(260) Only phase II or III clinical studies can determine whether or not there is a correlation between pharmacodynamic parameters determined *in vitro* and clinical efficacy, or even if a relationship exists between plasma concentration thresholds and, on the one hand minimal efficacy in patients, and/or on the other hand, life-threatening major bleedings.

(261) In summary, **D2/D11**, relating to healthy subjects only, does not, neither explicitly nor implicitly, disclose information that would be indicative or conclusive of the clinical efficacy of the claimed dosage regimen. This, however, would be required for a novelty-destroying anticipation of a second medical use claim.

Accordingly, the claimed subject matter is novel over **D2/D11**.

F.5 D29 is no prior art under Art. 54(2) EPC

(262) O10 at p. 4-6 asserts that the claimed subject matter would lack novelty over document **D29**.

As will be shown below, **D29 was not available to the public** prior to the effective filing date of the Opposed Patent. Being no prior art under Art. 54(2) EPC it cannot be taken into account when assessing novelty and inventive step.

(263) O10's novelty attack is premised on two assertions – specifically that: (1) EudraCT would be a public database, and (2) the database entry EudraCT no. 2004-002171-16 would have been available before the effective filing date of the Opposed Patent. Both assertions are wrong.

(264) First, EudraCT is not a public database. EudraCT is the EU's electronic database of clinical trials. It contains clinical trial information submitted by sponsors and informs a selected group of registered users about ongoing clinical trials in all EU Member States and European Economic Area (EEA) countries, enabling an overview of multi-state trials. The information in EudraCT is not available to the general public, but only to a select group of registered users who are bound to confidentiality. This includes study sponsors, national regulatory authorities, European commission, and EMA. Registered users can log in to the system to perform tasks in the approval process relating to their roles.

(265) **D29** is a printout of a webpage from the EU clinical trials register portal (www.clinicaltrialsregister.eu). The date on the bottom right of p. 2-5 of **D29** indicates that the webpage was only accessed on December 29, 2015. O10 has provided no proof that the webpage was already online and/or its content publicly available before January 31, 2005, the effective filing date of the Opposed Patent.

(266) Where lack of novelty is alleged, the burden of proof invariably lies with the party claiming that the information in question was made available to the public before the effective filing date (see "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter I.C.3.5.1, citing, e.g., **T 193/84**, **T 73/86**, **T 162/87**, **T 293/87**, **T 381/87**, **T 245/88** and **T 82/90**).

O10 has not discharged its burden of proof.

(267) As evidenced by the attached EMA press release of March 22, 2011 (**D70**) and the attached correspondence between Dr. Alexander Nowak, authorized representative of the Patentee, with Ms. Raffaella Chersoni, a member of the EMA service desk (**D71**), the EU clinical trials register (https://www.clinicaltrialsregister.eu) was only launched on **March 22, 2011.** As stated in para. 1 of the press release (**D70**), the online register gives, *for the first time* (i.e. on March 22, 2011), public access to information on interventional clinical trials for medicines *authorized* in the European Economic Area (EEA). Rivaroxaban had not yet been authorized at the effective filing date of the Opposed Patent (see **D48a**, final page, point 9, stating *"30 September 2008"* as date of first authorization). The public EU clinical trials register was only launched on March 22, 2011. Thus, there can be no doubt that **D29** does not qualify as prior art pursuant to Art. 54(2) EPC.

(268) Finally, even if **D29** were considered prior art, it does not disclose *the result* of the clinical trial it describes. According to **T 715/03**, such disclosure would however be necessary to

anticipate a second medical use claim. As explained in more detail in section F.4.2.2 above, the Board in **T 715/03** held that even if a prior art document discloses that advanced clinical investigations, such as phase II or III studies, are ongoing, but fails to disclose the final result of these studies, this document is not novelty-destroying for a claimed therapeutic treatment.

(269) In summary, **D29** cannot be prejudicial to the novelty of the claimed subject matter as it does not belong to the prior art relevant to the Opposed Patent. Even if it were considered as prior art, which it should not, the claimed subject matter is novel over the disclosure of **D29.**

G INVENTIVE STEP (ART. 100(a), 56 EPC)

G.1 Summary of opponents' inventive step arguments

(270) Opponents' inventive step arguments rely on the following documents as closest prior art:

Opponents	Closest prior art	See our rebuttal arguments in
All opponents	**D2/D11**	sections G.3-G.9 below
O1, O4, and O5	**D1/D1a**	section G.10.1 below
O4, O8, O9, and O12	**D3/D12** or **D15/D17**	section G.10.2 below
O9	**D16** or **D27**	section G.10.3 below

Several opponents fail to consider the EPO's problem-and-solution approach. Those who do, fail to apply it correctly. In particular, none of the opponents determine the correct distinguishing features. Instead, they only rely on the use of a rapid-release tablet and ignore the therapeutic once-daily dosage regimen, which is an important distinguishing feature for all closest prior art documents considered (see sections G.4 and G.10.1-3 below).

(271) Based on this error, O1, O2, O3, O4, O6, O8, O9, O11, and O13 formulate the technical problem as merely being the *provision of a useful or alternative oral dosage form*, the solution to which they consider obvious or a merely arbitrary choice (see, however, sections G.4, G.5 and G.8 below).

(272) The **correct problem-and-solution approach**, starting from **D2** or **D11** as closest prior art, is applied in sections G.3 to G.9 below.

(273) The opponents assert that the claimed once-daily dosage regimen for rivaroxaban would have been obvious for the following reasons (our rebuttal sections are indicated in parentheses):

- Once-daily administration would have been obvious *per se* (see section G.7 below). In particular,

  1. **no conventional wisdom or prejudice** taught away from the claimed dosage regimen (see section G.7.1 below).

  2. a desired **increase in patient compliance** would teach towards a once daily dosage regimen (see section G.7.5 below).

- **Rapid-release tablets** would have been an obvious choice (see section G.8 below).

- Rivaroxaban would have been known to have **a relatively large therapeutic window**, which would indicate feasibility of once-daily dosing (see section G.7.4 below). In particular,

  1. several opponents erroneously infer the therapeutic window from prior art phase I **pharmacodynamics** and safety data (see sections G.7.4.2, G.9.3.2-G.9.3.5 below).

  2. **D1, D6**, and **D16** would teach rivaroxaban to have a relatively large therapeutic window (see section G.7.4.3 below).

  3. the reference to **D14 (Rowland and Tozer)** in para. [0010] of the Opposed Patent would not support Patentee's argument during prosecution that the skilled person would not have expected rivaroxaban's half life to be sufficient for effective once-daily dosing (see section G.7.4.6 below).

- The ***in vitro*** **pharmacodynamic assay results** determined in phase I studies (**D2/D11, D3/D12, D15/D17**) would have suggested a once-daily dosage regimen to be effective (see section G.9.3 below). In particular,

  1. **D2/D11** and **D15/D17** would provide evidence for a **sustained therapeutic effect** of rivaroxaban (see section G.9.3.1 below).

  2. the phase I study results for rivaroxaban (**D2/D11, D3/D12, D15/D17**) would be indicative of clinical efficacy (see sections G.9.3.2-G.9.3.5 below).

- The claimed dosage regimen would have been obvious in light of the known once-daily dosage regimens of low molecular weight heparins (LMWHs) such as **enoxaparin** (**D13**) or **nadroparin** (**D34**) (see section G.9.4 below).

- O2, O3, and O6 assert that the once-daily dosage regimen of rivaroxaban would have been obvious in light of the sustained effects that had been observed for **TAP** (**D6**) (see section G.9.5 below).

- O12 argues that rivaroxaban's mechanism of action would suggest a sustained effect, which would indicate feasibility of a once-daily dosage regimen (see section G.9.6 below).

- O9 argues that the claimed dosage regimen would have been obvious from a combination of **D2/D11** with either **D16** or **D27** (see section G.9.7 below).

- O1, O4, and O5 argue that the claimed dosage regimen would have been obvious when starting from **D1 as closest prior art** (see section G.10.1 below).

- O4, O8, O9 and O12 argue that the claimed dosage regimen would have been obvious when starting from **D3/D12** or **D15/17 as closest prior art** (see section G.10.2 below).

- O9 argues that the claimed dosage regimen would have been obvious when starting from **D16** or **D27 as closest prior art** (see section G.10.3 below).

(274) As will be demonstrated in the following sections, the opponents' arguments are neither correct, nor properly substantiated, nor in line with the case law of the Technical Boards of Appeal of the EPO. None of the prior art documents cited by the opponents teach or suggest that the claimed dosage regimen of rivaroxaban, i.e. its administration as a rapid-release tablet once daily for at least five consecutive days, would be safe and efficacious in the prophylaxis and therapy of thromboembolic disorders.

Arriving at the claimed invention involved an inventive step.

G.2 The claimed invention

(275) At the priority date of the Opposed Patent, rivaroxaban was known to be an orally administrable direct factor Xa inhibitor in early clinical development for the treatment and prevention of thromboembolic disorders. First results from phase I safety and *in vitro* pharmacodynamic studies were also known (see, for example, **D2/D11**, **D3/D12** and **D15/D17**). However, testing in patients suffering from, or at risk for, a thromboembolic disorder had yet to be completed and published. Consequently, it was not known whether or not, or under what dosage regimen, rivaroxaban would in fact be safe and efficacious in treating thromboembolic disorders.

(276) Based on the unanimous teaching of several of the phase I study reports cited by the opponents, the skilled person at the priority date of the Opposed Patent assumed rivaroxaban to have a half life of 3-6 hours (see, e.g., **D2**, l. 16: "4-6 h"; **D3**, l. 15: "3-4 h"). Conventional wisdom further led the skilled person to assume that when a drug is dosed in no more than a therapeutically active amount, which is desired to minimize side effects, the drug must be administered approximately every half life (see section G.7.1 below, and Opposed Patent at para. [0010]).

(277) Surprisingly, Patentee found that once-daily oral administration of rivaroxaban in the form of a rapid-release tablet, despite its reported half life of 3-6 hours, demonstrated safety and efficacy in a range similar to twice-daily dosaging. The data included in para. [0018]-[0020] and [0035]-[0046] of the Opposed Patent clearly demonstrate the safety and efficacy of once-daily administration of rivaroxaban (see section G.6.1 below). That the effect is credibly achieved across the full claim scope is also supported by post-published data obtained in the

numerous clinical trials that led to the marketing approval of rivaroxaban for the treatment of a range of thromboembolic disorders (see section G.6.2 below).

G.3 The closest prior art

(278) **D2** (or the almost identical **D11**) should be considered as the closest prior art. **D2/D11** reports on a phase I multiple dose escalation trial for rivaroxaban in healthy human males.

(279) By contrast, **D1** (used as closest prior art by O1, O4, and O5) only teaches rivaroxaban as one species within a broader genus of oxazolidinone derivatives and does not include results of clinical trials for rivaroxaban. **D16** and **D27** (used as closest prior art by O9) only report on *in vitro* or pre-clinical test results for rivaroxaban. In **D3/D12** and **D15/D17** (used as alternative closest prior art by O4, O8, O9, and O12), rivaroxaban was tested in healthy human males, however, only single dose regimens were used rather than the more relevant multiple dose regimen used in **D2/D11**.

(280) Against this background of prior art, **D2/D11** can be considered as the "*most promising springboard*" towards the invention (see "Case Law of the Boards of Appeal", Eighth edition 2016, Chapter I.D.3.4.2). Accordingly, it should be considered as the closest prior art.

(281) Taking **D2/D11** as closest prior art is also consistent with the view of the International Preliminary Report on Patentability and the Examining Division of the EPO. In addition, all opponents considered **D2/D11** to be the closest prior art or one of two possible closest prior art documents.

In the following sections G.4 to G.9, the problem-and-solution approach will be exercised starting from **D2/D11** as closest prior art.

G.4 The distinguishing features vis-à-vis the claimed invention

(282) The distinguishing features of the claimed invention vis-à-vis **D2/D11** have already been explained under "Novelty" in section F.4 above.

(283) In summary, **D2/D11** fails to disclose the following features:

- a rapid-release tablet of rivaroxaban,
- the claimed dosage regimen: once-daily administration of rivaroxaban for at least five consecutive days for the treatment of a thromboembolic disorder.

G.5 The objective technical problem

(284) The technical effect of the distinguishing features is that a *surprisingly safe and efficacious dosage regimen* is achieved (for a discussion of the data demonstrating this technical effect, see section G.6 below). Thus, starting from **D2/D11** as closest prior art, the **objective technical problem** underlying the Opposed Patent can be regarded as:

> ***The provision of a safe and effective oral dosage regimen for rivaroxaban for the therapeutic and prophylactic treatment of thromboembolic disorders.***

G.6 The invention solves the objective technical problem

(285) The claimed dosage regimen solves the objective technical problem. The technical effect underlying the formulation of the objective technical problem is achieved.

(286) Proof for this is provided both by the data contained in the Opposed Patent (see section G.6.1 below) as well as post-published data obtained in the clinical trials that led to the marketing approval of rivaroxaban for the treatment of a range of thromboembolic disorders (see section G.6.2 below).

G.6.1 Data contained in the Opposed Patent

(287) The data reported in para. [0018]-[0020], [0042]-[0044] and Table 1-1 of the Opposed Patent clearly demonstrate the **clinical efficacy** of once-daily ("od") administration of rivaroxaban. There were fewer occurrences of composite endpoint events (15.1%) compared to untreated conditions (see known values for placebo in para. [0018] of the Opposed Patent), i.e., fewer cases of deep vein thrombosis (DVT), pulmonary embolisms (PE), or death with the once-daily dosaging of rivaroxaban. Moreover, the efficacy of once-daily administered rivaroxaban was in the same range as standard therapy with enoxaparin, an LMWH administered by subcutaneous injection (occurrences of composite endpoint events: 15.1% with 30 mg od rivaroxaban vs. 16.8 % with 40 mg od enoxaparin; cf. Table 1-1 of the Opposed Patent).

(288) The data reported in para. [0018]-[0020], [0045]-[0046], and Table 1-2 of the Opposed Patent also clearly demonstrate the **clinical safety** of once-daily administration of rivaroxaban. The occurrence of any major bleeding events was low, again perfectly in line with results from bid administration, and approximately in the range of standard therapy.

(289) Surprisingly, despite the reported short half life of 3-6 h (see, e.g., **D2**, l. 16: "4-6 h"; **D3**, l. 15: "3-4 h"), indicative of at least a twice-daily ("bid") administration regimen, the od administration was perfectly in line with bid administration with regard to efficacy and safety. By comparing the total daily dose administered, it could be demonstrated that efficacy, on the

one hand, and major bleeding, an expected side effect, on the other hand, following od administration matched well with the efficacy and side effects following bid administration. See para. [0020], [0044], and [0046] of the Opposed Patent and the following comparison of data points taken from Tables 1-1 and 1-2 of the Opposed Patent:

Efficacy results			
Total daily dose of rivaroxaban	20mg	30mg	40mg
Administration	10 mg bid	30 mg od	20 mg bid
Incidence rate	20.0%	15.1%	10.2%

Safety results			
Total daily dose of rivaroxaban	20mg	30mg	40mg
Administration	10 mg bid	30 mg od	20 mg bid
Incidence rate	2.9%	4.5%	6.5%

(290) Some opponents argue that it would not have been surprising that the efficacy of a 30 mg od dose would be higher than a 10 mg bid dose (i.e. 20 mg total daily dose) and lower than a 20 mg bid dose (i.e. 40 mg total daily dose). See, e.g., O1, p. 22, 3rd para. This is, however, not the point. The surprising effect underlying the invention is that the 30 mg od dose is exactly where the skilled person would have expected a 15 mg bid dose to be. That is, the od dosage regimen seems to be as safe and efficacious as the bid dosage regimen.

(291) This was surprising because the skilled person would not have expected the short half life of rivaroxaban to be sufficient for once-daily dosaging. As the skilled person knows, drug serum concentrations fluctuate upon multiple dose oral drug administrations (see section G.7.2 below). The peak serum concentration (C_{max}) is reached due to maximum drug uptake after administration. Depending on the half life of the drug at issue and the administration frequency, the serum concentration quickly declines again to reach a minimum (or trough) serum concentration(C_{trough}) shortly before the next round of administration. Once-daily administration of the total daily dose leads to greater fluctuations in drug plasma levels (i.e. levels fluctuate between a higher C_{max} and a lower C_{trough}) as compared to dividing up the total daily dose into more frequent administrations, such as twice- or thrice-daily. Given the short reported half life for rivaroxaban of 3-6 hours (see, e.g., **D2**, l. 16: "4-6 h"; **D3**, l. 15: "3-4 h"), the skilled person would have expected once daily administration of the total daily dose to be associated with too high C_{max} and insufficient C_{trough} levels, which he would have feared to increase the risk of the known adverse events of bleeding and thrombus formation, respectively. For a detailed discussion of this point, see sections G.7.2 and G.7.3 below.

(292) O2, O3, and O13 fare no better with their arguments that the data in the Opposed Patent would even show a beneficial effect for twice-daily dosaging. In this respect they assert that the 20 mg bid regimen would show a greater reduction in VTE than the 30 mg once daily regimen (see O2/3, p. 6; O13, para. bridging p. 9-10). Obviously these two dosage regimens are not directly comparable because the *total daily doses* are different, which, when discussing the safety results, is also acknowledged by O2, O3, and O13 (see O2/3, p. 7, 1st para.; O13 para. bridging p. 9-10 and p. 10, 2nd para.).

(293) The data presented in para. [0046] and Table 1-2 of the Opposed Patent also clearly demonstrate the **safety** of once-daily administration of rivaroxaban. The occurrence of any major bleeding events was low, approximately in the range of standard therapy, and again perfectly in line with results from bid administration. As discussed above, also this was surprising, because C_{max} levels are higher when administering the total daily dose all at once as compared to dividing it up into several administrations throughout the day, and, given the skilled person's expectation that bleeding, the major safety concern with anticoagulants, would be driven by high C_{max} levels, which therefore should be avoided when possible (see sections G.7.2 and G.7.3 below).

(294) At the effective filing date of the Opposed Patent, the phase II clinical trial **data contained in the Opposed Patent were <u>the first</u> to demonstrate that the use of rivaroxaban (irrespective of any specific dosage regimen) is safe and clinically effective in the treatment of thromboembolic disorders**. In particular, the data in the Opposed Patent demonstrate that rivaroxaban is safe and effective when administered as a **rapid-release tablet once daily for at least five consecutive days**, which was all the more surprising given its known short half life.

G.6.2 <u>Post-published data</u>

(295) The data included in the Opposed Patent have meanwhile been confirmed and expanded to include many different indications in a vast number of clinical and post-marketing studies. In light of this wealth of evidence, opponents cannot dispute that the claimed dosage regimen for rivaroxaban is safe and efficacious and therefore solves the problem underlying the invention across a broad spectrum of thromboembolic indications.

(296) As already outlined in sections C.1 and E.2 above, rivaroxaban (tradename: Xarelto®) has meanwhile been approved in the claimed dosage regimen in more than 130 countries worldwide and has been successfully launched in more than 80 countries, including Australia, Canada, China, Japan, the US, and within the European Union. Rivaroxaban has been approved for more indications in the area of venous and arterial thromboembolism than any

of the other non-vitamin-K-dependent oral anticoagulants (Bayer Annual Report 2015, p. 70, **D46**).

(297) The European Medicines Agency (EMA) has authorized rivaroxaban as an oral anticoagulant given once daily as a rapid-release tablet for the following indications (see **D48a** and **D48b**):

1. Prevention of **venous thromboembolism** (VTE) in adult patients undergoing elective hip or knee replacement surgery.

2. Prevention of **stroke and systemic embolism** in adult patients with non-valvular atrial fibrillation (SPAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke, or transient ischemic attack.

3. Treatment of **deep vein thrombosis** (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

(298) Similarly, the US FDA has authorized rivaroxaban for the following indications (see **D49**).

1. To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

2. For the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and for the reduction in the risk of recurrence of DVT and of PE.

3. For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement.

(299) More than 20 million Xarelto® prescriptions have been written in the US alone to treat or help reduce the risk of DVT and PE blood clots and strokes. In fact, Xarelto® is now the most prescribed blood thinner in its class in the US (*https://www.**xarelto-us**.com*). Xarelto® has achieved blockbuster status with annual sales of 2.252 billion EUR worldwide in 2015 (Bayer Annual Report 2015, p. 156, **D46**).

(300) Being the first oral direct factor Xa inhibitor to gain regulatory approval (see, e.g., **D23**, title and abstract), **Xarelto® satisfied a long-standing yet unmet medical need** (see, e.g., **D16**, p. 514, right col., end of 1st para. or **D51**, p. 1, 1st para.), which is recognized by the many prestigious awards that the inventors won for their development of **Xarelto®** in the claimed dosage regimen. See section C.1 above. The Patentee's surprising finding and subsequent development of rivaroxaban's **once-daily dosage regimen** is one of the key factors that has contributed to its huge success. Taken together, (1) the fulfillment of this long-felt and hitherto unmet medical need, (2) Xarelto®'s commercial success and (3) the simplicity of the inventive solution serve as **secondary indications of inventive step** (see the Guidelines for Examination

in the EPO 2016, G-VII-10.3 and "Case Law of the Boards of Appeal", Eighth edition 2016, Chapters I.D.10.4, 10.5 and 10.7).

(301) To show specifically that the problem underlying the invention has been credibly solved across the full scope of the claims, Patentee would like to point the Opposition Division to the following four pieces of evidence:

- The RECORD 1-3 phase III clinical trials (see section G.6.2.1 below)
- The ROCKET AF phase III clinical trial (see section G.6.2.2 below)
- The EINSTEIN DVT and EINSTEIN PE phase III clinical trials (see section G.6.2.3 below)
- The ODIXa HIP2 and ODIXa-OD-HIP phase IIb clinical trials (see section G.6.2.4 below).

G.6.2.1 The EMA's 2008 CHMP AR (D59): prevention of venous thromboembolism (the RECORD 1-3 phase III trials)

(302) The EMA's 2008 Committee for Medicinal Products for Human Use Assessment Report (CHMP AR 2008) for the initial marketing authorization of rivaroxaban for the prevention of venous thromboembolism, "VTE" (the collective term for deep vein thrombosis, "DVT", and pulmonary embolism, "PE") is attached as **D59.** It provides objective evidence from a major regulatory authority and summarizes the substantive body of preclinical and clinical data proving that rivaroxaban administered once daily in the form of a rapid-release tablet for at least five consecutive days is safe and efficacious in treating thromboembolic disorders.

(303) Starting on p. 24 under "main studies", **D59** describes the Patentee's clinical phase III program for rivaroxaban in VTE prevention (**RECORD**[8] 1-3 clinical trials). The RECORD 1-3 phase III trials were able to confirm the phase II data reported in the Opposed Patent. They involved 9581 patients and demonstrated a statistically significant superiority in efficacy for once-daily administration of rivaroxaban compared to the standard of care treatment with enoxaparin, a LMWH administered by subcutaneous injection. See, for example, the efficacy data presented in the top table on p. 33 of **D59**, representative portions of which are summarized below:

RECORD 1 Hip surgery (MITT population)	Primary efficacy endpoint (prox. and/or dist. DVT, nonfatal PE, and death)	M.-H.-weighed difference to enoxaparin	P value
rivaroxaban 10 mg od	1.1%	- 2.62 %	< 0.001
enoxaparin 40 mg od	3.7%		

[8] RECORD stands for: "Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE"

RECORD 3 Knee surgery (MITT population)	Primary efficacy endpoint (prox. and/or dist. DVT, nonfatal PE, and death)	M.-H.-weighed difference to enoxaparin	*P* value
rivaroxaban 10 mg od	9.6 %	- 9.15 %	< 0.001
enoxaparin 40 mg od	18.9 %		

(304) **D59** interprets and discusses the results of the pivotal RECORD 1-3 phase III trials as follows:

> *"On the background of MITT incidence rates of 3.7% and 18.9% in the* [enoxaparin] *comparator groups in the RECORD 1 and RECORD 3 trials, respectively, absolute reductions* [with rivaroxaban] *of 2.6 and 9.2%, respectively, appear* ***statistically significant and therapeutically impressive.*** *"* (**D59**, p. 33, 1st para., emphasis added)

> *"The* ***clinical phase III program demonstrated the superiority of rivaroxaban*** **vs** ***enoxaparin*** *concerning efficacy in the direct short term treatment comparison, the direct extended treatment comparison as well as the comparison of extended treatment with rivaroxaban* vs *short-term treatment with enoxaparin.* ***There is a clear superiority of rivaroxaban 10mg od to standard comparator enoxaparin 40mg od in the prevention of venous thromboembolism in patients undergoing major orthopaedic surgery of the lower limb.*** *"* (**D59**, p. 35, penultimate para., emphasis added)

(305) To the skilled person, VTE (DVT and PE) prevention is a prime example of thromboembolic disorders, and one which is typically used for proof-of-concept studies to demonstrate clinical safety and efficacy of a new anticoagulant (see section E.3.4.2 above and **D23**, p. 413, left col., *"Klinische Studien"*). The substantive body of clinical evidence summarized in **D59** on rivaroxaban's successes in VTE prevention therefore renders the technical effect credible for the entire class of thromboembolic disorders.

G.6.2.2 The ROCKET AF phase III trial: Prevention of Stroke and Systemic Embolism in patients with AF (D72)

(306) The body of clinical trials for VTE prevention is complemented by a further phase III clinical trial program demonstrating rivaroxaban's safety and efficacy in treating **thromboembolic disorders derived from *cardiogenic thromboembolism*** such as (ischemic) stroke, systemic embolism, and transitory ischemic attacks in patients with nonvalvular atrial fibrillation (AF): the pivotal **ROCKET-AF**[9] phase III study (see Patel et al., 2011, **D72**). Based *inter alia* on the results from this study, the EMA in 2011 extended the indication for the use of rivaroxaban in

[9] ROCKET-AF stands for "Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation"

the claimed dosage regimen (i.e. once-daily as a rapid-release tablet) to the prevention of stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors, such as congestive heart failure, hypertension, age > 75 years, diabetes mellitus, prior stroke, or transient ischemic attack (see **D48b**, point 4.1 of Xarelto®'s SmPC, and **D73**, an excerpt from the Bayer Annual Report 2011, p.110).

(307) The corresponding NEJM paper reporting the results from the pivotal ROCKET-AF phase III study is attached (see **D72**). In this double-blind trial, 14,264 patients with non-valvular AF who were at an increased risk for stroke were randomly assigned to receive either rivaroxaban (at a once-daily dose of 20 mg as a rapid-release tablet) or dose-adjusted warfarin (see **D72**, p. 883 under "METHODS" and p. 884 under "STUDY TREATMENT"). The use of a rapid-release tablet of rivaroxaban administered once daily could be shown to be safe and efficacious in preventing stroke and systemic embolism in patients with non-valvular AF. Importantly, this dosage regimen for rivaroxaban was demonstrated to be non-inferior to the standard of care, warfarin therapy (see **D72**, p. 883 under "CONCLUSIONS"), which comes with many disadvantages, such as the need for continued monitoring of anticoagulation status.

(308) As seen in Table 2 and Fig. 2A of **D72**, rivaroxaban was even *"superior to warfarin" "in the analyses of patients receiving at least one dose of a study drug who were followed for events during treatment"* (see comment in **D72**, p. 888, right col., l. 12 to 16 from the bottom and Fig. 2A on p. 889):

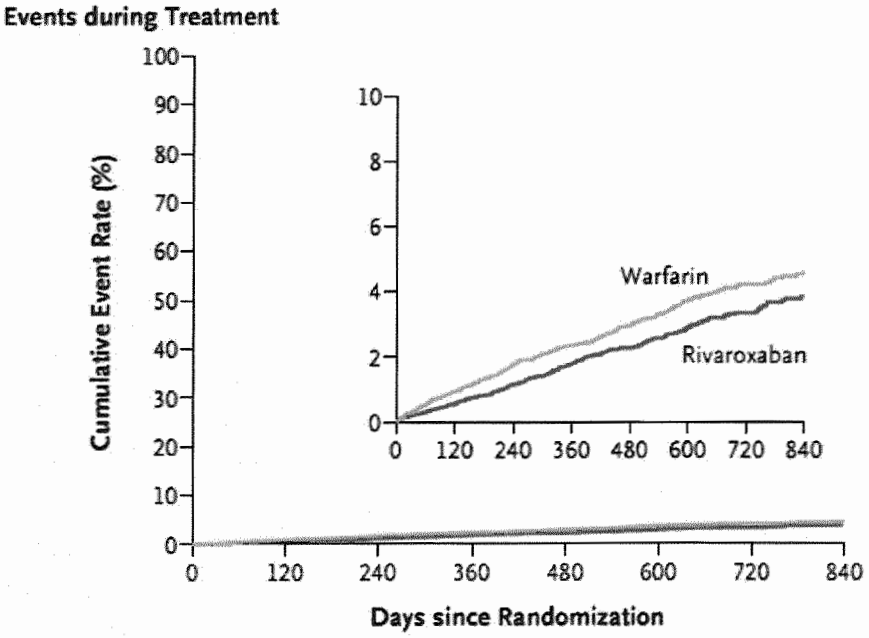


Fig. 2 (reproduction of **D72**, p. 889, Fig. 2A)

(309) In summary, the substantive body of clinical evidence provided by the ROCKET-AF phase III study renders the technical effect particularly credible for the class of thromboembolic disorders derived from cardiogenic thromboembolism (see selected indications in para. [0024] and entire para. [0025] of the Opposed Patent).

G.6.2.3 Treatment of VTE (EINSTEIN DVT and EINSTEIN PE phase III trials, D74-D76)

(310) The EMA in 2011 also extended the indication for the use of rivaroxaban administered once daily as a rapid-release tablet to the treatment of VTE (DVT and PE) based on the results of two pivotal phase III trials: **EINSTEIN DVT**[10] (see **D74**) and **EINSTEIN PE**[11] (see **D75**), the pooled results of which are summarized in Prins et al. (see **D76**).

(311) These studies involved a total of 8282 patients and demonstrated clinical efficacy of rivaroxaban in the treatment of VTE (see **D76**, p. 3 under "Results"). In particular, treatment with rivaroxaban administered once daily resulted in similar efficacy as compared to standard anticoagulant therapy, which was enoxaparin overlapping with and followed by a vitamin K antagonist (VKA). Importantly, however, significantly lower rates of major bleeding were observed with rivaroxaban (see **D76**, p. 1 under "Conclusion" and p. 9 under "Discussion"). In fragile patients, for whom VKA therapy is associated with increased complications, the incidence of major bleeding was, for example, reduced from 4.5% with standard therapy to 1.3% with rivaroxaban (see **D76**, p. 9, left col., final para. and right col., 1st para.).

(312) As explained in section G.6.2.1 above, VTE (DVT and PE) is a prime example of a thromboembolic disorder, which the skilled person knows to be typically used for proof-of-concept studies to demonstrate clinical safety and efficacy of a new anticoagulant for treatment of thromboembolic disorders. The substantive body of clinical evidence provided by the EINSTEIN DVT and EINSTEIN PE studies and rivaroxaban's clinical successes in the treatment of VTE therefore render the technical effect of the claimed treatment credible for thromboembolic disorders in general.

[10] Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis
[11] Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism

G.6.2.4 Difference between od vs. bid dosaging of rivaroxaban (ODIXa HIP2 and ODIXa-OD-HIP)

(313) The clinical trials described in sections G.6.2.1 to G.6.2.3 above compared the claimed once-daily dosage regimen of rivaroxaban to the respective standard of care treatments with enoxaparin or warfarin. The studies demonstrated at least non-inferiority, and in some instances also superiority of once-daily rivaroxaban as compared to the standard of care. Regarding a comparison of once-daily to twice-daily dosaging of rivaroxaban, Patentee would like to point the Opposition Division to the following two phase IIb studies it conducted: ODIXa[12]-HIP2 and ODIXa-OD-HIP. As will be explained in more detail below, the results of these studies indicate differences in efficacy between once-daily ("od") and twice-daily ("bid") dosaging of rivaroxaban.

(314) The ODIXa-HIP2 and ODIXa-OD-HIP phase IIb studies involved patients undergoing elective primary total hip replacement (adult men and postmenopausal women). Similar exclusion criteria applied and identical safety and efficacy endpoints were assessed in both studies. The efficacy results are summarized in Table 1 and Figure 3 below:

TABLE 1
Efficacy end points (incidence of any deep vein thrombosis, nonfatal pulmonary embolism, and all-cause death)

ODIXa-OD-HIP (PP Population; n=618)

	Rivaroxaban OD						Enoxaparin
Total daily dose	5 mg (n = 94)	10 mg (n = 113)	20 mg (n = 106)	30 mg (n = 104)	40 mg (n = 94)	60 mg (n/a)	40 mg (n = 107)
Primary efficacy endpoint, *n* (%)	14 (14.9)	12 (10.6)	9 (8.5)	14 (13.5)	6 (6.4)	-	27 (25.2)
95% confidence interval (%)	8.4, 23.7	5.6, 17.8	4.0, 15.5	7.6, 21.6	2.4, 13.4	-	17.3, 34.6

ODIXa-HIP2 (PP Population; n=548)

	Rivaroxaban BID						Enoxaparin
Total daily dose	5 mg (n = 104)	10 mg (n = 109)	20 mg (n = 101)	30 mg (n/a)	40 mg (n = 99)	60 mg (n = 29)	40 mg (n = 106)
Primary efficacy endpoint, *n* (%)	16 (15.4)	15 (13.8)	12 (11.9)	-	18 (18.2)	2 (6.9)	18 (17.0)
95% confidence interval (%)	9.1, 23.8	7.9, 21.7	6.3, 19.8	-	11.1, 27.2	0.8, 22.8	10.4, 25.5

[12] Oral Direct Inhibitor of Factor Xa

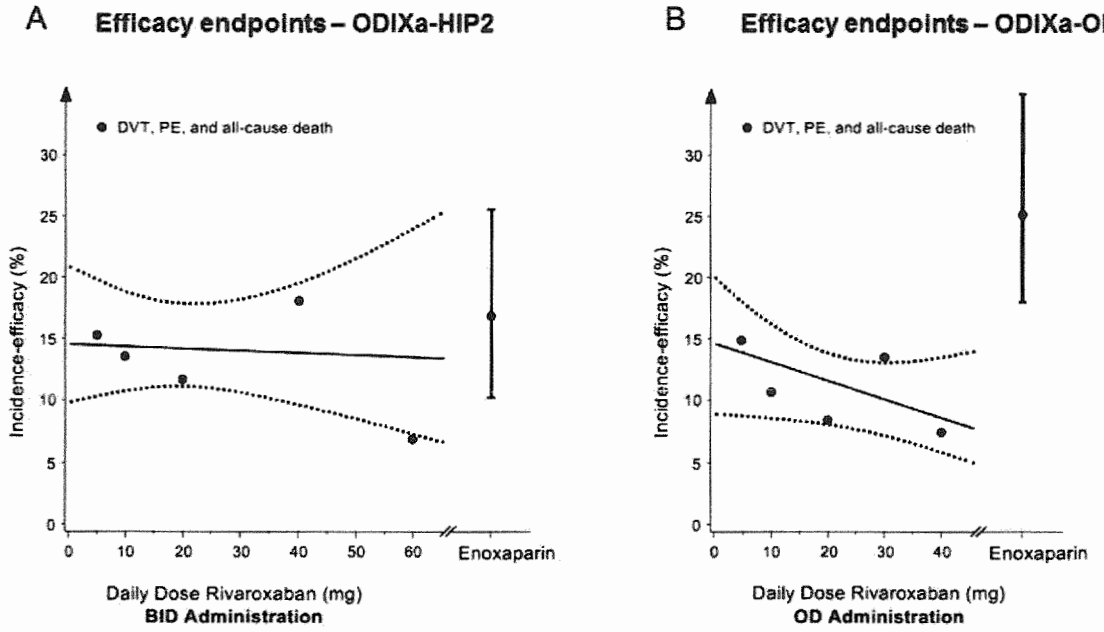


Fig. 3 (Efficacy Results from (A) ODIXa-HIP2 and (B) ODIXa-OD-HIP phase IIb studies)

(315) When comparing, within each study, the rivaroxaban treatment to the respective internal control enoxaparin treatment, the bid dosage regimen of rivaroxaban (ODIXa-HIP2 study) resulted in similar efficacy as the in-study control treatment with enoxaparin (see Fig. 3A above, the error bar of the internal enoxaparin control treatment overlaps with most of the rivaroxaban efficacy data points). In contrast, the od dosage regimen of rivaroxaban (ODIXa-OD-HIP study) resulted in efficacy that was superior to (lower incidences of efficacy endpoints) the treatment with the in-study enoxaparin at similar daily doses (see Fig. 3B above, the error bar of the internal enoxaparin control treatment does not substantially overlap with the rivaroxaban efficacy data points).

(316) Regarding safety, the od dosage regimen (ODIXa-OD-HIP study) did not increase bleeding risk above that seen with either the bid dosage regimen (ODIXa-HIP2 study) or the control treatment with enoxaparin. See Table 2 and Fig. 4A and 4B below:

TABLE 2

Incidence of major, postoperative bleeding

ODIXa-OD-HIP (Safety Population; n=845)

	Rivaroxaban OD						Enoxaparin
Total daily dose	5 mg	10 mg	20 mg	30 mg	40 mg	60 mg	40 mg
	(n = 128)	(n = 142)	(n = 139)	(n = 142)	(n = 137)	(n/a)	(n = 157)
Major postoperative bleeding, n (%)	3 (2.3)	1 (0.7)	6 (4.3)	7 (4.9)	7 (5.1)	-	3 (1.9)
95% confidence interval (%)	0.5, 6.7	0.0, 3.9	1.6, 9.2	2.0, 9.9	2.1, 10.2	-	0.4, 5.5

ODIXa-HIP2 (Safety Population; n=704)

	Rivaroxaban BID						Enoxaparin
Total daily dose	5 mg	10 mg	20 mg	30 mg	40 mg	60 mg	40 mg
	(n = 132)	(n = 136)	(n = 133)	(n/a)	(n = 134)	(n = 37)	(n = 132)
Major postoperative bleeding, n (%)	1 (0.8)	3 (2.2)	3 (2.3)	-	6 (4.5)	2 (5.4)	2 (1.5)
95% confidence interval (%)	0.0, 4.1	0.5, 6.3	0.5, 6.5	-	1.7, 9.5	0.7, 18.2	0.2, 5.4

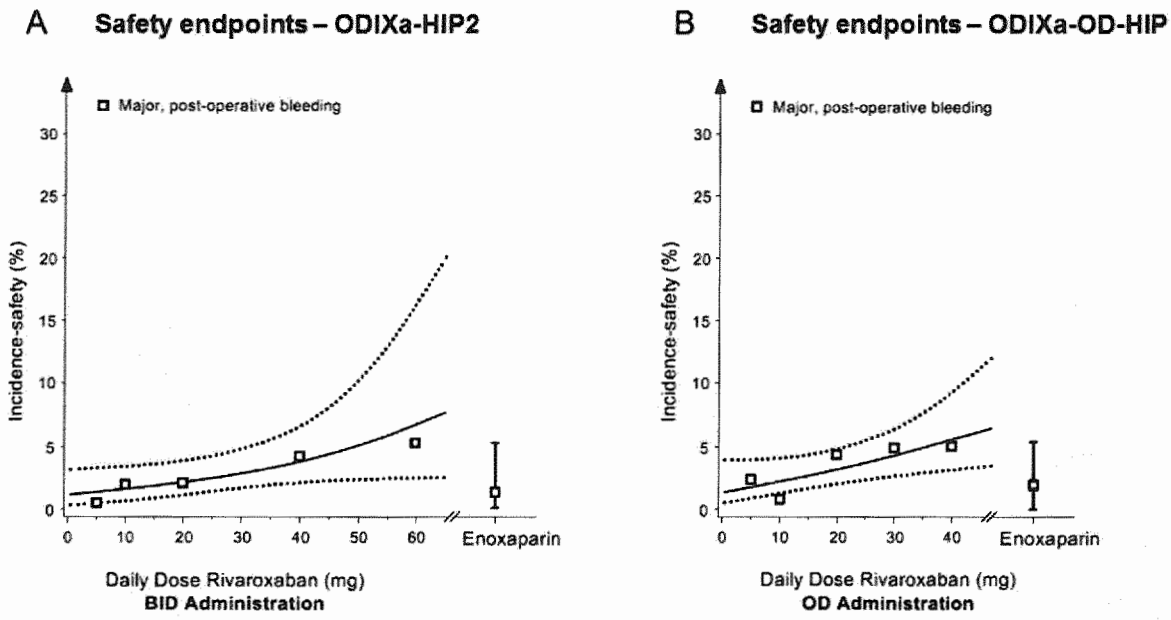


Fig. 4 (Safety Results from (A) ODIXa-HIP2 and (B) ODIXa-OD-HIP phase IIb studies)

G.6.3 The invention credibly solves the problem across the whole claim scope

(317) The opponents' assertions that the objective technical problem would not have been solved credibly across the whole scope of the claims is premised on the following assertions, which already have been rebutted in sections E.3.3, E.3.4.1, and E.3.4.2 concerning sufficiency of disclosure above:

1. That the term *"no more than once daily"* would also allow for non-working embodiments with no administration at all (see, e.g., O13, p. 7 final para.). For our rebuttal, see the respective sufficiency of disclosure section E.3.3 above.

2. That the claims would need to recite a specific quantitative dose range (see, e.g., O10, p. 19, 2nd para.). For our rebuttal, see the respective sufficiency of disclosure section E.3.4.1 above.

3. That the term *"treatment of thromboembolic disorders"* in claim 1 would cover *any* thromboembolic disorder and that it would not be credible that the technical effect is achieved within the whole scope of claim 1 (see, e.g., O4, p. 11, final 3 para.). For our rebuttal, see the respective sufficiency of disclosure section E.3.4.2 above.

(318) Each assertion is wrong. All three points have already been extensively rebutted in above sections E.3.3, E.3.4.1, and E.3.4.2, respectively, which address the question of sufficiency of disclosure across the whole claim scope under Art. 83 EPC. These rebuttal arguments apply *vice versa* to the question of whether or not it is credible that the technical effect is achievable across the whole claim scope, which is relevant under Art. 56 EPC.

(319) Briefly, as explained in section E.3.3 above, if grounded by the Opposed Patent's specification and the skilled person's understanding, the claim term *"no more than once daily"* means the same as exactly *"once daily"*. Thus, O13's objection that the claims would cover non-working embodiments involving days without any administration is moot.

(320) O10 has argued that – because the claims would lack any limitation as to the **quantitative dose** amount used in the dosage regimen – it would also cover doses for which no effect would have been shown (see. O10, p. 19-20). However, the claims do not need to recite a specific quantitative dose range (e.g., in milligrams) for inventive step to be acknowledged.

(321) The claims of the Opposed Patent do not recite a specific quantitative dose because the instant invention relates to the novel and surprising finding that rivaroxaban can be efficacious in a certain dosage regimen (i.e., using once-daily dosaging for at least five consecutive days in a rapid-release oral dosage form), independent of its efficacy in any given dose amount. See section E.3.4.1 above.

(322) As described in sections C.1 and E.2 above, rivaroxaban (tradename: Xarelto®) has already been approved in more indications in the area of venous and arterial thromboembolism than any of the other non-vitamin-K-dependent oral anticoagulants (Bayer Annual Report 2015, p. 70, **D46**). In addition to the currently approved indications, the use of rivaroxaban in the claimed dosage regimen is also being investigated in a broad range of other thromboembolic disorders. Thus, it is credible, that rivaroxaban in the claimed dosage regimen provides a safe and efficacious treatment option across a wide range of thromboembolic disorders. See section E.3.4.2 above.

(323) The data discussed in sections G.6.1 and G.6.2 above already render credible rivaroxaban's therapeutic effect for the entire class of thromboembolic disorders, as the formation of a thrombus involves factor Xa and thromboembolic disorders in general involve a common underlying disease contributor and pathophysiology: a hypercoagulation state, which is effectively counteracted by administering an anticoagulant. Before the effective filing date of the Opposed Patent it was already established that anticoagulants can provide effective treatment options for the entire range of thromboembolic disorders (see, e.g., chapter 4 in **D63** discussed in section E.3.4.2 above). See also **D6**, p. 156, left col., final para.:

> *"If the mechanistic, safety, and efficacy advantages of fXa inhibition ring true, the potential therapeutic uses for fXa inhibitors are virtually unlimited. Any thrombotic indication that has an underlying pathology of fibrin deposition or thrombin-dependent platelet activation and aggregation would certainly benefit from fXa inhibition."* (emphasis added)

(324) Against this background the burden of proof rests with the opponents to show that the claimed dosage regimen does not solve the problem across the whole claim scope.

G.7 Non-obviousness of the claimed once-daily dosage regimen

(325) Absent any publication of results from phase II or III clinical studies, the skilled person at the effective filing date of the Opposed Patent, without knowledge of the invention and the data contained in the Opposed Patent, could not have known that rivaroxaban would in fact be safe and efficacious in the treatment of a thromboembolic disorder, let alone in accordance with the claimed dosage regimen. In particular, the skilled person would not have known or expected that a rivaroxaban dosage regimen involving administration of a rapid-release tablet only once daily for at least five consecutive days would be safe and efficacious in the treatment of a thromboembolic disorder.

(326) The fact that once-daily administration was as effective and safe as (and, in some instances even superior to) twice-daily administration was surprising and could not have been predicted

based on the prior art or the skilled person's common general knowledge (see sections G.7.1 to G.7.7 below).

Arriving at the claimed solution therefore involved an inventive step.

G.7.1 The claimed invention is contrary to conventional wisdom; no reasonable expectation of success

(327) **Conventional wisdom** would have led the skilled person to believe that therapeutic efficacy of a drug with a half life of 3-6 hours (see, e.g., **D2**, l. 16: "4-6 h", cited in para. [0017] of the Opposed Patent and **D3**, l. 15: "3-4 h") required more frequent dosaging, such as twice-daily dosaging. In the prior art, the primacy of pharmacokinetic values such as half life in determining a likely successful oral dosage regimen was accepted conventional wisdom. See, for example, Birkett in "Pharmacokinetics Made Easy" 2002 (**D25a**), chapter "Half-life" at p. 23, final "key point":

> *"The **half-life determines** the duration of action after a single dose of a drug, the time taken to reach steady state with constant dosing and **the frequency with which doses can be given.**"* (emphasis added)

(328) See also **D37** cited by O11, p. 225, section 5.2.5:

> *"An understanding of the pharmacokinetic properties of a drug is one of the major sources of information used in designing a dosing regimen. [...]*
>
> - *[...]*
> - *The **half-life will determine** how the maintenance dosing rate should be **divided in time** to keep fluctuations in plasma concentration within acceptable limits".*
>
> (emphasis added)

(329) O9 on p. 8, 2nd para. and p. 12, 6th para. repeatedly concedes that the skilled person would have considered dosaging at intervals of **one dose per half life** as the starting point, convenient guide, and rule of thumb, and only pleads that it wouldn't have been a *"hard and fast rule"*.

(330) O8 on p. 8, 2nd para. points to exceptional circumstances that could indicate an unusual prolongation of therapeutic effect beyond what would have been expected based on a drug's half life (e.g. prodrugs, irreversible binding, or active drug metabolites). Similarly, O9 in the para. bridging p. 12-13 of its Opposition speculates that high selectivity, high competitiveness, long residence time in appropriate tissue, or effectiveness via multiple mechanisms would all be exceptional circumstances where sustained therapeutic effects can be observed. O12 at p. 6, 4th para. incorrectly bases its example on an irreversible inhibition, which is not the case for rivaroxaban. O8, O9 and O12 fail to offer any nexus as to why such exceptional

circumstances should apply to rivaroxaban, let alone would have been expected to apply to rivaroxaban at the effective filing date of the Opposed Patent.

(331) Contrary to opponents' assertions, such exceptional circumstances were not apparent and do not apply to rivaroxaban, which was known to be, and is, a *direct*, *competitive* and *reversible* factor Xa inhibitor (see, e.g., **D16**, p. 519, "Discussion", 1st para.). Also speaking against an exceptional prolongation of effect beyond what was expected based on half life, rivaroxaban is directly active in plasma, and does not show any signs of prodrug activity or active metabolites.

(332) In the case of rivaroxaban, the skilled person would have relied on his conventional wisdom to select a bid or tid dosage regimen based on rivaroxaban's short reported half life of only 3-6 hours (see, e.g., **D2**, l. 16: "4-6 h", cited in para. [0017] of the Opposed Patent and **D3**, l. 15: "3-4 h"). The skilled person searching for an effective dosage regimen of rivaroxaban would have relied on conventional wisdom and would have looked at half life and pharmacokinetics of rivaroxaban. Clearly, these considerations teach away from using once-daily administration of a rapid-release tablet.

(333) That half life was the primary determinant for dosaging frequency also specifically in the field of anticoagulants is confirmed by **D77**, the Annual Review of Medicine 2005 article by Linkins and Weitz (online publication date: 13.08.2004), which is cited in para. [0008] of the Opposed Patent. This review focuses on novel anticoagulant drug candidates having reached at least phase II clinical testing (see **D77**, p. 64, penult. para.). **D77** clearly teaches that these drugs are all dosed based on half life and at intervals of one to two times their respective half life:

> *"**Fondaparinux** exhibits complete bioavailability after subcutaneous injection, and with a plasma half-life of **17 h**, the drug is administered **once daily**."*
> (**D77**, p. 66, 2nd para., emphasis added)
>
> *"A more negatively charged derivative of fondaparinux, **idraparinux** binds antithrombin with higher affinity than fondaparinux. This endows idraparinux with a plasma half-life of **80 h**, similar to that of antithrombin (22). **Consequently**, idraparinux is given subcutaneously **once a week**."* (**D77**, p. 68, 2nd para., emphasis added)
>
> *"**Ximelagatran** is a prodrug of **melagatran** [...]. Ximelagatran levels in the blood peak 30 min after oral administration. Once absorbed, ximelagatran undergoes rapid biotransformation to melagatran, [...] levels of melagatran peak within 2 h. Melagatran has a half-life of **4–5 h** in patients. **Because** of this relatively **short half-life**, ximelagatran is given **twice daily**."*
> (**D77**, p. 70, 2nd and 3rd para., emphasis added)

In all these instances, **D77** naturally assumes a clear **causal link between** the known **half life** of a given anticoagulant and its prescribed **dosaging frequency** (*"with a plasma half-life of [...], the drug is administered once daily", "Consequently, [...] is given [...] once a week";*

"Because of this relatively short half-life, [...] is given twice daily"). In the case of rivaroxaban, the half life of which had been reported to be in the range of that stated for ximelagatran in **D77** (3-6 h for rivaroxaban vs. 4-5 h for ximelagatran), this presumed causal link would have taught towards at least a twice-daily dosage regimen. Arriving at the claimed once-daily dosage regimen was not obvious.

G.7.1.1 The ximelagatran example taught towards a bid administration of rivaroxaban

(334) In their review, Linkins and Weitz highlight **ximelagatran** as having great potential due to its oral mode of administration (**D77**, p. 70-73). The pharmacokinetics of ximelagatran are similar to those of rivaroxaban, specifically in time to C_{max} (ximelagatran and rivaroxaban: both within 2 h, see **D77**, p. 70, 3rd para. and **D3**, l. 8-9) and half life (ximelagatran: 4-5 h, see **D77**, p. 70, 3rd para. vs. rivaroxaban: 3-6 h, see, e.g., **D2**, l. 16: "4-6 h"; **D3**, l. 15: "3-4 h"). **D77** notably defines the dosage regimen of ximelagatran as twice daily specifically *"because of this relatively short half-life"* (see quote above from **D77**, p. 70, end of 3rd para., emphasis added). The bid regimen was also used in all clinical studies with this compound (see *id.*, p. 70, final para. to p. 72, final para.).

(335) Importantly, **D77** nevertheless notes in Table 2 that ximelagatran would have a *"wide therapeutic window"*, obviating the need for routine coagulation monitoring, an advantage over warfarin therapy (see **D77**, p. 71, Table 2, penultimate line). Thus, contrary to the opponents' repeated assertions, a *"wide therapeutic window"* does not deter the skilled person from administering a novel anticoagulant (such as ximelagatran) in accordance with its reportedly short half life of 4-5 hours, i.e. at least twice-daily.

(336) The ximelagatran example readily illustrates that at the effective filing date of the Opposed Patent, the use of orally administered anticoagulants with similar pharmacokinetic profiles to rivaroxaban taught towards a bid administration for anticoagulants with half lives of ca. 4-5 hours.

(337) **D77** at p. 70, 5th para. teaches that with ximelagatran, serious bleeding complications would need to be managed symptomatically if they occurred, as no specific antidote was available for ximelagatran. Similarly, the skilled person at the effective filing date of the Opposed Patent knew that no specific antidote existed for rivaroxaban. Similar to ximelagatran, the skilled person would thus have avoided the higher C_{max} values associated with once-daily dosaging due to fear of bleeding complications and would have opted for a more frequent dosaging. For a more detailed discussion, see section G.7.3 below.

(338) In summary, it was well known to a person of ordinary skill in the art that a drug having a half life of 3-6 hours usually cannot be efficacious and/or safe with once-daily oral administration of a rapid-release form. **D2/D11** and **D3/D12** both report a half life for rivaroxaban that would lead the skilled person to expect that multiple daily dosages would be required. The skilled person would not have been motivated to administer rivaroxaban only once daily and in a rapid-release dosage form because there was no reasonable expectation that such a dosage regimen would be therapeutically efficacious and safe.

G.7.2 With once-daily dosaging, skilled person would have feared too high fluctuations in drug concentration given the short half life of rivaroxaban

(339) As will be demonstrated below, the skilled person trying to solve the problem underlying the invention had no reasonable expectation of success for trying out the claimed solution.

(340) With once-daily dosaging, the skilled person would have feared too high fluctuations in drug concentration given the short half life of rivaroxaban. O5 essentially admits to this and correctly explains the underlying principles on p. 12, 3rd para. of its opposition:

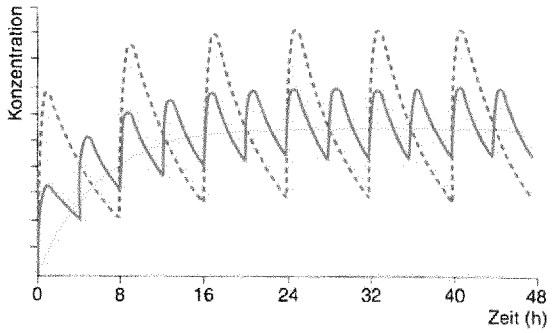
> *„Technisch betrachtet ist **der vorteilhafteste Zustand** der, bei dem im Blutplasma **konstant eine Wirkstoffkonzentration** vorhanden ist, die über der MEC* [minimal effective concentration] *liegt, die aber **weit** von der MTC* [minimal toxic concentration] *entfernt liegt. Je größer das Dosierungsintervall ist, umso eher liegt — aufgrund der Fluktuation der Wirkstoffkonzentration (vgl. D7 [=**D20**], Abb. 1.37 auf Seite 56) — die Wirkstoffkonzentration außerhalb der therapeutischen Breite, also über der MTC (beispielsweise bei einer zur Kompensation eingesetzten erhöhten Wirkstärke) und unter der MEC. Je näher die Wirkstoffkonzentration im Blutplasma an die MTC heranreicht, umso höher wird der Anteil der Patienten, bei denen schlussendlich Komplikationen auftreten, schließlich kann man nicht davon ausgehen, dass die MTC eine scharfe Grenze darstellt, unter der keine Komplikationen auftreten und über der stets Komplikationen auftreten. Die konstante Konzentration im Steady-State kann jedoch im meist nicht-praktikablen Idealfall nur durch konstante intravenöse Verabreichung erreicht werden. Fluktuationen in der Wirkstoffkonzentration können jedoch auf einem niedrigen Niveau gehalten werden, wenn das Dosierungsintervall bei einer oralen Verabreichung **kurz** gewählt wird. So gesehen ist es technisch mit einer **vorteilhaften Wirkung** verbunden, mehr als einmal täglich Rivaroxaban zu verabreichen. Gegenüber einer mehrmals täglichen Verabreichung stellt eine einmal tägliche Verabreichung eine **Verschlechterung** dar, und das Merkmal „nicht mehr als einmal täglich" stellt lediglich die* Erkenntnis *dar, dass diese Dosierung ausreichend, aber mit Sicherheit nicht optimal ist; eine Erkenntnis, die darüber hinaus vom Fachmann aufgefunden werden kann."* (emphasis and explanations in square brackets added)

(341) As O5 concedes, it amounts to common general knowledge that once-daily administration of the total daily dose leads to temporarily higher C_{max} levels, and that, as a result, the skilled person would expect an increased likelihood of adverse effects, as compared to when the total daily dose is divided into two or more daily doses. It is also expected to lead to much

higher fluctuations in drug concentration, especially if the half life is short in comparison to the dosaging interval. It was surprising that the expected increased likelihood of adverse effects did not occur with the claimed once daily dosage regimen of rivaroxaban.

(342) The fear of marked drug concentration fluctuations and how this is connected to the dosaging frequency is also nicely explained, for example, in **D78a,** the standard textbook by Aktories et al. (formerly Forth, Henschler Rummel) „Allgemeine und spezielle Pharmakologie und Toxikologie", 9th ed. (2004) at p. 73, left col., 2nd and 3rd para. and Fig. 1.65 on p. 74:

> *„Größere Schwankungen der Plasmakonzentration können von praktischer Bedeutung sein. Es* ***besteht nämlich die Gefahr,*** *dass entweder* ***toxische Konzentrationen*** *erreicht werden oder die* ***minimale wirksame Konzentration unterschritten*** *wird.*
>
> *In diesem Fall wäre zu überlegen, das Dosierungsschema zu ändern. Wird die Erhaltungsdosis auf* ***kleinere Einzeldosen*** *aufgeteilt, die in* ***kürzeren Dosierungsintervallen*** *verabreicht werden, so werden die* ***Schwankungen der Plasmakonzentration kleiner*** *(Abb. 1.65)."* (emphasis added)



„Abb. 1.65 Fluktuation der Plasmakonzentration in Abhängigkeit von Einzeldosis und Dosierungsintervall."

Fig. 5 (reproduction of **D78a,** Fig. 1.65 on p. 74)

See also **D78b** at p. 83, left col., 2nd para.

> *„Mehrmalige perorale Einnahme von Einzeldosen verursacht bei Arzneistoffen mit kurzer Eliminationshalbwertszeit* ***starke Schwankungen des Plasmaspiegels*** *und dies umso mehr, je unregelmäßiger die Medikamente eingenommen werden."*
> (emphasis added)

(343) This correlation between dosing frequency and unwanted fluctuations of plasma concentration was also known specifically in the context of factor Xa inhibitors, see **D79,** Hauptmann et al., 1999 (cited in para. [0008] of the Opposed Patent) *"State of the art article: Synthetic Inhibitors of Thrombin and Factor Xa: From Bench to Bedside"*, at p. 217, right col., 2nd para.:

"For a drug that should be given orally once or twice a day appropriate half-life is an important parameter in order to avoid marked oscillations of plasma levels between peaks and troughs at repeated administration." (emphasis added)

(344) An identical teaching can also be found in **D80a**, the standard pharmacology textbook Mutschler, 8th ed. (2001) „Arzneimittelwirkungen" at p. 50, right col. and Fig. A 2-29 and 2-30 on p. 51:

*„Ist die **Eliminationshalbwertszeit gering im Verhältnis zum Dosierungsintervall,** wird die Substanz im Intervall **praktisch vollständig eliminiert**. Die mit einer nachfolgenden Dosis erreichte Plasmakonzentration ist dann nahezu gleich der durch die vorangegangene Dosis erreichten Konzentration (s. Abb. A 2-29).*

*Liegt die **Eliminationshalbwertszeit in der gleichen Größenordnung wie das Dosierungsintervall** oder ist sie sogar noch größer, ist am Ende jedes Dosierungsintervalls noch eine merkliche Substanzmenge im Organismus vorhanden. Eine zweite Dosis führt dann zu einer deutlich höheren Plasmakonzentration als die vorangegangene Dosis. Bei nachfolgenden Dosen steigt die Plasmakonzentration weiter an, gleichzeitig nimmt die pro Zeiteinheit eliminierte Substanzmenge zu, bis die während des Dosierungsintervalls ausgeschiedene Menge der aus der vorangegangenen Dosis aufgenommenen Menge entspricht (Abb. A 2-30).*

Die Plasmaspiegel schwanken dann zwischen nahezu konstanten Maximal- ($C_{ss,max}$) und Minimalwerten ($C_{ss,min}$; Talspiegel, Trough-Wert), ein Zustand, der als **Pseudo-steady-state** *bezeichnet wird."* (emphasis added)

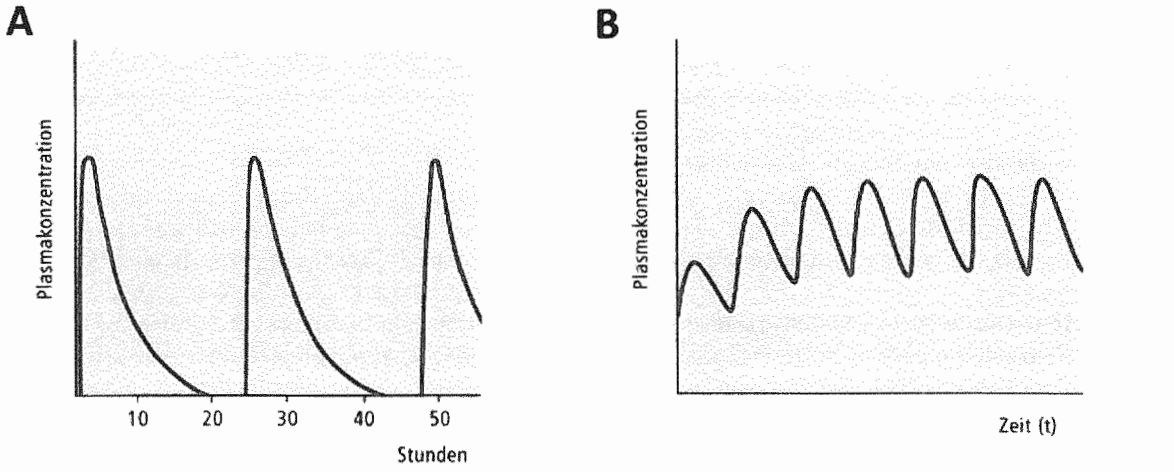


Abb. A 2–29. Plasmaspiegelverlauf nach mehrfacher oraler Gabe eines Pharmakons mit geringer Eliminationshalbwertszeit ($t_{1/2}$ = 3 Stunden) und großem Dosierungsintervall (τ = 24 Stunden)

Abb. A 2–30. Zunahme der Plasmakonzentration und Erreichen eines Steady-state-Plasmaspiegels nach mehrfacher oraler Gabe eines Pharmakons (Kumulation)

Fig. 6 (reproduction of (**A**) Fig. A 2-29 and (**B**) Fig. 2-30 on p. 51 of **D80a**)

(345) This again underlines that a rule of thumb and conventional wisdom existed that drugs are to be administered approximately every half life in order to avoid intermittent periods with no

measurable drug plasma concentration (as schematically depicted in **Fig. 6A** above; also acknowledged by O9 at p. 8, 2nd para. and p. 12, 6th para.) and excessive peak-trough fluctuations. The goal was to achieve a pseudo-steady state with trough-levels above baseline (as schematically depicted in **Fig. 6B** above).

(346) O5 concedes this when discussing similar diagrams taken from **D20**, the textbook of Derendorf (see O5, p. 11, 1st para.). O5 concludes on this basis that the dosage regimen should be chosen such that the steady-state drug plasma concentration is always below the minimal toxic concentration (MTC) and above the minimal effective concentration (MEC).

(347) What O5 fails to consider, however, is that based on the reported short half life of rivaroxaban (3-6 hours, see **D2/D11** and **D3/D12**) the skilled person would not even have expected that a once-daily dosage regimen would lead to an accumulation towards a steady state in the first place. Rather, he would have expected a plasma concentration profile mimicking that shown in Fig. A 2-29 of **D80a** (see **Fig. 6A** above), i.e. with intermittent periods close or equal to baseline, i.e. below whatever was expected to be the MEC. Thus O5's reasoning at p. 11, 1st para. and the cited passages from **D20** in fact support the notion that conventional wisdom taught away from administering rivaroxaban in a once-daily dosage regimen.

(348) Also **D67**, the textbook of Jaehde et al., 2nd ed. 2003, „Lehrbuch der klinischen Pharmazie" at p. 134, right col., final para. to p. 135, left col., 1st para. confirms that the dosaging interval is chosen based on half life:

> *„Die **Festlegung des Dosierungsintervalls erfolgt auf der Basis der Halbwertszeit des Arzneistoffes** (s. Kap. 4.3.1). Ob kontinuierliche Arzneistoffkonzentrationen oder auch Zeiten ohne systemische Arzneistoffbelastung aufrechterhalten werden sollen, hängt vom Therapiefeld und der Wirkweise des Arzneistoffs ab."* (emphasis added)

As alluded to in this quote from **D67**, there are examples where drug-free intermittent periods could be acceptable. Two representative examples are given in the following (clearly, treatment of thromboembolic disorders with rivaroxaban is not one of them):

(1) In pain treatment with quickly acting drugs, it may, for example, be sufficient to only treat pain peaks occurring irregularly. Thus, a pseudo-steady state of pain killers is not always necessary and drug-free intermittent periods can be acceptable. This is not the case for anticoagulant therapy, where the risk of thromboembolism is constant and anticoagulant-free intermittent periods were not thought to be acceptable.

(2) In the case of irreversible binding of an inhibitor to its target, time periods with no measurable plasma concentrations may also be acceptable if essentially all target sites are already occupied by the inhibitor. This is, for example, the case for antithrombotic

therapy with aspirin, which irreversibly inhibits COX1. The plasma half life of aspirin is only 15 to 20 minutes. However, because platelets as anuclear cells with limited protein expression cannot generate new COX1, the irreversible effects of aspirin last for the life of the platelet, i.e. several days (see **D31**, p. 39S, right col., 3rd para. to p. 40S, left col., 1st para.). This readily explains the efficacy of once-daily dosaging of aspirin in antithrombotic therapy despite its short half life. Rivaroxaban, however, is a reversible inhibitor and was therefore expected to require a pseudo-steady state or close to constant plasma drug concentration to be efficacious.

(349) For the therapeutic and prophylactic treatment of thromboembolic diseases with a reversible factor Xa inhibitor, such as rivaroxaban, it is clear that a pseudo-steady state is aimed for and that time periods without any systemic drug concentration measurable should be avoided. The risk of thromboembolism is not predictable and remains constantly imminent over time. Accordingly, the plasma concentration of a factor Xa inhibitor should also remain effective over time. The skilled person would have aimed for an administration approximately every half life to keep trough levels effective while maintaining a pseudo-steady state close to the optimal drug plasma concentration.

(350) The skilled practitioner would thus have tried to ensure that a safe and efficacious pseudo-steady state is achieved without any drug-free intermittent periods occurring. Against this background and the reported half life of rivaroxaban of only 3-6 hours, the skilled person would clearly have chosen at least a bid regimen to avoid the plasma concentration fluctuations depicted schematically in **Fig. 6A** above.

(351) Whereas once-daily dosaging is in principle desirable (see also para. [0009] of the Opposed Patent), in practice it is usually not achievable for drugs with short half lives. In contrast to the suggestion of O1 to assume "a maximum dose strategy" (O1, p.14, 3rd full para.), maintaining an effective level of anticoagulant by simply increasing the dose ignores the gravity of the life-threatening bleeding consequences inherent to anticoagulation therapy. The skilled person would have expected this bleeding to be associated with high peak concentrations, which he would also have avoided by ensuring a pseudo-steady state with only minimal fluctuations in plasma drug concentrations, distant from this MTC level. As such, he would not have considered a maximum dose strategy appropriate or even conceivable in the context of a novel anticoagulant.

(352) This view is confirmed by **D9**, the standard textbook Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10th ed. (2001), p. 25, left col., figure legend:

> *"Increasing the dose also prolongs a drug's duration of action but at the risk of increasing the likelihood of adverse effects. Accordingly, unless the drug is nontoxic*

> (e.g., *penicillins*), ***increasing the dose is not a useful strategy*** *for extending a drug's duration of action. Instead,* ***another dose of drug should be given*** *to maintain concentrations within the therapeutic window.*" (emphasis added)

(353) Also Birkett in "Pharmacokinetics Made Easy" (2002, **D25a**) emphasizes that the length of the effect is determined by half life and that increasing the dose is not a useful strategy. See *id.* at p. 20, 1st bullet point:

> *"...the longer the half life the longer the plasma concentration will stay in the effective range. However, the duration of action is a logarithmic, not linear, function of the dose so that* ***increasing the dose is an inefficient way of increasing the duration of action.***" (emphasis added)

(354) As a rule of thumb, the skilled person would have administered a new drug at dosaging intervals approximately equal to the drug's half life in order to avoid marked fluctuations in drug concentrations and high peak concentrations, possibly lying outside the therapeutic window, which the skilled person knew would only be determined later on in phase II and III studies (see sections G.7.4.2 and G.9.3.2 below).

See, for example, **D9**, p. 26, left col., final para. – right col., 1st para.

> *"In general, marked fluctuations in drug concentrations between doses are not desirable. If absorption and distribution were instantaneous, fluctuation of drug concentrations between doses would be governed entirely by the drug's elimination half-life.* ***If the dosing interval (T) was chosen to be equal to the half-life****, then the total fluctuation would be* ***twofold****;* ***this is often a tolerable variation.***" (emphasis added)

(355) The above line of reasoning is also in agreement with the case law of the Technical Boards of Appeal of the EPO. In **T 1319/04**, the Board gave the following reasoning regarding its finding of **non-obviousness of a once-daily dosage regimen** over the prior art's twice-daily dosage regimen:

> *"...the skilled person would not have envisaged changing the usual regimen for the treatment of hyperlipidaemia by oral administration* ***from twice daily to once per day*** *prior to sleep.*
>
> *In fact, having regard to the known hepatotoxicity of nicotinic acid,* ***common sense would rather prompt the skilled person to adopt a regimen with reduced amounts and more frequent intakes rather than a regimen where all the toxic drug is taken at once.***" (**T 1319/04**, point 2.4.10 of the Reasons, emphasis added).

(356) This inventive step reasoning is fully applicable to the present case. The hepatotoxicity feared to be associated with high doses of nicotinic acid in **T 1319/04** corresponds to the risk of major bleeding incidences, which at the priority date of the Opposed Patent were thought to

be associated with C_{max} and consequently feared when administering the complete daily dose of a novel oral anticoagulant to patients all at once (see the following section G.7.3).

G.7.3 Skilled person would have refrained from once-daily dosaging due to fear of C_{max}-associated bleeding

(357) Bleeding or hemorrhaging is a potentially life-threatening risk in all anticoagulant therapy – from injected agents such as unfractionated heparin (UFH) and low molecular weight heparins (LMWHs) through to oral agents, such as warfarin and the new oral anticoagulants (NOACs), i.e. dabigatran, apixaban, edoxaban, and rivaroxaban. Achieving a balance between sufficient anticoagulation to prevent blood clotting and avoidance of bleeding complications was at the effective filing date and still is today a constant challenge.

(358) The clinical impact of bleeding related to anticoagulant use is important for several reasons. (1) It can reduce the net benefit of therapy (the benefits of anticoagulation need to outweigh the risk of potentially serious bleeding); (2) wary clinicians may unnecessarily avoid therapy in patients who could potentially benefit; (3) bleeding complications, even if they occur rarely, impact negatively on public opinion, physician's acceptance, and even financial performance due to risk of pharmaceutical product liability lawsuits, especially, e.g., in the US.

(359) Certainly, the skilled person did not take bleeding risks lightly and would have expected that high C_{max} levels (which are reached when administering total daily doses all at once) would be associated with an increased temporal risk of bleeding during peak times. Also here, "common sense", as the Board put it in **T 1319/04**, would have prompted the skilled person to adopt a dosage regimen with reduced amounts and more frequent intakes (i.e. a bid or tid regimen) rather than a once-daily regimen where the total daily dose is taken all at once.

(360) This is especially true regarding what was known about the half life of rivaroxaban and the lack of any experience from dose-ranging studies *in patients*. The case underlying **T 1319/04** concerned a new dosage regimen for a *known and successfully applied* therapeutic drug treatment. In contrast, rivaroxaban, at the priority date of the Opposed Patent, had not yet been shown in phase II or phase III clinical trials to be safe or efficacious in *treating patients* suffering from, or at risk for, thromboembolism. Thus, the skilled person would have been even more cautious when selecting a dosage regime for rivaroxaban as a new drug and would have tried to avoid high C_{max} levels associated with once-daily dosaging.

(361) That the incidences of bleeding events would be so similar between od and bid dosage regimens of rivaroxaban was an unexpected and surprising finding, which the inventors only unraveled in the phase II clinical studies that led to the Opposed Patent. See the discussion of

the data contained in the Opposed Patent in section G.6.1 above and the comparison of safety profiles in ODIXa-HIP2 and ODIXa-OD-HIP trials presented in section G.6.2.4 and Fig. 4 above).

(362) **D23** (cited by O5) provides post-published evidence that safety, in particular in light of the bleeding risk, was an important aspect of the clinical trials for rivaroxaban. See **D23**, p. 413, left col., penult. para.:

> *„Ein **wichtiger Aspekt der klinischen Studien*** [mit rivaroxaban] *war — neben dem Nachweis der klinischen Wirksamkeit — die **Prüfung der Sicherheit, insbesondere in Bezug auf das Blutungsrisiko**."* (emphasis and explanation in square brackets added)

(363) Conventional wisdom at the priority date of the Opposed Patent was that peak plasma concentration was a key contributor to adverse effects such as bleeding. In the case of rivaroxaban, the close correlation between pharmacokinetics (PK) and pharmacodynamics (PD) found in the phase I studies (see, e.g., **D3**, l. 20-21 or **D15**, l. 28-30) also suggested that bleeding would be associated with C_{max}.

(364) That this then happened to not be the case was surprising and could not have been predicted based on the prior art. In fact, even today, the mechanism responsible for the observed comparability of safety profiles between od and bid regimens of rivaroxaban has yet to be fully elucidated. Relying on conventional wisdom and the initial PK/PD correlations from the phase I studies, the skilled person would thus have chosen at least a bid dosage regimen for rivaroxaban to reduce the fluctuations between peak and trough levels.

(365) Several opponents allege that the skilled person would not have feared bleeding complications with rivaroxaban because the class of factor Xa inhibitors would have been known to have a "relatively large therapeutic window". That this is a gross misrepresentation of facts will be explained in section G.7.4 below. At the effective filing date of the Opposed Patent, the therapeutic window for rivaroxaban was neither known nor expected to be large enough for once-daily dosaging.

(366) However, even if the skilled person had already known the therapeutic window for rivaroxaban, which he did not, he would still have avoided excessive peak plasma concentrations, because bleeding complications remain dangerous and rather unpredictable even if the therapeutic range is known. See, e.g., Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10th ed. 2001 (**D9c**), p. 1525, left col., 2nd para. in respect of heparins:

> *"Bleeding is the primary untoward effect of heparin. Historically, major bleeding was reported in 1% to 33% of patients who received various forms of heparin therapy, and in one study there were 3 fatal bleeding episodes among 647 patients (Levine and Hirsh, 1986). Recent studies suggest that major bleeding occurs in <3% of patients*

> *treated with intravenous heparin for venous thromboembolism (Levine* et al.*, 1998). The incidence of bleeding is no worse in patients treated with low-molecular-weight heparin for this indication. Although the number of bleeding episodes appears to increase with the total daily dose of heparin and with the degree of* ***prolongation of the aPTT, these correlations are weak,*** *and* ***patients can bleed with aPTT values that are within the therapeutic range.*** *Often an underlying cause for bleeding is present, such as recent surgery, trauma, peptic ulcer disease, or platelet dysfunction."*

Due to this insecurity, skilled practitioners when choosing a dose for a new anticoagulant will typically keep a safety margin to the MTC, the minimum drug concentration they believe might be associated with the risk of bleeding.

(367) Staying at the lower end of the therapeutic window to avoid high C_{max} values and keeping a safety margin to the upper end of the therapeutic window also corresponds to what the regulatory authorities demand for safety reasons. See, e.g., **D81**, Schwarz, 3rd ed. 2005, „Klinische Prüfungen von Arzneimitteln und Medizinprodukten", p. 63, 2nd para. under subheading „Studienarten der Phase II — Therapeutische Erprobung (explorativ)":

> *„Als Ergebnis der Dosisfindungsstudien* [in Phase II] *muß feststehen, welches die minimal wirksame Dosis, die mittlere und die maximal wirksame Dosis bei der betreffenden Zielpopulation mit dem jeweiligen Schweregrad der zu behandelnden Erkrankung ist. Die optimale Dosis — aus der Sicht von Zulassungsbehörden — liegt wenig über der minimal wirksamen oder zwischen der minimal wirksamen und der mittleren wirksamen Dosis."* (emphasis and explanation in square brackets added)

See also para. [0010] of the Opposed Patent which contains a similar teaching.

(368) The skilled person would have tried to avoid high C_{max} values and would therefore have applied more frequent dosaging instead of once-daily dosaging for a new anticoagulant such as rivaroxaban. This tendency to work with more frequent dosaging, i.e. smaller dosaging intervals, to be on the safe side is also emphasized in **D20** cited by O5. See **D20** at p. 52, 3rd para.:

> ***„Zur Sicherheit wird man sich mit den Dosierungsintervallen immer nach unten hin orientieren,*** *d.h. für ein berechnetes maximales Intervall von 11 Stunden könnte die Dosierungsempfehlung dreimal täglich (τ = 8 Stunden) lauten."* (emphasis added)

(369) The skilled person's fear of bleeding is compounded in the case of direct factor Xa inhibitors because, in contrast to the known treatments with heparin and vitamin K antagonists (VKA), **no antidote** was available to counteract life-threatening bleeding events when they occur.

G.7.3.1 Bleeding complications in clinical trials of anticoagulants developed in parallel (razaxaban, idraparinux) were a warning to the skilled person

(370) Several opponents seem to suggest that specifically for the more recently developed anticoagulants, such as heparin derivatives and factor Xa inhibitors, the bleeding risk would have been negligible. Opponents have no basis for making these contentions. Importantly, they are directly contradicted by the bleeding complications experienced in clinical trials of anticoagulants developed in parallel to rivaroxaban. These are summarized in **D77**, which highlights the ongoing risk of bleeding that was still known to be inherent to clinical trials investigating explorative anticoagulation therapy at the effective filing date of the Opposed Patent. For example,

- two patients receiving 5 mg of idraparinux (a heparin-related pentasaccharide) once weekly in phase II clinical trials suffered fatal bleeds. The dose used in the phase III studies was consequently halved to 2.5 mg (see **D77**, p. 68, 3rd para.).

- As another example, in the phase II trial of **razaxaban** (an orally administered factor Xa inhibitor like rivaroxaban), only the lowest dose (25 mg) was found to be safe and effective. The three higher-dose razaxaban arms of the study (50 mg, 75 mg and 100 mg) were stopped prematurely because of increased bleeding (see **D77**, p. 69, 1st para.).

(371) Thus, despite the fact that heparin analogs (such as idraparinux) and factor Xa inhibitors (such as razaxaban) had been classified as drugs with a *"relatively large therapeutic window"* (compared to conventional heparin or warfarin therapy) in selected prior art documents (see, e.g., **D1**, **D6**, or **D16**, as discussed in section G.7.4.3 below), already two-fold differences in doses were known to exceed the therapeutic window, with clinical development being stopped due to major bleeding events. Clearly, the term *"relatively wide therapeutic window"*, relied on by the opponents, needs to be put into perspective.

(372) In fact, the investigators of the early phase II trials for rivaroxaban in **D35** expressly contrast their (post-published) findings on the safety of twice-daily administered rivaroxaban doses to the excessive major bleeding observed with the three highest doses in the razaxaban phase II trial. See **D35**, p. 2484, right col., 1st para.:

> *"The observed incidence of major, postoperative bleeding was higher in the 20 and 30 mg b.i.d. doses* [of rivaroxaban], *although none of the doses was significantly higher than enoxaparin and none was stopped because of excessive bleeding. This contrasts with a recent study investigating the oral, direct FXa inhibitor razaxaban, in which the highest three doses were stopped due to excessive major bleeding.".*
> (emphasis and explanation in square brackets added)

Thus **D35**, which was published in the priority year of the Opposed Patent, confirms that the skilled person working in the clinical development of rivaroxaban had the negative razaxaban example on his mind and was influenced by the lack of safety observed with the higher razaxaban doses. Against this background he would not have expected rivaroxaban to have a large therapeutic window. This was in fact one of the reasons why the Patentee chose to conduct the first phase II clinical trials for rivaroxaban with a **twice-daily**, not a once-daily, dosage regimen (see **D35** and reference 18 cited therein). The twice-daily dosage regimen was the obvious and the *a priori* safer choice given rivaroxaban's short reported half life.

(373) Against this background of known bleeding complications with idraparinux and razaxaban even within a two-fold dose range, it would simply not have been ethically acceptable to subject patients that have undergone hip- or knee-replacement surgery, i.e. that have large internal wounds, to a "*maximum dose strategy*". The corresponding argument put forth, for example, by O1 is far-fetched and lacks merit (cf. O1, p. 14, 3rd para. and p. 17, 1st para.).

(374) In fact, Patentee indeed had to overcome **initial concerns** raised by several of the **clinical trial ethics committees** regarding the planned once-daily administration for rivaroxaban in the initial phase II trials. Ethics committees review the appropriateness of a suggested clinical trial protocol as well as the risks and benefits to study participants. They need to ensure that clinical trial participants are exposed to minimal risks in relation to any benefits that might result from the research. For rivaroxaban, responsible ethics committees indicated that they would feel more comfortable with a bid or tid dosage regimen. Thus, amongst those skilled in the art, serious concerns existed whether once-daily dosaging of rivaroxaban in the form of a rapid-release tablet would be safe and/or efficacious.

(375) The skilled person seeking a safe and efficacious dosage regimen for rivaroxaban would have followed the **bid example of ximelagatran** (described, for example, in **D77**, p. 70-72, see section G.7.1.1 above) due to the similarities in pharmacokinetics, oral dosaging, and planned treatment indications (e.g. venous thromboprophylaxis, treatment of venous thromboembolism, atrial fibrillation, and acute coronary syndromes, see **D77**, p. 71-72).

(376) This skilled person would have approached the clinical situation cautiously, refraining from administering higher doses in a once-daily regimen in light of the **known bleeding complications** with factor Xa inhibitors such as **razaxaban** and because there was **no known antidote** available for rivaroxaban. Thus, any actual bleeding occurrences would have to be managed, as with ximelagatran, 'symptomatically' (see **D77**, p. 70, 5th para.).

(377) A bid administration to achieve a certain total daily dose would have conferred the targeted efficacy without the elevated risk of increasing the likelihood of and prolonging any bleeding

occurrences. This, and not a once-daily dosage regimen with a rapid-release tablet, would have been the obvious thing to do.

(378) That the fear of C_{max}-associated bleeding with once-daily dosaging is still today considered a concern, is evidenced by post-published document **D22** cited by O5. **D22** in its abstract states the following in connection with novel oral anticoagulants such as rivaroxaban:

> *"the **twice-daily** dosing regimen is **less prone** than the once-daily dosing regimen to **hazardously high peaks** **or hazardously low troughs** in anticoagulant concentrations and associated actions. As in other fields of oral drug treatment, the **continuity** of drug action is greater with twice-daily than with once-daily dosing".* (emphasis added)

See also **D22**, p. 519, right col., l. 2-4:

> *"One can see that the **peak-to-trough variability** is larger for once-daily dosing, which could be **related to increased risks of bleeding or thrombotic events**, respectively."* (emphasis added)

(379) This is in line with the expectation the skilled person had at the effective filing date of the Opposed Patent. In light of the fear of C_{max}-associated bleeding, the above-referenced prior art experiences with other anticoagulants taught away from subjecting patients to the claimed once-daily dosage regimen for test purposes. The claimed solution did not at all appear to be an obvious option for the skilled person to pursue when searching for a safe and efficacious dosage regimen for the novel anticoagulant rivaroxaban at the effective filing date of the Opposed Patent.

G.7.4 The therapeutic window for rivaroxaban was neither known nor expected to be large enough for once-daily dosaging

(380) Several opponents seem to suggest that the class of factor Xa inhibitors would have been known to have a "large therapeutic window" (see O1, p.21, 1st para.; O2/O3, p. 9, para. (58) and (59); O5, p. 11, final para.; O6, p. 6, para. 4.6.9; O8, p. 11, 1st para.; and O9, p. 12, penult. para.). There is no basis for these assertions, especially since **anticoagulants as a class** are characterized by a **relatively narrow therapeutic window**.

G.7.4.1 Meaning of the terms "therapeutic index", "therapeutic range", and "therapeutic window"

(381) It is important to note that the terms "therapeutic index", "therapeutic range", and "therapeutic window" sometimes have conflicting and varying meanings. These terms are not necessarily used synonymously by those skilled in the art.

(382) For example, **D9,** the 1985 version of which is cited at para. [0011] of the Opposed Patent (Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, attached as **D9a**), contrasts the terms "therapeutic index" and "therapeutic window" on p. 51 (see **D9d**) and on p. 25 (see **D9**), respectively, as follows:

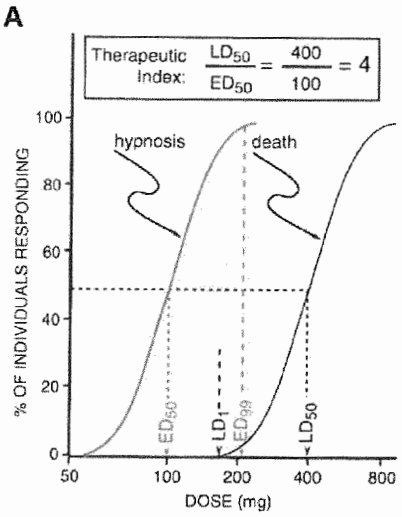


Figure 3–3. Frequency distribution curves and quantal concentration–effect and dose–effect curves.

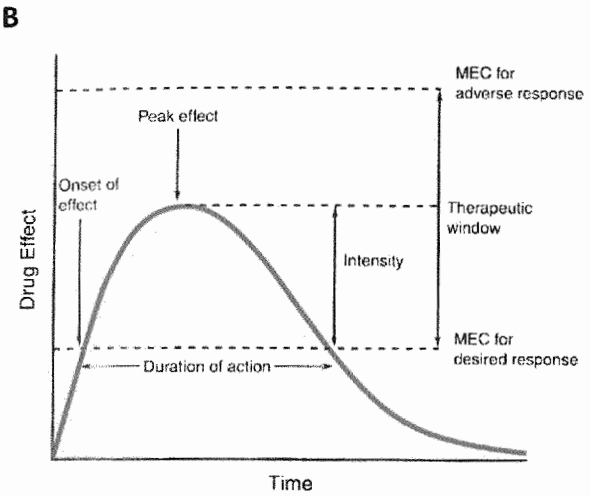


Figure 1–6. Temporal characteristics of drug effect and relationship to the therapeutic window.

Fig. 7 (reproduction of (A) Fig. 3-3 on p. 51 of **D9d,** and (B) Fig. 1-6 on p. 25 of **D9**)

Accordingly, whereas the therapeutic index is the ratio of LD50 to ED50, and is determined in pre-clinical (i.e., animal) studies where up to lethal doses are administered, the therapeutic window is determined in phase II or III studies by the minimum concentration required to achieve therapeutic efficacy and the minimum concentration at which adverse effects occur. See section G.9.3.2 below. **D14**, cited at para. [0010] of the Opposed Patent, uses "therapeutic index" and defines it as *"[u]sually toxic maintenance dose/usual therapeutic maintenance dose"* (see **D14**, p. 90, footnote a). Thus, the prior art does not use the terms "therapeutic index" and "therapeutic window" consistently.

(383) This is also reflected in the opponents' imprecise usage of the terms "therapeutic index" and "therapeutic window" (see, e.g., O1 at p. 18, 5th and 6th para., O2/O3 at para. (60), O6 at p. 6, para. 4.6.9, O8 at p. 11, 2nd para., O9, p. 8, 2nd para., penultimate sentence, all of which suggest that "therapeutic index", and "therapeutic window" would be the same).

(384) In the scientific literature, the term "therapeutic window" is often used only generically and conceptually, i.e. without a particular numerical range indicated or even known. Also **D9** on p. 25, right col., final para. states

> *"For many drugs, however, the effects are difficult to measure (or the drug is given for **prophylaxis), toxicity and lack of efficacy are both potential dangers**, and/or the therapeutic index is narrow. In these circumstances, doses must be titrated carefully, and drug dosage is limited by toxicity rather than efficacy. Thus, the therapeutic goal is to **maintain steady-state drug levels** within the **therapeutic window**. For most drugs, the actual concentrations associated with this desired range are not and need not be known."* (emphasis added)

(385) The above illustrates that the skilled person, when reading phrases such as *"relatively large therapeutic window"* (see **D6** at p. 154, left col., 2nd para.), *"relatively wide therapeutic window"* (see **D16** at p. 520, left col., 4th para.), or *"greater therapeutic range"* (see **D1**, para. [0373]), would have recognized these as being only vague and relative concepts. He would not have understood these to provide a concrete suggestion of what dosage regimen would in fact be safe and effective.

G.7.4.2 The boundaries of the therapeutic window cannot be inferred from phase I PD data

(386) O1 correctly points out that *"[i]n order to determine how often rivaroxaban can be administered, the therapeutic window and half-life of rivaroxaban need to be known"* (O1, p. 19, final para.). Similarly, O5 seems to concede that the boundaries of the therapeutic window, i.e. the minimally toxic (MTC) and minimally effective concentration (MEC), would need to be known for calculating an optimal dosage regimen (O5, p. 12, 3rd para.).

(387) As explained below, however, the boundaries of the therapeutic window of a given drug candidate are, if at all, only determined in phase II and III studies when the drug is tested in patients (see section G.9.3.2 below). The MTC and MEC can only be determined in this context. This context, however, was only provided by the data contained in the Opposed Patent, which had not been publicly available at the effective filing date of the Opposed Patent. Without knowledge of the invention and the data contained in the Opposed Patent, the skilled person could not have inferred rivaroxaban's therapeutic window from the mere phase I *in vitro* pharmacodynamics (PD) and safety data disclosed in the prior art.

(388) O1 and O5's attempt (O1, p. 20; O5, p. 11) to infer the boundaries of the therapeutic window of rivaroxaban from selected pieces of *in vitro* PD and safety data determined according to **D2** and **D15** in healthy subjects are misleading, scientifically incorrect, and beside the point.

(389) That *in vitro* prothrombinase-induced clotting time (PICT) or thrombin generation (TG) was prolonged after a 5 mg dose of rivaroxaban in healthy individuals according to **D15** does not even remotely support O1's conclusion that a single 5 mg dose would be *"above the minimum therapeutic level"* (O1, p. 20, 2nd para.). The same applies to O5 who erroneously assumes that the single 5 mg dose administered to healthy subjects in **D15**/**D17** would have

shown an effect on thromboembolic disorders (cf. O5, p. 11, 2nd para. referring to **D15**: *„Eine Wirkung auf thromboembolische Erkrankungen wird bereits bei Verabreichung von 5 mg erzielt"*). The subjects of **D15/D17** were healthy (see *id.*, title). Effects on thromboembolic disorders could not have been measured. As explained in more detail in section G.9.3.3 below, PD surrogate parameters determined *in vitro* in phase I studies in healthy subjects are not predictive of the *clinical* efficacy of a dosage regimen (such as the particular dosaging regimen claimed in the Opposed Patent).

(390) O1 and O5's line of argumentation for inferring the ceiling of the therapeutic window is similarly inappropriate. To this end, O1 relies on **D2/D11** reporting that a 30 mg bid dosage regimen (i.e. 60 mg per day) was safe and well tolerated in healthy male adults (O1, p. 20, penultimate para.). O5 mistakes the single 80 mg dose administered to healthy volunteers in **D3/D12** to represent the MTC (O5, p. 11, 2nd para).

(391) What opponents fail to consider in their leap of reasoning is that **healthy volunteers**, such as those used in the phase I study according to **D2/D11** or **D15/D17**, **do not have the same risk of bleeding complications as patients** in need of prophylaxis or treatment with an anticoagulant (these, e.g., have undergone hip or knee replacement surgery and have large internal wounds that can cause internal bleeding). Against this background it seems superfluous to say that the safety limits determined in healthy subjects in phase I cannot be transferred to patients in need of prophylactic or therapeutic treatment of a thromboembolic disease.

(392) This is nicely illustrated by the clinical development of the factor Xa inhibitor **razaxaban**, where only the lowest dose (25 mg) was found to be safe and effective in phase II studies. The three higher-dose razaxaban arms of the study (50 mg, 75 mg and 100 mg) were **stopped prematurely because of increased bleeding** (see **D77**, p. 69, 1st para., see also section G.7.3.1 above). Importantly, it can be assumed that all four doses of razaxaban cited above had in previous phase I studies been considered "safe" based on the data obtained from healthy study participants (otherwise they would not have been included in the phase II study design). This again underscores how well aware the skilled person was at the priority date of the Opposed Patent that safety data from phase I trials need to be interpreted with great caution, especially regarding the bleeding risk, which is fundamentally different *in patients* at risk of or suffering from thromboembolic disorders.

(393) Thus, O1's and O5's conclusion that the skilled person, based on the phase I data reported in **D2/D11** and **D15/D17** would have considered rivaroxaban to have a high therapeutic index or window is unfounded.

G.7.4.3 The prior art only referred to a "relatively" large therapeutic window for factor Xa inhibitors; in general, anticoagulants were considered narrow therapeutic window drugs

(394) Of note, none of the opponents stated any prior art absolute values connected to the boundaries of the allegedly large therapeutic window of rivaroxaban. This is of no wonder as they cannot. The phase II data contained in the Opposed Patent were the first that would have provided an understanding on how large the therapeutic window of rivaroxaban might be. These data were simply not publicly available before the effective filing date of the Opposed Patent.

(395) The expected therapeutic windows/ranges for factor Xa inhibitors were also only termed "relatively large" (see, e.g., **D6** at p. 154, left col., 2nd para.), "relatively wide" (see **D16** at p. 520, left col., 4th para.), or "greater" (see, e.g., **D1**, [0373]) in the prior art, i.e., relatively large or greater compared to known alternative anticoagulant therapies, heparin and warfarin. These alternative therapies require companion anticoagulation monitoring due to their very narrow therapeutic window. See, for example,

D6 at p. 155, left col. 1st para., l. 5-7 and right col, end of 3rd para.:

> *"[...] heparin administration **must be monitored carefully** to maintain plasma drug concentrations **within a safe and effective window**."*
>
> *"The significant bleeding complications and difficulty maintaining plasma concentrations of warfarin within the targetted range has led to the labeling of **warfarin** (Coumadin®) as a "**narrow therapeutic index drug**."* (emphasis added);

D14 cited in para. [0010] of the Opposed Patent at p. 89, 4th para.:

> *"[...] a drug with a low therapeutic index, e.g., heparin [...]"* or

D82, the textbook of Page et al., "Integrated pharmacology", 2nd ed. 2002, at p. 210, right col., final para.:

> *"The pharmacotherapeutic range of **heparin** is relatively **narrow** and bleeding is the major complication."* (emphasis added)

(396) These quotations already demonstrate that – compared to other drugs in general – anticoagulants as a class, including factor Xa inhibitors, were understood to in fact have a **relatively narrow therapeutic window**. This is also self-evident to the skilled person given the delicate balance between under- and overdosing that is imminent to the class of anticoagulant drugs, whose efficacy and toxicity are necessarily intertwined. See, e.g. the introductory abstract to the chapter on anticoagulants in the textbook Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (**D9c**, p. 1519):

> *"In the normal situation,* ***a delicate balance prevents both thrombosis and hemorrhage and allows physiological fibrinolysis without excess pathological fibrinogenolysis.*** *The drugs described in this chapter have very different mechanisms of action, but all are designed to achieve the same aim: namely, to alter the balance between procoagulant and anticoagulant reactions.* ***The efficacy and toxicity of these drugs are necessarily intertwined.*** *For example, the desired therapeutic effect of anticoagulation can be offset by the toxic effect of bleeding due to overdosing of anticoagulant. Similarly, overstimulation of fibrinolysis can lead to systemic destruction of fibrinogen and coagulation factors."* (emphasis added)

(397) Also the phase II safety data of other factor Xa inhibitors, such as **razaxaban** (see section G.7.3.1 above), taught the skilled person to interpret the term *"relatively large therapeutic window"* used in the literature cautiously and to put it into perspective. As described in section G.7.3.1 above, in phase II trials with the orally administered factor Xa inhibitor razaxaban, only the lowest dose (25 mg) was found to be safe and effective. The three higher-dose razaxaban arms of the study (50 mg, 75 mg and 100 mg) were stopped prematurely because of increased bleeding (see **D77**, p. 69, 1st para.).

(398) Thus, despite the fact that **D1**, **D6**, and **D16** (referring to **D6**) may have generically alluded to the class of factor Xa inhibitors as having a *"relatively large"*, *"relatively wide"*, or *"greater"* therapeutic window (compared to conventional heparin or warfarin therapy), the skilled person knew from substantial own clinical experience with such factor Xa inhibitors that even two-fold differences in dose could, as was the case for razaxaban, exceed the ceiling of the therapeutic window, with clinical development being stopped due to major bleeding events. A two-fold difference between efficacy and toxicity is – *in absolute terms* – considered a **small therapeutic window** by those skilled in the art (see, e.g., **D9**, p. 25, right col., final para.). Thus, compared to other drugs, factor Xa inhibitors such as razaxaban or rivaroxaban were known to have a relatively small therapeutic window.

Again, the term *"relatively wide therapeutic window"*, relied on by the opponents, needs to be put into perspective.

(399) At the effective filing date, the skilled person was aware that no results from phase II clinical studies with rivaroxaban had yet been reported. Against this background, he would not have given the generic and vague statements *"relatively wide therapeutic window"* cited by the opponents any weight, and would instead have relied on his influential clinical experience with other factor Xa inhibitors. In light of his knowledge of the razaxaban phase II trial results (see section G.7.3.1 above), the skilled person would not have expected a factor Xa inhibitor such as rivaroxaban to have a very wide therapeutic window.

(400) In fact, as explained in section G.7.3.1 above, the investigators of the early phase II trials for rivaroxaban in **D35** expressly contrast their (post-published) findings on the safety of twice-

daily administered rivaroxaban doses with the excessive major bleeding observed with the three highest doses in the razaxaban phase II trial. See **D35**, p. 2484, right col., 1st para.:

> *"The observed incidence of major, postoperative bleeding was higher in the 20 and 30 mg b.i.d. doses* [of rivaroxaban], *although none of the doses was significantly higher than enoxaparin and none was stopped because of excessive bleeding. This contrasts with a recent study investigating the oral, direct FXa inhibitor razaxaban, in which the highest three doses were stopped due to excessive major bleeding".* (emphasis and explanation in square brackets added)

Thus, the skilled person working in the clinical development of rivaroxaban had the negative razaxaban example on his mind and was influenced by the lack of safety observed with the higher razaxaban doses. Against this background he would not have expected rivaroxaban to have a large therapeutic window. This was in fact one of the reasons why the Patentee chose to conduct the **first phase II clinical trials for rivaroxaban** with a **twice-daily**, not a once-daily, dosage regimen (see **D35** and reference 18 cited therein). The twice-daily dosage regimen was the obvious and safer choice given rivaroxaban's short reported half life.

(401) As described under section G.7.3 above, the skilled person knew that even singular, potentially unrelated bleeding events under anticoagulant therapy can have a significant impact on public opinion, physician's acceptance, and even financial performance due to risk of pharmaceutical product liability lawsuits if safety is not handled with the utmost care. Therefore, cautious dose selection and risk mitigation were of primary importance in anticoagulant drug development.

(402) Regardless of what the skilled person might have speculated the therapeutic window of rivaroxaban to be, he would have tried to keep plasma levels as low as possible, avoiding high peak concentrations and thereby minimizing the risk of bleeding events as much as possible. The skilled person was cautious and would have immediately discarded the *"maximum dose strategy"* and *"try and see"* approach advocated by some of the opponents as way too risky and untenable.

(403) Finally, the fact that an anticoagulant is described by some scholars as having a *"relatively wide therapeutic window"* does not lead the skilled person to adopt od dosaging if the half life was known to be as short as that reported for rivaroxaban (i.e., 3-6 h, see, e.g., **D2**, l. 16: "4-6 h"; **D3**, l. 15: "3-4 h"). See the ximelagatran example discussed in section G.7.1.1 above: **D77** states in Table 2 on p. 71 that ximelagatran would have a *"[w]ide therapeutic window"*. In the corresponding text passage at p. 70, 3rd para, **D77** states that the half life is 4-5 hours and that *"[b]ecause of this relatively short half-life, ximelagatran is given twice daily"* (emphasis added).

(404) Similarly, also **the Patentee for its initial phase II trials of rivaroxaban chose a twice-daily dosage regimen** (see **D35** and reference 18 cited therein). That this was the obvious thing to do is also supported by the **concurrently developed** oral factor Xa inhibitor competitor drug product, **apixaban**, which has a reported half life of approx. 12 hours and is approved in a **twice-daily dosage regimen** (see **D83**, the SmPC for apixaban, p. 23, 2nd para. and p. 2-3, section on posology, respctively). For apixaban, the vast majority of all published clinical studies that led to its regulatory approval were naturally conducted with the bid dosage regimen, given the 12 hour half life of apixaban.

(405) This again underlines that for a drug such as rivaroxaban, whose half life was reported to be even less than half of that of apixaban, the obvious dosage regimen would have been a thrice-daily regimen, possibly a twice-daily regimen, but certainly not the claimed once-daily administration in the form of a rapid-release tablet.

G.7.4.4 The therapeutic window of anticoagulants was known to be small in comparison to other, non-toxic drugs.

(406) As an anticoagulant, rivaroxaban disrupts the delicate hemostatic balance (see section G.7.3 above). For this entire class of medicaments, efficacy and bleeding are necessarily intertwined (see the introductory abstract to the chapter on anticoagulants in **D9c**, Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, p. 1519). When administering anticoagulants, the skilled person *walks the tightrope between coagulation and bleeding*.

(407) Thus, the skilled person knew that the therapeutic window of anticoagulants, irrespective of whether being a traditional (heparin/warfarin) or novel anticoagulant (thombin- or factor Xa inhibitors), would always remain relatively small in comparison to other, non-toxic drugs.

(408) This is confirmed by many of the prior art documents cited by the opponents, which refer to **anticoagulants** as having a narrow therapeutic window or being low therapeutic index drugs (see, e.g., **D6** at p. 155, left col., 1st para. and right col, end of 3rd para.; **D14**, p. 89, 4th para; and see also **D82** at p. 210, right col., final para.). Only relative to these, factor Xa inhibitors were expected to have "*relatively large*" (see, e.g., **D6** at p. 154, left col., 2nd para.), "*relatively wide*" (see **D16** at p. 520, left col., 4th para.), or "*greater*" (see, e.g., **D1**, para. [0373]) anticipated therapeutic windows. See section G.7.4.3 above.

(409) Some of the opponents go as far as putting the expected therapeutic window for rivaroxaban on the same level as the large therapeutic windows of known non-toxic drugs such as **antibiotics** (for example, penicillins such as amoxicillin) to conclude that large therapeutic windows would be synonymous with infrequent dosaging and allowing for "*maximum dose*

strategies" (cf. O1, p. 14 referring to **D9**; O2/O3, para. (60) referring to **D7**). The skilled person immediately recognizes this leap in reasoning to be manifestly deficient and misleading.

(410) In the prior art cited, almost all examples for *"large therapeutic index"* or *"non-toxic"* drugs that allow for infrequent dosaging under the *"maximum dose"* strategy are antibiotics. See, for example,

- **D9**, p. 25, right col, end of 2nd para. referring to *"penicillins and most β-adrenergic receptor antagonists"* and p. 26, right col., 2nd para. referring to *"amoxicillin"*;
- **D7**, p. 255, final para. referring to *"benzylpenicillin"*;
- **D14**, p. 89, 4th para. referring to *"penicillin"*.

(411) The **comparison between rivaroxaban and antibiotics** is entirely inappropriate. Penicillins (including amoxicillin), for example, specifically inhibit steps in the synthesis of the thick peptidoglycan cell walls of gram-positive bacteria. Human cells do not possess a peptidoglycan cell wall. Therefore, they cannot be affected by this drug. Clearly, this explanation for the essential non-toxicity and wide therapeutic window of penicillins (which according to **D37**, p. 226, Table 5.1 can be administered in *"supramaximal"* amounts) does not apply to rivaroxaban, which directly interferes with hemostasis in humans.

G.7.4.5 D14 supports non-obviousness of the claimed dosage regimen

(412) O1, O5, and O8 contend that the statement in para. [0010] of the Opposed Patent, i.e.

> *"When the drug substance is applied in no more than a therapeutically effective amount, which is usually preferred in order to minimize the exposure of the patient with that drug substance in order to avoid potential side effects, the drug must be given approximately every half live (see for example: Malcolm Rowland, Thomas N. Tozer ...* [=**D14**] *)",*

would not be supported by **D14**, the reference cited.

(413) In this respect opponents point to p. 89, final para. of **D14**:

> *"Half-Lives Between 30 Min und 8 Hr*
>
> *For such drugs, the major considerations are therapeutic index and convenience of dosing.*
>
> *A* ***drug with a high therapeutic index*** *need only be administered once every 1 to 3 half-lives, or even less frequently.*
>
> *A* ***drug with a low therapeutic index*** *must be given approximately every half-life, or more frequently, or be given by infusion."* (emphasis added)

This is exactly the passage that the Patentee intended to reference in para. [0010] of the Opposed Patent. As an anticoagulant, rivaroxaban was known to have a small therapeutic window in comparison to other, non-toxic drugs (see the preceding section G.7.4.4 above). This is also confirmed by **D14** itself, where in the paragraph preceding the above-referenced one, heparin is cited as an example for a "low therapeutic index" drug (see **D14**, p. 89, 4th para.).

(414) The skilled person reading the above-cited passage from **D14** in its context and based on his common general knowledge would have understood rivaroxaban to be a drug with a low therapeutic index. For such drugs, **D14** clearly states at p. 89, final para. that they "*must be given approximately every half-life*" or even more frequently.

(415) The opponents' erroneous interpretation of the above-cited passage from **D14** is premised on its misrepresentation that rivaroxaban would have been considered a "*drug with a high therapeutic index (large therapeutic window)*" (see, e.g., O1, p. 18, penult. para, cf. also O5, p. 10, penult. para. and p. 11, final para.; O6, para. 4.6.9). Opponents are mistaken.

(416) As explained in sections G.7.4.3 and G.7.4.4 above, rivaroxaban, as an anticoagulant, belonged to a class of drugs that the skilled person generally knew to have a narrow therapeutic window. At the effective filing date of the Opposed Patent, the therapeutic window for rivaroxaban was neither known nor expected to be large enough for od dosaging (for a detailed discussion, see section G.7.4.2 above). All references cited by the opponents only allude to a "*relatively* high" or "larg*er*" therapeutic window of rivaroxaban (compared to conventional heparin or warfarin therapy), not a "high" or "large" window in absolute terms (see section G.7.4.3 above).

(417) Finally, even if, for the sake of argument, one would follow the opponents' mischaracterization of rivaroxaban being a "*drug with a high therapeutic index*", then **D14** would still teach an administration once every 1 to 3 half lives. Given the reported half life of rivaroxaban of 3-6 hours (see, e.g., **D2**, l. 16: "4-6 h"; **D3**, l. 15: "3-4 h") this would result in a dosage interval of between once every 3 hours and once every 18 hours (= 3 x maximally reported half life of 6 h). Thus, the largest calculated dosaging interval (18 h) lies exactly between od (24 h) and bid (12 h). To be on the safe side, the skilled person in such cases chooses a more frequent dosaging. See **D20** cited by O5, which at p. 52, 4th para. suggest a tid (every 8 h) instead of a bid (every 12 h) regimen for a calculated interval of 11h:

> ***„Zur Sicherheit wird man sich mit den Dosierungsintervallen immer nach unten hin orientieren,*** *d.h. für ein berechnetes maximales Intervall von 11 Stunden könnte die Dosierungsempfehlung dreimal täglich (τ= 8 Stunden) lauten."* (emphasis added)

(418) Thus, even if the skilled person had erroneously referred to the dosaging recommendation for high therapeutic index drugs in **D14**, which he would not have, he would still only have arrived at a **twice-daily**, not a once-daily, dosage regimen for rivaroxaban given its short reported half life.

(419) O5 at p. 10, para. 3-4 misstates the once-daily dosage regimen of rivaroxaban to have been *"about twice its half life"* (*„Dosierungsintervall von etwas mehr als dem doppelten der Halbwertszeit"*). This is incorrect. At the effective filing date of the Opposed Patent, rivaroxaban was unanimously assumed to have a half life of 3-6 hours (see, e.g., **D2**, l. 16: "4-6 h"; **D3**, l. 15: "3-4 h"). Therefore, the claimed od dosaging interval was between 4 times and 8 times rivaroxaban's reported half life. It was not obvious for a skilled person at the effective filing date of the Opposed Patent to administer rivaroxaban only once every 4 to 8 times its half life.

(420) In summary, and contrary to O1's, O5's, and O8's assertions, **D14** cited in para. [0010] of the Opposed Patent fully supports the conventional wisdom that Patentee relied on during prosecution, i.e. that it was well known to a person skilled in the art that a half life of less than 10 hours is typically not sufficient for a once-daily administration (see Patentee's submission in examination proceedings dated January 24, 2011 and section G.7.1 above).

G.7.5 Desired increase in patient compliance does not provide reasonable expectation of success

(421) Several opponents assert that the skilled person would have been motivated to administer rivaroxaban once daily using a rapid-release tablet for patient convenience and compliance. For this reason alone, once-daily administration would have been *"obvious* per se" (see O1, p. 13, last line) or a *"matter of common sense"* (O6, p. 5, 4.6.1).

(422) Patentee does not dispute that once-daily dosaging can be *desirable* to improve patient compliance. However, whereas once-daily dosaging is *desirable*, this is *not easily achievable* in practice because most drugs are not sufficiently efficacious and safe when administered once daily.

(423) An expected increase in compliance is of no value if the skilled person has no reasonable expectation of success that the dosage regimen will be safe and efficacious. Safety and efficacy are by far the overruling criteria for any drug development and take precedent over any compliance advantages the skilled person might have envisaged or speculated on. In fact, despite the opponents' repeated assertion that once-daily administration would be obvious, the majority of approved drugs requiring long-term dosaging need to be administered at least twice-daily, especially if no sustained-release dosage form is available.

(424) The fact that rivaroxaban may be administered safely and efficaciously once daily in a rapid-release dosage form was not at all obvious in light of its half life and in the absence of any clinical safety and efficacy studies in patients. This is true even if the claimed dosage regimen could have the advantage of increased patient compliance and ease of administration.

(425) The opponents' assertions that the skilled person would have been motivated to administer rivaroxaban once daily for patient convenience and compliance is based on hindsight and completely unrelated to the decisive question of whether or not the skilled person had a reasonable expectation of success regarding therapeutic efficacy and safety of a once-daily dosaging of rivaroxaban as a rapid-release tablet. That the benefits associated with once-daily administration of rivaroxaban are plausible in retrospect is unrelated to the question of whether the solution itself was obvious. See the "Case Law of the Boards of Appeal", 7th edition 2016, Chapter I.D.10.7, final para.:

> *"A solution is not obvious simply because its success is plausible. That success is plausible once a solution is known does not necessarily mean that the solution itself was already obvious to the skilled person. Whether success is plausible and whether the solution itself is obvious are two distinct matters requiring separate investigation (**T 862/11**)."*

(426) Even if one assumed that the skilled person had a preference for once-daily dosaging, which – *exactly in light of non-compliance issues* – is not necessarily the case (see section G.7.6 below below), he would have ruled out this possibility due to the short half life that had been reported for rivaroxaban and the safety concerns that had been reported in the clinical development of other factor Xa inhibitors such as razaxaban (see section G.7.3.1 above).

(427) As once-daily administration was not obvious *"per se"*, O1's argument that any surprising effects associated with the claimed dosage regimen would amount to mere "bonus effects" (see O1 at p. 22, penult. para, referring to **T 506/92**) is also moot.

G.7.6 Non-compliance and the "missed dose argument" speak against once-daily dosaging

(428) Undisputedly, lack of patient compliance, and in particular, lack of medication adherence, was recognized by those skilled in the art to be a ubiquitous problem in long-term drug therapy already at the effective filing date of the Opposed Patent. See, e.g., **D14**, p. 93, 2nd para.:

> *"Lack of compliance is a major problem in pharmacotherapy. The most frequent pattern of noncompliance is the occasional omitted dose or failure to take several consecutive doses".*

(429) Because the skilled person knew that doses would eventually be missed in practice due to patient non-compliance, he would have chosen a dosage regimen that mitigates the risks

associated with a missed dose as much as possible. In light of his common general knowledge, which is illustrated by **Fig 7-6 of D14** reproduced as Fig. 8 below, he would have chosen at least a twice-daily dosage regimen for rivaroxaban to achieve this aim, as will be explained in the following.

(430) O1, pointing to Fig 7-6 of **D14**, alleges that it would be clear for a drug with a large therapeutic window to be administered less frequently and in larger doses, even if this results in large variations in concentrations, since these would still be within the therapeutic window and therefore safe.

(431) First, even for O1's alleged example of a "large therapeutic window" drug (**D14**, Fig. 7-6) the least frequent dosaging shown (od) still corresponds to 1.5 times the half life of that drug ($t_{1/2}$ = 15.9 h). Thus, even if the skilled person had transferred this teaching to rivaroxaban, which he had no reason for, this would only have resulted in a dosaging interval of 4.5 to 9 h (1.5 times the reported half life of rivaroxaban), i.e. at least a bid or tid administration.

(432) O1, however, entirely misses the point of Fig 7-6 of **D14**. The schematic and corresponding figure legend clearly teach that – even for large therapeutic window drugs – more frequent dosaging is much preferred over once-daily administration because of the less severe effects of missing a dose:

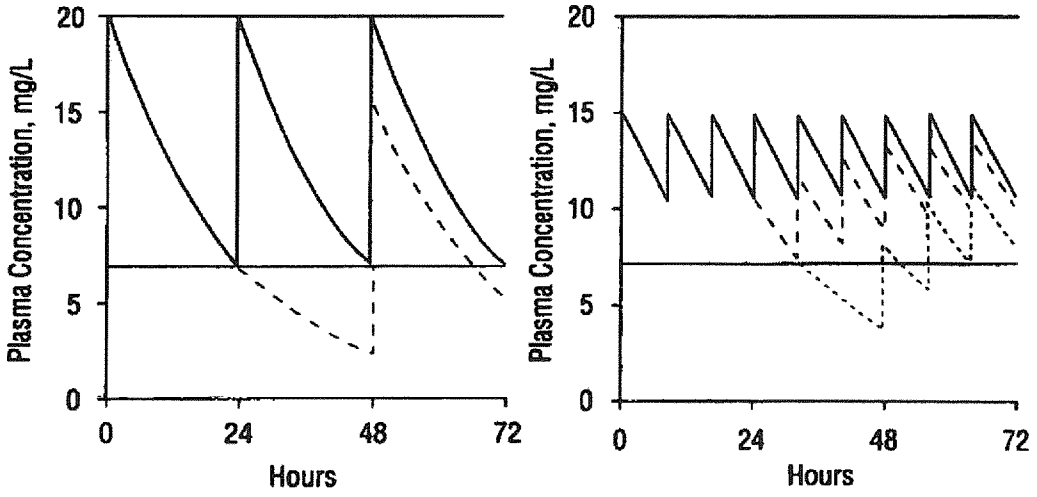


Fig. 7–6. From a kinetic perspective, the impact of a missed dose is greater the larger the dose and the less frequent the administration. Consider steady-state multi-dose conditions for a drug with a therapeutic window of 7 to 20 mg/L (color screened), a volume of distribution of 23.1 L, and a half-life of 15.9 hr. **Panel A:** When a 300-mg dose is given once daily to maintain therapeutic concentrations, a missed dose results in a trough concentration of 2.5 mg/L, a value well below the lower limit of the therapeutic window. **Panel B:** When a 100-mg dose is given every 8 hr (colored long dashed line), the lowest concentration achieved after a single missed dose is 7.3 mg/L, a value within the therapeutic concentration range. If 3 consecutive doses are missed (colored short-dashed line) the minimum concentration (3.7 mg/L) is still above that observed when a single daily dose of 300-mg is missed. The figure was adapted from concepts presented by Levy G., A pharmacokinetic perspective on medicament noncompliance. Clin. Pharmacol. Ther. 54:242-244. 1993.

Fig. 8 (reproduction of Fig. 7-6 on p. 93 of **D14**)

Referring to Fig. 7-6, **D14** at p. 93, 3rd para. notes that

> *"...even omitting three consecutive doses of the 8 hourly regimen (the equivalent of a once-daily dose) does not produce as low a concentration as the omission of a single daily dose."*

Thus, precisely because the skilled person was aware of eventual patient non-compliance, he had good reasons for administering rivaroxaban more frequently than once daily.

(433) That this reasoning even still applies today is evidenced by document **D22** (published in 2015 and cited by O5 in its para. bridging p. 12-13) which states the following in respect of non-vitamin K antagonist oral anticoagulants (NOACs) with half lives of ~12 hours (see **D22**, abstract):

> *"the twice-daily dosing regimen is less prone than the once-daily dosing regimen to hazardously high peaks or hazardously low troughs in anticoagulant concentrations and associated actions. As in other fields of oral drug treatment, the continuity of drug action is greater with twice-daily than with once-daily dosing, despite the fact that a few more doses are skipped with twice-daily than with once-daily dosing. This paradox is explained by the disproportionately greater impact on drug action of skipping a once-daily than a twice-daily dose."* (emphasis added)

(434) The opponents' pointing to para. [0009] of the Opposed Patent does not prove otherwise. That section describes the inventors' own reflections on possible advantages of the inventive once-daily dosage regimen and cannot be equated to an admission of common general knowledge at the effective filing date of the Opposed Patent (cf. the contrary assertions of opponents: O1, p. 13, section 7.1.3; O4, p. 12; O6, p. 5, para. 4.6.1; O9, p. 11, penult. para.; O10, p. 11, 1st para.).

In summary, expected non-compliance and the "missed dose argument" speak against once-daily dosaging, and certainly do not render the claimed invention obvious.

G.7.7 In the field of drug development, skilled person adopts no "try and see" attitude

(435) O6 at point 4.6.1 takes the position that the selection of a dosage regimen would amount to no more than "trial and error". O6 ignores the particulars of the technical field at issue.

(436) In assessing inventive step in the present case, it is important to note that **in the field of late-stage drug development**, which necessarily involves the testing in humans, **the skilled person does not resort to "trial and error" or adopt a "try and see" attitude**. In decision **T 293/07** the Board established (see *id.*, point 37 of the Reasons) that the testing of humans could not be considered to represent known routine tests and accordingly, the skilled person was **not in a "try and see" situation**. Also, in decision **T 847/07** (see *id.*, point 70 of the

Reasons) the Board considered it questionable whether the skilled person would adopt a "try and see" attitude at all in cases where human testing would be necessary in order to determine whether or not a compound has a certain property.

(437) The same reasoning applies to the present case, where the safety and efficacy of the claimed dosage regimen could only be determined in phase II or III clinical trials, the results of which were not yet publicly available at the effective filing date of the Opposed Patent.

(438) Clinical trials on humans are certainly not routine tests; the skilled person, who generally was extremely cautious with anticoagulants due to their inherent danger of bleeding, would therefore not adopt a "try and see" attitude in trying to find a suitable (i.e. safe, efficacious, and lastly convenient) dosage regimen. Rather, in treating patients for the first time in phase II or III studies, he would – *without knowledge of the invention and the data contained in the Opposed Patent* – have only tested obvious dosage regimens for which there was a clear and reasonable expectation of success. As described herein above and below, this clearly was not the case for rivaroxaban's once-daily dosage regimen, when properly assessed from the vantage point of a skilled person at the effective filing date of the Opposed Patent.

G.8 Non-obviousness of *the combination* of once-daily dosaging and rapid-release tablet

(439) Most problem-and-solution approaches exercised by the opponents are deficient in that they only argue based on one of the two distinguishing features described in section G.4 above (i.e. the use of a rapid-release tablet). Based on this error, they formulate the technical problem as merely being the *provision of a useful or alternative oral dosage form*, the solution to which they consider obvious or a merely arbitrary choice (see, e.g., O1, p.23; O2/3, p. 5, para. (31); O4, p. 9, last sentence under number ii); O6, p. 4, 1st para.; O8, p. 9, 3rd para.; O9, p. 10, 2nd para.; O11, p. 8, penult. para.; O13, p. 8, 2nd para. and p. 9, 1st para).

In this respect, opponents refer to a host of documents showing that rapid-release tablets were well known (see, e.g., **D4**, **D5**, **D18**, and **D43-45**).

(440) Patentee does not contest that rapid-release tablets as such were well known. The claimed *therapeutic once-daily dosage regimen* of rivaroxaban is, however, particularly non-obvious, when properly assessed in combination with the oral dosage form being a *rapid-release tablet* as claimed. To avoid hindsight bias, it is imperative to assess both of these distinguishing features in combination when following the EPO's problem-and-solution approach (see sections G.3 to G.5 above).

(441) Regarding the problem of providing a safe and efficacious oral dosage regimen, the release properties of the oral dosage form used (i.e., rapid-release or sustained-release) are

inseparably connected to the chosen dosaging interval (i.e. once-daily or more frequently). **Both features** are interlocked and **together solve the same technical problem.** O10's attempt to bifurcate the problem-and-solution approach into two partial and separate technical effects and problems (see *id.*, p. 14 and 17) is therefore clearly inadmissible (see the Guidelines for Examination in the EPO 2016, G-VII 5.2, final para. and G-VII 6 and 7, all citing T 389/86).

(442) The combination of once-daily dosaging of rivaroxaban in the form of a rapid-release tablet was particularly non-obvious. If the skilled person had at all considered once-daily dosaging for rivaroxaban, which he would not have (see section G.7 above), he would have only chosen this **in combination with a *sustained-release*, not a *rapid-release* dosage form** due to the reported half life of 3-6 hours for rivaroxaban (see, e.g., **D2**, l. 16: "4-6 h"; **D3**, l. 15: "3-4 h").

(443) For example, the standard pharmacology textbook by Aktories et al. (formerly Forth, Henschler Rummel) „Allgemeine und spezielle Pharmakologie und Toxikologie", 9th ed. (19.10.2004, **D78b**) teaches the following at p. 83, left col., 2nd para. – right col., 1st para.:

> *„Bei Arzneiformen mit verlängerter Freisetzung des Arzneistoffs wird meist unterschieden zwischen Retardpräparaten zur peroralen und Depotpräparaten zur parenteralen Anwendung.* ***Mehrmalige perorale Einnahme von Einzeldosen verursacht bei Arzneistoffen mit kurzer Eliminationshalbwertszeit starke Schwankungen des Plasmaspiegels*** *und dies umso mehr, je unregelmäßiger die Medikamente eingenommen werden. Retardpräparate gewährleisten über längere Zeit eine relativ gleichmäßige Freisetzung und eine daraus folgende ausreichend konstante Plasmakonzentration des Arzneistoffs (s. Abb. 1.75). Die verminderte Einnahmehäufigkeit verbessert überdies die vorschriftsmäßige Einnahme (Compliance)."* (emphasis added)

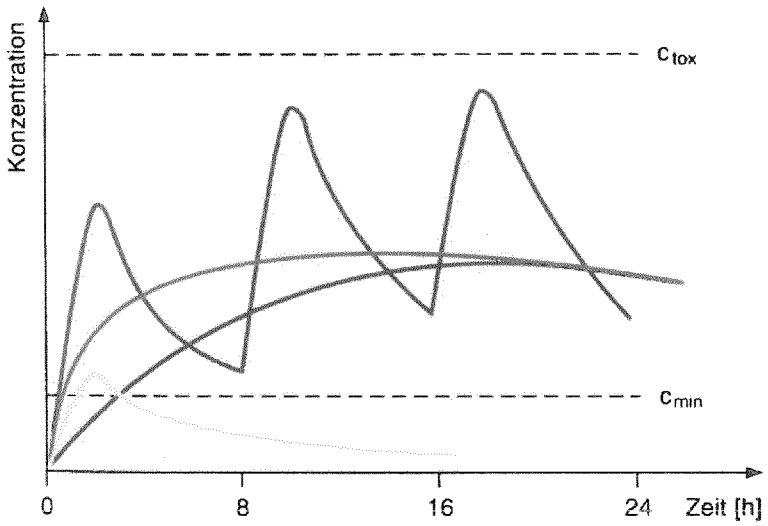


Fig. 9 (reproduction of Fig. 1.75 on p. 83 of **D78b**)

> ***„Abb. 1.75 Plasmakonzentration eines retardierten Arzneistoffs im Vergleich zu intermittierender Zufuhr in Einzeldosen.***
>
> ***Einzeldosen,*** *in diesem Beispiel alle 8 Stunden (blaue Kurve), führen zu* ***starken „Ausschlägen"*** *der Plasmakonzentration, die nahe an der therapeutischen Unwirksamkeit (c_{min}) oder dem* ***Auftreten von unerwünschten Nebenwirkungen*** *(c_{tox}) liegen können. Retard- oder Depot-Arzneiformen setzen den Arzneistoff langsamer und mit relativ konstanter Geschwindigkeit über längere Zeit frei (grüne Kurve). Wenn sich dadurch der Wirkungseintritt bei c_{min} verzögert, ist es sinnvoll, eine zusätzliche schnell freisetzbare Initialdosis zu applizieren (gelbe Kurve). Die resultierende Plasmakonzentration (rote Kurve) zeigt einen schnellen Wirkungseintritt und anschließend einen relativ konstanten Plasmaspiegel."* (emphasis added)

(444) Similarly, the textbook of Meier et al., 1981, „Biopharmazie, Theorie und Praxis der Pharmakokinetik" (**D84**), teaches at p. 324, 1st para.:

> *„Der Schwankungsbereich im Steady State ist direkt korreliert mit der Eliminationshalbwertszeit $t_{1/2}$ eines Wirkstoffs und dem Dosierungsintervall τ, Gl. (11.29). Je kleiner τ im Verhältnis zu $t_{1/2}$ gewählt wird, desto kleiner werden die Variationen zwischen $c^{ss}{}_{pmax}$ und $c^{ss}{}_{pmin}$ (Abb. 11.12). Die geringste Schwankung im Steady State wird natürlich dann erreicht, wenn die Dosis gleichmäßig und kontinuierlich infundiert wird (Abb.11.10). Retardpräparate und Formen mit gesteuerter Wirkstoff-Freigabe führen ebenfalls zu geringeren Variationen der steady-state Plasmaspiegel bei weniger häufiger Verabreichungsfrequenz (Kap. 9.4, s.S. 264)."* (emphasis added)

(445) The above textbook excerpts, which can be considered general common knowledge, demonstrate that sustained-release dosage forms were well known and customary. Against this background and the many deliberations of the skilled person when bringing a new drug to the market, O2's and O3's only argument against a sustained-release dosage form, i.e. that the skilled person would not have considered it due to the *"additional formulation complexities"*, is not convincing [see O2 and O3 at para. (49)].

(446) In summary, if the skilled person had at all considered a once-daily administration of rivaroxaban, he would have implemented this by using a sustained-release, not a rapid-release tablet, in order to maintain plasma concentrations within the expected therapeutic range.

G.9 Starting from D2/D11, the claimed solution was not obvious in light of D3/D12 or D15/D17

As explained in section G.3 above, **D2/D11** should be considered as the closest prior art for determining inventive step in the present case. The majority of opponents (see O1, O4, O5, O6, O7, O8, O9, O10, O11, and O13) allege that starting from **D2/D11** the claimed solution would have been obvious in light of the teaching of **D3/D12** or **D15/D17**. As will be explained in more detail in the following subsections, this clearly is incorrect. The claimed dosage

regimen for rivaroxaban is inventive vis-à-vis the combined teachings of **D2/D11, D3/D12** and **D15/D17.**

(447) **D2/D11, D3/D12** and **D15/D17** report on some of the very first testings of rivaroxaban in humans. All documents exclusively concern tests performed in healthy human volunteers (see their respective titles, which recite *"healthy male subjects"* or *"healthy volunteers"* as study population).

(448) **D3/D12** and **D15/D17** report the results of administering a **single dose only** of rivaroxaban to healthy volunteers. Each volunteer only received one dose, and the doses varied among the different volunteers. **D2/D11** reports a **multiple-dose escalation study** in healthy human volunteers in which six different dosage regimens were tested, each for five days. Only one of these dosage regimens involved a once-daily administration, and that was in the lowest overall dose amount (5 mg) tested. See **D2/D11**, line 4 discussing dosages of 5 mg od, bid, or tid and 10 mg, 20 mg, or 30 mg bid for five days.

(449) However, none of **D2/D11, D3/D12** or **D15/D17** discuss what dosage would be safe and efficacious in patients suffering from or at risk of thromboembolic disorders. Indeed, they cannot teach or suggest efficacious dosages because they report results in healthy volunteers only, who are not at a heightened risk for thromboembolism (see section F.4.2 above). From healthy volunteers, only the general safety of the drug can be evaluated and certain first insights on PK/PD-properties obtained. However, with healthy volunteers as reported in **D2/D11, D3/D12** or **D15/D17**, the skilled person does not and cannot determine the therapeutic window or the efficacy of a dosage regimen (see sections G.7.4.2 above and section G.9.3 below). In addition, it is also clear to the skilled person that the risk of bleeding in ill patients in need of either therapy or prophylactic treatment is entirely different from the situation in healthy male adults, who are specifically chosen for phase I studies because they have no increased risk of bleeding or thromboembolism (see section F.4.2 above). Therefore, **D2/D11, D3/D12** and **D15/D17** also fail to teach what dosage regimens might be safe in treating a thromboembolic disorder as claimed.

(450) Thus, as discussed under novelty above (see section F.4.2), an important distinguishing feature between the closest prior art and the claimed invention is that **D2/D11** does not teach *therapeutically safe and effective* dosage regimens.

(451) Most problem-and-solution approaches exercised by the opponents are deficient in that they ignore this primary distinguishing feature and only argue based on the second distinguishing feature, i.e. the use of a rapid-release tablet. Based on this error, they formulate the technical problem as merely being the *provision of a useful or alternative oral dosage form*, the

solution to which they consider obvious or a merely arbitrary choice (see, e.g., O1, p.23; O2/3, p. 5, para. (31); O4, p. 9, last sentence under number ii); O6, p. 4, 1st para.; O8, p. 9, 3rd para.; O9, p. 10, 2nd para.; O11, p. 8, penult. para.; O13, p. 8, 2nd para. and p. 9, 1st para).

(452) It is, however, exactly the combination of (1) a *rapid-release* tablet and (2) the *therapeutic od dosage regimen* that renders the claimed subject matter inventive over the prior art. To avoid the unfair perspective gained by hindsight, it is imperative to include both of these distinguishing features when following the EPO's problem-and-solution approach (see sections G.3 to G.5 above).

G.9.1 D2/D11 does not suggest the claimed solution

(453) **D2/D11** does not suggest that a once-daily dosage regimen employing a rapid-release tablet of rivaroxaban would be safe and efficacious *in treating a thromboembolic disorder*. As explained in section F.4.2, and in particular section F.4.2.3, above and contrary to the opponents' repeated assertions, **D2/D11** does not disclose *any* dosage regimen for *treating a thromboembolic disorder* because it only concerns the test administration to healthy subjects. In addition, among the many dosage regimens tested in **D2/D11**, the skilled person certainly would not have chosen the sole once-daily regimen mentioned.

(454) The skilled person reading **D2/D11** immediately understands that this phase I dose escalation study **was performed in anticipation of a bid dosage regimen** in subsequent phase II studies. Only one out of the six dosage regimens tested in **D2/D11** involved a once-daily administration. All others involved either a twice-daily (4 times: 5 mg, 10 mg, 20 mg, or 30 mg bid) or thrice-daily (5 mg tid) administration. Also in practice, this was the case: The **first phase II studies for rivaroxaban** following the phase I results reported in **D2/D11** only tested bid regimens (see **D35** submitted by O11 and ref. 18 in **D35**). This illustrates that pursuing a bid regimen for rivaroxaban, and not the claimed od regimen, was the obvious thing to do. The latter is also supported by the **concurrently developed** oral factor Xa inhibitor **apixaban**, which has a reported half life of approx. 12 hours and was clinically tested and approved in a **twice-daily dosage regimen** (see **D83**, the SmPC for apixaban, p. 23, 2nd para. and p. 2-3, section on posology, respectively).

(455) Importantly, **D2/D11** does not compare od, bid, and tid for the purpose of comparing efficacy and safety of administration frequency. The single od dosage was merely used as the lowest control regimen out of convenience in explicitly-stated 'dose-escalation' studies. The same purpose would have been reached by administering 2.5 mg bid to achieve the 5 mg dose level. The goal was to test escalating doses, not how they were administered.

(456) Of note, in **D2/D11** the once-daily administration was only performed for the lowest total daily dose (5 mg) tested. In phase I dose escalation studies, it is common practice to start with a very low dose. The textbook of Jaehde et al., 2nd ed. 2003, „Lehrbuch der klinischen Pharmazie" (**D67**), at p. 131, right col., final para. to p. 132, left col., 1st para. and Fig. 9.2 characterizes these low starting doses as "subtherapeutic" (see Fig. 10 below, bottom right arrow: *„subtherapeutisch"*):

> *„In Abb. 9.2 ist ein Dosisitrationsschema für eine Erstanwendung beim Menschen beispielhaft dargestellt. Es werden 8 Behandlungsgruppen gebildet. Von einer **sehr niedrig gewählten Anfangsdosis** erfolgt bei Verträglichkeit jeweils eine entsprechende Dosissteigerung, anfangs um Faktoren 5 und 4 später dann um 1,3-1,2."* (emphasis added)

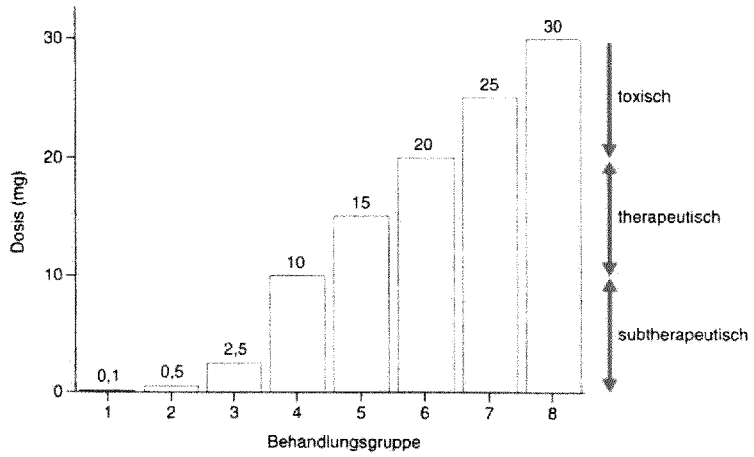


Abb. 9.2: Dosistitration bei der Erstanwendung am Menschen.

Fig. 10 (reproduction of Fig. 9.2 on p. 131 of **D67**)

(457) From **Fig. 10** (Fig. 9.2 of **D67**) above it is clear that the skilled person expects the initial and lowest dose tested in a dose escalation study to only have minimal pharmacodynamic effects. The skilled person would not have selected the 5 mg od dosage regimen disclosed in **D2** to treat a thromboembolic disorder because he would not have expected this to be efficacious.

(458) The common general knowledge exemplified by **Fig. 10** above also directly refutes the unsupported assertion of O8 on p. 8, 1st para., whereby the mere fact that the 5 mg od regimen was included in **D2/D11** should signify that it was expected to be efficacious in treating thromboembolic disorders. Clearly, this is not the case. Similarly, also O8's assertion that the skilled person would have considered all six dosage regimens disclosed in **D2/D11** as equal is clearly untenable in view of the common general knowledge exemplified by **Fig. 10**.

(459) If, for the sake of argument, one were to follow the opponents' line of reasoning that **D2/D11** would have taught towards an od dosage regimen, one can just as easily conclude by the use

of tid administration in **D2/D11** that it taught towards a more frequent administration than bid. Obviously, neither is the case. If at all, **D2/D11 taught towards a bid dosage regimen.** This is also confirmed by the fact that the first phase II trials for rivaroxaban following the results of **D2/D11** exclusively tested bid dosage regimens of rivaroxaban (see **D35** submitted by O11 and ref. 18 in **D35**).

(460) The opponents have no basis for their repeated assertions that an od dosage regimen for rivaroxaban *"would have been obvious [...] simply by following the explicit teaching of **D2**"* [see, e.g. O2/3, p. 8, para. (50)]. From **D2/D11** the skilled person could not infer any information as to what dosage regimen would be safe and efficacious in patients suffering from or at risk of thromboembolic disorders. In particular, the skilled person would not have selected the lower 5 mg od administration reported in **D2/D11** which he would have understood to be a mere control regimen.

G.9.2 Neither D3/D12 nor D15/D17 suggest the claimed solution

(461) Almost all opponents rely on **D3/D12** for arguing obviousness of using a tablet as oral dosage form and assert that the pharmacodynamics results reported in **D3/D12** and **D15/D17** would show sustained effects, which would teach towards an od regimen. They assert that the combination of **D2/D11** with **D3/D12** and/or **D15/D17** would render the claimed dosage regimen obvious.

(462) Patentee disagrees. First of all, the skilled person would not have consulted **D3/D12** or **D15/D17** when attempting to find a safe and efficacious dosage regimen for the treatment of thromboembolic disorders because these references only concern early test administrations in healthy volunteers. It is clear to the skilled person that the risk of bleeding as well as the dosages required to achieve the desired anticoagulant effect in ill patients in need of either therapeutic or prophylactic treatment is entirely different from the situation in the healthy male adults studied in **D3/D12** and **D15/D17**, who are specifically chosen for phase I studies because they have no increased risk of bleeding or thromboembolism (see section F.4.2 above)

(463) As will be shown in sections G.9.3.1 to G.9.3.5 below, pharmacodynamic effects and surrogate parameters measured in healthy subjects in phase I studies were known to not be predictive of clinical efficacy of a dosage regimen (such as the particular dosage regimen at issue here). Thus, the skilled person would not have believed the pharmacodynamic data obtained from healthy volunteers in the phase I studies according to **D2/D11**, **D3/D12**, or **D15/D17** to teach what dosage regimen would be safe and efficacious for treating patients suffering from or at risk of a thromboembolic disorder, let alone that a particular efficacious

dosage regimen could be administering a rapid-release tablet once daily for at least five consecutive days.

(464) As discussed in section G.9.3.1 below, the close PK/PD correlations reported in **D3/D12** and **D15/D17** even teach away from the claimed od regimen. In addition, both **D3/D12** and **D15/D17** are single-dose studies and for this reason alone cannot have predictive value in respect of a multi-dose dosage regimen of the type claimed here.

(465) In summary, the skilled person had no reasonable expectation of success regarding safety and efficacy of a once-daily treatment regimen with rivaroxaban as a rapid-release tablet because of the short half life of rivaroxaban, the lack of efficacy testing in patients, and the serious safety issues that he knew could be associated with high dosing of oral factor Xa inhibitors from the parallel clinical development of razaxaban (see section G.7.3.1 above).

(466) In particular, a reasonable expectation of success with the claimed dosage regimen and form cannot be inferred from **D3/D12** and **D15/D17**, since they all only disclose safe and tolerable single doses in healthy people, and because the prior art had accepted the primacy of pharmacokinetic values such as half life in determining a likely successful oral dosage regimen for patients in need of treatment.

G.9.3 Phase I study results (D2/D11, D3/D12, D15/D17) did not suggest that a once-daily dosage regimen would be effective

G.9.3.1 D2/D11 and D15/D17 provide no evidence for a sustained therapeutic effect of rivaroxaban

(467) In their inventive step arguments many opponents (see O1, p. 20; O4, p. 13; O6, p. 5, para. 4.6.3; O8, p. 12; O9, p. 8, final para. and p. 14, penultimate para.; O10, p. 15, penult. para.; O12, p. 8) rely on the od regimen tested in **D2/D11** and the following sentences taken from **D15/D17** and read out of context:

> *"A single 30 mg dose exerted a sustained effect in some assays of thrombin generation for up to 24 hours". (**D17**, final para., similar statement in **D15**, l. 18-19)*

(468) Opponents apparently interpret this isolated statement, which is directed to a subgroup of *in vitro* thrombin generation assays measured in healthy subjects, to mean that also in case a single dose of 30 mg of rivaroxaban is orally administered to a patient, there would be a therapeutic effect *in vivo* for up to 24 hours. Opponents have no basis for drawing this conclusion. It amounts to a mere *ex post facto* analysis and is also factually incorrect.

(469) As explained in more detail below, the results of *in vitro* thrombin generation or clotting assays, as reported in **D15/D17**, are not predictive of clinical efficacy *in vivo*. First of all,

D2/D11 and **D15/D17** report results of phase I studies involving healthy volunteers. Such results can *per se* not be predictive of clinical outcome, and therefore clinical efficacy, which is only determined in phase II and III studies in patients (see sections G.9.3.2-G.9.3.3 below). Specifically, *in vitro* thrombin generation and clotting assays, such as the ones measured in **D2/D11**, **D3/D12** and **D15/D17**, are in and of themselves no reliable predictor of clinical efficacy (see section G.9.3.4 below). Dose-pharmacodynamic response relationships determined with such *in vitro* assays rarely even correlate with the dose-clinical efficacy relationships observed in patients and can therefore not suggest the clinical efficacy of the claimed dosage regimen (see section G.9.3.5 below).

(470) The pharmacodynamics data reported in **D2/D11** and **D15/D17** indicate the effect of rivaroxaban on certain *in vitro* thrombin generation and clotting assays after administration to healthy subjects. The data do not, however, support an *unambiguous* finding that rivaroxaban would exert sustained effects, even *in vitro*. Rather, the results from the individual *in vitro* assays available showed contradicting results in that only some showed prolonged effects at all (see below). The skilled person would not have known which assay would indicate the true effect that could be used to predict clinical efficacy and safety of a dosage regimen (such as the particular dosage regimen claimed here). The skilled person would only have known this after performing investigations in later clinical trials (i.e. in patients in need of therapeutic or prophylactic treatment), but not from the *in vitro* thrombin generation or phase I data available at the priority date of the Opposed Patent.

(471) **D17**, because it is longer and contains data tables, would be read in conjunction with the almost identical **D15**. **D17** states that sustained effects on thrombin generation were seen only in "*some assays*". **D15/D17** is silent as to the level of the sustained effect after 24 hours. **D15/D17** measured thrombin generation using a number of different tests. **D17** only ambiguously states that in some assays, effects were seen for up to 24 hours. No specific test was described, and many of the tests were debated in the field at the time for lack of reliability and predictive value (see section G.9.3.4 below). The differences in extended effects observed according to **D15/D17** could have merely been a consequence of the individual set-up of the tests themselves and/or differences in sensitivity. If all tests were indicative of thrombin generation, but not all showed the same profile of changes, then the skilled person would gain no useable information from this **incoherent set of results**. Certainly, he would not have based such important decisions as selecting a safe anticoagulant dosage regimen on these incoherent findings.

(472) When taking the data table of **D17** into account, which reports 2-hour and 12-hour time points, it is apparent that for most assays, the effects were already more than halved after 12 hours.

D15 explicitly states that peak changes were observed between 2 and 4 hours post administration. In addition, **D15** states that, e.g., PITT was (only) *"sustained over 12 hours"* (**D15**, l. 24) and PICT was *"prolonged over 12 hours with both doses"* (**D15**, l. 28). Thus, it can be expected that little effect, if any, remained after 24 hours. No mention is made as to how effects were monitored, or is it disclosed which actual measure of thrombin generation remained prolonged at 24 hours.

(473) That little effect, if any, remained after 24 hours is also consistent with the PD-assay results reported in the rivaroxaban phase I studies **D11** and **D12,** which indicate that the majority of the effects had vanished already after 12 hours:

> *"Full profiles of all pharmacodynamic (PD) parameters (Factor Xa inhibition, PT, aPTT, HepTest) were performed [...] Comparable profiles were observed for all PD parameters. Relevant changes in the PD parameters were still present after 12 hours. BAY 59-7939 inhibited Factor Xa activity in a dose-dependent manner, with maximum effects 2-3 hours after administration. Effects were maintained for 8-12 hours at the 5 mg dose, and ~12 hours at the 10, 20, and 30 mg doses."* (**D11**, l. 8-9 and 15-20, emphasis added)
>
> *"Full PD profiles (Factor Xa inhibition, PT, aPTT, HepTest) were determined for 24 hours after drug administration. [...] The inhibitory effect of BAY 59-7939 was almost completely reversed after 24 hours [...]. PT prolongations also reverted to baseline after 24 hours".* (**D12**, l. 7-8 and 17-20, emphasis added)

(474) The fact that in **D11** effects were said to be maintained for 8-12 hours, however, relevant "changes" in PD-parameters were still present after 12 hours is consistent with an interpretation that the bulk effect had vanished after 12 hours. Certainly, this quote from **D2/D11** does not support O4's conclusion at p. 12, penult. para. that the *in vivo* antithromboembolic effects of rivaroxaban would have been known to last much longer than was expected based on its half life. Even if one were to assume that the skilled person would base his dosage considerations exclusively on the *in vitro* PD effect time spans observed in phase I studies with healthy individuals, which he would not, then the 12-hour time span for PD effects still only speaks towards a bid, not an od, dosage regimen (contrary to the assertions of O10 at p. 11, 1st para. and O13 at p. 7, 1st para.).

(475) O12 at p. 10, 5th para. automatically concludes from the 24-hour time span for the observed effect reported in **D15/D17** for some thrombin generation assays that rivaroxaban would need to be administered once daily. If this reasoning were correct, one would also need to apply it *vice versa* to the 12-hour time span observed for the other PD-effects reported in **D2/D11**, **D3/D12** and **D15/D17**. This would, however, lead to the conclusion that a **bid regimen** was expected to be necessary to achieve therapeutic efficacy.

(476) In addition, **D3/D12** and **D15/D17** unanimously state that a **close correlation between PD and PK profiles** was observed for rivaroxaban. See, for example:

"Pharmacodynamic and pharmacokinetic time profiles showed a close relationship with a correlation coefficient between 0.6 and 0.9, depending on the parameters used". (**D3**, l. 20-21, emphasis added)

"There was close correlation between BAY 59-7939 plasma concentrations and inhibition of Factor Xa activity as well as with decreases in ETP; the correlation was modest with PITT." (**D15**, third-to-last sentence, emphasis added)

The PK time profile of rivaroxaban is governed by its reported half life of 3-6 hours (see, e.g., **D2**, l. 16: "4-6 h"; **D3**, l. 15: "3-4 h"). The reported close correlation between PK- and PD-profiles would have been interpreted by the skilled person to mean that overall, no substantially sustained PD-effects for rivaroxaban had been observed. Thus, the skilled person would have relied on PK-considerations such as half life to determine the dosaging frequency likely to be safe and efficacious in subsequent phase II studies. These considerations would have led the skilled person to adopt at least a twice-daily dosage regimen, as outlined in section G.7 above.

(477) Clearly, the opponents' repeated recitation of the sentence *"A single 30 mg dose exerted a sustained effect in some assays of thrombin generation for up to 24 hours"* from **D15/D17** has to be read in the context of **D15/D17's** overall disclosure and the teachings of the related remaining prior art documents **D2/D11** and **D3/D12**.

(478) The overall picture obtained from the PD assay results reported in **D2/D11**, **D3/D12**, and **D15/D17**, taken together with the short half life of rivaroxaban and the reported close PD/PK correlations would create an image of a PD time profile for the skilled person resembling the following standard PK-profile reported, for example, in the textbook **D80a** at p. 51, for an od-dosed drug with a half life of 3 hours:

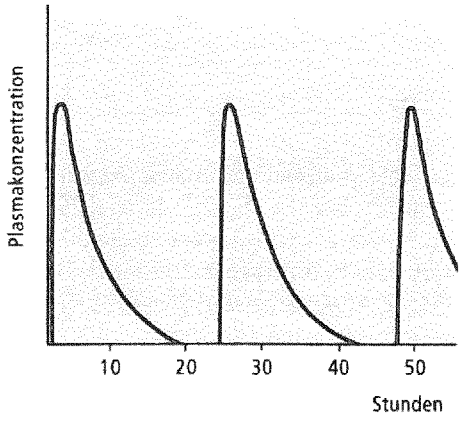


Abb. A 2–29. Plasmaspiegelverlauf nach mehrfacher oraler Gabe eines Pharmakons mit geringer Eliminationshalbwertszeit ($t_{1/2}$ = 3 Stunden) und großem Dosierungsintervall (τ = 24 Stunden)

Fig. 11 (reproduction of Fig. A 2-29 on p. 51 of **D80a**)

(479) As this representative plasma concentration time profile demonstrates, in the intermittent periods shortly before the next dose is administrated, the plasma concentration and therefore the effect of rivaroxaban would have been believed to have completely vanished. For the reasons set out in sections G.7.2 and G.7.3 above, the skilled person would have considered such a PK/PD profile undesirable due to hazardously high peak and hazardously low trough levels. Instead, he would have tried to achieve accumulation to a pseudo-steady state with higher trough levels and less peak-trough fluctuations by choosing a more frequent dosage regimen than the claimed once-daily regimen.

G.9.3.2 Clinical efficacy and the boundaries of the therapeutic window are only determined in phase II and III studies

(480) The pharmacodynamic parameters determined in **D2/D11**, **D3/D12**, and **D15/D17** in healthy subjects are not predictive of the clinical efficacy of a dosage regimen. The textbook **D67** states in this respect on p. 133, left col., 2nd para.:

> *„Der **gesicherte Nachweis der Wirksamkeit** einer neuen Substanz **wird in keinem Fall im Rahmen von Phase-I-Studien am Probanden erbracht**. Definitionsgemäß werden Probanden in die Untersuchung einbezogen, die im Rahmen der Ein- und Ausschlussbedingungen der Studien als **gesund** gelten. Da aber das **Vorliegen entsprechender Krankheitssymptome** für die Bewertung der Wirksamkeit ausschlaggebend ist, **kann dies beim Gesunden nicht getestet werden**. Für einzelne pharmakodynamische Effekte (u. a. Blutdrucksenkung) kann auch beim Probanden evtl. eine entsprechende Wirkung beobachtet werden. Die **Aussagekraft dieser Befunde** für den Hypertoniker ist jedoch **fragwürdig**, weil die pathophysiologischen Mechanismen der Erkrankung und deren pharmakodynamische Beeinflussung sehr verschieden sein können."* (emphasis added)

(481) It thus belonged to the **common general knowledge** of the skilled person that clinical efficacy and the related boundaries of the therapeutic window are only determined in phase II and III studies, when the drug is first tested in patients. This background of common general knowledge clearly contradicts the opponents' assertion that the dosage regimens tested in the phase I study of **D2/D11** would have been *"attempts to determine effective dosage forms and regimens for the treatment of thromboembolic disorders"* (see, e.g., O1, p. 16, 5th para.).

(482) There can be no doubt that the skilled person would not have considered the phase I study results reported, e.g., in **D2/D11**, **D3/D12**, or **D15/D17**, to be predictive of the clinical efficacy of the claimed dosage regimen for rivaroxaban.

G.9.3.3 Phase I pharmacodynamic surrogate parameters are not predictive of clinical endpoints

(483) Several opponents seem to suggest that the pharmacodynamic (PD) surrogate parameters reported in **D2/D11**, **D3/D12**, or **D15/D17** (i.e. the clotting and thrombin generation assays PT,

aPTT, HepTest, TG, ETP, PITT, and PICT) – *that were measured exclusively in healthy individuals* – could be taken at face value to demonstrate clinical efficacy of the claimed dosage regimen. Clearly, this is not the case.

(484) See, e.g., section 5.2.4 of Annex I to EU Directive 2001/83 (**D69**, p. 149, discussed under "Novelty" in in section F.4.2.3 above), which expressly states that:

> *"The demonstration of **pharmaco-dynamic effects** in human beings shall **not** in itself be **sufficient** to justify conclusions regarding any particular potential therapeutic effect."* (emphasis added)

(485) That PD surrogate parameters determined in phase I studies do not determine effects on clinical endpoints is also confirmed by the textbook **D67**, which states at p. 133, left col., 2nd para. using hypertension as an example:

> *„Für einzelne pharmakodynamische Effekte (u. a. Blutdrucksenkung) kann auch beim Probanden* [in Phase I Studien] *evtl. eine entsprechende Wirkung beobachtet werden. Die **Aussagekraft dieser Befunde** für den Hypertoniker ist jedoch **fragwürdig**, weil die pathophysiologischen Mechanismen der Erkrankung und deren pharmako-dynamische Beeinflussung sehr verschieden sein können."*
> (emphasis and explanation in square brackets added)

(486) O10 thus clearly commits a logical fallacy when concluding that **D17**'s suggestion that rivaroxaban could effectively inhibit thrombin generation in *healthy* individuals would be tantamount to (note the *"i.e."* in O10, p. 15, end of 2nd para.) rivaroxaban being efficient *in the treatment of a thromboembolic disorder*.

(487) Even if the PD surrogate parameters reported in **D2/D11**, **D3/D12**, or **D15/D17** had been measured in *patients*, they would still not be predictive of the safety and efficacy of therapy or prophylaxis of a particular dosage regimen (as claimed in the Opposed Patent), which can only be determined via assessment of clinical endpoints in phase II or phase III studies. Stapff in his textbook „Arzneimittelstudien", 2nd ed. 2001 (**D85**), p. 48, 1st para. states in this respect:

> *„Es ist auch zu beachten, dass die Wirkung eines Arzneimittels zwar durch sog. Surrogat-Parameter geprüft werden kann, **Aussagen über die Wirksamkeit und die therapeutische Effizienz aber nur durch klinische Endpunkte getroffen werden können**. Ein Arzt verordnet ja nicht deshalb einen Lipidsenker, damit der LDL-Wert des Patienten um einige mg/dl abfällt („**Laborkosmetik**"), sondern damit das kardiovaskuläre Risiko des Patienten gemindert wird, er also keinen Herzinfarkt oder Schlaganfall erleidet („**Evidence-based medicine**"). Die alleinige Orientierung einer Osteoporose-Therapie anhand der Knochendichtewerte ist sogar gefährlich, da zu dichter Knochen je nach Therapie spröde und „glasig", damit sogar brüchiger werden kann.*
>
> *Die **Verwendung von Surrogat-Parametern** muss deshalb in manchen Fällen **sehr kritisch gesehen** werden und sollte nur zu Beginn der Arzneimittelentwicklung akzeptiert werden."* (emphasis added)

(488) As will be shown in the following section, these concerns particularly apply to the field of anticoagulation. Here, correlating surrogate markers with clinical endpoints, therapy progress, or even successful prophylaxis is particularly difficult.

G.9.3.4 *In vitro* clotting or thrombin generation assays do not predict clinical efficacy of a dosage regimen

(489) In the field of thromboembolic diseases, it has been observed that often the results of *in vitro* clotting or thrombin generation assays are not predictive of clinical efficacy or indicative of the bleeding risk of a particular dosage regimen or able to distinguish between the two. A given anticoagulant may behave differently in different tests, showing effects in one *in vitro* clotting test and none or reduced effects in another. It may be therapeutically active at plasma concentrations that show no effects in certain *in vitro* clotting or thrombin generation assays, but pronounced effects in others. Thus, the skilled person would not have given singular results from certain *in vitro* clotting or thrombin generation tests (such as the thrombin generation tests described in **D15**/**D17**) much weight in terms of whether those results could predict the clinical efficacy of the type of specific dosage regimen claimed here.

(490) On the other hand, a dependable minimum drug concentration associated with the risk of bleeding is also almost impossible to determine precisely, and bleeding can occur in patients even with drug concentrations thought to be within the therapeutic range. Coagulation assays such as aPTT are not always informative here. See, e.g., the textbook **D9c** at p. 1525, left col., 2nd para.

> *"Bleeding is the primary untoward effect of heparin. Historically, major bleeding was reported in 1% to 33% of patients who received various forms of heparin therapy, and in one study there were 3 fatal bleeding episodes among 647 patients (Levine and Hirsh, 1986). Recent studies suggest that major bleeding occurs in <3% of patients treated with intravenous heparin for venous thromboembolism (Levine* et al*., 1998). The incidence of bleeding is no worse in patients treated with low-molecular-weight heparin for this indication. Although the number of bleeding episodes appears to increase with the total daily dose of heparin and with the degree of* ***prolongation of the aPTT, these correlations are weak****, and* ***patients can bleed with aPTT values that are within the therapeutic range****. Often an underlying cause for bleeding is present, such as recent surgery, trauma, peptic ulcer disease, or platelet dysfunction."*
> (emphasis added)

(491) Due to this uncertainty, skilled practitioners in choosing a dosage regimen for a new anticoagulant are cautious and will seek to keep a safety margin to the minimum drug concentration they believe might be associated with the risk of bleeding.

(492) For factor Xa inhibitors, it was particularly questionable whether or not certain clotting assays would be predictors of antithrombotic effects at all. See the following passages from **D79** (emphasis added):

p. 214, right col., 2nd para.:

*"Taken together, **factor Xa inhibitors exert antithrombotic effects at doses that produce only moderate ex vivo anticoagulation**, measured in APTT or PT assays (Table 5). **This gives rise to the question** whether the APTT truly reflects the anticoagulant state produced by these inhibitors and, moreover, **whether it is a reliable predictor of the antithrombotic effect**.";*

p. 215, right col., 2nd para.:

*"In light of recent findings from in vitro and in vivo comparative studies, one may assume that **the anticoagulant efficacy of factor Xa inhibitors, measured in terms of common clotting assays, does not parallel their antithrombotic efficacy**. More data comparing the ex vivo anticoagulant effects [...] have to be gathered in order to corroborate this assumption that could be of potential clinical significance for monitoring antithrombotic therapy by ex vivo clotting assays. From a therapeutical point of view, **effective doses or plasma levels are of less importance than the benefit (antithrombotic effect)–risk (haemorrhage) ratio** when comparing thrombin and factor Xa inhibitors.";*

p. 225, left col., 2nd para.:

*"However, one has to consider that extrapolation from experience with oral anticoagulants and heparin, when monitoring the treatment with low molecular weight heparins and hirudin by **PT and APTT**, has **yielded problems. Similar problems may be expected for monitoring** synthetic thrombin inhibitors and, **especially, for factor Xa inhibitors.**";*

p. 225, right col., 3rd para.:

*"There are other **unresolved issues. Which clotting assay can best predict the antithrombotic effect** when the value of the APTT assay is uncertain? [...]*

*What is the **therapeutic window** in different **clinical settings**?";*

and, finally, the sentence bridging p. 225 and p. 226:

*"Ultimately, **controlled clinical trials must be performed** to evaluate the usefulness of factor Xa inhibitors as antithrombotic drugs with the advantage of low bleeding risk".*

These quotes clearly demonstrate that isolated results from *in vitro* clotting assays performed in early clinical studies on *healthy* volunteers (as in **D2/D11, D3/D12**, and **D15/D17**) would not have been interpreted by the skilled person as – *on their own* – allowing any conclusions about the clinical efficacy of the claimed dosage regimen.

(493) This is further compounded by the problem of **incoherent results** between assays. Whereas rivaroxaban should theoretically show the same kinetics in a factor Xa activity assay and the various possible *downstream* thrombin generation assays, this was not the case (see the discussion of the data presented in **D2/D11** and **D15/D17** in section G.9.3.1 above). Sustained

effects for up to 24 hours were only seen *"in some assays of thrombin generation"* (see **D17**, final para., emphasis added). These differences in results could have merely been a consequence of the individual set-up of the tests themselves and/or differences in sensitivity. If all tests were indicative of thrombin generation, but not all showed changes, then the skilled person would gain no useable information from these incoherent results.

(494) Only subsequent phase II and III studies can establish whether or not a meaningful correlation between *in vitro* clotting or thrombin generation assay results and clinical efficacy and/or bleeding risk indeed exists. Such results, however, simply did not yet belong to the prior art at the effective filing date of the Opposed Patent.

(495) For rivaroxaban, even today, no single *in vitro* clotting or thrombin generation assay has been established to allow for a reliable prediction of therapeutic or prophylactic outcome of a particular dosage regimen. See, e.g., the 2009 booklet **D52** that was handed out to physicians prescribing Xarelto (rivaroxaban) for thrombosis prophylaxis at p. 5, left col.:

> *„Hinweis: Xarelto® und Quick-Werte bzw. INR*
>
> - ***Direkte Faktor-Xa-Inhibitoren beeinflussen unabhängig von ihrer Wirkstärke die globalen Gerinnungstests*** *(z. B.* ***aPTT, PT****/Quick-Wert/INR)*
> - *Die antikoagulatorische Wirkung der direkten Faktor-Xa-Inhibitoren ist nicht mit der von Vitamin K- Antagonisten vergleichbar, auch nicht bei vergleichbaren INR-/Quick-Werten.*
> - *Der Quick-Wert [PT] kann während der Xarelto®-Therapie* ***unterhalb des Normbereichs liegen, ohne dass dies in Verbindung mit einem erhöhten Blutungsrisiko steht"***. (emphasis added)

(496) Similarly, also the EMA's CHMP AR 2008 (**D59**) for rivaroxaban emphasizes that results of *in vitro* clotting parameters such as PT cannot be extrapolated to predict clinical efficacy of the claimed dosage regimen:

> *"An exploratory evaluation of the relation between PT and bleedings in phase III studies was conducted but* ***PT threshold predictive of bleedings was not identified.*** *Similar analysis for phase II data was also provided. The bleeding risk does increase with dose, but* ***the dose-bleeding event relationship appears to be shallow. Neither PK parameters (AUC, C_{max} or C_{min}) nor PT can be used as indicator of bleeding risk*** *due to the shallow concentration-response and overlapping concentrations/PT in patients with and without bleeding events in the studied dose range in the studied population."* (**D59**, p. 22, penultimate para., emphasis added)

While PD parameters such as PT may correlate with clinical outcomes when large patient samples are studied, the isolated results of individual clotting assays were not expected to

and have not been shown to be a reliable indicator of clinical efficacy and bleeding risk of a particular dosage regimen (as claimed in the Opposed Patent).

(497) Therefore, the results from *in vitro* clotting and thrombin generation tests determined in healthy volunteers as reported in **D2/D11**, **D3/D12**, or **D15/D17** cannot and would not have informed the clinical efficacy of the claimed dosage regimen of rivaroxaban.

G.9.3.5 Dose-response relationships determined with *in vitro* assays in healthy subjects rarely correlate with the dose-clinical efficacy relationship observed in patients

(498) The skilled person would not have expected the final determination of dose-clinical efficacy relationships in phase II/III studies to mimic the dose-pharmacodynamic response relationships that had been observed in the phase I studies for rivaroxaban that were performed in healthy subjects.

(499) It belonged to the general knowledge of the skilled person that dose-pharmacodynamic response relationships determined with *in vitro* assays rarely correlate with the dose-clinical efficacy relationship observed in patients, and could therefore not have been used by the skilled person to predict the clinical efficacy of the claimed dosage regimen.

(500) See, for example, Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10th ed. 2001 (**D9d**), p. 49, right col., final para.:

> *"As discussed in Chapter 2, the relationship between the concentration of a drug and the magnitude of the observed response may be complex, even when responses are measured in* ***simplified systems*** **in vitro**, *although* ***typical sigmoidal concentration-effect curves*** *usually are seen (see Chapter 2). When drugs are administered* ***to patients****, however, there is no single characteristic relationship between the drug concentration in plasma and the measured effect; the concentration-effect curve may be concave upward, concave downward, linear, sigmoid, or an inverted-U shape."*
> (emphasis added)

(501) Thus, even if a first dose-response relationship was determined by way of *in vitro* clotting assays in phase I studies in healthy individuals, the skilled person would not have concluded from this information, reliably and beyond mere speculation, the shape of the dose-clinical efficacy relationship when patients were treated with the drug using the claimed dosage regimen.

(502) Again, this demonstrated that the phase I results provided in **D2/D11**, **D3/D12**, or **D15/D17** cannot inform the dosaging efficacy of rivaroxaban in patients suffering from, or at risk for, a thromboembolic disorder.

G.9.4 Inventive step in light of the known dosage regimen of LMWHs such as enoxaparin (D13, D41) or nadroparin (D34)

(503) Several opponents assert that the claimed once-daily dosage regimen would have been obvious in light of the known once-daily dosage regimen of LMWHs such as enoxaparin (see O1 and O6, referring to **D13**, and O12 referring to **D41**) or nadroparin (see O11, referring to **D34**).

(504) With an allegedly similar half life (4-5 hours) and also showing (*inter alia*) anti-factor Xa activity, the dosage regimen for enoxaparin would have been directly transferable to rivaroxaban. Being administered by injection, enoxaparin would be rapidly available in the blood, with no slow release form being necessary. This would underline that factor Xa inhibitors in general could be administered once daily while being therapeutically effective. See O1, p. 17, section 7.2.1 and O6, p.5, para. 4.6.5 to 4.6.6, referring to **D13**, and O12, p. 7, section 3.1.3 and p. 10, 2nd para. referring to **D41**. Similarly, O11 points to **D34** to assert that the claimed dosage regimen would have been obvious because for subcutaneous administration of a particular LMWH, nadroparin, once-daily injection was known to be at least as effective and safe as the same total daily dose divided over two injections for the treatment of acute deep vein thrombosis.

Each assertion is wrong.

(505) First, rivaroxaban and LMWHs, such as enoxaparin and nadroparin, are completely different classes of compounds, both structurally as well as functionally. While rivaroxaban is a small molecule chemical compound (an oxazolidinone derivative) with a defined chemical structure and uniform composition, enoxaparin and nadroparin are low molecular weight fractions of naturally occurring heparin, i.e. they are complex polycomponent mixtures of glycosaminoglycan oligomers of varying lengths, chemical subunit composition, and modification (see, e.g., **D13**, p. 1045, left col., final para. and p. 1050, left col., penultimate para.). Documents **D86** and **D87** are additionally submitted to demonstrate the chemical and compositional complexity of LMWHs (see **D86**, "Summary", "Introduction" and "Results" section and **D87**, p. 1421, right col., penultimate para. to p. 1422, left col., 5th para.). For example, according to **D86**, enoxaparin contains oligomeric glycosaminoglycan components ranging in their degree of polymerization from 2-3 subunits (see **D86**, Fig. 2, < 6weight %) to greater than 16 subunits (see **D86**, Fig. 2, ca. 20 weight %).

(506) It is important to note that for such complex mixtures of naturally occurring glycosaminoglycans of varying lengths, chemical subunit composition, and modification it is virtually impossible to determine a meaningful half life. Even when only looking at a single oligomer species, its drug blood plasma concentration cannot be accurately determined

because glycosaminoglycans are also normally present in biological tissue (see **D13**, p. 1049 under section 2.2). In addition, the different glycosaminoglycan species present in LMWHs will also not show the same rate of absorption into the blood stream following subcutaneous injection. The difficulty of assessing drug blood plasma concentration of LMWHs *directly* is further compounded by the fact that higher molecular weight glycosaminoglycan oligomers will be metabolized to lower molecular weight oligomers in the body, which still retain biological activity. It is thus difficult to decide which oligomer species to select for half life determination.

(507) For these reasons, half lives stated for heparins or LMWHs in the literature are no true *pharmacokinetic* half lives (calculated from plasma concentration measurements), but usually *"biological", pharmacodynamic* half lives, in which the effect on a certain anticoagulation factor is measured (see **D13**, p. 1048, para. bridging left and right col.). For example, the half life of 4-5 hours for enoxaparin relied on by the opponents is the *"apparent t1/2β of the anti-Xa activity of enoxaparin"* (see **D13**, p. 1051, left col., l. 10-11, emphasis added). Thus, it is clear to the skilled person that the half life of rivaroxaban (*pharmacokinetic* half life) and that of LMWHs (*pharmacodynamic* half life) that had been reported in the literature cannot be compared directly.

(508) Second, the differences in composition and structure between rivaroxaban and LMWHs are also reflected in the different functional properties of the two medicaments: While **rivaroxaban** is a *direct, reversible* active site inhibitor with specificity only towards one target (factor Xa, see **D16**, Table 1 or **D23**, p. 412, right col., 2nd para.), **LMWHs** act on *multiple targets* in the anticoagulation pathway and also inhibit factor Xa only *indirectly* by catalyzing activation of antithrombin (see, e.g., **D13**, p. 1045, right col., under section 1.1 and **D23**, p. 412, right col., 1st para.). In addition, LMWHs have more unspecific interactions and, importantly, also inhibit coagulation by stimulating release of a further mediator: tissue factor pathway inhibitor (TFPI, see, e.g., **D13**, p. 1046, right col., under section 1.2).

(509) Along these lines, **D13** cited by O1, O6, and O11 also emphasizes that some of the anticoagulant activity of enoxaparin may be mediated by a compound *released by* enoxaparin (see **D13**, p. 1051, left col., l. 14-15) and that compared to regular heparin, the relation between plasma concentration and activity is less straightforward for enoxaparin, for which anti-Xa activity is said to have persisted for days after discontinuation (see **D13**, p. 1048, right col., 2nd para.). Also the reported sustained inhibitory effect of enoxaparin on fibrinopeptide A generation is thought to be due to the release of endogenous mediators such as TFPI or glycosaminoglycans (see **D13**, p. 1048, left col., 2nd para.). These explanations for the sustained effects of enoxaparin beyond what was expected solely based on its half life do not

apply to rivaroxaban for which no reasonable expectation of success for a once-daily dosage regimen existed.

(510) Being strongly charged polyanions, LMWHs also bind unspecifically (albeit less than unfractionated heparin) to plasma proteins and endothelial cells (see **D13**, p. 1047, under section 1.4). It is not surprising that biologically more complex entities such as peptides, antibodies, or oligomeric glycosaminoglycans may interact in the body with components outside of the blood plasma and therefore show sustained effects independent of their half life in blood plasma. The skilled person had no reason to transfer this knowledge to the small molecular chemical compound rivaroxaban, which does not show this binding behavior.

(511) In addition, **D87** confirms that the various antithrombotic activities of LMWH are produced by specific saccharide species in the complex mixture of glycosaminoglycans they are composed of (see **D87**, p. 1421, right col., 3rd para.). All of these LMWH species, including those which have low affinity for antithrombin, bind to multiple proteins, such as platelet factor 4, TFPI, growth factors, and other proteins, which combined with antithrombin binding of other LMWH species in the mixture mediates the full antithrombotic effect of LMWHs (see **D87**, p. 1422, left col., 4th para.). It is also clear that many LMWH metabolites will still contain the pentasaccharide signature sequence responsible for antithrombin binding (see **D86**, p. 866, left co., 1st para. and **D87**, p. 1422, left col., 3rd para.). These active metabolites can also serve to readily explain the sustained anticoagulant effects observed with enoxaparin.

(512) In summary, rivaroxaban and LMWHs have fundamentally different mechanisms of action. LMWHs do not have a half life in the classical sense due to active metabolites and the release of downstream mediators such as TFPI, which may explain the pronounced sustained effects observed. The skilled person would have expected the reasons for LMWHs to be administrable in a once-daily dosage regimen to be rooted in this more complex mechanism of action. He had no reason to transfer enoxaparin's dosage regimen to rivaroxaban.

(513) This is especially true as **D13** cited by the opponents even cautions transferability of its findings for enoxaparin to the remaining class of LMWHs. See, for example,

D13, p. 1054, left col., penultimate para., last 6 lines:

> *"It is not safe to assume, for example, that all LMWHs will be safe and effective in patients undergoing hip replacement simply because one LMWH has been proven to be so. This is illustrated by the differing results seen for enoxaparin and nadroparin in that indication."*

and **D13**, concluding sentence, see para. bridging p. 1054-1055:

> *"It must be borne in mind that the findings of safety and efficacy cannot be extrapolated to other LMWHs, as each drug must undergo specific evaluation in the circumstances in which it is intended to be used".*

If the safety and efficacy results for enoxaparin cannot even be transferred to nadroparin, another LMWH, it is clear that the skilled person would not transfer the dosage regimen of either enoxaparin (**D13, D41**) or nadroparin (**D34**) to rivaroxaban, which – structurally and functionally – is an entirely different class of compound.

(514) Finally, the opponents fail to take the **different modes of administration** into account. Whereas **enoxaparin** and **nadroparin** are administered ***subcutaneously***, the skilled person was trying to solve the problem of providing a safe and efficacious ***oral*** **dosage regimen for rivaroxaban.** Relationships between half life and dosaging frequency for a given subcutaneously administered drug (e.g., enoxaparin or nadroparin) cannot be transferred to a different orally administered drug.

(515) In addition, and contrary to O1's assertion, subcutaneous injection, unlike intravenous injection, does not lead to an immediate availability of the drug in the blood stream. See, e.g., **D9**, p. 7, right col., 2nd para., l. 4-6:

> *"The rate of absorption following subcutaneous injection of a drug often is sufficiently constant and slow to provide a* ***sustained effect****".*

See also **D9e**, p. 1343, left col., 1st para.:

> "Deep subcutaneous (intrafat) *injection of heparin has been used to slow the rate of absorption and thereby prolong the therapeutic concentration in blood".*

Thus, the skilled person may well have explained the possibility of once-daily administration of enoxaparin with the sustained effects caused by its subcutaneous administration.

(516) In decision **T 847/07** (see points 65-66 of the Reasons) the Board decided that the skilled person would not extrapolate a particular mode of administration (subcutaneous injection) that was known for one factor of the coagulation cascade (factor IX) to another factor in the cascade (factor VIII). The Board held that the mere fact that both protein factors take part in the coagulation cascade would not lead the skilled person to assume that the stability properties of the two coagulation factors are similar. In particular, it was known that the two factors have different functions in the overall coagulation pathway and differ in protein primary structure.

(517) This reasoning fully applies to the present case, where the opponents assert that once-daily oral administration of rivaroxaban would have been obvious based on the known once-daily

subcutaneous administration of enoxaparin or nadroparin. Not only do the routes of administration differ between rivaroxaban and these LMWHs, but also the chemical structure and mechanisms of action are fundamentally different as explained above.

(518) Given the different structural and functional properties of these two classes of medicaments, in combination with the opposing modes of administration, the skilled person would not find it obvious to extrapolate the od dosage regimen known for LMWHs to a new small molecule direct factor Xa inhibitor such as rivaroxaban.

G.9.5 Inventive step in light of the sustained inhibition reported for TAP (D6)

(519) O2, O3, and O6 assert that the once-daily dosage regimen of rivaroxaban would have been obvious in light of the sustained effects that had been observed for tick anticoagulation peptide (TAP) in pre-clinical and *in vitro* studies (see O2/3 at p. 8, and O6, p. 5-6, para. 4.6.7, both referring to **D6**). These pre-clinical and *in vitro* results lead the authors of **D6** to propose that factor Xa inhibitors would have a *"relatively large therapeutic window"* compared to conventional therapy. This aspect of **D6** has already been discussed in section G.7.4.3 above.

(520) The opponents' comparison of TAP with other factor Xa inhibitors, such as rivaroxaban, suffers from at least the same defects as explained for enoxaparin above. TAP is a protein (60 amino acids, see **D6**, p. 152, left col., final para.) and therefore chemically and functionally entirely distinct from the small molecule active site inhibitor rivaroxaban. O2 and O3 concede this when referring to TAP as an *"unrelated Xa inhibitor"* [see O2/3, p. 8, para. (53)]. In addition, TAP was only administered parenterally (**D6** at p. 153, left col., final para.), which therefore cannot be directly compared to orally administered rivaroxaban.

(521) Given the different structural and functional properties of rivaroxaban and TAP, in combination with the opposing modes of administration, the skilled person would not find it obvious to extrapolate any sustained effects observed for TAP to rivaroxaban.

(522) In addition, **D6** does not recite the half life of the drug candidates reported therein. Without more information, the skilled person would simply assume that the observed sustained effects might be due to a longer half life of the drug. This is not unusual amongst therapeutic protein drug products. Moreover, **D6**'s description of TAP is limited to pre-clinical, i.e. animal, studies. The skilled person does not use pre-clinical data obtained for one type of inhibitor class (protein) to draw conclusions for a completely different class of inhibitors (small molecule chemical compound), let alone a possible therapeutic dosage regimen in humans.

(523) Of note, **D6** at p. 152, right col. states that TAP was discontinued from development for undisclosed reasons. This information would also have deterred the skilled person from making any conclusions based on the TAP pre-clinical findings.

(524) O2, O3, and O6 attempt to rely on **D6** for concluding that the observed sustained effects would not have been limited to TAP, but that any factor Xa inhibitor would have been expected to provide such a sustained drug effect following short-term inhibitory action. Therefore, od administration would have been obvious. **D6** does not support such a conclusion.

(525) As explained earlier, **D6** is almost exclusively concerned with pre-clinical data in the field of factor Xa inhibtors. **D77**, which provides a similar summary for the *clinical data* available in 2004, i.e. 3 years after the publication date of **D6** and closer to the priority date of the Opposed Patent, demonstrates that in the actual phase II and III studies, anticoagulants and factor Xa inhibtors in particular were all dosed based on half lives and at intervals of 1-2 times their respective half life (see section G.7.1 above). Thus, it is simply not true that the teaching of **D6** would have caused the skilled person to administer factor Xa inhibitors in less frequent dosage regimens than what would have been expected as (a) optimal based on their half lives and (b) practiced in the more advanced clinical development closer to the priority date of the Opposed Patent. For the skilled person, the latter would have clearly taken precedent over the general statements derived from unrelated pre-clinical data in the much earlier published document **D6**.

(526) Finally, **D6** repeatedly emphasizes, what is anyhow apparent to the skilled person, i.e. that clinical development is inherently uncertain. See, e.g., the following passages in **D6**:

> *"Which experimental condition is more comparable to the situation in patients with arterial thrombosis is still uncertain, especially in regard to how these new agents perform in the **model** versus the **clinical** setting."* (**D6**, para. spanning p. 153-154, emphasis added);
>
> *"Although the **hurdles for discovering a fXa inhibitor** that has the appropriate pharmacokinetic properties are quite **challenging**, these data are encouraging and suggest that orally active fXa inhibitors may be coming closer to realization."* (**D6**, p. 156, left col., 1st para., last 5 lines, emphasis added)
>
> *"Indeed, with every new bit of preclinical and clinical data, we will gain a better understanding of how these agents work, how to **administer them safely and effectively**, and how to evaluate and monitor their activity. However, the **ultimate outcome** of this collective, long-term **research effort** will only be clearly known when **large-scale clinical trials** are performed comparing direct fXa inhibitors with the current standard of care for each specific indication. Based on the preclinical and clinical data available thus far, the next few years should be an **exciting period** for evaluating the potential of what may be the next generation of antithrombotic agents, direct fXa inhibitors." (**D6**, p. 156, final para.)*

(527) These quotations from **D6** demonstrate the uncertainty that the skilled person faced and put the limited conclusions presented in **D6** based on pre-clinical data unrelated to rivaroxaban into perspective. Identifying factor Xa inhibitors with appropriate PK-properties for oral administration was considered a *challenging hurdle* and finding specific dosage regimens for *"safe and effective"* oral administration is explicitly highlighted as forming part of that challenge. If, based on **D6**, everything had already been obvious, its author would not have described the time to come as an *"exciting period"* (see **D6**, p. 156, right col., final para., 3rd line from end).

(528) The fact that none of the early drug candidates described in **D6** ever gained regulatory approval underscores the uncertainty of drug development.

G.9.6 Rivaroxaban's mechanism of action did not suggest a sustained effect (O12)

(529) O12 in its section entitled *"Scientific background"* asserts that rivaroxaban would act on two steps in the coagulation cascade:

(I) inhibiting the **generation of factor Xa** from factor X and

(II) inhibiting **factor Xa activity**, i.e. the generation of thrombin from prothrombin.

In support of this assertion, O12 points to **D15** and **D42**. However, only the latter even mentions factor Xa generation and neither of the documents supports O12's assertion (see below). Regardless, O12 then goes on to conclude that a sustained effect could have been expected based on rivaroxaban's alleged multi-pronged mechanism of action.

O12 has no basis for making these assertions.

(530) First, O12's assertion of a multi-pronged mechanism of action for rivaroxaban is not convincing without any explanation of how rivaroxaban is supposed to mediate the inhibition of the formation of factor Xa. It belonged to the common general knowledge of the skilled person that in the coagulation cascade two enzymes catalyze the proteolytic cleavage (and thereby activation) of factor X to factor Xa (see, e.g. the textbook **D80b**, p. 497, Fig. B 4-5):

- **factor IXa** with its cofactor, **factor VIII** (in a complex known as **intrinsic Xase**), and
- **factor VIIa** with its cofactor, **tissue factor** (in a complex known as **extrinsic Xase**).

(531) As also acknowledged by the simplified scheme on p. 5 of O12, the intrinsic (contact activation) and extrinsic (tissue factor) pathways converge at the point of factor Xa generation to continue in the final common pathway (also known as the 'thrombin pathway'). It goes

without saying that factor Xa activity is downstream of factor Xa generation, and final endpoints such as thrombin generation or blood clotting are even further downstream of both. Thus, even if, for the sake of argument, one assumed that rivaroxaban would inhibit not only factor Xa activity but also factor Xa generation, only the net effect of both would be measurable in the factor Xa activity, clotting assays, or thrombin generation assays described, for example, in **D2/D11**, **D3/D12**, **D15/D17**, and **D42**.

O12's arguments to the contrary are fallacious.

(532) Second, O12's assertion that rivaroxaban would target factors other than factor Xa in the blood coagulation cascade is similarly unconvincing. O12 at p. 6, final para. points to **D15** and **D42** as allegedly showing that rivaroxaban would inhibit more than one reaction of the blood coagulation cascade.

(533) **D15**, however, only concludes that rivaroxaban effectively inhibits thrombin generation regardless of whether coagulation was initiated via the intrinsic or extrinsic pathway. This also makes perfect sense given that rivaroxaban's target, i.e. factor Xa, is situated downstream, and in fact at the converging point, of both pathways.

(534) **D42** also does not support O12's asserted multi-pronged mechanism of action. In fact the assays described in **D42** do not distinguish properly between factor Xa generation and factor Xa activity because the single final readout is a kinetic measurement of activity (determination of IC_{50} values) using substrates for factor Xa and thrombin. Less substrate turnover and an associated increase in IC_{50} values, however, can be indicative of both inhibition of factor Xa generation as well as inhibition of factor Xa activity because factor Xa generation is necessarily upstream of any factor Xa action. Against this background, and contrary to O12's assertion, the skilled person would not conclude from the scarce information reported in **D42** that rivaroxaban inhibits both factor Xa activity and factor Xa generation.

(535) This is also in line with what the skilled person knew from scientific papers and reviews summarizing the data available on rivaroxaban's activity and mechanism of action. These unanimously describe rivaroxaban as a highly selective inhibitor of factor Xa (see, e.g., **D16**, Summary and Table 1). If rivaroxaban also directly inhibited factor Xa generation from factor X, it would need to inhibit the serine protease activities of the intrinsic (i.e. factor IXa) and/or extrinsic (i.e. factor VIIa) Xase complexes as well. Clearly, this is not the case. See, e.g., **D16**, p. 516, right col., 3rd para. referring to Table 1 on p. 517 which demonstrates a more than 10 000-fold greater selectivity of rivaroxaban for factor Xa compared to both factor IXa (intrinsic Xase) and factor VIIa (extrinsic Xase).

(536) The skilled person would assign more weight to peer-reviewed publications, such as **D16**, compared to vague statements made in a (non-peer-reviewed) conference abstract such as **D42**, the assay readout of which he easily identifies as inappropriate for properly distinguishing between factor Xa activity and generation.

(537) Finally, it should be noted that those skilled in the art do not use the term *"generation"* in its literal sense when referring to *in vitro* anticoagulation assays. See, e.g., **D15**, which describes several *"thrombin generation"* assays, in all of which only thrombin activity [substrate turnover, endogenous thrombin potential (ETP), and platelet-induced thrombin-generation time (PITT)] or downstream clot formation (PICT) is measured. Hence, these *"thrombin generation"* assays cannot distinguish between thrombin generation and activity. They are called *"thrombin generation"* assays because they involve the coagulation cascade and generation of thrombin, in contrast to purely biochemical assays in which a compound is tested for inhibition of already purified (and thus already formed) thrombin. Similarly, the skilled person would have interpreted the conclusion in **D42** that rivaroxaban inhibited "not only formed Factor Xa, but also its generation" (**D42**, l. 12-13 from end) in the sense that it not only inhibited purified or artificially activated (formed) Factor Xa, but also showed inhibition in one of the "Factor Xa generation" assays described, which involve activation of the coagulation cascade and hence *de novo* factor Xa *generation* via either the extrinsic or the intrinsic pathway.

(538) In summary, the basic assumption underlying O12's inventive step argument is already incorrect. Rivaroxaban is a highly selective inhibitor of factor Xa activity and is not characterized by a multi-pronged mechanism of action impacting factor Xa generation.

(539) Finally, even if one assumed a multi-pronged mechanism of action for rivaroxaban, this would not explain or make obvious any sustained effect of rivaroxaban beyond what was expected based on rivaroxaban's plasma concentration and half life. O12's assertions to the contrary are unsupported and lack merit. At the effective filing date of the Opposed Patent, the skilled person would certainly have considered plasma concentration as the best indicator of how long a given factor Xa inhibitor could be efficacious for. O12's assertion at p. 6, 3rd para. that *"[a]s soon as an inhibitor interacts with more than one reaction of a cascade, such as the blood coagulation, the mere concentration of the inhibitor in the blood is not predictive for the time scale of its efficacy"* is simply incorrect.

(540) Importantly, unlike the hypothetical example given by O12 at p. 6, penult. para. regarding the consequences of an irreversible inhibitor, rivaroxaban was known to be a *competitive and reversible* inhibitor of factor Xa (see, e.g., **D16**, p. 519. 1st para.). O12's argument is fallacious for this very reason. In addition, the hypothetical example of O12 makes it sound as if

generation of factor Xa was a time-consuming and rate-limiting step. O12 has no basis for making this assertion. Factor Xa regeneration is quick. It does not depend on *de novo* protein synthesis, but is simply the result of cleavage of (abundantly available) inactive factor X to Xa by either the intrinsic or extrinsic Xase.

(541) Thus, even if one were to assume that rivaroxaban directly inhibited one of the Xase enzymes or upstream processes (which it does not), then one would expect this inhibition to subside immediately and factor Xa regeneration to promptly follow reductions in inhibitor plasma concentration. Thus, O12 has no basis for asserting that *"if a drug not only inhibits Factor Xa but also the formation of Factor Xa from Factor X, there will be a delay in the increase of the concentration of Factor Xa when the concentration of the inhibitor decreases"* (O12, p. 6, 2nd para., l. 3-5). Again, the skilled person would have had no reason to assume that plasma concentration would not be a good indicator of anticoagulant effects of rivaroxaban.

(542) In summary, the Opposition Division should assign no weight to O12's inventive step arguments, which are factually incorrect and based on a misrepresentation of rivaroxaban's mechanism of action.

G.9.7 D2/D11 in combination with D16 or D27 (O9)

(543) O9's position that the claimed dosage regimen would have been obvious from a combination of **D2/D11** with either **D16** or **D27** is not convincing.

(544) **D16** summarizes the *in vitro* properties of rivaroxaban, its antithrombotic efficacy in animal models, its effect on blood plasma hemostasis *in vitro* and the pre-clinical pharmacological profile based on which rivaroxaban was chosen for clinical development (see **D16**, p. 514, right col., final para.).

(545) **D16** is cautious regarding how transferable its *in vitro* and animal model findings are to the treatment of humans, (i.d., p. 520, left col., 3rd para., l. 4-5 from end: *"Although these results may not be directly applicable to humans..."*, and 5th para., l. 4-5: *"The clinical relevance of these data needs to be investigated..."*) and only generally refers to abstracts **D2** and **D3** (ref. 18 and 17, respectively, of **D16**) as reporting the first tests of rivaroxaban in humans. Thus, for inventive step purposes, the teaching of **D16** does not go beyond that of **D2** or **D3**.

(546) O9's argument that the skilled person would know from a combination of **D2/D11** with **D27** that rivaroxaban would in fact be effective *in vivo* in humans in the treatment of thromboembolic disorders is similarly unavailing.

(547) **D27** is a high-level abstract, only 9 lines in length, and does not report any results or data. The skilled person would not base the dosage selection for late-stage clinical development on such scarce information. **D27** merely states that *"[l]ead optimization led to the discovery of BAY 59-7939, a highly potent and selective direct FXa inhibitor with excellent in vivo antithrombotic activity and high oral bioavailability"* (l. 5-6) and then concludes that rivaroxaban *"was selected for clinical development for the prevention and treatment of thromboembolic diseases"* (last 2 lines). **D27** offers no basis for O9's assertion that the clinical efficacy of rivaroxaban in treating thromboembolic disorders had been established (see O9, p. 11, 4th para.). Rather, **D27** expressly states that rivaroxaban had only just been selected for clinical development without stating any results thereof. The skilled person, who was following the development of novel oral anticoagulants closely, knew that at the publication date of **D27**, no efficacy data from human clinical studies was available. Without doubt, he would have understood the "*excellent* in vivo *antithrombotic activity*" to refer to results from animal studies.

Thus, also **D27** cannot supplement the missing teaching of clinical efficacy in **D2/D11**.

G.10 Other problem-and-solution approaches exercised by the opponents

G.10.1 D1 as closest prior art (O1, O4, and O5)

(548) O1, O4, and O5 use **D1** as an alternative starting point to **D2/D11** for the assessment of inventive step. **D1**, however, is clearly not the closest prior art. **D1** discloses rivaroxaban as a species within a broader genus of oxazolidinone derivatives. It includes *in vitro* and pre-clinical test results, but does not test rivaroxaban in humans. Thus, **D2/D11** which reports a phase I dose escalation study in humans is much more suited to serve as closest prior art.

(549) However, also starting from **D1** as closest prior art does not render the claimed invention obvious. As explained under novelty in section F.3 above, **D1** does not teach or suggest a once-daily administration of a rapid-release tablet of rivaroxaban for at least five consecutive days.

(550) Thus, the distinguishing features, and therefore also their technical effect and the resulting objective technical problem, are identical to what has been discussed in connection with **D2/D11** as closest prior art in sections G.4 and G.5 above. The **objective technical problem** vis-à-vis **D1** can therefore also be formulated as:

> ***The provision of a safe and effective oral dosage regimen for rivaroxaban for the therapeutic and prophylactic treatment of thromboembolic disorders.***

G.10.1.1 Non-obviousness based on D1 alone

(551) To arrive at the claimed invention starting from **D1**, the skilled person would first have to select rivaroxaban as lead compound among the many oxazolidinone derivatives taught by **D1**. In the arteriovenous rat shunt model experiments reported in para. [0387]-[0391] of **D1**, seven other compounds were tested besides rivaroxaban, five of which showed identical activity to rivaroxaban (see Table 1 of **D1**, ED50 values of 3 mg/kg). Thus, the data contained in **D1** do not single out rivaroxaban as being preferred.

(552) Next, the skilled person would need to opt for an oral dosage form. Of the eight compounds tested in the arteriovenous rat shunt model experiments of **D1**, only two were administered orally (examples 44 and 123). Both showed identical activity. Thus, the data contained in **D1** also do not highlight rivaroxaban as being the preferred orally administered factor Xa inhibitor.

(553) Opponents rely on para. [0367] to [0372] of **D1** for an alleged implicit disclosure of the features *"rapid-release tablet"* and *"once-daily administration for at least five consecutive days"*. First of all, there is no such implicit disclosure in **D1** (see novelty section F.3 above). Second, these paragraphs form part of the general description of **D1** and applying the case law of the Technical Boards of Appeal of the EPO cannot be seen to teach any features *in combination* with rivaroxaban.

(554) The feature *"tablet"* needs to be selected from a long list of possible administration forms in para. [0367] of **D1**. Opponents do not contest that the particular claim feature *"rapid-release tablet"* is nowhere disclosed in **D1**.

(555) Opponents further rely on an inadmissible *argumentum e contrario* based on the final sentence in para. [0368] of **D1** which reads:

> *"In the case of the administration of relatively large amounts, it may be advisable to divide these into several individual administrations over the course of the day".*

(556) **D1** does not contain any pharmacokinetic information on the compounds reported therein. No half life, bioavailability, or human plasma concentrations are mentioned. The skilled person, who followed the development of novel factor Xa inhibitors closely, was also aware that at the filing date of **D1**, no testing in humans had yet been performed for any of the compounds mentioned in **D1**, including rivaroxaban. Against this background of lacking pharmacokinetic information, the skilled person would have perceived para. [0368] of **D1** not as a suggestion for a concrete dosage regimen for any of the compounds mentioned in **D1**, but only as **generic language** common to patent applications filed in the early stages of drug discovery and lead optimization, where pharmacokinetic data is still lacking.

(557) In addition, para. [0368] of **D1** leaves open what *"relatively large amounts"* are supposed to mean. Regarding departing from the *"amounts mentioned"* (before), para. [0368] of **D1** teaches that this may depend *"on the body weight or on the type of administration route, on the individual response to the medicament, on the manner of its formulation and the time or interval at which administration takes place"*, i.e. many different factors with no single one being singled out as preferred. Para. [0368] of **D1** also leaves entirely open, whether or not in case of *"an administration of relatively small amounts"*, it may also *"be advisable"* to divide these amounts into several individual administrations over the course of the day. In fact, given the reported short half life of rivaroxaban, the skilled person would have presumed exactly this. As explained in more detail in section G.7 above, the skilled person would have refrained from choosing a once-daily dosage regimen for rivaroxaban based on the information that was publicly available prior to the present invention. This holds true in particular for the dosaging of relatively small amounts, where the skilled person would have feared hazardously low trough levels (i.e. devoid of efficacy) between administrations.

(558) At the effective filing date of the Opposed Patent, the skilled person knew of rivaroxaban's short half life of 3-6 hours (see, e.g., **D2**, l. 16: "4-6 h"; **D3**, l. 15: "3-4 h") and the bleeding complications experienced with other factor Xa inhibitors in clinical development (see the razaxaban example discussed in section G.7.3.1 above). This information, which was published between the earliest publication date of **D1** (see **D1a**: July 5, 2001) and the effective filing date of the Opposed Patent (January 31, 2005), would have taken precedent over any generic statements regarding possible dosaging recommendations in the earlier published document **D1**. This particularly applies because **D1** concerned an entire genus of factor Xa inhibitors and contained no human pharmacokinetic data or information on safe and medically effective dosage regimens (that is, from phase II or III clinical trials) specifically for rivaroxaban.

(559) Finally, even if the skilled person had considered para. [0368] or [0372] of **D1** in his development of a safe and efficacious dosage regimen for rivaroxaban, arriving at the claimed solution still involved an inventive step. First, **D1** does not teach towards any specific dosage regimen (such as the once-daily dosage regimen claimed here). Instead, **D1** only generically provides that the formulations administered should have an acceptable amount (i.e. dose) of medicament. See **D1**, para. [0367]:

> *"The novel active compounds of the general formula (I) can be converted in a known manner into the customary formulations [...]. Here, the therapeutically active compound should in each case be present in a concentration [...] i.e. in amounts which are sufficient in order to achieve the dosage range indicated."* (emphasis added)

(560) **D1** offers suggestions for amounts, but does not link these amounts to any particular dosaging intervals. Opponents quote para. [0368] or [0372] of **D1** in favor of it teaching towards a dosage regimen (see, for example, O1, p.15, last paragraph). The relevant portions of para. [0372] of **D1** read:

> *"...it may be necessary in the case of intravenous or oral administration to depart from the amounts mentioned, namely depending on the [...] interval at which administration takes place. [...] In the case of the administration of relatively large amounts, it may be advisable to divide these over the course of the day, namely into several individual doses or as a continuous infusion".* (emphasis added)

(561) Opponents interpret the final sentence in para. [0368] and [0372] of **D1** out of context when considering it to mean that the authors envisioned a once-daily administration per default. These paragraphs clearly separate the dose included in one formulation, i.e. 'amount' in one administration, from the interval at which each dose is administered (compare first with final sentence in para. [0368] and [0372] of **D1**), i.e. the dosage regimen. Thus, the skilled person reads para. [0368] and [0372] of **D1** as a teaching towards the administration of a dose itself and not a dosage regimen.

(562) Moreover, *"in order to achieve the dosage range indicated"* (see **D1**, p.15, para. [0367], last 2 lines) requires that the dosage range indicated be known to be efficacious and safe in the treatment of a thromboembolic disorder. No prior art, including **D1**, provides such information. This, as described previously in sections F.4.2 and G.9.3.2, can only be determined in phase II and III studies, neither of which had been completed before the effective filing date of the Opposed Patent.

(563) Therefore, starting from **D1**, the skilled person would only have been armed with the knowledge that, generally, if doses exceeded a certain amount, they could be administered *"over the course of the day"*. Contrary to the opponents' assertions, the opposite of *"administration over the course of the day"* (cf. **D1**, para. [0368] and [0372], final sentences) is not necessarily a once-daily dosage regimen, but could just as well be a twice-daily regimen administered not throughout the day, but in the morning and the evening of a given day. Thus, even if one were to follow opponents' *argumentum e contrario*, **D1** does not suggest a once-daily dosage regimen.

(564) As explained in sections G.7.1 to G.7.4 above, without knowledge of the therapeutic window of rivaroxaban, the skilled person would have been taught by his common general knowledge that a more frequent administration of rivaroxaban would be necessary based on its short reported half life alone.

(565) **D1** does not teach otherwise. In particular, para. [0373] of **D1** only teaches that the oxazolidinone derivatives of **D1** were expected to have a greater therapeutic range as compared to conventional anticoagulant therapy without indicating any absolute values for the expected therapeutic range:

> *"Compared to the conventional preparations for treating thromboembolic disorders, the compounds of the general formula (I) according to the invention [...] are distinguished in particular by the fact that a greater therapeutic range is achieved by the selective inhibition of factor Xa. For the patient, this means a lower risk of, bleeding, and for the treating physician, this means that the patient is easier to adjust. Moreover—owing to the mechanism—the onset of action is more rapid. Above all, however, the compounds according to the invention permit an oral administration form, which is a further advantage of the therapy with the compounds according to the invention."* (emphasis added)

(566) The greater therapeutic range, lower risk of bleeding, and more rapid onset of action mentioned in **D1** are characteristics that were thought to be associated with the more selective mechanism, but are in and of themselves no more than speculation with regard to a particular dosage regimen, let alone the claimed dosage regimen. See section G.7.4 above for a discussion of why the therapeutic window for rivaroxaban was neither known nor expected to be large enough for od dosaging

G.10.1.2 Non-obviousness based on D1 in combination with the other art cited

(567) Regarding non-obviousness of the claimed solution vis-à-vis **D1** and possible combinations with other prior art documents, all arguments discussed for **D2/D11** as closest prior art in sections G.7 to G.9 above equally apply to the problem-and-solution approach based on **D1** as closest prior art. For brevity, they will not be reiterated here.

G.10.2 D3/D12 or D15/D17 as closest prior art (O4, O8, O9, and O12)

(568) O4, O8, O9, and O12 argue that besides **D2/D11**, also **D3/D12** or **D15/17** could be considered as the closest prior art. In **D3/D12** and **D15/D17**, rivaroxaban was tested in healthy volunteers, and only single doses were administered. Thus, **D2/D11** which reports a phase I *multiple dose* escalation study in humans clearly is better suited to serve as closest prior art.

(569) However, also when starting from **D3/D12** or **D15/D17** as closest prior art document, inventive step of the claimed dosage regimen must be acknowledged under the problem-and-solution approach. Neither **D3/D12** nor **D15/D17** teaches or suggests a once-daily administration of a rapid-release tablet of rivaroxaban for at least five consecutive days *for the treatment of a thromboembolic disorder*.

(570) Thus, the distinguishing features, and therefore also their technical effects and the resulting objective technical problem, are identical to what has been discussed in connection with **D2/D11** or **D1** as closest prior art in sections G.4, G.5 and G.10.1 above. Thus, the **objective technical problem** vis-à-vis **D3/D12** or **D15/D17** can be formulated as:

> ***The provision of a safe and effective oral dosage regimen for rivaroxaban for the therapeutic and prophylactic treatment of thromboembolic disorders.***

(571) The claimed solution was not obvious, also when starting with **D3/D12** or **D15/D17** as closest prior art. As explained in sections G.9.2 and G.9.3 above, **D3/D12** and **D15/D17** only report phase I study results that did not suggest that the claimed dosage regimen would be medically effective. In particular, **D3/D12** and **D15/D17** provide no evidence for a sustained therapeutic effect of rivaroxaban (see section G.9.3.1 above). Phase I pharmacodynamic surrogate parameters, and in particular the *in vitro* thrombin generation and clotting assays reported in **D3/D12** and **D15/D17**, cannot provide the information about clinical endpoints or efficacy that would be necessary to suggest clinical efficacy of a particular dosage regimen (see sections G.9.3.3 and G.9.3.4 above). Clinical efficacy and the boundaries of the therapeutic window are only determined in phase II and III studies, which had not been available at the effective filing date of the Opposed Patent (see section G.9.3.2 above).

(572) All arguments discussed for **D2/D11** as closest prior art in sections G.7 to G.9 above equally apply to the problem-and-solution approach based on **D3/D12** or **D15/D17**. For brevity, they will not be reiterated here.

(573) In summary, also when starting from **D3/D12** or **D15/D17** as closest prior art, inventive step of the claimed dosage regimen must be acknowledged.

G.10.3 D16 or D27 as closest prior art (O9)

(574) O9 argues that besides **D2/D11**, also **D16** or **D27** could be considered as the closest prior art. **D16** and **D27** only report *in vitro* and pre-clinical test results (see section G.9.7 above). Thus, **D2/D11**, which reports a first phase I dose-escalation study for rivaroxaban in humans, clearly is more suited to serve as closest prior art.

(575) Also when starting from **D16** or **D27** as closest prior art, arriving at the claimed dosage regimen required an inventive step. Reporting only on *in vitro* and pre-clinical test results, **D16** and **D27** alone do not provide any teaching or suggestion in the direction of the claimed dosage regimen.

(576) As explained in detail above, the claimed dosage regimen was contrary to conventional wisdom and there was no reasonable expectation of success for administering rivaroxaban once daily. In particular, none of the prior art documents cited by the opponents suggest that a once-daily dosage regimen could be therapeutically safe and effective. Again, all arguments that were discussed in this respect for **D2/D11** as closest prior art in sections G.7 to G.9 above equally apply to the problem-and-solution approach based on **D16** or **D27** as closest prior art. For brevity, they will not be reiterated here.

(577) In summary, also starting from **D16** or **D27** as closest prior art does not render the claimed invention obvious. An inventive step must be acknowledged.

H AUXILIARY REQUESTS

(578) As outlined above, Patentee is of the firm opinion that the patent as granted meets the requirements of the EPC and trusts that the Opposition Division will reject the oppositions and maintain the patent as granted.

(579) As a mere precautionary measure, patentee herewith provides **auxiliary requests** (ARs) for the event that, after the discussion of the main request, the Opposition Division considers it necessary to delete the term "no more than" in claim 1 (see AR1, AR3, AR10 to AR15 and AR22 to AR27), to define a dose amount in claim 1 (see AR2, AR3, and AR16 to AR27), or to further define the term "thromboembolic disorders" in claim 1 (see AR4 to AR27).

(580) AR10 to AR27 are simple combinations of ARs 4 to 9 with ARs 1 to 3 (see sections H.10 to H.12 below).

H.1 Auxiliary Request 1 (AR1)

(581) Claim 1 of AR1 is based on claim 1 as granted, in which the wording *"no more than"* was deleted. Support for this amendment can be found, e.g., in claim 3 of WO'474, the application as originally filed (see also WO'474, p. 1, l. 1 to 5, p. 3, l. 15 to 18 and 23 to 26, as well as p. 4, l. 20 to 23). Thus, AR1 complies with Art 123(2) EPC.

(582) The amendment of *"no more than once daily"* to *"once daily"* in claim 1 of AR1 does not change the scope of the granted claims given the synonymous usage of these terms in the Opposed Patent (see section E.3.3 above). Even if one were to adopt the interpretation of some of the opponents that *"no more than once daily"* would also include *"less than once daily"* (which it does not when grounded by the claim's context and the Opposed Patent's specification, see section E.3.3 above), the change to *"once daily"* would only further delimit the scope of the granted claims. Thus, AR1 also complies with Art. 123(3) EPC.

(583) AR1 is filed in case the Opposition Division unexpectedly considers the feature *"no more than once daily"* in granted claim 1 to include *"less than once daily"* administration.

H.2 Auxiliary Request 2 (AR2)

(584) Claim 1 of AR2 is based on claim 1 as granted, however, the dose range to be administered was defined as being from *"5 to 30 mg"*. This corresponds to the most preferred dose range recited on p. 10, l. 16 of WO'474. Thus, AR2 complies with Art 123(2) EPC. AR2 also complies with Art. 123(3) EPC as it further delimits the scope of the granted claims by defining the dose range to be administered.

(585) AR2 is filed in case the Opposition Division unexpectedly comes to the conclusion that granted claim 1 would not be enabled or inventive across its entire scope.

H.3 Auxiliary Request 3 (AR3)

(586) AR3 is a combination of AR1 and AR2 and complies with Art. 123(2) and (3) EPC for the reasons stated in sections H.1 and H.2 above.

(587) AR3 is filed in case the Opposition Division unexpectedly comes to the conclusion that granted claim 1 would not be enabled or inventive across its entire scope and considers the feature *"no more than once daily"* in granted claim 1 to include *"less than once daily"* administration.

H.4 Auxiliary Request 4 (AR4)

(588) Claim 1 of AR4 is based on claim 1 as granted, however, the term "thromboembolic disorder" was further defined to be selected from the group consisting of:

- Acute coronary syndrome spectrum
- ST Segment Elevation Myocardial Infarction (STEMI) (also known as Q-wave MI),
- Non ST Segment Elevation Myocardial Infarction (NSTEMI)(also known as Non Q-wave MI)
- unstable angina (UA),
- stable angina pectoris,
- vascular re-occlusions and restenoses after angioplasty or aorto-coronary bypass,
- peripheral arterial occlusion disorders,
- pulmonary embolisms,
- deep vein thromboses,
- renal thrombosis,
- transitory ischaemic attacks,
- stroke,
- disseminated intravascular coagulation (DIC),
- economy class syndrome,
- disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are selected from cerebral ischemic diseases, stroke, systemic embolism and ischemic attacks, and
- disorders derived from thromboembolic complications which can arise within patients with microangiopathic hemolytic anaemia, extracorporal circulation, or prosthetic heart valves as well as from the thromboembolic complication venous thromboembolism in tumor patients.

This list of types of thromboembolic disorders corresponds to the list of possible types of thromboembolic disorders described on p. 9, l. 6-25 of WO'474 as being included in the term "thromboembolic disorder", wherein the following amendments have been made:

- The diseases specifically objected to by O5 (see *id.*, p. 7, 3rd para.: *"inhibition of tumor growth and development of metastasis"*, *"rheumatic diseases of the musculoskeletal*

system", *"Alzheimer's disease"*, *"diabetic retinopathy"*, and *"diabetic nephropathy "*) were deleted.

- In addition, the diseases *"inhibition of old-age macula-degeneration"* and *"other microvascular diseases"* were deleted.

- Optional further definitions (e.g., *"especially in patients with risk of venous thrombosis, atherosclerotic diseases, inflammatory diseases, as rheumatic diseases of the musculoskeletal system"*, *"especially in patients with acute, intermittent or persistent arrhythmia of the heart such as atrial fibrillation or alongside cardioversion, or in patients with valvular heart disease or artificial heart valves"*, *"such as hemodialysis"* and *"in particular in patients undergoing surgical interventions, chemotherapy or radiotherapy"*) were deleted as well for the sake of brevity and clarity.

Arriving at the list of diseases in claim 1 of AR4 corresponds to performing moderate deletions from a single list of some length. Thus, AR4 complies with Art 123(2) EPC. AR4 also complies with Art. 123(3) EPC as it further delimits the scope of the granted claims by further defining the thromboembolic disorder to be treated.

(589) AR4 is filed in case the Opposition Division unexpectedly comes to the conclusion that granted claim 1 would not be enabled or inventive across its entire scope.

H.5 Auxiliary Request 5 (AR5)

(590) Claim 1 of AR5 corresponds to claim 1 of AR4, in which the following diseases were deleted: *"acute coronary syndrome spectrum as ST Segment Elevation Myocardial Infarction (STEMI) (also known as Q-wave MI), Non ST Segment Elevation Myocardial Infarction (NSTEMI) (also known as Non Q-wave MI) and unstable angina (UA), as well as stable angina pectoris, vascular re-occlusions and restenoses after angioplasty or aorto-coronary bypass, peripheral arterial occlusion disorders"*. The corresponding diseases were also deleted from the shorter list recited in granted claim 2.

(591) Compared to claim 1 as granted, the term "thromboembolic disorder" in claim 1 is therefore further defined according to AR5 to be selected from the group consisting of:

- pulmonary embolisms,
- deep vein thromboses,
- renal thrombosis,
- transitory ischaemic attacks,
- stroke,
- disseminated intravascular coagulation (DIC),
- economy class syndrome,

- disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are selected from cerebral ischemic diseases, stroke, systemic embolism and ischemic attacks, and
- disorders derived from thromboembolic complications which can arise within patients with microangiopathic hemolytic anaemia, extracorporal circulation, or prosthetic heart valves as well as from the thromboembolic complication venous thromboembolism in tumor patients.

(592) Arriving at the list of diseases in claim 1 of AR5 corresponds to performing moderate deletions from a single list of some length disclosed on p. 9, l. 6-25 of WO'474 (see explanations in section H.4 for AR4 above, which apply *vice versa* to AR5). Thus, AR5 complies with Art 123(2) EPC. AR5 also complies with Art. 123(3) EPC as it further delimits the scope of the granted claims by further defining the thromboembolic disorder to be treated.

(593) AR5 is filed in case the Opposition Division unexpectedly comes to the conclusion that granted claim 1 would not be enabled or inventive across its entire scope.

H.6 Auxiliary Request 6 (AR6)

(594) Claim 1 of AR6 corresponds to claim 1 of AR5, in which the following further diseases were deleted: "renal thrombosis", "disseminated intravascular coagulation (DIC)", "economy class syndrome", and the "disorders derived from thromboembolic complications". The "disorders derived from cardiogenic thromboembolism" were limited to "systemic embolism".

(595) Compared to claim 1 as granted, the term "thromboembolic disorder" in claim 1 is therefore further defined according to AR6 to be selected from the group consisting of:

- pulmonary embolisms,
- deep vein thromboses,
- transitory ischaemic attacks,
- stroke,
- disorder derived from cardiogenic thromboembolism, wherein the disorder derived from cardiogenic thromboembolism is systemic embolism.

(596) Arriving at the list of diseases in claim 1 of AR6 corresponds to performing deletions from a single list of some length disclosed on p. 9, l. 6-25 of WO'474 (see explanations in sections H.4 for AR4 and H.5 for AR5 above, which apply *vice versa* to AR6). Thus, AR6 complies with Art 123(2) EPC. AR6 also complies with Art. 123(3) EPC as it further delimits the scope of the granted claims by further defining the thromboembolic disorder to be treated.

(597) AR6 is filed in case the Opposition Division unexpectedly comes to the conclusion that granted claim 1 would not be enabled or inventive across its entire scope.

H.7 Auxiliary Request 7 (AR7)

(598) Claim 1 of AR7 corresponds to claim 1 of AR5, in which the following further diseases were deleted: "renal thrombosis", "stroke", "disseminated intravascular coagulation (DIC)", "economy class syndrome", and the "disorders derived from thromboembolic complications". The "disorders derived from cardiogenic thromboembolism" were limited to "stroke and systemic embolism in patients with atrial fibrillation". This amendment is supported by l. 17-19 on p. 9 of WO'474. Dependent claim 2 was deleted. Compared to claim 1 as granted, the term "thromboembolic disorder" in claim 1 of AR7 is further defined to be selected from the group consisting of:

- pulmonary embolisms,
- deep vein thromboses,
- transitory ischaemic attacks,
- disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are stroke and systemic embolism in patients with atrial fibrillation.

(599) Arriving at the list of diseases in claim 1 of AR7 corresponds to performing deletions from a single list of some length disclosed on p. 9, l. 6-25 of WO'474 (see explanations in sections H.4 for AR4 and H.5 for AR5 above, which apply *vice versa* to AR7). Thus, AR7 complies with Art 123(2) EPC. AR7 also complies with Art. 123(3) EPC as it further delimits the scope of the granted claims by further defining the thromboembolic disorder to be treated.

(600) AR6 is filed in case the Opposition Division comes to the conclusion that granted claim 1 would not be enabled or inventive across its entire scope.

H.8 Auxiliary Request 8 (AR8)

(601) Claim 1 of AR8 corresponds to a combination of claims 1 and 2 as granted, wherein the following diseases were deleted from the list recited in granted claim 2: *"ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass"*. Compared to claim 1 as granted, the term "thromboembolic disorder" in claim 1 of AR8 is further defined to be

- pulmonary embolisms,
- deep vein thromboses, or
- stroke.

(602) These 3 types of disorders were selected from the list of preferred thromboembolic disorders recited in originally filed claim 4 (see also WO'474, p. 9, l. 31 to p. 10, l. 2). This selection corresponds to performing deletions from a single list of some length. Thus, AR8 complies

with Art 123(2) EPC. AR8 also complies with Art. 123(3) EPC as it further delimits the scope of the granted claims by further defining the thromboembolic disorder to be treated.

(603) AR8 is filed in case the Opposition Division unexpectedly comes to the conclusion that granted claim 1 would not be enabled or inventive across its entire scope.

H.9 Auxiliary Request 9 (AR9)

(604) Claim 1 of AR9 corresponds to claim 1 of AR7, in which the following diseases were deleted: "transitory ischaemic attacks" and "systemic embolism". The "disorders derived from cardiogenic thromboembolism" were limited to "stroke in patients with atrial fibrillation". This amendment is supported by l. 17-19 on p. 9 of WO'474. Compared to claim 1 as granted, the term "thromboembolic disorder" in claim 1 of AR9 is further defined to be selected from the group consisting of:

- pulmonary embolisms,
- deep vein thromboses, and
- a disorder derived from cardiogenic thromboembolism, wherein the disorder derived from cardiogenic thromboembolism is stroke in patients with atrial fibrillation.

(605) Arriving at the list of diseases in claim 1 of AR9 corresponds to performing deletions from a single list of some length disclosed on p. 9, l. 6-25 of WO'474 (see explanations in sections H.4 for AR4, H.5 for AR5, and H.7 for AR7 above, which apply *vice versa* to AR9). Thus, AR9 complies with Art 123(2) EPC. AR9 also complies with Art. 123(3) EPC as it further delimits the scope of the granted claims by further defining the thromboembolic disorder to be treated.

(606) AR9 is filed in case the Opposition Division unexpectedly comes to the conclusion that granted claim 1 would not be enabled or inventive across its entire scope.

H.10 Auxiliary Requests 10 to15 (AR10-AR15)

(607) AR10 to AR15 resemble combinations of AR1 as described above (deletion of "no more than" in claim 1) with AR4 to AR9, respectively, as described above. No further amendments were made.

For ease of reference, the content of AR10 to AR15 is summarized in the following table.

AR	Corresponds to combination of	Amendment based on AR1	Definition of "thromboembolic disorder" based on AR4-AR9
AR10	AR1 + AR4	Deletion of *"no more than"* in claim 1	- ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina (UA), stable angina pectoris, vascular re-occlusions and restenoses after angioplasty or aorto-coronary bypass, peripheral arterial occlusion disorders, pulmonary embolisms, deep vein thromboses, renal thrombosis, transitory ischaemic attacks, stroke, treatment of disseminated intravascular coagulation (DIC), "economy class syndrome", - disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are selected from cerebral ischemic diseases, stroke, systemic embolism and ischemic attacks, or - disorders derived from thromboembolic complications which can arise within patients with microangiopathic hemolytic anaemia, extracorporal circulation, or prosthetic heart valves as well as from the thromboembolic complication venous thromboembolism in tumor patients
AR11	AR1 + AR5	*see above*	- pulmonary embolisms, deep vein thromboses, renal thrombosis, transitory ischaemic attacks, stroke, disseminated intravascular coagulation (DIC), "economy class syndrome", - disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are selected from cerebral ischemic diseases, stroke, systemic embolism and ischemic attacks, or - disorders derived from thromboembolic complications which can arise within patients with microangiopathic hemolytic anaemia, extracorporal circulation, or prosthetic heart valves as well as from the thromboembolic complication venous thromboembolism in tumor patients
AR12	AR1 + AR6	*see above*	- pulmonary embolisms, deep vein thromboses, transitory ischaemic attacks, stroke, or a disorder derived from cardiogenic thromboembolism, wherein the disorder derived from cardiogenic thromboembolism is systemic embolism
AR13	AR1 + AR7	*see above*	- pulmonary embolisms, deep vein thromboses, transitory ischaemic attacks, or disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are stroke and systemic embolism in patients with atrial fibrillation
AR14	AR1 + AR8	*see above*	- pulmonary embolisms, deep vein thromboses or stroke
AR15	AR1 + AR9	*see above*	- pulmonary embolisms, deep vein thromboses, or a disorder derived from cardiogenic thromboembolism, wherein the disorder derived from cardiogenic thromboembolism is stroke in patients with atrial fibrillation

(608) Since AR10 to AR15 are mere combinations of AR1 with AR4 to AR9 presented above, they comply with the requirements of Art. 123(2) and (3) EPC for the same reasons as stated for AR1 and AR4 to AR9 above.

(609) AR10 to AR15 are filed in case the Opposition Division unexpectedly comes to the conclusion that granted claim 1 would not be enabled or inventive across its entire scope and considers the feature *"no more than once daily"* in granted claim 1 to include *"less than once daily"* administration.

H.11 Auxiliary Requests 16 to 21 (AR16-AR21)

(610) AR16 to AR21 resemble combinations of AR2 as described above (addition of *"in a dose of 5 to 30 mg"* in claim 1) with AR4 to AR9, respectively, as described above. No further amendments were made.

For ease of reference, the content of AR16 to AR21 is summarized in the following table.

AR	Corresponds to combination of	Amendment based on AR2	Definition of "thromboembolic disorder" based on AR4-AR9
AR16	AR2 + AR4	Addition of *"in a dose of 5 to 30 mg"* in claim 1	- ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina (UA), stable angina pectoris, vascular re-occlusions and restenoses after angioplasty or aorto-coronary bypass, peripheral arterial occlusion disorders, pulmonary embolisms, deep vein thromboses, renal thrombosis, transitory ischaemic attacks, stroke, treatment of disseminated intravascular coagulation (DIC), "economy class syndrome", - disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are selected from cerebral ischemic diseases, stroke, systemic embolism and ischemic attacks, or - disorders derived from thromboembolic complications which can arise within patients with microangiopathic hemolytic anaemia, extracorporal circulation, or prosthetic heart valves as well as from the thromboembolic complication venous thromboembolism in tumor patients

AR17	AR2 + AR5	*see above*	- pulmonary embolisms, deep vein thromboses, renal thrombosis, transitory ischaemic attacks, stroke, disseminated intravascular coagulation (DIC), "economy class syndrome", - disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are selected from cerebral ischemic diseases, stroke, systemic embolism and ischemic attacks, or - disorders derived from thromboembolic complications which can arise within patients with microangiopathic hemolytic anaemia, extracorporal circulation, or prosthetic heart valves as well as from the thromboembolic complication venous thromboembolism in tumor patients
AR18	AR2 + AR6	*see above*	- pulmonary embolisms, deep vein thromboses, transitory ischaemic attacks, stroke, or a disorder derived from cardiogenic thromboembolism, wherein the disorder derived from cardiogenic thromboembolism is systemic embolism
AR19	AR2 + AR7	*see above*	- pulmonary embolisms, deep vein thromboses, transitory ischaemic attacks, or disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are stroke and systemic embolism in patients with atrial fibrillation
AR20	AR2 + AR8	*see above*	- pulmonary embolisms, deep vein thromboses or stroke
AR21	AR2 + AR9	*see above*	- pulmonary embolisms, deep vein thromboses, or a disorder derived from cardiogenic thromboembolism, wherein the disorder derived from cardiogenic thromboembolism is stroke in patients with atrial fibrillation

(611) Since AR16 to AR21 are mere combinations of AR2 with AR4 to AR9 presented above, they comply with the requirements of Art. 123(2) and (3) EPC for the same reasons as stated for AR2 and AR4 to AR9 above.

(612) AR16 to AR21 are filed in case the Opposition Division unexpectedly comes to the conclusion that granted claim 1 would not be enabled or inventive across its entire scope.

H.12 Auxiliary Requests 22 to 27 (AR22-AR27)

(613) AR22 to AR27 resemble combinations of AR1 and AR2 as described above (deletion of "no more than and addition of *"in a dose of 5 to 30 mg"* in claim 1) with AR4 to AR9, respectively, as described above. No further amendments were made.

For ease of reference, the content of AR22 to AR27 is summarized in the following table.

AR	Corresponds to combination of	Amendment based on AR1 and AR2	Definition of "thromboembolic disorder" based on AR4-AR9
AR22	AR1 + AR2 + AR4	Deletion of *"no more than"* in claim 1 and addition of *"in a dose of 5 to 30 mg"* in claim 1	- ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina (UA), stable angina pectoris, vascular re-occlusions and restenoses after angioplasty or aorto-coronary bypass, peripheral arterial occlusion disorders, pulmonary embolisms, deep vein thromboses, renal thrombosis, transitory ischaemic attacks, stroke, treatment of disseminated intravascular coagulation (DIC), "economy class syndrome", - disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are selected from cerebral ischemic diseases, stroke, systemic embolism and ischemic attacks, or - disorders derived from thromboembolic complications which can arise within patients with microangiopathic hemolytic anaemia, extracorporal circulation, or prosthetic heart valves as well as from the thromboembolic complication venous thromboembolism in tumor patients
AR23	AR1 + AR2 + AR5	*see above*	- pulmonary embolisms, deep vein thromboses, renal thrombosis, transitory ischaemic attacks, stroke, disseminated intravascular coagulation (DIC), "economy class syndrome", - disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are selected from cerebral ischemic diseases, stroke, systemic embolism and ischemic attacks, or - disorders derived from thromboembolic complications which can arise within patients with microangiopathic hemolytic anaemia, extracorporal circulation, or prosthetic heart valves as well as from the thromboembolic complication venous thromboembolism in tumor patients
AR24	AR1 + AR2 + AR6	*see above*	- pulmonary embolisms, deep vein thromboses, transitory ischaemic attacks, stroke, or a disorder derived from cardiogenic thromboembolism, wherein the disorder derived from cardiogenic thromboembolism is systemic embolism
AR25	AR1 + AR2 + AR7	*see above*	- pulmonary embolisms, deep vein thromboses, transitory ischaemic attacks, or disorders derived from cardiogenic thromboembolism, wherein the disorders derived from cardiogenic thromboembolism are stroke and systemic embolism in patients with atrial fibrillation
AR26	AR1 + AR2 + AR8	*see above*	- pulmonary embolisms, deep vein thromboses or stroke

AR27	AR1 + AR2 + AR9	*see above*	- pulmonary embolisms, deep vein thromboses, or a disorder derived from cardiogenic thromboembolism, wherein the disorder derived from cardiogenic thromboembolism is stroke in patients with atrial fibrillation

(614) Since AR22 to AR27 are mere combinations of AR1 and AR2 with AR4 to AR9, respectively, presented above, they comply with the requirements of Art. 123(2) and (3) EPC for the same reasons as stated for AR1, AR2 and AR4 to AR9 above.

(615) AR22 to AR27 are filed in case the Opposition Division unexpectedly comes to the conclusion that granted claim 1 would not be enabled or inventive across its entire scope and considers the feature *"no more than once daily"* in granted claim 1 to include *"less than once daily"* administration.

I CONCLUDING REMARKS

(616) As shown above, the subject matter of the Opposed Patent fulfills the requirements of the European Patent Convention.

(617) Patentee's request to reject the opposition and to maintain the patent as granted is therefore justified.

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Enclosure
Auxiliary Requests 1 to 27 (marked-up and clean copy versions)
Annex A – Cross-reference table with consolidated list of opponents' documents **D1-D45**
Annex B – Complete list of documents **D1-D87** on file
Annex C – Feature Analysis of granted claims 1 and 2
New documents **D1a**, **D9a-D9e**, **D25a** and **D46-D87** submitted by Patentee