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Title of invention:
SerpinF2-Binding Molecules and Methods of Use

Patent Proprietor:
Translational Sciences Inc.

Opponent:
Bayer Intellectual Property GmbH

Headword:
SerpinF2-Binding Molecules/Translational Sciences

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

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Case Number: T 0219/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 15 February 2024

Respondent: (Patent Proprietor)	Translational Sciences Inc. 1840 Overton Park Avenue Memphis, TN 38122 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Appellant: (Opponent)	Bayer Intellectual Property GmbH Alfred-Nobel-Strasse 10 40789 Monheim (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 22 December 2021 concerning maintenance of the European Patent No. 2753359 in amended form.**

Composition of the Board:

Chair	R. Hauss
Members:	A. Chakravarty
	L. Bühler

Summary of Facts and Submissions

I. In an interlocutory decision, the opposition division decided that European patent No. 2 753 359, entitled "*SerpinF2-Binding Molecules and Methods of Use*", as amended according to auxiliary request 3 met the requirements of the EPC. The patent was filed as an international application under the PCT, which was published as WO 2013/036596 (the "application as filed" or "the application").

II. Both the patent proprietor and the opponent filed appeals against this decision. The patent proprietor subsequently withdrew its appeal but maintained its request that the opponent's appeal be dismissed. The opponent is therefore the appellant and the patent proprietor is the respondent in the appeal proceedings.

III. In the decision under appeal, the opposition division considered a main request and three auxiliary requests. It held that the main request, auxiliary request 1 and auxiliary request 2 were not allowable because they did not meet the requirements of Article 123(2) EPC.

IV. In relation to auxiliary request 3, the opposition division held that document D8 represented the closest prior art for the purpose of assessing inventive step and that the claimed subject-matter would not have been obvious to the skilled person starting from the disclosure in this document, even when considered in the light of the disclosure in, *inter alia*, documents D3, D6 and D26 (for document numbering, see point VI., below).

V. Claim 1 of the respondent's main (and sole) request in the appeal proceedings (identical to auxiliary request 3 held to be allowable by the opposition division) reads as follows:

"1. A SerpinF2-binding antibody that reduces SerpinF2 activity or concentration, for use in a method of preventing or treating brain hemorrhage or brain edema resulting from cerebral ischaemia due to thrombotic ischaemic stroke in a human patient in need thereof".

α2-antiplasmin (α2-AP) is another name for SerpinF2 that is used in the prior art.

VI. The following documents are referred to in this decision.

D3: Nagai N. *et al.*, Blood, 2001, 97(10), 3086-3092.

D6: Nagai N. *et al.*, Journal of Thrombosis and Haemostasis, 2003, 1, 307-313.

D8: Chen F. *et al.*, Radiology, 2007, 244(2), 429-438.

D20: Durukan A. and Tatlisumak T., 2007, Pharmacology, Biochemistry and Behaviour, 87, 179-197.

D25: Pakola S. *et al.*, 2009, Clinical Therapeutics, 31, 1688-706.

D26: Thijs V.N. *et al.*, Stroke, 2009, 40, 3789-3795.

VII. The appellant's submissions relevant to the decision are summarised as follows.

Inventive step (Article 56 EPC) - Claim 1
The starting point in the prior art and the objective technical problem

Document D8, which disclosed an animal study comparing the effects of microplasmin and tissue plasminogen activator (tPA), was a suitable starting point for the assessment of inventive step. Its relevance had been questioned by the respondent because of the rat stroke model used in this study. In the respondent's view and with reference to document D20, the photo-thrombotic model used was not suitable to demonstrate a relevant effect because it lacked a penumbra and only a thromboembolic model as provided in the opposed patent could demonstrate the claimed therapeutic effect.

However, in the decision under appeal the opposition division had held that animal models different from the thromboembolic model were suitable to render the claimed therapeutic benefits credible in the clinic (see point 7.3.1.3, first paragraph). Importantly, the animal model used in document D8 was different from the animal models discussed in document D20 because it clearly had a penumbra and was therefore a relevant animal model for ischaemic stroke and effects on haemorrhage and edema. Based on this, document D8 represented the closest prior art.

Starting from the disclosure in document D8, the objective technical problem formulated in the decision under appeal, 'the provision of an alternative treatment of brain haemorrhage and edema resulting from cerebral ischaemia due to ischaemic thrombotic stroke in a human patient in need thereof', was correct.

Obviousness

The question to be answered was whether the person skilled in the art would have expected an α2-AP-binding antibody to have the desired therapeutic effect defined in claim 1, when considered in the light of the knowledge in the art of the mechanism of action of microplasmin and its interaction with α2-AP.
The basic flaw in the opposition division's reasoning was an erroneous understanding of the teaching of D8.

Specifically, the opposition division had been wrong to state that according to document D8 the improvement of neurologic deficits by microplasmin was due to direct thrombolysis "or" to the neutralisation of α2-AP (see decision under appeal, reasons 7.3.1.3 on page 15). The opposition division had failed to appreciate that document D8 actually taught that direct thrombolysis was due to the neutralisation of α2-AP (see the paragraph bridging pages 436 and 437). With respect to the non-thrombolytic neuroprotective effect, document D8 referred to, *inter alia*, document D6 (reference [14] of D8), which in turn linked also the non-thrombolytic neuroprotective effect to reduction of circulating α2-AP (see D6: page 312).

In the same passage of the decision under appeal, the opposition division had further stated that the "*multiple possible modes of action of microplasmin are also corroborated in D26 that not only looks at α2-antiplasmin but also at protease levels*". However, document D26 disclosed that it was in fact the reduction of α2-AP levels that was responsible for reduced protease levels - "*The strong reduction in α2-AP levels observed in the higher doses tested in this study resulted in a systemic effect of microplasmin as*

demonstrated by the reduced fibrinogen levels, reflecting the nonfibrin-specific lytic activity of microplasmin due to the lack of kringle domains" (see D26, sentence bridging the left and the right hand column on page 3794). Thus the suggestion that the effect of protease was independent from the effect of α2-AP was wrong. Moreover, document D26 (see page 3794, left hand column) confirmed that both the fibrinolytic activity and the neuroprotective effect were due to α2-AP depletion.

It had been clearly established that the reduction of haemorrhage reported in document D8 was due to the reduction of α2-AP levels. The question whether the skilled person would have considered that this reduction could also be achieved by a SerpinF2- (i.e. α2-AP)- binding antibody instead of microplasmin had to be answered in the affirmative.
The skilled person would have envisaged using such an antibody, as disclosed for example in document D3.

The opposition division in its decision had stated that document D3 did not disclose that reduction of α2-AP levels could reduce edema or haemorrhage. However, this was not relevant for obviousness. Rather, the question was whether document D3 suggested that an α2-AP binding antibody could be used as an alternative to microplasmin to reduce α2-AP levels. This was clearly the case. In view of these considerations, the skilled person would have had a reasonable expectation that an antibody capable of neutralising α2-AP would be suitable to solve the problem of the provision of an alternative treatment of brain haemorrhage resulting from cerebral ischaemia due to ischaemic thrombotic stroke in a human patient.

Admittance of "late" submissions

The respondent had made a number of submissions that represented amendments of its appeal case and which should not be admitted under Article 13(2) RPBA. These included the arguments and related allegations of fact, presented for the first time in its letter of 8 December 2023. These were:

i) that document D26 contained clinical data (efficacy data) relating to the treatment or prevention of stroke-induced brain haemorrhage.

ii) that the experiments in document D8 were not representative of "*cerebral ischemia due to thrombotic ischaemic stroke in a human patient*" because the rat photothrombotic model did not adequately simulate human thrombotic stroke.

iii) that the explicit purpose of document D8 was to study the haemorrhagic (side) effect of microplasmin, and not to investigate the potential capability of microplasmin for treating or preventing stroke-induced brain haemorrhage.

iv) that the anti-haemorrhage data in document D8 was not reliable because $\Delta R2^*$ values allegedly were not statistically significant and haemorrhage was allegedly crudely assessed via mere visual inspection.

v) the submission that document D3 related to a structurally and functionally different construct to that mention in document D8 (i.e. miniplasmin), made in support of the argument that the person skilled in the art starting from document D8 would not have turned to document D3.

vi) the submission that document D26 in Table 2 demonstrated failure of the treatment of brain haemorrhage or edema.

vii) the evidence by virtue of quotes in footnotes 8 and 9 of the respondent's letter of 8 December 2023.

The respondent had not provided any justification for the late submission of these newly alleged facts and had not demonstrated that there were any exceptional circumstances, justified with cogent reasons, for their admittance. Hence, the above arguments and related allegations of fact must be disregarded, in line with Article 13(2) RPBA.

Moreover, the new allegations were wrong.

In relation to point v), miniplasmin lacked four of the five kringle domains of plasmin, while microplasmin lacked all five kringle domains. However, both constructs bound to α2-AP and reduced α2-AP levels *in vivo*. Moreover, document D3 also disclosed depletion of α2-AP by plasmin and a Fab fragment neutralizing α2-AP. The focus of D3 was therefore on α2-AP depletion by different constructs and its effect on cerebral ischaemic injury. Hence, the teaching of document D8 and that of document D3 was compatible, as both documents taught that α2-AP inhibition is the mechanism responsible for the observed therapeutic effects.

Moreover, the fact that document D3 did not mention brain haemorrhage was irrelevant, because document D8 already disclosed that microplasmin had a therapeutic effect on brain haemorrhage, and the objective

technical problem was to provide an alternative treatment of brain haemorrhage.

In relation to point vi), document D26 did not disclose the 'failure' of the treatment of brain haemorrhage or edema but specifically referred to the preclinical data, including in document D3, and to transient α2-AP depletion as a mechanism for neuroprotective effects and vascular integrity of microcirculation in the penumbra. Document D26 thus motivated the skilled person to provide an α2-AP-depleting therapy for treating stroke-induced brain haemorrhage.

VIII. The respondent's submissions relevant to the decision are summarised as follows.

Inventive step (Article 56 EPC) - Claim 1
The starting point in the prior art and the objective technical problem

Claim 1 related to the prevention or treatment of brain edema induced by cerebral ischaemia due to thrombotic ischaemic stroke with α2-AP-binding antibodies in a human patient.

Document D26 addressed the same problem, whereas document D8 did not. Indeed, document D8 used a photo-thrombotic model which was not representative of human ischaemic stroke, because it did not contain a penumbra (see document D20, page 182). Thus, a photo-thrombotic model as disclosed in D8 was undesirable for preclinical drug studies where the chief target was penumbra, such as ischaemic stroke. Therefore, document D8 was not a suitable starting point for the assessment of inventive step. In this context, and contrary to what was claimed by the appellant, the opposition

division had not stated that animal models in general were suitable to render claimed therapeutic benefits plausible in the clinic. Paragraph 7.3.1.3 of the decision under appeal referred to comparability of thromboembolic and middle cerebral artery (MCA) ligation occlusion models, irrespective of whether the corresponding tests were carried out with animals or clinically.

Even if document D8 were taken to represent the closest prior art, the claimed invention would not have been obvious to the skilled person. In its appeal, the appellant had argued that the opposition division's understanding of document D8 was wrong, particularly where it made a distinction between thrombolysis and the neutralisation of α2-AP. However, the opposition division's conclusions and its decision on inventive step assessed starting from document D8 were correct.

The objective technical problem starting from document D8 was essentially the same as that formulated in the decision under appeal, except for the reference to an "alternative" treatment in the objective technical problem, because document D8 did not relate to treatment in humans. The problem was therefore the provision of a treatment of brain haemorrhage and edema resulting from cerebral ischaemia due to ischaemic thrombotic stroke in a human patient in need thereof. However, the consideration whether the objective technical problem should contain the word "alternative" was not considered material to the respondent's case.

Obviousness

Document D8 stated that "*the improvement of neurologic deficits in our study may be attributed to both of*

these therapeutic effects of microplasmin" (see page 436, last two lines, to page 437, line 2). In identifying two different therapeutic effects, a clear distinction between thrombolysis and the neutralisation of the α2-AP was made. This became even clearer from page 436, right column, last paragraph, which stated that "*Although the detailed mechanisms are still unknown, the therapeutic effects of microplasmin may be realized on two levels. The first is the partial recanalization of the occluded vessels […]. The second is the nonthrombolytic neuroprotective effect […]*". Here, document D8 again made a clear distinction. From this the skilled person would have understood that the mechanism of action of microplasmin was unknown, at best unclear. This was because document D8 stated that the detailed mechanisms behind the therapeutic effects were still unknown.

At the oral proceedings the respondent explained with reference to document D25 (page 1697), that the skilled person would have understood that microplasmin had proteolytic activity on fibrin which was why it had thrombolytic activity. α2-AP inhibited this activity. α2-AP depletion allowed the thrombolytic activity of microplasmin to be attained. The thrombolytic effect (recanalisation of blood-vessels) was distinct from an anti-haemorrhage effect. Moreover, the non-thrombolytic neuroprotective effect was also distinct from an anti-haemorrhage effect because neuroprotection should be understood differently from reducing haemorrhage.

Furthermore, the skilled person would have doubted the reliability of the anti-haemorrhage result reported in document D8. Document D8 disclosed that rats treated with 10 mg/kg microplasmin exhibited an apparently reduced haemorrhagic rate relative to the placebo

group. However, the skilled person would have considered that result to be potentially anomalous in view of the results provided for the slightly lower dose of 7.5 mg/kg. In particular, given that the 7.5 mg/kg had no statistically significant effect on haemorrhage incidence, the skilled person would have found it strange that a slightly higher dose (10 mg/kg) apparently provided complete inhibition of haemorrhage.

The skilled person would also have found it difficult to reconcile the alleged reduction of haemorrhage incidence with the fact that 10 mg/kg microplasmin dose was seen to have essentially no effect on any parameter associated with blood-brain barrier breakdown and intracerebral haemorrhage.

For these reasons, the skilled person would not have considered the anti-haemorrhage effect in D8 to be reliable. Instead, the skilled person would have considered the result for the 10 mg/kg dose to be an artefact, possibly resulting from testing a particularly small cohort of rats (only 9 rats received 10 mg/kg, whereas there were 13 rats in the 7.5 mg/kg cohort).

The deficiencies in document D8 could not be remedied by the disclosure in document D26 either. The multiple possible modes of action of microplasmin were corroborated in document D26 which not only reported α2-AP levels but also protease levels. The multiple effects of microplasmin on coagulation, the complement system, skin rashes, etc., were not seen with α2-AP-deficiency or inhibition in any reports, indicating that microplasmin acted through different mechanisms. Finally, document D26 showed that microplasmin had caused a fatal brain haemorrhage. It did not prevent

other, non-fatal brain haemorrhages, nor did it improve perfusion or neurological outcome. These findings with human stroke, which was predominantly caused by thromboembolism, indicated that the effects of microplasmin did not predict that α2-AP inhibition or depletion would reduce brain haemorrhage or edema.

Moreover, after reading document D8, the skilled person would have been prompted to look into the possibility of using microplasmin to treat or prevent human stroke-induced brain haemorrhage. In doing so, the skilled person would have identified the microplasmin Phase II clinical trial report, document D26. This document provided data showing that microplasmin did not treat or prevent human stroke-induced brain haemorrhage. The failure disclosed in document D26 was seen despite microplasmin providing a 'strong reduction in α2-AP levels'. The skilled person would have understood from document D26 that even a 'strong reduction in α2-AP levels' would not be an effective treatment or prevention for human stroke-induced brain haemorrhage. Document D26 also provided data showing that microplasmin did not treat or prevent human stroke-induced brain haemorrhage (and may even exacerbate this specific pathological aspect of stroke). Indeed, document D26 reported that: "No dose effect was seen [for microplasmin] on the rate of asymptomatic intracerebral haemorrhage" (see page 3794, left hand column, first paragraph of discussion).

Furthermore, the skilled person would not have turned to document D3 because it did not even refer to microplasmin, but instead tested a larger construct with different functionality, namely miniplasmin.

Even if the skilled person had read document D3, they would still not have reasonably expected a neutralising anti-α2-AP antibody to be useful for treating or preventing stroke-induced brain haemorrhage. The fact that D3 related to miniplasmin and not to microplasmin would have added to the skilled person's uncertainty with respect to extrapolating from the preliminary (and contradictory) microplasmin results in document D8.

Finally, the claimed invention related to treating brain haemorrhage or brain edema resulting from cerebral ischemia due to thrombotic ischaemic stroke and not to reducing the haemorrhagic side effects of tPA. Document D8 was only concerned with this latter effect and therefore did not show or suggest treatment of stroke-induced haemorrhage. Thus, even if the thrombolytic and the non-thrombolytic neuroprotective effects discussed in document D8 were linked to α2-AP depletion, this was unrelated to the anti-haemorrhagic effect mentioned in the claim. There was nothing in document D8 to suggest that the claimed effect was also based on α2-AP depletion.

Requests

IX. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

It also requested the board not to admit, under Article 12 RPBA, the respondent's line of argument to the effect that only document D26, but not document D8 should be considered as the starting point for the assessment of inventive step. Furthermore, it requested the board not to admit, under Article 13(2) RPBA, the related allegations of fact that were presented for the

first time in the respondent's letter of 8 December 2023.

These were that:

- document D26 contained clinical data (efficacy data) relating to the treatment or prevention of stroke-induced brain haemorrhage; whereas

- the experiments in document D8 were not representative of "*cerebral ischemia due to thrombotic ischaemic stroke in a human patient*" because the rat photothrombotic model did not adequately simulate human thrombotic stroke; and

- the explicit purpose of document D8 was to study the haemorrhagic (side) effect of microplasmin, and not to investigate the potential capability of microplasmin for treating or preventing stroke-induced brain haemorrhage.

The further allegations made in the respondent's letter of 8 December 2023, namely

- new allegations of fact in relation to the reliability of the anti-haemorrhage data in document D8;

- new allegations made in support of the argument that the person skilled in the art starting from document D8 would not have turned to document D3;

- the allegation that document D26 in Table 2 demonstrated failure of the treatment of brain haemorrhage or edema;

- the evidence by virtue of quotes in footnotes 8 and 9 of the respondent's letter of 8 December 2023,

should also not be admitted under Article 13(2) RPBA.

Finally, the following submissions made by the respondent for the first time at the oral proceedings before the board should not be admitted under Article 13(2) RPBA.

- the argument that the protease activity of microplasmin was the mechanism involved in direct thrombolysis;

- the objective technical problem as formulated by the opposition division was incorrect;

- D8 did not show an effect of microplasmin in preventing or treating brain haemorrhage or brain edema resulting from cerebral ischaemia due to thrombotic ischaemic stroke;

- the effects in document D8 in relation to brain haemorrhage related to reduced side effects in comparison with those observed with tissue plasminogen activator (tPA).

X. The respondent requested that the appeal be dismissed and the patent be maintained on the basis of the request deemed allowable in the decision under appeal.

Reasons for the Decision

Main request - claim 1

1. The claimed subject-matter is a purpose-limited product as provided for in Article 54(5) EPC. The product is *"a SerpinF2-binding antibody that reduces SerpinF2 activity or concentration"*, where SerpinF2 is an alternative name for α2-antiplasmin (α2-AP). The therapeutic purpose or use is *"preventing or treating brain hemorrhage or brain edema resulting from cerebral ischaemia due to thrombotic ischemic stroke in a human patient in need thereof"*.

Inventive step (Article 56 EPC)

The starting point in the prior art and the objective technical problem

2. The appellant contended that the claimed subject-matter was not inventive starting from the disclosure in document D8 and also that it was not inventive when considered starting from the disclosure in document D26.

3. The respondent argued that inventive step should be assessed starting from document D26 representing the closest prior art. Inventive step should not be assessed starting from document D8 because this document was more remote from the claimed invention than document D26. In its view the claimed subject-matter would not have been obvious to the skilled person starting from the disclosure in document D26.

4. It is however settled case law of the boards of appeal that if a skilled person had a choice of several workable routes, i.e. routes starting from different documents, which might lead to the invention, the rationale of the problem-and-solution approach requires that the invention be assessed relative to all these possible routes, before an inventive step can be acknowledged (see Case Law of the Boards of Appeal, 10th edition, 2020, I.D.3.1). Moreover, it is also established case law that a claimed invention must not be obvious in relation to any piece of prior art. The selection of one document as the so-called "closest prior art", in cases where this is appropriate, merely serves the purpose of avoiding the need to consider a multitude of potential, more distant starting points (*ibid*). Nonetheless, inventive step can, in principle, be assessed starting from any prior-art disclosure. The relative remoteness of a particular document does not prohibit its consideration as a starting point in a full analysis according to the problem-and-solution approach. If the starting point is too remote from the claimed subject-matter in terms of structural features and purpose, the problem-and-solution approach will simply not result in the finding that the claimed subject-matter is obvious.

5. Since the appellant based its objection of lack of inventive step on an approach starting from the disclosure of document D8, and this approach had also been considered in the decision under appeal, the board found it appropriate to first adopt this approach. Since this resulted in a finding of lack of inventive step (as set out below) it was not necessary to address the alternative approach starting from the disclosure of document D26.

6. As summarised in the decision under appeal (starting on page 11), document D8 discloses the comparison of the therapeutic effects of microplasmin (a truncated form of plasmin that combines a direct thrombolytic activity with a neuroprotective property; see D8, page 430, left hand column, second paragraph), with those of tissue plasminogen activator ("tPA") in a rat stroke model (*Id.*, title). It reports that the incidence of intracerebral haemorrhage was significantly higher ($P < .05$) in the tPA-treated group (10 mg/kg) than in the control group and both microplasmin-treated groups (7.5 mg/kg and 10 mg/kg), with the lowest incidence found in the 10 mg/kg microplasmin group (*Id.*, page 433, right-hand column, '*intracerebral hemorrhage*' and the table on page 434). According to the disclosure in document D8, microplasmin was able to exert thrombolytic and neuroprotective effects in a rat stroke model. Although the mechanism for these effects is said to be not fully understood, it is stated that it involves lowering the level of circulating α2-AP, i.e. SerpinF2 (*Id.*, page 436, paragraph bridging the middle and right columns). The board is persuaded that the skilled person would understand from document D8 that lowering the level of circulating α2-AP is suitable means for reducing the risk of intracerebral haemorrhage in treatment of acute ischaemic stroke. This is confirmed by the disclosure in the box on page 430, headed "*Implication for patient care*", where it is stated "*Microplasmin may serve as a potential alternative to tissue plasminogen activator in the treatment of patients with ischemic stroke, with comparable effects and lower hemorrhage rat[e]*".

7. Both claim 1 and document D8 have the same aim, namely the prevention of brain haemorrhage resulting from cerebral ischaemia due to thrombotic ischaemic stroke.

In other words both aim at the therapeutic effect recited in the claim.

8. The differences between the claimed subject-matter and the disclosure in document D8 are:
i) that the claim specifies a human patient, whereas document D8 reports experiments done in rats, and
ii) that instead of microplasmin, the therapeutic agent is an antibody capable of binding and reducing the activity or concentration of α2-AP.

9. In view of these differences, the objective technical problem can be seen as 'finding an alternative agent for the prevention of brain haemorrhage resulting from cerebral ischaemia due to thrombotic ischaemic stroke in a human patient'.

Obviousness

10. The question to be answered in assessing obviousness is whether or not the skilled person starting from the disclosure in document D8 and seeking an alternative to microplasmin, would have turned to an antibody capable of binding α2-AP, as defined in the claim, as a solution to this problem.

Would the skilled person have considered the results reported in document D8 to be applicable to a human patient?

11. As set out in section 6. above, the skilled person knew from document D8 (Box: *"Implication for Patient Care"*) that microplasmin may serve as a potential alternative to tissue plasminogen activator in the treatment of patients with ischaemic stroke, with comparable effects and lower haemorrhage rate. This conclusion was reached on the basis of experiments done in a rat stroke model.

The incidence of intracerebral haemorrhage resulting from cerebral ischaemic stroke could be reduced compared to both tPA treated rats and to control rats, by administration of microplasmin in a dose of 10 mg/kg (see page 433, right-hand column and the table in the left-hand column on page 434).

12. On the question of whether or not the skilled person would have considered the middle cerebral artery (MCA) occlusion model used in document D8 (see page 430, middle column, "*Animal Model*") appropriate to render it credible that the effects reported could be achieved in human patients, it is noted that the ultimate aim of document D8 was to find solutions for human patients. It is further apparent that the authors of document D8 considered that rat model they used appropriate for this purpose, as evidenced by the section "*Implication for Patient Care*" referred to above.

13. The respondent, by reference to document D20, suggested that a photo-thrombotic model, as utilised in document D8, was undesirable for preclinical drug studies where the chief target was the penumbra, e.g. those studying ischaemic stroke. However, as noted by the appellant, the model used in document D8 was a photo-thrombotic model combined with multiparametric magnetic resonance (MR) imaging with a perfusion-diffusion mismatch analysis. Document D8 discloses that perfusion-weighted (PW) and diffusion-weighted (DW) MR imaging can be used to determine the tissue at risk, namely the penumbra, because that tissue is characterised by a perfusion-diffusion mismatch.

14. Thus, concerns about unsuitability due to lack of penumbra do not apply to the model used in document D8. Thus, the board accepts that the rat model used in

document D8 was at the relevant date considered appropriate to provide meaningful results that would model the situation in humans.

Was microplasmin known to prevent haemorrhage by neutralisation of α2-AP?

15. The respondent was of the view that the skilled person, at the relevant date of the patent, would not have known that neutralisation of α2-AP was the reason for the therapeutic effects of microplasmin mentioned in document D8. Without a known link between the neutralisation of α2-AP and the reduction of haemorrhage, the skilled person would have had no reasonable expectation that administering an antibody capable of neutralising/antagonising α2-AP could represent a solution to the objective technical problem.

16. In the board's view, the skilled person seeking to prevent intracerebral haemorrhage would have understood from document D8 that microplasmin offered advantages over tPA because it was considered as a thrombolytic agent associated with a reduced risk of brain haemorrhage. Document D8 states "*It has been suggested that introduction of tPA aggravates degradation of microvascular barriers (ie, mainly basal lamina and blood-brain barrier) in ischemic injury. The breakdown of basal lamina — caused mainly by matrix metalloproteinase-9 induction by lipoproteinreceptor-relating protein — is associated with hemorrhagic transformation* " (see page 436, left columan; references removed) and "*Our results suggest that tPA treatment aggravated the blood-brain barrier damage that may herald a higher risk of hemorrhage*" (Id, middle column). Furthermore, as put forward by the

appellant, document D8 taught the skilled person that in a rat model of ischaemic stroke, the incidence of intracerebral haemorrhage resulting from cerebral ischaemic stroke could be reduced by administration of microplasmin in a dose of 10 mg/kg not only compared to tPA-treated rats but also to control rats (see page 433, right-hand column and the table in the left-hand column on page 434). According to document D8 (page 436, right column), "*...there was a dose-dependent neural and/or vascular protective effect with microplasmin, because a significantly lower hemorrhagic rate was found, particularly with a higher dose (10 mg/kg) of microplasmin*".

17. As to whether or not the skilled person would have considered that the above mentioned reduction in haemorrhagic side effects was achieved by depleting circulating α2-AP, a link is made on page 436 of D8, in the final paragraph of the middle column which states "*The exact dose of thrombolytic drugs seems critical not only in regard to the antistroke effects but also in regard to the hemorrhagic side effect, and the optimal dose of each drug also varies among species of animals. For our study, we used 10 mg/kg tPA, which is approximately equivalent to its standard clinical dose of 1 mg/kg for patients. The doses of 7.5 and 10 mg/kg microplasmin were considered appropriate for depleting circulating α2-antiplasmin to exert therapeutic effects without resulting in much safety concern*".

18. In this passage the depletion of α2-AP is mentioned in connection with both the thrombolytic antistroke effects and the haemorrhagic side effect.

19. The board also notes that document D8 proposes no other mechanism than depletion of α2-AP for the observed

lower haemorrhage rate. Although document D8 mentions a "*first* [...] *direct thrombolysis*" effect *"due to the neutralization of plasma α2-antiplasmin"* and a "*second* [...] *nonthrombolytic neuroprotective effect, which is supported by the fact that administration of microplasmin decreased the infarct volume even in a mouse model with permanent MCA occlusion (14, 25)* (see page 436, right-hand column, final paragraph), this cannot be understood as suggesting that the mechanism underlying the two therapeutic effects is different.

20. This view is reinforced by reference (14) in the above cited passage, which is document D6 in the present proceedings. Document D6 concerns the effect of recombinant human microplasmin in ischaemic stroke models in mice and in an extracorporeal loop thrombosis model in rabbits (see title and Summary). On page 312, right column, reference is made to previous studies where α2-AP gene deficient mice had smaller cerebral infarct size after middle cerebral artery (MCA) ligation and to the finding that reduction of α2-AP with a single bolus of human plasmin, or of an anti-α2-AP Fab fragment reduced infarct size. The authors of document D6 state "*This suggested that reduction of circulating α2-antiplasmin may constitute a new approach to reduce cerebral infarct size in ischaemic stroke in the absence of reperfusion, possibly via a neuroprotective mechanism of action*". This passage makes a direct link between lowering the level of α2-AP and neuroprotective effects.

21. The respondent further argued that the skilled person would have considered the anti-haemorrhage effect of microplasmin reported in document D8 to be unreliable because it was only seen for one of the tested doses of microplasmin.

22. This argument is not convincing. The board has seen no arguments which would explain why the skilled person would dismiss the results presented in the table on page 434 of document D8 of a statistically relevant reduction of intracerebral hemorrhage for the 10mg/kg group, especially since the authors of document D8 themselves considered that their findings suggested that "*Microplasmin may serve as a potential alternative to tPA in the treatment of patients with ischemic stroke, with comparable effects and lower hemorrhage rate*" (see page 437, middle column, final paragraph).

23. The respondent also put forward that the skilled person would not have ignored the fact that document D8 directed them to the microplasmin Phase II clinical trial disclosed in document D26, where they would have learned about the failure of microplasmin in preventing haemorrhage, despite providing a "*strong reduction in α2-AP levels*". From this they would have concluded that microplasmin had actually caused haemorrhage and so it could not reasonably be expected that microplasmin, let alone a α2-AP binding antibody, would solve the technical problem.

24. Document D26 reports a randomised, placebo-controlled, dose-ranging clinical trial that was designed to assess the safety and pharmacodynamic properties of intravenous microplasmin in patients with acute ischaemic stroke. Its main aim was to test the tolerability of microplasmin in patients with acute ischaemic stroke (see abstract). The study did not aim to assess the clinical efficacy of microplasmin in treating ischaemic stroke or in preventing intracerebral brain haemorrhage. D26 recalls that *"The observations that α2-antiplasmin (α2-AP) deficiency in*

mice and α2-AP depletion by neutralizing antibodies or a fter administration of plasmin reduced infact size led to the development of microplasmin for patients with ischemic stroke". The study was motivated by the fact that "*Acute stroke models in mice, rats, and rabbits have generally demonstrated that intravenous microplasmin is associated with a reduction in infarct size compared with placebo and that microplasmin may have a lower propensity to cause bleeding than recombinant tPA*" (see page 3789, right-hand column). Thus, the study disclosed in document D26 aimed at evaluating microplasmin as an alternative to tPA due to its lower propensity to cause haemorrhage. The conclusions reached in document D26 were that "*Microplasmin was well tolerated and achieved neutralization of a2-antiplasmin. Further studies are warranted to determine whether microplasmin is an effective therapeutic agent for ischaemic stroke*" (see abstract). Document D26 also links the neuroprotective effect as well as increased endogenous fibrinolytic activity to depletion of α2-AP (page 3794, left-hand column, "Discussion").

25. Furthermore, document D26 in its discussion (page 3794) notes that there was a decrease in the expression of MMP-2 compared with placebo and comments (with reference to earlier publications) that "*Increased levels of MMPs have been linked to intracerebral hemorrhages associated with tPA use. One potential advantage of microplasmin from preclinical work is the lower risk of intracerebral hemorrhage, which is one of the reasons why tPA is given infrequently*". Although document D26 does not suggest a direct link between reduction in α2-AP levels and decreased MMP-2 expression, this statement reinforces the message that

administration of microplasmin did not increase the risk of intracerebral haemorrhage.

26. In spite of one patient developing a fatal symptomatic intracranial haemorrhage, the authors maintained their view that microplasmin was a safe thrombolytic alternative to tPA and did not question the rationale that led them to undertake the study. Instead, they proposed further clinical investigations into the effectiveness of microplasmin for ischaemic stroke. Moreover, a single event is not statistically significant, thus the skilled person reading document D26 would not construe a disincentive based on this event.

27. The appellant referred to document D26 according to which "*No dose effect was seen [for microplasmin] on the rate of asymptomatic intracerebral hemorrhage*" (see page 3794, left hand column, first paragraph of discussion), to support the argument that document D26 taught the skilled person that microplasmin was ineffective for preventing intracerebral haemorrhage.

28. However in the board's view, the cited statement in document D26 is made in the context of the previous sentence: "*Microplasmin was well tolerated with only one treated patient who developed a fatal symptomatic intracranial hemorrhage*". Thus, it is to be understood as meaning that microplasmin did not cause additional, dose dependent intracerebral haemorrhage. Furthermore, the authors state that their study was not powered to detect clinical efficacy and that, as expected, no effect on clinical outcome was observed (see D26: Abstract: Methods, and page 3794: right column).

α2-AP-binding antibodies as an alternative to microplasmin

29. Neither document D8 nor D26 mentions antibodies blocking the activity of α2-AP (SerpinF2) as a potential alternative to microplasmin. Thus, neither the disclosure in document D8 alone, nor a combination of document D8 with document D26 would have led the skilled person directly to the claimed invention. However, the appellant suggested that the claimed subject-matter lacked an inventive step in view of the disclosure in document D8 in combination with that in document D3.

30. Document D3 is entitled "*Depletion of circulating α2-antiplasmin by intravenous plasmin or immunoneutralization reduces focal cerebral ischaemic injury* [FII] *in the absence of arterial recanalization*". From the title it is apparent that it comes from the same technical field as the claimed invention. It discloses experiments done in animal (mouse and hamster) models, describing a study of the effects on FII observed after reduction of circulating α2-AP by infusion of human plasmin, human miniplasmin or of the Fab fragment of a monoclonal antibody neutralising murine α2-AP.

31. The appellant's argument is essentially that document D3 discloses that antibodies binding α2-AP and blocking its effect represented an obvious equivalent to the microplasmin used in document D8 and could be used as an alternative for lowering circulating α2-AP levels.

32. The board agrees with the appellant that the skilled person seeking an alternative agent to microplasmin to achieve the same clinical effect would have learned

from document D3 that an antibody capable of neutralising α2-AP would be suitable. This is because document D3 discloses that depletion of α2-AP can be obtained with both plasmin and miniplasmin (a truncated from of plasmin, having the same serine protease domain, but lacking kringle domains; see e.g. document D6) and alternatively with a Fab fragment neutralising murine α2-AP (Fab-4H9). In the discussion section (see page 3091, right column) it is reported that "*The hypothesis that FII reduction was the result of α2-AP depletion and not of the proteolytic activity of injected plasmin was confirmed by the experiments with Fab-4H9, the Fab fragment of a murine monoclonal antibody neutralizing murine α2-AP*".

33. The board is persuaded that the skilled person starting from the disclosure in document D8 and seeking an alternative means to deplete α2-AP (the mechanism underlying the effects of microplasmin), would have learned from document D3 that an antibody neutralising α2-AP (i.e. a SerpinF2-binding antibody that reduces SerpinF2 activity) would be suitable.

Admittance of new facts and related lines of argument submitted by the respondent

34. The appellant objected under Article 12 RPBA and Article 13(2) RPBA to several lines of argument presented by the respondent and the related allegations of fact (see Section IX. above).

35. According to Article 13(2) RPBA (as amended by decision of the Administrative Council CA/D 5/19 Corr. 1 of 26 June 2019), any amendment to a party's appeal case made after after notification of a summons to oral

proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

36. With the exception of the facts and arguments dealt with below, this decision was reached taking these disputed lines of argument into account. Since the appellant is not adversely affected, no reasons for their consideration need be given.

37. The respondent's argument that the skilled person would not have turned to document D3 because it related to miniplasmin and not microplasmin, was first made in the letter dated 8 December 2023, i.e. after the board's communication under Article 15(1) RPBA issued on 9 October 2023 and there are no exceptional circumstances for its late submission, which have been justified with cogent reasons. The argument would be inadmissible under Article 13(2) RPBA. In any case, the argument is not persuasive as both document D8 and document D3 are concerned with α2-AP depletion and its effect on cerebral ischaemic injury.

38. Hence, the teachings of document D8 and document D3 are compatible, as they both teach that α2-AP inhibition is the mechanism responsible for the observed therapeutic effects.

39. The respondent's argument based on the premise that the claimed invention related to treating brain haemorrhage or brain edema resulting from cerebral ischaemia due to thrombotic ischaemic stroke and not to reducing the haemorrhagic side effects of tPA as taught in D8, is in the board's view also not to be taken into account under Article 13(2) RPBA because it was first made in

the letter dated 8 December 2023, i.e. after the board's communication under Article 15(1) RPBA issued on 9 October 2023 and there are no exceptional circumstances, which have been justified with cogent reasons by the respondent.

40. In any case this line of argument is not persuasive, because D8 demonstrates that rats treated with 10 mg/kg microplasmin had a significantly lower tendency to intracerebral haemorrhage than both control and tPA treated rats (see the table in the left hand column of page 434).

41. At the oral proceedings before the board, the respondent submitted that neither the thrombolytic effect nor the non-thrombolytic neuroprotective effect of microplasmin disclosed in document D8 were the same as an anti-haemorrhage effect and therefore the skilled person could draw no conclusions about use of microplasmin to prevent haemorrhage from the results disclosed in document D8.

42. These lines of argument were not present in any of the respondent's written submission and were therefore presented for the first time at the oral proceedings before the board, i.e. after the board's communication under Article 15(1) RPBA issued on 9 October 2023 and there are no exceptional circumstances, justified with cogent reasons provided by the respondent. Given that these arguments are also of a complex technical nature which the appellant and the board would have needed time to study, the board decided not to take them into account.

43. In view of the above considerations, the board concludes that the claimed subject-matter lacks an

inventive step in view of the disclosure in document D8 when taken in combination with that in document D3.

44. The respondent's sole claim request is not allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

I. Aperribay R. Hauss

Decision electronically authenticated