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Datasheet for the decision of 10 October 2019

Case Number: T 1842/15 - 3.3.04

Application Number: 09777111.7

Publication Number: 2310043

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Language of the proceedings: EN

Title of invention:
Von Willebrand Factor or Factor VIII and von Willebrand Factor for the treatment of coagulopathy induced by inhibitors of thrombocytes

Patent Proprietor:
CSL Behring GmbH

Opponent:
Baxter International, Inc.

Headword:
FVIII/vWF for the treatment of a bleeding event/CSL BEHRING

Relevant legal provisions:
EPC Art. 54(2), 56, 83, 123(2), 123(3)
RPBA Art. 13

Keyword:
Main request, auxiliary requests 1 to 11 - sufficiency of disclosure (no)
auxiliary request 12 - novelty (yes), sufficiency of disclosure (no)
auxiliary request 12A - inventive step (yes)

Decisions cited:

Catchword:

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Beschwerdekammern

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Case Number: T 1842/15 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 October 2019

Appellant: (Patent Proprietor)	CSL Behring GmbH Emil-von-Behring-Strasse 76 35041 Marburg (DE)
Representative:	Pohlman, Sandra M. df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Respondent: (Opponent)	Baxter International, Inc. One Baxter Parkway, DF3-3E Deerfield Illinois 60015 (US)
Representative:	Alt, Michael Bird & Bird LLP Maximiliansplatz 22 80333 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 20 July 2015 revoking European patent No. 2310043 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chair	P. de Heij
Members:	R. Morawetz
	B. Rutz

Summary of Facts and Submissions

I. The appeal by the patent proprietor (appellant) lies from the opposition division's decision revoking European patent No. 2 310 043. The patent is entitled "*Von Willebrand Factor or Factor VIII and von Willebrand Factor for the treatment of coagulopathy induced by inhibitors of thrombocytes*".

II. Claims 1, 2 and 10 as granted read as follows:

"1. A composition consisting of von-Willebrand-factor (vWF) or FVIII/vWF for use in the treatment and/or prevention of a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes, wherein the substance inhibiting thrombocytes is an inhibitor of the ADP receptor or a combination of a cyclooxygenase inhibitor and an inhibitor of ADP.

2. Use of a composition consisting of von-Willebrand-factor (vWF) or FVIII/vWF for the manufacture of a medicament for the treatment and/or prevention of a disorder related to a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes comprising administering a pharmaceutically effective amount of a von-Willebrand-factor (vWF) to a patient in need thereof wherein the substance inhibiting thrombocytes is an inhibitor of the ADP receptor or a combination of a cyclooxigenase inhibitor and an inhibitor of ADP.

10. A composition consisting of vWF and a composition consisting of FVIII for simultaneous, separate or sequential use for use in the treatment and/or

prevention of a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes, wherein the substance inhibiting thrombocytes is an inhibitor of the ADP receptor or a combination of a cyclooxigenase inhibitor and an inhibitor of ADP."

III. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Article 100(b) and 100(c) EPC. The opposition division decided that claims 1, 2 and 10 of the main request (claims as granted) failed the requirements of Article 123(2) EPC; that claims 1, 2 and 10 of auxiliary request 3 failed the requirements of Article 123(3) EPC; that claims 1, 2 and 9 of auxiliary request 6 failed the requirements of Article 123(3) EPC; that the set of claims of auxiliary requests 1, 2, 4, 5, 7 to 17 failed to meet the requirements of Article 83 EPC; that the subject-matter of claims 1, 2 and 10 of auxiliary request 18 failed to meet the requirements of Article 54 EPC; while auxiliary request 19 and the requests filed with the letter dated 22 May 2015 were not admitted into the opposition proceedings.

IV. With the statement of grounds of appeal, the appellant filed sets of claims of a main request and auxiliary requests 1 to 3 corresponding to auxiliary request 3, the main request, and auxiliary requests 6 and 9, in that order, considered by the opposition division. Auxiliary requests 4 to 24 equally filed with the statement of grounds were newly filed claim requests.

Claims 1, 2 and 10 of the **main request** read as follows:

"1. A composition consisting of von-Willebrand-factor (vWF) or FVIII/vWF for use in the treatment and/or prevention of a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes, wherein the substance inhibiting thrombocytes is an inhibitor of the ADP receptor or a combination of a cyclooxigenase inhibitor and an inhibitor of the ADP receptor.

2. Use of a composition consisting of von-Willebrand-factor (vWF) or FVIII/vWF for the manufacture of a medicament for the treatment and/or prevention of a disorder related to a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes comprising administering a pharmaceutically effective amount of a von-Willebrand-factor (vWF) to a patient in need thereof wherein the substance inhibiting thrombocytes is an inhibitor of the ADP receptor or a combination of a cyclooxigenase inhibitor and an inhibitor of the ADP receptor.

10. A composition consisting of vWF and a composition consisting of FVIII for simultaneous, separate or sequential use for use in the treatment and/or prevention of a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes, wherein the substance inhibiting thrombocytes is an inhibitor of the ADP receptor or a combination of a cyclooxigenase inhibitor and an inhibitor of the ADP receptor."

Claim 1 of **auxiliary requests 1 to 11** relates to a composition consisting of von-Willebrand-factor (vWF) alone or of FVIII/vWF for use in the treatment and/or

prevention of a bleeding event.

Claims 1, 2 and 10 of **auxiliary request 12** read as follows:

"1. A composition consisting of a factor VIII/von-Willebrand-factor (FVIII/vWF) combination for use in the treatment of a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes, wherein the substance inhibiting thrombocytes is an inhibitor of the ADP receptor or a combination of a cyclooxigenase inhibitor and an inhibitor of the ADP receptor.

2. Use of a composition consisting of FVIII/vWF for the manufacture of a medicament for the treatment of a disorder related to a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes comprising administering a pharmaceutically effective amount of a von-Willebrand-factor (vWF) to a patient in need thereof wherein the substance inhibiting thrombocytes is an inhibitor of the ADP receptor or a combination of a cyclooxigenase inhibitor and an inhibitor of the ADP receptor.

10. A composition consisting of vWF and a composition consisting of FVIII for simultaneous, separate or sequential use for use in the treatment of a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes, wherein the substance inhibiting thrombocytes is an inhibitor of the ADP receptor or a combination of a cyclooxigenase inhibitor and an inhibitor of the ADP receptor."

V. The opponent is the respondent in these appeal proceedings.

VI. The board scheduled oral proceedings as requested by the parties and issued a communication pursuant to Article 15(1) RPBA in which it indicated, *inter alia*, that it intended to hear the parties also on inventive step.

VII. During the oral proceedings, the appellant filed auxiliary requests 12A and 12B.

Claims 1 and 9 of **auxiliary request 12A** read as follows:

"1. A composition consisting of a factor VIII/von-Willebrand-factor (FVIII/vWF) combination for use in the treatment and/or prevention of a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes, wherein the substance inhibiting thrombocytes is an inhibitor of the ADP receptor or a combination of a cyclooxigenase inhibitor and an inhibitor of the ADP receptor.

9. A composition consisting of vWF and a composition consisting of FVIII for simultaneous, separate or sequential use for use in the treatment and/or prevention of a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes, wherein the substance inhibiting thrombocytes is an inhibitor of the ADP receptor or a combination of a cyclooxigenase inhibitor and an inhibitor of the ADP receptor."

Dependent claims 2 to 8 of auxiliary request 12A further define the composition of claim 1.

VIII. At the end of the oral proceedings, the chair announced the board's decision.

IX. The following documents are referred to in this decision:

D1 Koscielny J. and Alban S., Vascular Care (2008), vol. 14, pages 28 to 43

D2 Koscielny J. et al., Clin Appl Thrombosis/ Hemostasis (2004), vol. 10, pages 155 to 166

D3 Dickneite G. et al., Thromb Haemost (1998), vol. 80, pages 192 to 198

D4 US 2003/0125250

D11 Mannucci P.M. et al., Blood (1986), vol. 67, pages 1148 to 1153

D12 DiMichele D.M. and Hathaway Wm.E., American Journal of Hematology (1990), vol. 33, pages 39 to 45

D13 Metzler H. et al., Der Anaesthesist (2007), vol. 56, pages 401 to 412

D14 Declaration by Dr Metzler H., dated 1 March 2015

D15 M. Barthels and Poliwoda H., in Gerinnungsanalysen (1993), Georg Thieme Verlag, pages 280 to 283

D16 Schulman S. And Bijsterveld N.R., Transfusion Medicine Reviews (2007), vol. 21, pages 37 to 48

D17 Ranucci M. et al., Journal of Cardiothoracic and Vascular Anesthesia (2007), vol 21, pages 851 to 854

D18 Blajchman M.A. et al., J. Clin. Invest. (1979), vol. 63, pages 1026 to 1035

D19 Michelson A.D., CHEST (1995), vol. 108, Supplement, pages 506S to 522S

D20 Declaration by Dr Koscielny J., dated 23 March 2015

D21 Lethagen S. et al., Haemophilia (2000), vol. 6, pages 15 to 20

D22 Colucci G. et al., Blood (2014), vol. 123, pages 1905 to 1916

D24 Declaration by Dr Dickneite G., dated 31 March 2015

X. The appellant's arguments, submitted in writing and during the oral proceedings, a far as relevant to the present decision, are summarised as follows.

Main request
Extension of scope of protection (Article 123(3) EPC) - claims 1, 2 and 10

Claims 1, 2 and 10 as granted covered two alternatives with regard to the condition to be treated. The wording of alternative (i) recited in granted claims 1, 2 and

10 covered bleeding events associated with thrombopathy induced by an inhibitor of the adenosine diphosphate (ADP) receptor and did not exclude that other substances also contributed to the thrombopathy. The second alternative of claims 1, 2 and 10 of the main request, thrombopathy induced by a cyclooxygenase inhibitor and an inhibitor of the ADP receptor, was thus already encompassed by alternative (i) of granted claims 1, 2 and 10.

Main request and auxiliary requests 1 to 11
Sufficiency of disclosure (Article 83 EPC) - claim 1

A composition consisting of only von-Willebrand-factor (vWF) for use in the treatment and/or prevention of a bleeding event

An effect of vWF alone in the treatment of a bleeding event was made plausible by the patent. In the examples, Haemate®, a vWF-containing Factor VIII (FVIII) concentrate, was used. There was no reason to doubt that the effects observed with Haemate® were predictive of the effects of vWF alone because Haemate® contained about 2.5 times more vWF activity than FVIII.

The respondent had failed to provide "*serious doubts, substantiated by verifiable facts*" that vWF alone had no effect.

Paragraph [0002], lines 18 to 20, of the patent stated that the fibrinogen receptor on the thrombocyte surface (GPIIb/IIIa) induced thrombocyte aggregation after the binding of fibrinogen "*or vWF*". The patent thus attributed an effect to vWF alone.

The post-filed data reported in document D24 further

supported the claimed medical use with vWF alone.*A composition consisting of FVIII/vWF for use in the treatment and/or prevention of a bleeding event*

The patent provided data showing that bleeding events induced by administration of an inhibitor of the ADP receptor (in combination with a cyclooxygenase inhibitor) could be treated and also prevented by administration of FVIII/vWF.

It was unrealistic to demand that to establish sufficiency of disclosure it had to be shown that no bleeding at all occurred.

The skilled person would have understood that prevention and also treatment of a bleeding event was shown by a reduction of blood loss in an animal receiving FVIII/vWF in comparison to an untreated control animal. The increase in bleeding due to clopidogrel was prevented.

Auxiliary request 12
Novelty (Article 54(2) EPC)

Document D4

The medical use disclosed in document D4 differed from the claimed medical use. Document D4 was silent on a thrombopathy induced by an inhibitor of the ADP receptor (and a cyclooxygenase inhibitor), and no effect was shown regarding such a thrombopathy. The generic disclosure of platelet dysfunctions in document D4 did not anticipate the claimed specific thrombopathy induced by ADP receptor inhibitors.

The examples of document D4 did not establish that

bleeding induced by an inhibitor of the ADP receptor (and a cyclooxygenase inhibitor) could be treated or prevented by FVIII/vWF. Hence, the effect disclosed in the patent led to a new clinical situation vis-à-vis document D4, and it also identified a new subgroup of subjects being treated in line with decisions T 836/01 and T 1642/06.

Documents D1 and D13

Established case law required the disclosure of the therapeutic effect of the substance to anticipate a medical use claim.

Document D1 (see Figure 3) and document D13 (page 409, lines 8 to 11) provided speculative statements relating to the administration of FVIII/vWF upon bleeding events induced by aspirin and clopidogrel and suggested using FVIII/vWF in combination with cortisone. No explanation, let alone any data, supporting a therapeutic effect for the administration of FVIII/vWF (with cortisone) was provided.

Sufficiency of disclosure (Article 83 EPC) - claims 2 and 10

No further arguments were submitted for claim 2.

According to claim 10, vWF and FVIII could be administered separately or sequentially as long as the administration resulted in an effective treatment.

Auxiliary request 12A

Admission

The request should be admitted because the prevention aspect of the independent claims was sufficiently disclosed.

Inventive step (Article 56 EPC)

Closest prior art

Document D17 dealt with the same clinical situation as claim 1 but was not a realistic starting point because it was a report relating to a single patient and because it was primarily concerned with platelet mapping.

Document D1 dealt with the same medical use as claimed and was a more suitable starting point.

Technical problem

The claimed subject-matter differed from the disclosure of document D1 and document D17 in that it established FVIII/vWF as an effective treatment/prevention for bleeding events induced by an inhibitor of the ADP receptor, optionally in combination with a cyclooxygenase inhibitor.

Hence, regardless which document was taken to represent the closest prior art, the technical problem could be formulated as the provision of an effective treatment/ prevention for drug-induced bleeding events in this patient group.

Obviousness

Document D17 read in the light of the skilled person's common general knowledge

Document D17 did not suggest that FVIII/vWF could be used in the treatment/prevention of bleeding events induced by aspirin and clopidogrel. Let alone would there have been any reasonable expectation of success because document D17 had to be read in light of the common general knowledge of the skilled person at the effective date of the patent. At that date, the mechanism of action of desmopressin was not fully understood and could not be solely linked to vWF.

Common general knowledge

The teaching of documents D1 and D13 belonged to the common general knowledge. Pursuant to these documents, the administration of FVIII/vWF was only a theoretical option, and cortisone had to be given together with FVIII/vWF. Cortisone was known to have an effect on the bleeding time, see title of document D18.

At the effective date of the patent, it was known that desmopressin raised the level of vWF but also that the effect of desmopressin on the reduction of bleeding could not be clearly linked to its effect on vWF; see document D11, page 1152, right-hand column, last paragraph; document D12, page 41, right-hand column, end of fourth paragraph, abstract, page 42, right-hand column, page 44, right-hand column, second paragraph; document D21 page 19, right column, second paragraph.

Document D22 provided an independent expert opinion of how the skilled person would have understood the prior art documents, see page 1905, right-hand column.

Established case law supported that document D22 could be relied on as evidence.

Of the documents relied on by the respondent, documents D3, D4, D16 and D19 were not concerned with bleeding events induced by an inhibitor of the ADP receptor.

Document D3 related to the use of FVIII/vWF in a different clinical situation and disclosed that Haemate® had no effect on platelet aggregation in aspirin/hirudin treated pigs, see page 196, right-hand column, first paragraph, and page 198, left-hand column, first paragraph; Figure 5. Document D16 related to the same clinical situation as document D3 and cited this document.

Document D4 related to platelet dysfunctions due to genetic defects and the examples related to thrombocytopenia, a situation where platelet numbers were low but not where the ADP receptor was blocked. Paragraph [0014] was not relevant to clopidogrel induced thrombopathy.

Document D19 related to antiplatelet agents other than inhibitors of the ADP receptor and merely provided a speculative statement on page 510S, left-column, second full paragraph.

Document D2 disclosed that patients suffering from drug-induced impaired hemostasis should not be treated with vWF or FVIII/vWF, see page 157, right-hand column.

Document D17 in combination with the teaching of

document D3

The skilled person would not have combined the teaching provided in document D17 with the teaching in document D3. Even if the skilled person would have consulted document D3, this document would not have provided them with a reasonable expectation of success because document D3 reported that there was no difference in platelet aggregation upon administration of Haemate®.

Document D1 in combination with the teaching of document D17 or document D4

Document D1 required cortisone as part of the proposed treatment with FVIII/vWF. Cortisone was known to have an effect on the bleeding time, see title of document D18, and the skilled person would have had no reason to leave it out. The combination with the teaching of document D17 would have provided no reasonable expectation of success because the mechanism of action of desmopressin was uncertain.

Document D4 related to a different clinical situation, was silent on the blocking of ADP receptors and could not be combined with document D1. Paragraph [0014] did not relate to patients with a block in aggregation due to inhibitors of ADP-receptors and provided no suggestion that blocked platelet aggregation could be solved with Haemate®. The skilled person would have been aware from document D3 that Haemate® had shown no effect on platelet aggregation.

XI. The arguments of the respondent, submitted in writing and during the oral proceedings, as far as relevant to

the present decision, are summarised as follows.

Main request

Extension of scope of protection (Article 123(3) EPC) - claim 1

Alternative i) of granted claim 1 could not be construed to provide a non-exhaustive list of inhibitors, i.e. to encompass a combination of an inhibitor of the ADP receptor with one or more arbitrary inhibitors of thrombocytes.

ADP receptor inhibitors were not to be considered a subgroup of ADP inhibitors.

Main request
Sufficiency of disclosure (Articles 100(b) and 83 EPC) - claim 1

A composition consisting of vWF alone for use in the treatment and/or prevention of a bleeding event

The use of vWF alone was not plausibly disclosed by the patent. The examples only investigated the effect of a combination of FVIII and vWF. No experimental data that indicated that the administration of vWF alone enabled the treatment of a bleeding event were provided. Haemate® contained a substantial amount of FVIII which could be the active ingredient. The patent did not disclose how Haemate® acted, and there was no common general knowledge with respect to its mechanism.

The same level of skill had to be used in the assessment of inventive step and sufficiency of disclosure. If there were uncertainties in the prior

art about how desmopressin worked in clopidogrel-treated patients, these uncertainties also existed when sufficiency of disclosure was at issue.
Paragraph [0002] of the patent contained the same information as document D17.

A composition consisting of FVIII/vWF for use in the treatment of a bleeding event

The treatment of a bleeding event required the occurrence of a bleeding event and afterwards the addition of an active ingredient to effectively treat the bleeding event.

None of the examples in the opposed patent provided an experimental set-up that would be consistent with the treatment of a bleeding event in a real-life clinical situation. In the examples, Haemate® was administered first, and blood loss was measured afterwards.

A composition consisting of FVIII/vWF for use in the prevention of a bleeding event

None of the examples of the patent qualified as an example of prevention. The mere fact that Haemate® was given before the occurrence of a bleeding event did not mean prevention since the act of preventing by definition meant effectual hindrance. Only reduction of bleeding had been shown.

Auxiliary requests 1 to 11

Auxiliary requests 4 to 11 should not be admitted into the appeal proceedings because they were not converging and contained different permutations of amendments.

The same objections with regard to sufficiency of disclosure regarding claim 1 of the main request applied to auxiliary request 1 to 11.

Auxiliary request 12
Novelty (Article 54 EPC)

Document D4

Document D4 did not explicitly mention that the platelet dysfunction was caused by an antiplatelet drug, e.g. an ADP receptor inhibitor. However, drug-induced platelet dysfunction had been well described in the prior art literature, see document D17, page 852, right-hand column, first paragraph under discussion and table 4 of document D2. The patient group as defined in claim 1 was completely included in the patient group of document D4.

Document D4 already disclosed the effective treatment of any kind of thrombopathy and implicitly also the treatment of a thrombopathy caused by a combination of acetylsalicylic acid (ASA)/clopidogrel. Thus, no new patient group and no new technical effect had been established.

Document D1

Document D1 suggested the administration of FVIII/vWF concentrate in case of a bleeding event associated with a thrombopathy induced by aspirin and clopidogrel. The skilled clinician would have understood the question mark in Figure 3 as referring to cortisone only.

Document D13

Document D13 provided a list of commonly used substances with hemostatic effect. One treatment option was the administration of FVIII/vWF concentrates.

Sufficiency of disclosure (Article 83 EPC) - claims 2 and 10

Claim 2, which read "*administering a pharmaceutically effective amount of a von-Willebrand-factor (vWF) to a patient*", related to the treatment with vWF alone.

The absence of a definition of the timing of the administration of vWF and FVIII in claim 10, see "*simultaneous, separate or sequential use*", again resulted in treatment with vWF alone.

Auxiliary request 12A

Admission

The set of claims of this request should not be admitted because the re-addition of the prevention aspect broadened the scope in comparison to the set of claims of auxiliary request 12. The prevention aspect of the claim was not sufficiently disclosed for the reasons given with respect to the main request.

Inventive step (Article 56 EPC)

While various lines of argument as regards lack of inventive step were put forward in the written submissions, during the oral proceedings before the board, only the lines of argument based on document D17 as closest prior art, taken alone or in combination

with the teaching of document D3, and based on document D1 as closest prior art in combination with the teaching of documents D17 or D4 were maintained.

Closest prior art

Document D17 was a suitable starting point because it related to the treatment or prevention of the same clinical condition and summarised the effects underlying the treatment with desmopressin, thus providing a link to FVIII/vWF.

The other suitable starting point was document D1. Document D1 disclosed the use of desmopressin to treat the claimed condition, explained vWF's role in the hemostatic effect of desmopressin, see page 34 and also proposed the use of FVIII/vWF (plus cortisone), see Figure 3.

Technical problem

The difference between document D17 and the claimed invention was that FVIII/vWF was used instead of desmopressin.

The difference between document D1 and the claimed invention was that it was not explicitly disclosed that FVIII/vWF alone should be used.

The objective technical problem could be defined as the provision of an alternative treatment to the use of desmopressin.

Obviousness

Document D17 read in the light of the skilled person's

common general knowledge

Document D17 hinted at the use of FVIII/vWF for the reversal of a drug-induced platelet dysfunction by disclosing the rationale underlying desmopressin's use, see page 853, right-hand column. Starting from document D17, the skilled person, using their common general knowledge, would have arrived at the claimed subject-matter in an obvious manner.

Common general knowledge

It belonged to the common general knowledge that desmopressin led to an increase in plasma vWF and FVIII, see document D1, page 34, right-hand column. There was no indication in document D1 that cortisone had anything to do with bleeding.

Moreover, the mode of action of FVIII/vWF for reversal of a thrombopathy in a patient under dual platelet therapy based on ASA/clopidogrel was well known in the clinical community and the prior art literature at the effective date of the patent, and it belonged to the common general knowledge of the skilled person as evidenced by document D19, see page 510S; document D17, page 853, passage bridging left and right column; document D16, see page 44, left-hand column under "*Desmopressin (...) and von Willebrand factor Concentrate*"); document D2, see page 162; document D3, see page 197, right-hand column, first and third paragraph; document D4, see paragraphs [0001],[0019], [0022] and claims 1 and 10; document D15, see page 281.

Documents D11, D12 and D21 relied on by the appellant were old and had lost their relevance, see document D14, and document D22 was post-published.

Document D17 in combination with document D3

Document D3 provided a pointer to the use of FVIII/vWF. It explained the mechanistic principles and hemostatic effect of vWF and concluded that vWF could be used for the prevention of a bleeding event caused by platelet dysfunction induced by antithrombotic agents. Importantly, document D3 would have taught the skilled person that the anti-bleeding effect of desmopressin was in fact mediated by vWF, see page 192, right-hand column; page 197, right-hand column.

Document D1 in combination with the teaching of document D17 or document D4

Document D1 disclosed that desmopressin led to an increase of vWF.

Document D17 taught the mechanistic action of desmopressin and concluded that the rationale for using desmopressin was that GPIIb-IIIa-dependent platelet aggregation was mediated by the cross-binding of fibrinogen or vWF to the receptor.

Also, document D4 had acknowledged the technical rationale of using vWF and/or FVIII to enhance platelet adhesion and aggregation for all kinds of platelet dysfunctions, see paragraph [0014].

Therefore, starting from desmopressin or FVIII/vWF plus cortisone in document D1, it would have been obvious to use FVIII/vWF alone (without cortisone) in view of the teaching of document D17 or document D4.

XII. The appellant requested, as far as relevant to the present decision, that:
- the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the set of claims of the main request or, alternatively, that the opposition be rejected and that the patent be maintained as granted (auxiliary request 1) or, further alternatively, that the patent be maintained on the basis of one of the sets of claims of auxiliary requests 2 to 12, 12A, 12B or 13 to 24, in their numerical order, of which auxiliary requests 12A and 12B were filed during the oral proceedings
- documents D32, D33 and D37 be not admitted into the proceedings
- documents D34 and D35 be admitted into the proceedings
- the attack on inventive step starting from document D17 be held inadmissible.

XIII. The respondent requested that:
- the appeal of the patent proprietor be dismissed
- auxiliary requests 4 to 11, 12A and 13 to 24 not be admitted into the appeal proceedings
- documents D32, D33 and D37 be admitted into the proceedings
- an inventive-step attack starting from document D17 be admitted into the proceedings.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

Main request

Extension of scope of protection (Article 123(3) EPC) - claims 1, 2 and 10

2. The set of claims of the main request is identical to the set of claims of auxiliary request 3 underlying the decision under appeal. The opposition division held that claims 1, 2 and 10 of that request did not comply with the requirements of Article 123(3) EPC (see decision under appeal, point 16.3). This finding is disputed by the appellant.

3. Claims 1, 2 and 10 as granted are directed to the treatment and/or prevention of a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes, in which the substance inhibiting thrombocytes is (i) an inhibitor of the adenosine diphosphate (ADP) receptor or (ii) a combination of a cyclooxygenase inhibitor and an inhibitor of ADP (emphasis added, see section II).

4. Claims 1, 2 and 10 alternative (ii) of the main request have been amended vis-à-vis claims 1, 2 and 10 alternative (ii) as granted to read "*a combination of a cyclooxigenase inhibitor and an inhibitor of the ADP receptor*" (emphasis added, see section IV).

5. In the board's judgement, the relevant part of granted claims 1, 2 and 10 would have been understood by the skilled person to read "a bleeding event associated with a thrombopathy induced by an inhibitor of the ADP receptor". The wording of alternative (i) in the context of claims 1, 2 and 10 as granted (see point 3 above) does not exclude that other substances besides the inhibitor of the ADP receptor also contribute to

the thrombopathy. Therefore, any prevention of a bleeding event associated with a thrombopathy induced by an inhibitor of the ADP receptor, whether it is used alone or in combination, e.g. with a cyclooxygenase inhibitor, falls within the protection conferred by claims 1, 2 and 10 alternative (i) as granted.

6. The protection conferred by the second alternative of claims 1, 2 and 10 of the main request, i.e. the treatment and/or prevention of a bleeding event associated with a thrombopathy induced by a cyclooxygenase inhibitor and an inhibitor of the ADP receptor, is thus encompassed within the protection provided by alternative (i) of granted claims 1, 2 and 10.

7. Since the board's finding is not based on the assumption that granted claim 1 provides a non-exhaustive list of inhibitors or that ADP receptor inhibitors are to be considered a subgroup of ADP inhibitors, the respondent's lines of argument (see section XI) fail.

8. The board concludes that amended claims 1, 2, and 10 of the main request do not extend the scope of protection conferred by the claims vis-à-vis the protection conferred by the claims of the granted patent.
The main request complies with the requirements of Article 123(3) EPC.

Sufficiency of disclosure (Article 83 EPC)

9. Claim 1 is drafted as a medical use claim in accordance with Article 54(5) EPC and relates to a composition consisting of von-Willebrand-factor (vWF) alone or in combination with Factor VIII (FVIII) for use in the

treatment and/or prevention of a bleeding event.

10. In interpreting Article 83 EPC, it has been established in the jurisprudence of the boards of appeal that the claimed invention must be sufficiently disclosed at the effective date based on the application as a whole taking into account the common general knowledge of the skilled person. It is also established jurisprudence that where, as in this case, a therapeutic application is claimed in accordance with Article 54(5) EPC, attaining the claimed therapeutic effect is a functional technical feature of the claim. As a consequence, under Article 83 EPC, unless this would already have been known to the skilled person at the effective date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application. Post-published data may be taken into account, but only to backup findings in the application (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, sections II.C.1 and II.C.7.2).

A composition consisting of vWF alone for use in the treatment and/or prevention of a bleeding event

11. The opposition division held that the use of a composition consisting of vWF alone in the treatment and/or prevention of a bleeding event was not sufficiently disclosed (see decision under appeal, points 18.4.2 and 18.4.4). The appellant disputes these findings.

12. The board notes that in Example 1 of the patent, the effect of Haemate® P in rats treated with the ADP-receptor inhibitor clopidogrel was studied. Platelet inhibition was induced by the administration of

clopidogrel on day 0 and day 1. On day 2, the rats received platelets and Haemate® P either separately or in combination. The tail tip was cut 15 minutes later, and the blood loss was determined by monitoring bleeding over a period of 30 minutes. It was found that monotherapy with 200 U/kg Haemate® P resulted in a significant decrease in blood loss compared to in rats treated with clopidogrel/isotonic saline. Example 2 reports data obtained in pigs after administration of clopidogrel over a period of three days, followed by administration of aspirin on the third day and treatment with Haemate® P 15 minutes later. Blood loss was determined after spleen wounding and was reduced after treatment with Haemate® P.

13. It is evident from the preceding point that the patent provides data showing an effect on blood loss for Haemate® P, a product which comprises both vWF and FVIII. However, the use of vWF alone has not been exemplified in the patent, and no data are reported for such a use.

14. The patent provides no explanation as regards the mechanism underlying the effect seen with Haemate® P in Examples 1 and 2. In the board's judgement, since Haemate® P contains also a substantial amount of FVIII, no conclusion with respect to vWF's effect can be drawn from the fact that the content of vWF in Haemate® P is about 2.5 times higher than the content of FVIII. The board is thus not persuaded by the appellant's argument that an effect of vWF alone in the treatment of a bleeding event is made plausible by the effect seen in the examples with Haemate® P.

15. Moreover, in the board's judgement, the statement in the patent that "[t]*he fibrinogen receptor on the*

thrombocyte surface, Glycoprotein IIb/IIIa (GP IIb/ IIIa), induces the aggregation of thrombocytes after the binding of its agonist fibrinogen (or vWF)" (see paragraph [0002], lines 18 to 20) provides no explanation why vWF would have been expected to counteract the inhibition of platelet aggregation caused by a pharmacologic blockade of the ADP-dependent receptors. In the light of the skilled person's common general knowledge (see point 38 below), this statement would not have been sufficient to disclose to the skilled person that vWF was indeed suitable for the claimed treatment.

16. As regards the available common general knowledge (see also point 10 above), it was undisputed between the parties that the teaching of documents D1 and D13 would have belonged to the common general knowledge of the skilled person at the effective date of the patent. According to these documents, desmopressin (deamino-D-arginine vasopressin (DDAVP)) is the first treatment option for the management of perioperative bleeding events in patients undergoing emergency operations while receiving antithrombotic agents such as clopidogrel and ASA (see document D1, page 34, right-hand column, first and second paragraph and document D13, page 409, lines 3 to 7). Document D1 furthermore states that desmopressin leads to an increased mobilisation of vWF from the endothelium and to an increase in thrombocyte adhesion and aggregation (*ibid.*).

17. However, the parties disagreed on whether or not it was commonly known before the effective date of the patent that desmopressin's effect on the reduction of bleeding could be attributed directly to vWF or FVIII/vWF. The appellant relied on documents D11, D12, D21 and D22 in

this context, while the respondent relied on documents D2, D3, D4, D15, D16, D17 and D19 and declaration D14.

18. While the parties' submissions with respect to this issue were made primarily in the context of inventive step, the board agrees with the respondent that in line with established jurisprudence the same level of skill has to be applied when, for the same invention, the two questions of sufficient disclosure and inventive step are being considered (see Case Law of the Boards of Appeal, 9th edition 2019, section II.C.4.1).

Common general knowledge

Documents D11, D12, D21 and D22 - relied on by the appellant

19. According to document D21 "*desmopressin is often used for haemostatic treatment in platelet dysfunction, but the effect kinetics of platelet responses and the mechanism of action are poorly known*" (see page 15, left-hand column, first paragraph). While desmopressin is known to increase plasma levels of vWF (see document D11, page 1152, right-hand column, last paragraph), it is also known that the effectiveness of desmopressin is not solely due to an increase in plasma levels of vWF and that "*additional factors must be advocated to explain the hemostatic effectiveness of DDAVP*" (i.e. desmopressin; *ibid.*). Indeed, it had been found that "*there was no correlation between platelet responses and quantitative or qualitative changes of vWF in plasma*" (see document D21, page 15, right-hand column, first paragraph) and also that "*the bleeding time response did not correlate with changes in the levels of von Willebrand factor (vWF) or ristocetin cofactor activity*" (see document D12, page 39,

abstract).

20. Documents D11, D12 and D21 were published in 1986, 1990 and 2000, respectively, thus some time before the effective date of the patent. Hence, the question arises whether the mechanism underlying desmopressin's effect and in particular vWF's or FVIII/vWF's role in this effect was better understood by the effective date of the patent.

21. The board agrees with the appellant that document D22, a scientific article in a peer-reviewed journal, can be relied on as an independent expert opinion to address this question, although it was published five years after the filing date of the patent (see also Case Law of the Boards of Appeal, 9th edition 2019, section I.C.2.8.5).

22. According to the summary provided on page 1905, lines 1 to 3, desmopressin "*is clinically efficacious in patients with mild platelet function disorders but it is not known which mechanisms mediate this effect*". As regards the mechanism underlying hemostasis induced by desmopressin, document D22 states that it "*might be mediated by DDAVP-induced rise of circulating vWF high-molecular-weight multimers, leading to an increased platelet adhesion to the injured vessel wall: however, although this mechanism is biologically plausible, it has not yet been proven. Conversely the documented efficacy of DDAVP in patients with type 3 VWD (lacking VWF in endothelial stores)*[12,13] *and in patients with Bernard-Soulier syndrome (lacking glycoprotein Ib [GPIb], the platelet receptor for VWF)*[14,15] *clearly indicates that additional mechanisms are responsible for the in vivo hemostatic effects of DDAVP as well*." (see page 1905, right-hand column, lines 9 to

14).

Documents D2, D3, D4, D15, D16, D17 and D19 and declaration D14 - relied on by the respondent

23. Document D3 relates to the treatment of skin bleeding induced by recombinant hirudin (rH), a thrombin inhibitor. While the authors "*suggest that the anti-bleeding effect of DDAVP is also mediated by vWF*" (see page 197, right-hand column, first paragraph), they state that "[f]*or a mechanism we propose that vWF causes binding of platelets to the exposed subendothelium via GP Ib/V/IX.*" (see page 197, right-hand column, third paragraph). Importantly, it is shown in document D3 that Haemate, i.e. FVIII/vWF, has no effect on platelet aggregation in aspirin/rH treated pigs (see page 196, right-hand column, first paragraph and Figure 5).

24. Document D16 also discloses (see page 44, left-hand column, last two paragraphs) that desmopressin shortened the bleeding time in rabbits treated with hirudin and observes that "*there was a rise of von Willebrand factor and factor VIII. However, there was no effect at all on bleeding time from an infusion with a pure factor VIII concentrate. Therefore it is plausible that the supernormal levels of von Willebrand factor (...) are responsible for reversing the bleeding.*" (emphasis added, see page 44, left-hand column, last two paragraphs).

25. Document D19 relates to antithrombotic therapy in children and proposes that for the treatment of bleeding due to antiplatelet agents "*transfusions of platelet concentrates and/or the use of products that enhance platelet adhesion (plasma products containing*

high concentrations of von Willebrand factor or D-des amino arginine vasopressin) may be helpful" (emphasis added, page 510S, left-hand column, third paragraph).

26. As explained in the patent, thrombocytes have two functions in relation to the plasmatic coagulation, (i) the adhesion to the subendothelium and (ii) the aggregation among each other (see paragraph [0012] of the patent). Thrombocytes bind primarily to the subendothelial collagen via their GP Ib receptor for vWF. The following aggregation of thrombocytes and a subsequent retraction and contraction of the aggregated platelets induce a haemostatic plug during secondary hemostasis (see paragraph [0005] of the patent). The thrombopathy in claim 1 is induced by substances that inhibit the aggregation of the thrombocytes, not their adhesion.

27. It is evident from points 23 and 24 above that documents D3 and D16 concern bleeding induced by a thrombin inhibitor and thus a clinical condition different from the claimed one. Moreover, while document D16 is silent about why it would be plausible that vWF reverses bleeding, documents D3 and D19 propose as a mechanism for the effect seen with desmopressin that vWF causes adhesion of the platelets. However, any effect of vWF or FVIII/vWF on platelet adhesion is of no relevance to the claimed treatment which concerns a clinical situation in which aggregation is inhibited, not adhesion. Finally and importantly, document D3 explicitly discloses that FVIII/vWF has no effect on platelet aggregation in aspirin/rH treated rats. Aspirin (ASA) is a cyclooxygenase inhibitor and thus falls within the inhibitors used pursuant to claim 1.

28. The board concludes from points 23 to 27 above that it cannot be inferred from the disclosure of documents D3, D16 or D19 that vWF or FVIII/vWF has an effect on the aggregation of platelets in the presence of a pharmacological blockade of the ADP-dependent receptors.

29. As regards the further documents relied on by the respondent, document D2 discloses that "*DDAVP may lead to improvement of hemostasis by increasing the levels of coagulation factor VIII, vWF, and tissue plasminogen activator*" (see page 162, right-hand column, second paragraph) but provides no information on the effect of FVIII or vWF on platelet aggregation in the presence of a pharmacological blockade of the ADP-dependent receptors. Moreover, document D2 teaches that patients suffering from acquired platelet dysfunctions who did not respond to treatment with desmopressin (non-responders) were given aprotinin or tranexamic acid but not FVIII/vWF (see page 157, right-hand column).

30. Document D15 discloses that vWF has several functions including mediating platelet adhesion and platelet aggregation after platelet activation (see page 281, first paragraph) but is silent about the effect of FVIII or vWF on platelet aggregation in the presence of a pharmacological blockade of the ADP-dependent receptors.

31. Document D17 discloses the use of desmopressin in a patient who received clopidogrel and aspirin prior to surgery to prevent bleeding events (see page 851, left-hand column and page 852, left-hand column) and also that the rationale for using desmopressin - which increases the level of plasma vWF - "*relies on the observation that GPIIb-IIIa-dependent platelet*

aggregation is mediated by the cross-binding of fibrinogen or von Willebrand factor to the receptor. Therefore, the direct stimulation of the GPIIb-IIIa receptor may elicit platelet aggregation even in the presence of a pharmacological blockade of the ADP-dependent receptors." (emphasis added, page 853, right-hand column).

32. In the board's judgement, it is evident (see preceding point) that the authors of document D17 are not certain what the mechanism underlying desmopressin's effect is. That vWF directly stimulates the GPIIb-IIIa receptor in the presence of a pharmacological blockade of the ADP-dependent receptors is in any case not shown in document D17.

33. Document D4 relates to the use of FVIII/vWF for treating bleeding disorders caused by (i) thrombocytopenia, a platelet disorder caused by a reduction in the number of circulating platelets and (ii) platelet dysfunctions caused by genetic deficiencies (see paragraphs [0001], [0004] and [0019], [0022] and claims 1 and 10). While document D4 mentions that it is known that "*vWF plays an important role in platelet adhesion and aggregation through functioning as an adhesive molecule between collagen of the wounded blood vessel wall and platelets or between platelets themselves*" (see paragraph [0014]), it is silent about any effect of vWF in the presence of a pharmacological blockade of the ADP-dependent receptors.

34. Finally, the respondent relies on document D14, an expert declaration drawn up after the effective date of the patent, to support their argument that at the effective date of the patent, it was well known that vWF or FVIII/vWF had a central role in hemostasis and

that the documents relied on by the appellant were old (see page 5, fifth paragraph to page 7, first paragraph).

35. The board notes that the author of document D14 (see page 7, first paragraph) does not dispute the disclosure of documents D11 and D12 but submits that they have lost their relevance because of scientific developments in the field as evidenced by documents D16 and D17.

36. However, it has been established in points 24 and 26 above that document D16 relates to a different clinical situation and does not explain why it would be plausible that vWF reverses bleeding while document D17 merely proposes that the direct stimulation of GPIIb-IIIa-dependent receptor "*may elicit platelet aggregation*" but provides no evidence that vWF or FVIII/vWF achieve this in the presence of a pharmacologic blockade of the ADP-dependent receptors (see points 30 and 31 above). The board concludes that the respondent has not established that scientific developments in the field rendered the disclosure of documents D11, D12 or D21 obsolete.

37. In the board's judgement, the documents relied on by the respondent do not support their submission that the mode of action of FVIII/vWF for reversal of a thrombopathy in a patient under dual antiplatelet therapy based on ASA/clopidogrel was well known at the effective date of the patent.

Conclusion with respect to the common general knowledge

38. The board concludes from points 19 to 37 above that while desmopressin was known prior to the effective

date of the patent to induce an increase in plasma levels of vWF and FVIII, it can be inferred from documents D11, D12 and D21 that the effect of desmopressin could not be clearly linked to vWF or FVIII/vWF and that there were uncertainties in the prior art as to the role of vWF and FVIII in desmopressin's effect on bleeding in clopidogrel-treated patients. From document D22, it is apparent that these uncertainties still existed at the effective date of the patent.

39. With respect to the assessment of the disputed findings of the opposition division (see point 11 above), this means in particular that the suitability of vWF alone for use in the treatment and/or prevention of a bleeding event associated with a thrombopathy induced by an inhibitor of the ADP receptor or a combination of a cyclooxygenase inhibitor and an inhibitor of the ADP receptor cannot be inferred to have formed part of the skilled person's common general knowledge at the effective date of the patent.

40. In line with established jurisprudence of the boards of appeal (see point 10 above), the appellant cannot rely on the post-filed data of document D24 to remedy the lack of sufficiency of disclosure.

41. The board, having regard to the facts and arguments presented to it, concludes that the patent does not disclose the suitability of vWF alone to achieve the claimed therapeutic effect so that there is insufficiency of disclosure with respect to this aspect of claim 1.

A composition consisting of FVIII/vWF for use in the treatment and/or prevention of a bleeding event

42. The opposition division further held that while the use of a composition consisting of FVIII/vWF for use in the treatment of a bleeding event was sufficiently disclosed, the use of the same composition for the prevention of a bleeding event was not (see decision under appeal, point 18.4.4). The respondent disputes the first finding and the appellant the latter.

43. Example 1 of the patent has been summarised above (see point 12). It shows that the administration of FVIII/ vWF shortly before bleeding is artificially induced by cutting the rat's tail reduces blood loss. The board does not share the respondent's interpretation that "*prevention*" required "*effectual hindrance*" of any bleeding at all. Effectual hindrance of bleeding in the context of a tail cut - to stay with the experimental set-up - would only be possible if the blood coagulates completely, in other words, if the rat is already dead for some time. In the board's opinion, the skilled person would have expected some bleeding to occur if the tail was cut as long as the test animal was alive. Therefore, the board is satisfied that the observed reduction in blood loss would have reflected for the skilled person the suitability of FVIII/vWF for the claimed prevention of a bleeding event in clopidogrel-treated patients in the sense that it would reduce the severity of the bleeding.

44. As set out in point 12 above, the patent provides evidence that in situations were platelet inhibition is induced by the administration of clopidogrel, Haemate® P is capable of reducing the bleeding if it is administered before the bleeding is induced. In the

board's opinion, no reasons were provided by the respondent why the skilled person would have had any reason to doubt that Haemate® P would not have the same effect - reduction of blood loss - in a situation where a bleeding event occurred first and FVIII/vWF was administered subsequently. Therefore, the board is satisfied that the observed reduction in blood loss would have suggested to the skilled person also the suitability of FVIII/vWF for the claimed treatment of a bleeding event in clopidogrel-treated patients.

45. When asked during the oral proceedings in the context of auxiliary request 12A, the respondent confirmed that no other objections were maintained/raised against the claimed subject-matter.

46. The board, having regard to the facts and arguments presented to it, concludes that the patent discloses the suitability of FVIII/vWF to treat and prevent a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes so that this aspect of claim 1 is sufficiently disclosed.

Auxiliary requests 1 to 11

Sufficiency of disclosure (Article 83 EPC)

47. Claim 1 of auxiliary requests 1 to 11 relates, *inter alia*, to a composition consisting of vWF alone for use in the treatment and/or prevention of a bleeding event. Admittance of the set of claims of auxiliary requests 4 to 11 into the appeal proceedings was contested by the respondent. There is no need to give reasons for the admittance of auxiliary requests 4 to 11 by the board since none of auxiliary requests 1 to 11 can be allowed as they fail the requirements of Article 83 EPC for the

same reasons as indicated above for the main request (vWF alone) (see points 11 to 41). This was not disputed by the appellant.

Auxiliary request 12

Novelty (Article 54(2) EPC) - claim 1

48. In the decision under appeal, the disclosure of document D4 was held to anticipate the subject-matter of all independent claims of auxiliary request 18 while documents D1 and D13 were not considered novelty-destroying (see point 20.5 of the decision).

49. The appellant contested the opposition division's decision as regards their findings with respect to document D4, while the respondent maintained on appeal that the disclosure of each of documents D4, D1 and D13 anticipated the subject-matter of claim 1 of auxiliary request 12.

Document D4

50. Document D4 relates to the use of FVIII/vWF for treating bleeding disorders caused by (i) thrombocytopenia, a platelet disorder caused by a reduction in the number of circulating platelets, and (ii) platelet dysfunction (see paragraphs [0001], [0003], [0008], [0019] and [0022] of document D4). With respect to bleeding disorders caused by platelet dysfunction, paragraph [0004] of document D4 recites the following examples: "*thrombasthenia caused by deficiency of platelet membrane glycoproteins (GP) IIb/ IIIa and Bernard-Soulier's syndrome caused by deficiency of GP Ib*". In the examples of document D4, a hemostatic effect of FVIII (see Example 1) and vWF (see

Example 2) on bleeding in an animal model "*considered to be suitable for the evaluation of bleeding caused by thrombocytopenia*" (see page 3, left-hand column, lines 11 to 13) is shown.

51. The claim under consideration is concerned with the treatment of a specific condition of thrombopathy or platelet dysfunction, namely one that is induced by the administration of an ADP receptor inhibitor such as clopidogrel. This leads to a dysfunction in the aggregation of the thrombocytes, whereas the number of the thrombocytes is normal or marginally changed (see also paragraph [0013] of the patent).

52. It is undisputed that a group of patients having a platelet dysfunction induced by the administration of an ADP receptor inhibitor is not explicitly disclosed in document D4. The respondent's argument that these patients were "*completely included*" in the patient group of document D4, having a bleeding disorder due to platelet dysfunction, fails because the generic disclosure of platelet dysfunctions does not anticipate the present specific subgroup of patients. Since the patient group treated according to claim 1 has a pharmacological blockade of the ADP-dependent receptors, it is also clearly distinguishable from patients having a platelet dysfunction caused by a genetic deficiency of, for example, GPIb or GPIIb/IIIa disclosed in paragraph [0004] of document D4 by its physiological and pathological status.

53. As explained in point 50 above, in document D4 an effect is shown in the context of a thrombocytopenic animal model, i.e. in the context of (low numbers of) normally functioning thrombocytes. In the board's opinion, from the effect seen in this model, the

skilled person would not have concluded that the same effect would necessarily also be obtained in the context of a thrombopathy caused by a pharmacological blockade of the ADP-dependent receptors.

54. The board concludes that, contrary to the respondent's argument, document D4 therefore neither discloses the claimed patient group nor the functional feature of therapeutic effect of the use of FVIII/vWF (or vWF) for the treatment or prevention of a thrombopathy induced by inhibitors of ADP-dependent receptors.

55. Therefore, the disclosure of document D4 does not anticipate the subject-matter of claim 1 of auxiliary request 12 or any other claim of that request.

Documents D1 and D13

56. Document D1, a review article, relates to the management of perioperative bleeding events in patients at high risk for such bleeding events, e.g. patients undergoing emergency operations while receiving antithrombotic agents such as clopidogrel and ASA, and discloses that in the event of bleeding under ASA/ clopidogrel, the first treatment option is desmopressin (DDAVP) (see page 34, right-hand column, first and second paragraph). In the case of persistent perioperative bleeding during an emergency operation, document D1 proposes that antifibrinolytics, rFVIIa or "*vWF-haltiges F-VIII-Konzentrat (mit Kortison) ?)*" [vWF-containing FVIII concentrate (with cortisone) (?)] be given (see Figure 3). Treatment with vWF-containing FVIII concentrate (with cortisone) is not further explained in document D1. Nor does document D1 report on the outcome of the administration of a vWF-containing vWF-containing FVIII concentrate (with

cortisone).

57. Document D13 likewise relates to the management of perioperative bleeding events in patients receiving clopidogrel and ASA and suggests standard therapies such as administration of thrombocytes, desmopressin, or antifibrinolytics for treating clinical relevant bleeding events (see page 409, lines 3 to 7). As a further option which document D13 explicitly states to be purely theoretical, it mentions that FVIII/vWF concentrate and corticoids could be given (see page 409, lines 9 to 11). While document D13 states that reports of the effectiveness of desmopressin and antifibrinolytics exist (page 409, lines 6 to 7), document D13 is silent with respect to the effectiveness of FVIII/vWF.

58. Claim 1 is drafted as a second medical use claim, where novelty is derived from the intended medical use, and attaining the claimed therapeutic effect is a functional technical feature of the claim (see also decision T 1859/08 of 5 June 2012, Reasons, point 7). It is evident from points 56 and 57 that neither document D1 nor document D13 shows an effect of FVIII/vWF in the treatment/prevention of a bleeding event associated with a thrombopathy induced by substances inhibiting thrombocytes. Nor is an explanation provided in these documents why the skilled person would have expected such an effect to occur.

59. The respondent's argument that documents D1 and D13 anticipate the claimed subject-matter rests on the proposition that the coagulatory potential of a vWF-containing FVIII concentrate and the role of vWF and FVIII levels in the context of primary hemostasis to enhance platelet adhesion and to overcome a platelet

dysfunction would have been well within the knowledge of the skilled person before the effective date of the patent. Assuming for the respondent's benefit that the common general knowledge at the publication date of documents D1 and D13 was the same as before the effective date of the patent, this argument nevertheless fails because it has been established (see point 38 above) that the effect of desmopressin could not be clearly linked to vWF or FVIII/vWF. Therefore, in the board's judgement, the skilled person would have had doubts about the suitability of FVIII/vWF for the management of perioperative bleeding events in patients receiving clopidogrel and ASA.

60. The board concludes from the above that neither the disclosure of document D1 nor the disclosure of document D13 when read with the common general knowledge would have anticipated the subject-matter of claim 1 of auxiliary request 12 nor that of any other claim of that request.

61. In summary, the subject-matter of the claims of auxiliary request 12 is not anticipated by the disclosure of document D1, D4 or D13.

Sufficiency of disclosure (Article 83 EPC) - claims 2 and 10

62. Claim 2 requires that a pharmaceutically effective amount of vWF be administered to a patient. The board considers that this claim does not meet the requirements of Article 83 EPC for the same reasons as indicated above for the main request (see points 11 to 41). This was not disputed by the appellant.

63. Claim 10 is directed to a composition consisting of vWF and a composition consisting of FVIII for simultaneous,

separate or sequential use. The board considers that the skilled person would not reasonably have interpreted the claim to encompass extensive time spans between administration of vWF and FVIII when administered separately or sequentially. The respondent's argument that the claim relates to administration of vWF alone is thus not found persuasive. The board concludes that the claim meets the requirements of Article 83 EPC for the same reasons as indicated above for the main request (see points 42 to 46).

Auxiliary request 12A

Admission into the appeal proceedings

64. The set of claims of this request was filed during the oral proceedings before the board. It is based on the set of claims of auxiliary request 12 filed with the statement of grounds of appeal, with claim 2 deleted and independent claims 1 and 9 amended to include "*and/or prevention*" (see also section VII).

65. The respondent objected to the admission of this request into the appeal proceedings.

66. In the board's judgement, the amendments carried out resulted in a clearly allowable claim request since the board had found in the context of the main request that with respect to FVIII/vWF, the prevention aspect was sufficiently disclosed (see points 42 to 46 above).

67. Accordingly, the board, exercising its discretion pursuant to Article 13(1) RPBA, decided to admit this request into the appeal proceedings.

Inventive step (Article 56 EPC)

68. While the decision under appeal does not deal with the ground of opposition of inventive step, the appellant requested that the board also decide on inventive step. During the oral proceedings, the parties were heard on inventive step in the context of the set of claims of the main request and, as the board understands, the respondent maintained the same arguments for the set of claims of auxiliary request 12A.

Admittance of an inventive-step attack based on document D17 as closest prior art (Article 12(4) RPBA)

69. The appellant objected to the admittance of the inventive-step objection starting from document D17 as closest prior art. The board decided not to exercise its discretion to exclude an inventive-step attack based on document D17 as closest prior art. Since the attack was not successful, no reasons need to be given.

Closest prior art

70. The parties disagreed on which document represented the closest prior art for the claimed invention. While the appellant submitted that document D1 was the closest prior art, the respondent held that either document D1 or document D17 represented the closest prior art.

71. The teaching of document D1 has been summarised in point 56 above. It relates to the same clinical condition and patient group as the claimed treatment, namely patients who receive the anticoagulant therapy of aspirin (acetyl salicylic acid, ASA) in combination with clopidogrel. It discloses that the administration of desmopressin is the first treatment option in case

of a clinically relevant bleeding in these patients. Furthermore, it proposes that antifibrinolytics, rFVIIa or FVIII/vWF (with cortisone) could be given. The latter two proposals are followed by a question mark (?).

72. The teaching of document D17 has been summarised in point 31 above. It relates also to the same clinical condition and patient group as the claimed treatment and also discloses the rationale for using desmopressin (see paragraph bridging columns on page 853).

73. Both document D1 and document D17 thus relate to the treatment or prevention of the same clinical condition of acquired platelet dysfunction and share relevant technical features with the claimed invention.

74. Therefore, the board takes the view that the teaching in either document D1 or document D17 might be taken as the starting point for assessing inventive step and, in accordance with established case law, inventive step will be assessed with respect to either document (see Case Law of the Boards of Appeal of the EPO, 9th edition 2019, section I.D.3.1).

Technical problem

75. The subject-matter of claim 1 differs from the teaching of document D17 and document D1 in that a composition consisting of vWF/FVIII is used for the treatment or prevention of a bleeding event associated with a thrombopathy.

76. While the appellant submitted that this difference resulted in an effective treatment, the respondent

considered that it led to an alternative treatment.

77. The board notes that the therapeutic effect is a technical feature of a second medical use claim. Accordingly, the board sees no difference in substance between these two formulations of the problem.

78. The board thus agrees with the respondent that - regardless of whether document D17 or document D1 is taken as the starting point - the technical problem to be solved is the provision of an alternative coagulatory substance that elicits platelet aggregation in the presence of a pharmacologic blockade of the ADP-dependent receptors for preventing or treating a bleeding event.

Obviousness

79. The question which remains to be answered is whether the skilled person, aware of the teaching of the closest prior art document and faced with the technical problem, would have modified the teaching in the closest prior art document to arrive at the claimed invention in an obvious manner.

Document D17 read in the light of the skilled person's common general knowledge

80. While the board accepts the respondent's argument that document D17 would have provided the skilled person looking for an alternative coagulatory substance with a motivation to consider the coagulatory factors vWF and FVIII, the relevant question which needs to be addressed in the board's judgement is whether the skilled person could have reasonably predicted, before the effective date of the patent, that the results

obtained with desmopressin were obtainable by therapy with FVIII/vWF alone, bearing in mind that the claim concerns a composition consisting of FVIII/vWF.

81. It has been established in point 38 above that the effect of desmopressin on the reduction of bleeding could not be attributed directly to an effect of desmopressin on vWF or FVIII/vWF and that other factors were considered responsible for desmopressin's effect on bleeding. The respondent's argument, based on the proposition that the mode of action of FVIII/vWF for reversal of a thrombopathy in a patient under dual platelet therapy based on ASA/clopidogrel was well known in the clinical community, thus fails.

82. Moreover, in the board's view, the skilled person reading document D17 would have been aware that document D1, while mentioning that desmopressin induces, *inter alia*, an increased mobilisation of vWF, proposes to administer FVIII/vWF with cortisone but not FVIII/vWF alone and even places a question mark next to that proposal, just as does document D13, which proposes as a purely theoretically option the use of a combination of FVIII/vWF and cortisone. Contrary to the respondent's submission, cortisone was known to have an effect on bleeding at the effective date of the patent, (see, for instance, the title of document D18), and the skilled person would thus have had no reason to assume that treatment with FVIII/vWF alone would achieve the same effect as treatment with desmopressin.

83. The board thus agrees with the appellant that document D17, when read in the light of the common general knowledge of the skilled person, would not have provided any reasonable expectation that FVIII/vWF

would solve the problem formulated above.

Document D17 in combination with the teaching of document D3

84. In a further line of argument, the respondent relied on a combination of the disclosure of document D17 with the teaching of document D3.

85. The relevant teaching of document D3 has been summarised in point 23 above. It relates to the treatment of bleeding events induced in the presence of the thrombin inhibitor hirudin and thus to a different clinical situation. Even assuming, for the benefit of the respondent's argument, that the skilled person would have considered document D3, they would, in the board's judgement, not have envisaged the claimed treatment because document D3 discloses that Haemate® has no effect on platelet aggregation in aspirin/ hirudin treated pigs (see page 196, right-hand column, first paragraph and page 198, left-hand column, first paragraph; Figure 5). Moreover, document D3 proposes that desmopressin's effect on bleeding is caused by vWF's effect on platelet adhesion, not platelet aggregation (see page 197, right-hand column, first and third paragraph). Therefore, based on the teaching of document D3, the skilled person would in the board's view have had no reason to expect that Haemate® would be effective in the relevant patient group.

86. The board concludes that the claimed invention is not obvious starting from the teaching of document D17 as the closest prior art when read with the common general knowledge of the skilled person or in combination with the teaching of document D3.

Document D1 in combination with the teaching of document D17 or document D4

87. The respondent's line of argument based on document D1 as the starting point hinges on the proposition that document D4 or document D17 would have taught the skilled person that GPIIb-IIIa-dependent platelet aggregation was mediated by the cross-binding of vWF to the receptor.

88. However, the board notes that document D4 is silent with respect to the relevance of this mechanisms for the reversal of a pharmacological blockade of the ADP-dependent receptors, while document D17 merely speculates that direct stimulation of the GPIIb-IIIa receptor *"may elicit platelet aggregation even in the presence of a pharmacological blockade of the ADP-dependent receptors.*" (see page 853, right-hand columns).

89. Considering that the skilled person reading document D4 or document D17 before the effective date of the patent would have moreover been aware that the effect of desmopressin on the reduction of bleeding could not be attributed directly to vWF or vWF/FVIII and that other factors must be responsible for desmopressin's effect on bleeding (see point 38 above), they would, in the board's judgement, not have been prompted by document D4 or document D17 to use FVIII/vWF with a reasonable expectation of success of solving the problem.

90. Therefore, the board concludes that the claimed invention is not obvious starting from the teaching of document D1 as the closest prior art in combination

with the teaching of document D17 or document D4.

91. When asked at the oral proceedings, the respondent stated that they had no further objections against this claim request.

Conclusion

92. Since the patent can be maintained on the basis of the set of claims of auxiliary request 12A, the set of claims of auxiliary requests 12B and 13 to 24 need not be considered by the board. It was also not necessary to consider the admittance of documents D32 to D35 and D37 as these documents turned out not to be relevant for the present decision.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of the set of claims of auxiliary request 12A filed during oral proceedings on 10 October 2019, and a description to be adapted thereto.

The Registrar: The Chair:

A. Nielsen-Hannerup P. de Heij

Decision electronically authenticated