Düsseldorf Higher Regional Court, 2 U 42/23

Machine Translation

Date:	August 3, 2023
Court:	Düsseldorf Higher Regional Court (OLG Düsseldorf)
Panel:	2nd Civil Senate
Type of decision:	Judgment
File number:	2 U 42/23
ECLI:	ECLI:DE:OLGD:2023:0803.2U42.23.00

Lower court: Düsseldorf District Court (LG Düsseldorf), 4a O 85/22

Legal Summary:

OLG Düsseldorf, judgment of August 3, 2023 - I-2 U 42/23

1.
An adversarial decision on legal validity of the patent is not required if the decision to grant the patent has been taken in consideration of third-party objections. This applies in particular if the patent was granted by the TB-EPO or the Federal Patent Court (BPatG) in appeal proceedings.

1.
The dispensability of an opposition or nullity decision also applies if certain publications or third-party objections were no longer admitted and considered in the appeal instance for reasons of delay.

1.
A generics case suspending the contradictory legal validity decision also exists if generic products were therefore lawfully on the market during a transitional phase and have led to a certain price erosion,

because the patent grant was only issued following a legal remedy by the applicant, the existing marketing protection had already expired before the appeal decision, but the generics company was aware of the forthcoming patent grant before the first marketing.

1.
If the injunction patent has come about in the appeal proceedings by dealing with third-party objections, the refusal of a preliminary injunction is generally only appropriate under those conditions under which the infringement court can deviate from a positive decision on the legal validity (irrefutability, promising new attack).

Tenor:

I. Following the appeal, the judgment of the 4a Civil Chamber of the Düsseldorf District Court announced on January 26, 2023 is amended.

The request for preliminary injunction dated October 12, 2022 is dismissed.

II. The injunction plaintiff is ordered to pay the costs.

III. The amount in dispute for the appeal proceedings is set at € 3,000,000.

G r o u n d s : 1

I.

The facts of the case will not be presented in accordance with Sections 540 (2), 313a (1) sentence 1, 542 (2) sentence 1 Code of Civil Procedure (ZPO). 2

II.

The injunction defendant's admissible appeal is successful. 3

The District Court should correctly not have granted injunction plaintiff's request for a preliminary injunction. 4

5

A.

The patent (EP 2 959 894) relates to the provision of a sphingosine-1-phosphate (= S1P) receptor modulator for use in the treatment of relapsing-remitting multiple sclerosis (MS). 6

Multiple sclerosis is an autoimmune disease in which autoimmune activity is directed against antigens of the central nervous system (CNS). Inflammation in parts of the CNS leads to the loss of the myelin sheath around the nerve fibres (demyelination), the loss of nerve fibres and ultimately the death of neurons, oligodendrocytes and glial cells. MS is a chronic, progressive, disabling disease, with relapsing-remitting MS (RRMS) manifesting itself in recurrent attacks with focal or multifocal neurological disorders. 7

A fundamental problem with the treatment of MS is that the treatment is only partially effective and, despite anti-inflammatory and immunosuppressive treatment, in most cases there is only a short delay in the progression of the disease. 8

The drug class of S1P receptor modulators are well-known immunomodulators. They have the ability to modulate G-protein-coupled S1P receptors by binding to the receptors in the lymph nodes and thereby preventing certain lymphatic immune cells from migrating out of the lymph nodes (so-called "lymphocyte homing") and from there entering the bloodstream and ultimately the central nervous system. Thanks to the S1P modulators, a reduction of lymphocytes in the bloodstream is achieved, which, if the lymphatic immune cells were to reach the central nervous system, would be directed against the body's own structures through dysregulation and release so-called pro-inflammatory cytokines, which in turn would result in the harmful destruction of the myelin sheath of nerve cells. 9

A known representative of an S1P receptor modulator that is used against RRMS is the active substance 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol with the international non-proprietary name "F". 10

The injunction patent proposes its use in a daily oral dose of 0.5 mg. Accordingly, the single claim - in the form of a specific purpose claim - protects the combination of the following features: 11

- 1. S1P receptor modulator for use in the treatment of relapsing-remitting multiple sclerosis. 1123
- 2. The S1P receptor modulator is 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol in free form or in a pharmaceutically acceptable salt form. 1145
- 3. The S1P receptor modulator is administered orally in a daily dose of 0.5 mg. 1167

In comparison with dosages of the F active ingredient of 1.25 mg and 5 mg per day successfully tested on the priority date of the patent in suit, the injunction patent is 18

based on the finding that therapeutic success is already achieved with a daily dose of only 0.5 mg, the use of which is advantageous for the patient thanks to the lower amount of active ingredient.

B.

The District Court assumed that only the actual active ingredient F is relevant for compliance with the dosage information provided in the patent in suit and, based on this, found that the challenged generic product "D 0.5 mg hard capsules" literally makes use of the technical teaching of the patent in suit and that the injunction plaintiff, as the registered patent holder, is therefore entitled to an (injunctive) claim to cease and desist from further acts of offering and marketing (Section 139 (1) sentence 1 German Patent Act (PatG)) as well as an (injunctive) claim to destruction of the infringing products in the domestic possession and/or property of the injunction defendant (Section 140a (1) sentence 1 PatG) to be secured by the ordered official custody. These statements do not indicate an error of law. 19

C. 20

However, the District Court was wrong to affirm a reason for an injunction (Section 935 Code of Civil Procedure (ZPO)). The assumption that the legal validity of the injunction patent was secured to the extent required for the issuance of a preliminary injunction does not stand up to legal scrutiny. 21

1.

It corresponds to the established case law of the Senate (InstGE 9, 140 - Olanzapin; InstGE 12, 114 - Harnkatheterset; GRUR-RR 2011, 81, 82 - Gleitsattel-Scheibenbremse II; judgment of December 6, 2012, file no.: I-2 U 46/12, BeckRS 2013, 13744; GRUR-RR 2013, 236, 239 f. - Flupirtin-Maleat; judgment of November 7, 2013, file no.: I-2 U 94/12, GRUR-RS 2014, 04902 - Desogestrel; judgment of December 18, 2015, file no.: I-2 U 35/15, GRUR-RS 2016, 6208 para. 18 - diagnostic procedure; judgment of August 31, 2017, file no.: I-2 U 11/17, BeckRS 2017, 125974 para. 48; judgment of December 14, 2017, file no.: I-2 U 18/17, GRUR-RS 2017, 142305 para. 12 – Kombinationszusammensetzung; judgment of September 26, 2019, file no.: I-2 U 28/19, GRUR-RS 2019, 33227 = GRUR-RR 2020, 240 [Ls.] - MS-Therapie; GRUR-RR 2021, 249, 250 - Cinacalcet II; GRUR-RR 2021, 400, 402 - MS-Therapie II; GRUR-RS 2023, 5166 - Fumarsäureester) that the issuance of a preliminary injunction, in particular for injunctive relief, can only be considered if both the question of patent infringement and the existence of the right to injunctive relief can be answered so clearly in favor of the injunction plaintiff that an erroneous decision to be revised in any subsequent main proceedings is not seriously to be expected. 22

Of course, there cannot - and therefore must not - be absolute certainty in this sense, because the legal validity of a patent - unlike the question of infringement in many cases - typically depends on questions of assessment, the answer to which is not a mathematical task with a certain predictable outcome, which is why the fate of a patent can change significantly beyond the legal instances required for its legal validity. Frequently, only a momentary certainty reflecting the current legal validity situation at 23

the time of the decision on the request for an injunction is possible, which - for lack of a better alternative - must nonetheless be the fundamental guideline for the infringement court.

a) 24

However, particular caution is required with the decision to grant, which is made after a purely internal discussion between the applicant and the patent office. In view of the persistently high revocation and destruction rate of granted patents, according to which only about 3 out of 10 IP rights challenged with an opposition or nullity action prove to be legally valid to the extent granted (cf. the evidence in Kühnen, Handbuch der Patentverletzung, 15th ed, G para. 57), the fact that a patent has been granted cannot in itself support a preliminary injunction without further ado, but can generally only be assumed to have a sufficiently secure legal basis if the patent subject to the injunction has already survived first-instance opposition or nullity proceedings (Senate, InstGE 9, 140, 146 - Olanzapin; InstGE 12, 114 - Harnkatheterset; GRUR-RR 2011, 81, 82 - Gleitsattel-Scheibenbremse II; judgment of November 7, 2013, file no.: I-2 U 94/12, GRUR-RS 2014, 04902 - Desogestrel; judgment December 18, 2014, file no.: I-2 U 60/14, BeckRS 2015, 01829 para. 17; judgment December 18, 2015, file no.: I-2 U 35/15, GRUR-RS 2016, 6208 para. 18 – diagnostisches Verfahren; judgment of August 31, 2017, file no.: I-2 U 11/17, BeckRS 2017, 125974 para. 48; judgment of December 14, 2017, file no.: I-2 U 18/17, GRUR-RS 2017, 142305 para. 12 – Kombinationszusammensetzung; judgment of September 26, 2019, Ref.: I-2 U 28/19, GRUR-RS 2019, 33227 = GRUR-RR 2020, 240 [Ls.] - MS-Therapie; GRUR-RR 2021, 249, 250 - Cinacalcet II, GRUR-RR 2021, 400, 402 - MS-Therapie II; GRUR-RS 2023, 5166 - Fumaräureester). In order to make an injunction protection right suitable for preliminary injunction proceedings anticipating the main proceedings, a positive decision of the competent opposition or nullity instances equipped with technical expertise is therefore generally required in adversarial proceedings. 25

Whether the admissibility of this approach has changed as a result of the ECJ's preliminary ruling in Case C-44/21 (GRUR 2022, 811 - Phoenix Contact/Harting) (see Kühnen, loc. cit, Chap. G para. 81 et seq.; Deichfuß, GRUR 2022, 800; Keßler/Palzer, EuZW 2022, 562; Stierle, Mitt 2022, 277), does not need to be decided in the case in dispute because an adversarial decision on the legal status of the case in dispute is already superfluous according to the previous Senate case law. 26

b) 27

The requirement of a decision on the legal validity of the injunction that is favorable to the injunction plaintiff - not the need to convince the infringement court dealing with the request for an injunction of the legal validity of the right to injunctive relief (Senate, judgment of December 10, 2015 - I-2 U 35/15) - can be waived in special cases. They are characterized by circumstances that justify a situation of interest that deviates from the usual, under which the risk of an incorrect decision by the infringement court, which relies on the granting act, can and/or must be accepted. The exceptional cases recognized in previous case law - which are expressly non-exhaustive examples - can essentially be divided into three categories, namely those situations in which the act of grant can claim particular reliability (e.g. because of the involvement of a competitor in the granting procedure or the confirmatory decision on the validity of the patent by a renowned foreign court), in cases in which the patent proprietor requires special legal protection 28

(e.g. because of an imminent expiry of the property right or the infringement of the property right by a generic product), and in cases in which the attack on the validity of the property right can already be exposed as futile by the infringement court.

Accordingly, there is no need for an adversarial decision in favor of the injunction patent if, among other things, the injunction defendant (or another serious competitor) has already participated in the grant proceedings with its own objections, so that the grant of the patent is factually equivalent to a decision in bilateral opposition proceedings, or if (e.g. in view of the market situation or the disadvantages threatening from the infringement of the property right), there are exceptional circumstances which make it unreasonable for the injunction plaintiff to wait for the outcome of the opposition or nullity proceedings (cf. Senate, InstGE 12, 114, 121 - Harnkatheterset; judgment of November 7, 2013, file no.: I-2 U 94/12, GRUR-RS 2014, 04902 - Desogestrel; GRUR-RR 2013, 236, 240 - Flupirtin-Maleat; judgment of December 18, 2015, file no.: I-2 U 35/15, GRUR-RS 2016, 6208 para. 19 – Diagnostische Verfahren; judgement of December 14, 2017, file no.: I-2 U 18/17, GRUR-RS 2017, 142305 para. 12 - Kombinationszusammensetzung; most recently: GRUR-RS 2023, 5166 - Fumarsäureester). 29

aa) 30

In the case of third-party objections, it does not matter - contrary to the opinion of the District Court - whether those grounds for objection and those citations on which the respondent relies in the injunction and validity proceedings were examined in the grant proceedings. The mere fact that a competitor did not raise the objections in question in its third-party objection is an indication that they are not relevant. This is because a third-party will regularly only participate in a third-party granting procedure if it has its own economic interest in a patent not being granted. This interest will typically arise from the fact that he is already active on the relevant product market or at least intends to be so and hopes to gain his own freedom of action by averting the grant of a patent in favor of the applicant. This can only succeed if the applicant raises all available objections with its third-party objections and, in particular, does not omit the best arguments. 31

The above does not mean that documents and/or revocation/nullity reasons not cited in the context of third-party objections are irrelevant, but merely that, in order to avert an injunction despite the grant of a patent with third-party participation, it is rather up to the respondent to demonstrate to the infringement court that the new citations (which also include such publications which were submitted by a third-party but not considered in the grant proceedings for reasons of delay) are decisively closer to the subject matter of the invention than those considered in the grant proceedings, and to convince the court that reasons for revocation raised for the first time will be supported with the necessary certainty (Senate, GRUR-RR 2021, 249 - Cinacalcet II). 32

bb) 33

An "exceptional" situation regularly exists in the case of infringements by generics companies. While the damage caused by them in the event of a subsequent maintenance of the patent is often enormous and irreparable (e.g. in view of the price drop caused by the setting of fixed amounts), an unjustified injunction (due to the subsequent destruction of the patent) merely has the consequence that the generics 34

company is temporarily wrongly kept off the market, which can be fully compensated by corresponding claims for damages against the patent proprietor. It is all the more appropriate to refer the generics company to a later liquidation of damages if necessary, as it generally does not take any economic risks of its own for its market presence because the preparation has been sufficiently medically tested and established on the market thanks to the patent holder. At the same time, the effective enforcement of a patent is of particular importance in the pharmaceutical sector because patent protection represents the central incentive and driving force for pharmaceutical development - and thus ultimately for public health. Because of the immense costs associated with research and subsequent drug approval, commercial development activities only take place if the prospects of amortization are secure, and these in turn depend decisively on the effective enforcement of patent protection granted to the researching company.

A prohibition order must therefore be issued, even if the infringement court cannot obtain final and unambiguous certainty about the legal validity due to the lack of an expert decision on the legal validity, provided that the infringement court (on the basis of its own assessment possible in view of the technical matter concerned) is convinced (in the sense of sufficient prima facie evidence) that the protective right of injunction is legally valid because the lack of patentability of the subject matter of its invention cannot be established. From the point of view of the infringement court, either the better arguments must speak in favor of patentability, so that this can be positively affirmed, or the question of patentability must at least remain unresolved (with regard to the distribution of the burden of proof applicable in legal validity proceedings), so that the infringement court, if it had to decide on the case itself instead of the Patent Office or the Federal Patent Court (BPatG), would have to affirm its legal validity (Senate, GRUR-RR 2013, 236, 240 - Flupirtin-Maleat; judgment of November 7, 2013, file no: I-2 U 94/23, GRUR-RS 2014, 04902 - Desogestrel; judgment of February 19, 2016, file no.: I-2 U 54/15, BeckRS 2016, 6344 para. 13; judgment of December 14, 2017; judgment of December 14, 2017, file no.: I-2 U 18/17, GRUR-RS 2017, 142305 para. 12 – Kombinationszusammensetzung; GRUR-RR 2021, 249, 252 - Cinacalcet II; GRUR-RR 2021, 400, 403 - MS-Therapie II; most recently: GRUR-RS 2023, 5166 - Fumarsäureester). 35

c) 36

In the case in dispute, two of the exceptions recognized in the case law of the Senate are present, which make a decision on the validity of the injunction patent superfluous. 37

aa) 38

Firstly, the patent was granted taking into account the objections of third-parties, namely a whole series of generic competitors of the injunction plaintiff, whereby the decision to grant is of particular importance in the present case because it was not - as is usually the case - issued by the Examining Division responsible at first instance, but - with extensive reasons - by the Technical Board of Appeal of the European Patent Office, which will probably also make the decision on legal validity of the injunction patent in the current opposition proceedings before the EPO that will end the appeal. 39

40

The fact that the Technical Board of Appeal did not admit, for reasons of delay, various statements by third-parties which they submitted for the first time after the statement of grounds of appeal, despite their participation in the first instance examination proceedings and the patent request already pursued identically there, is of no legal significance. The third-party participation in the first instance examination proceedings already suspends an adversarial decision on the legal validity of the patent, because it can be assumed that a competitor, who is naturally uncertain about the outcome of the examination proceedings, would have submitted all arguments against the requested patent grant in good time that could have any serious prospect of success. Therefore, if the injunction patent had already been granted before the Examining Division, the 11 third-party objections raised there in vain would have been sufficient to obtain an injunction without a disputed decision on legal validity of the injunction patent. The result cannot be any different if a patent was not granted because the Examining Division - from the point of view of the appeal instance - made a legally erroneous decision and - as the corrective appeal decision shows - should have correctly decided to grant the injunction patent. The further 15 third-party objections raised in the course of the appeal proceedings therefore justify the assumption - until the infringer demonstrates the contrary - that they are no more relevant than those third-party objections that were already raised in the first instance examination proceedings.

This assumption is additionally supported by the fact that the rejection of new submissions in the appeal instance before the EPO must be preceded by an examination as to whether the documents in question are prima facie highly relevant for the assessment of patentability, which, if so, must result in their admission to the appeal proceedings (Case Law of the Boards of Appeal of the EPO, 10th ed., clause 5.13.2). Even if the decision of the Board of Appeal does not expressly refer to this relevance criterion, it does state that the rejected opinions could and should all have been presented in the proceedings before the Examining Division and that, in view of this, the Board decided not to take the opinions into account in the appeal proceedings. Contrary to the opinion of the District Court, these comments make it sufficiently clear that the Board of Appeal considered the admission of the new, belated third-party observations and made a decision in this respect (to the detriment of the third-parties). The subject of this decision can only have been the question of whether the established procedural delay of certain third-party objections should exceptionally be set aside in the interest of substantive justice because the late objections are highly relevant for the decision to grant. 41

bb) 42

Secondly, this is a generics case, which, due to its special economic features, already justifies exceptional circumstances in itself, which suspend a disputed decision on legal validity. The fact that the regulatory marketing protection of the injunction plaintiff (Art. 14 No. 11 Regulation (EC) 726/2004, Section 24b para. 1 sentence 2 AMG) expired on March 22, 2022 and the publication of the patent grant did not take place until October 12, 2022, so that there was a transitional period of approx. 7 months (March 22 to October 11, 2022) during which generic suppliers were able to enter the market, does not change this. 43

44

That the injunction plaintiff - in gross violation of its own economic interests! - should have deliberately delayed the granting of the patent without a reasonable objective reason. However, this is not even decisive. Even if the injunction plaintiff were to be accused of any delay, it would have remained without any effect if the Examining Division had handled the application on which the injunction patent is based - from the point of view of the appeal instance - without any legal errors. In that case, a decision granting the patent would already have been issued on November 19, 2020 (and not only with the corrective appeal decision), i.e. well before the expiry of the marketing protection, so that a period without protection rights could not have arisen. However, the injunction plaintiff does not have to suffer any legal disadvantage because the granting authority made an incorrect decision.

It is irrelevant whether, for the same reason, the injunction plaintiff cannot be blamed for the fact that, as a result of the temporary appearance of generic products from March 22 to October 11, 2022, a market situation has arisen which distinguishes the dispute from the typical generics cases because of the price erosion that has lawfully occurred to a certain extent as a result. Apart from the fact that the economic disadvantages to be accepted by the injunction plaintiff as a consequence of the erroneous rejection of its patent application by the Examining Division cannot be a justification for perpetuating the damage on the part of the injunction plaintiff even further, the District Court found without error of law (LGU 53-57) that the injunction plaintiff, should no injunctions be issued against the further distribution of generic products, is threatened with considerable additional sales losses due to the fact that F is threatened with the setting of fixed amounts. In any case, it is not reasonable to expect the injunction plaintiff to wait for the opposition decision before enforcing its patent. 45

At the same time, the injunction defendant is not more worthy of protection than an ordinary generics company, for which case law has so far assumed an exception to the requirement of a disputed legal validity decision. It is true that the acts of use carried out by the injunction defendant after the expiry of the marketing protection (March 22, 2022) until the publication of the injunction patent (October 12, 2022) were lawful. However, as the District Court (LGU 57/58) correctly recognized, it was already clear to the injunction defendant before the start of its very first act of distribution due to the decision of the Board of Appeal issued on February 8, 2022 ordering the grant of the patent that the injunction plaintiff would soon be entitled to a patent whose scope of protection would be unlawfully infringed by the generic product. All uses were therefore made in the certain knowledge and with the conscious acceptance that the uses would have to be discontinued immediately after publication of the patent grant. If the injunction defendant took up the distribution of its generic product - which was planned from the outset for a limited period of time - under such conditions because it considered the prospects for earnings to be sufficiently rewarding despite everything, it cannot now argue that a withdrawal from the market as a result of the grant of the patent would be associated with economically unreasonable consequences for it. Rather, only the risk that the injunction defendant deliberately took on with its generic product has materialized. 46

d) 47

48

Conversely, it follows from the regular necessity of a positive disputed legal validity decision that, as soon as it is available, it can in principle be assumed that the validity of the injunction patent is sufficiently secured (Senate, judgment of February 19, 2016, file no.: I-2 U 54/15, BeckRS 2016, 6344 para. 12; judgment of December 14, 2017, file no.: I-2 U 18/17, GRUR-RS 2017, 142305 para. 12 - Kombinationszusammensetzung; judgment of September 26, 2019, file no.: I-2 U 28/19, GRUR-RS 2019, 33227 = GRUR-RR 2020, 240 [Ls.] - MS-Therapie; GRUR-RR 2021, 249, 251 - Cinacalcet II; most recently: GRUR-RS 2023, 5166 - Fumarsäureester).

aa) 49

As the body that issues the injunction, the infringement court has a legal duty to seriously examine the prospects of success of the attacks directed against it, even after the conclusion of proceedings at first instance, in order to form its own opinion on the protectability of the invention as a basis for the requested injunction. However, this examination has natural, structural limits. In view of the statutory allocation of jurisdiction, which assigns the decision on legal validity of granted patents to the courts of first instance, which are staffed with technical experts, and in view of the fact that only they have in-depth relevant knowledge and experience in the relevant technical field, whereas the infringement courts are only able to make a lay assessment of technical issues due to their purely legal staffing, an infringement court, in its examination of legal validity of the patent, must in principle accept the decision on the maintenance of the injunction patent taken by the competent specialist instance (DPMA, EPO, BPatG) after a technically expert examination and, unless there are special circumstances in the individual case, draw the necessary conclusions by issuing the necessary injunctions to protect the patent proprietor (Senate, judgment of February 19, 2016, file no.: I-2 U 54/15, BeckRS 2016, 6344 para. 12; judgement of December 14, 2017; judgment of September 26, 2019, file no.: I-2 U 28/19, GRUR-RS 2019, 33227 = GRUR-RR 2020, 240 [Ls.] - MS-Therapie; GRUR-RR 2021, 249, 251 - Cinacalcet II; most recently: GRUR-RS 2023, 5166 - Fumarsäureester). 50

There is only reason to question the decision on legal validity of the patent and to refrain from issuing an injunction if the infringement court considers the reasoning of the opposition or nullity instance to be unreasonable or if the attack on the injunction patent is based on (e.g. new) promising aspects which have not yet been considered and decided upon by the authorities previously dealing with the case (Senate, judgment of December 6, 2012, file no.: I-2 U 46/12, BeckRS 2013, 13744; GRUR-RR 2021, 249, 251 f. - Cinacalcet II; most recently: GRUR-RS 2023, 5166 - Fumarsäureester). In contrast, it is generally not appropriate to reject the request for an injunction despite the IP right being upheld at first instance solely because the infringement court substitutes its own (lay) assessment of the technical facts for the assessment by the competent opposition or nullity instance (Senate, judgment of December 18, 2014, file no.: I-2 U 60/14, BeckRS 2015, 01829 para. 17; judgment of February 19, 2016, file no.: I-2 U 54/15, BeckRS 2016, 6344 para. 12; judgment of December 14, 2017; GRUR-RR 2021, 249, 252 - Cinacalcet II; most recently: GRUR-RS 2023, 5166 - Fumarsäureester). This is particularly prohibited if the subject matter is technically complex (e.g. from the field of chemistry, pharmacy or electronics), in relation to which the insights and assessment possibilities of the non-technically trained - Fumarsäureester). 51

While an infringement court can form its own at least reasonably well-founded opinion on complex technical subject matter, if necessary, insofar as it is a question of whether the subject matter of the injunction patent was clearly and directly disclosed in the underlying original application, and possibly also whether the question of novelty can still be considered reasonably independently, the decision as to whether the expert was able to arrive at the invention in an obvious manner from the prior art depends on a profound technical understanding and insight into the technical knowledge, skills and the way of thinking and proceeding of an average expert at the time of priority. Even an experienced infringement court, at least when it is not a matter of simple mechanical inventions but - as here - of complex inventions, generally has no expertise of its own (Senate, GRUR-RS 2023, 5166 - Fumarsäureester). On the other hand, it is the day-to-day task of opposition divisions, boards of appeal and nullity panels to consider, in the narrowly defined technical field assigned to them, what prior knowledge the relevant expert possessed at the relevant time, with what knowledge horizon the person therefore perceived the state of the art and with what strategy attempted to develop it further. Due to their constant and, in case of doubt, many years of dealing with precisely these questions, the courts of first instance have a wealth of experience that puts the handling of the criterion of inventive step on a legally secure basis (Senate, GRUR-RS 2023, 5166 - Fumarsäureester). Against this background, it is inadmissible for an infringement court, which has neither approximately comparable knowledge nor experience with regard to the development work of technicians, to place its own, necessarily entirely lay assessment above the considerations of a well-founded decision on legal validity. 52

At the same time, the technical advantage in knowledge and experience also limits the subject matter for which the priority of the decision on legal validity must be recognized. It does not exist where the infringement court's knowledge and experience deficits, which require it to exercise restraint, do not exist, which is the case if and insofar as purely patent law and/or intellectual property law issues are involved, the appropriate assessment of which does not depend on special technical expertise. 53

bb) 54

Due to the directly comparable interests and decision-making situation, the above also applies if, as in this case, the patent in suit is not (yet) subject to an adversarial legal decision, but is based on a well-founded decision to grant, which was reached subject to notable third-party objections. Under these circumstances, the infringement court must, in case of doubt, refrain from a deviating technical assessment of what the granting authority has decided and can only deviate from its technical assessment if there are really valid reasons. This applies not least because, in case of doubt, its judges will also decide on the attack on legal validity of the injunction patent. 55

It has already been recognized in the case law of the Senate that the decisions of a Technical Board of Appeal of the EPO in particular (the same would apply to the Technical Boards of Appeal of the Federal Patent Court) justify a high degree of trust in their correctness due to their superior position in the legal protection system, which is why a deviation of the infringement court from its findings is only conceivable in very 56

exceptional cases (Senate, judgment of January 21, 2016 - I-2 U 48/15). Since the quality of the decision taken, which is guaranteed by the position of the court of first instance, is decisive for the prominent significance, and not the formal legal process - an opposition or a grant procedure - in which it was reached, the restrictions mentioned for a deviating assessment of technical facts by the infringement court must of course also apply to a decision of the Board of Appeal which was issued after a rejected patent application.

cc) 57

In principle, they are not relativized by the fact that there are conflicting findings of a foreign court, also equipped with technical expertise, on the decision to grant, so that the technical experts disagree on considerable grounds as to whether a particular technical teaching is protectable or not. 58

If the contradictory decisions - such as here the decision to grant by the Technical Board of Appeal and various foreign infringement decisions which have negatively assessed the legal validity of the injunction patent - deal with identical technical facts because they deal with the same technical teaching (sic.: the injunction patent) and the same citations from the prior art, so that the argumentation of one authority is in indissoluble contradiction to the opposing argumentation of the other authority, the existing dispute can naturally not be conclusively decided by the infringement court, which is composed of technical laypersons and is legally prevented from securing external technical expert assistance, which it would need. However, this does not mean that under the aforementioned circumstances it must necessarily be assumed that the legal situation is not sufficiently certain. This is because not just any decision to the contrary that negates the protectability of the invention, which has been made somewhere with the involvement of technical expertise (be it a technical judge or an external expert), can be an obstacle to legal protection. Rather, it is necessary that the opposing finding originates from a decision-maker who has access to the right to injunctive relief because he is involved in the procession of instances provided for the assessment of its legal validity (Senate, judgment of August 31, 2017 - I-2 U 11/17). The fact that only their findings are relevant follows from the statutory jurisdiction regime, which assigns the question of patent grant and validity to technical decision-making bodies, whose findings the infringement courts must respect by following the provisional grant or validity decision with their injunction. However, the allocation of jurisdiction and responsibility established by law not only justifies the injunction in principle, but also limits the extent to which decisions contradicting the act of grant can invalidate the decision issued on the protective right to injunctive relief as a basis for a provisional conviction for patent infringement. This is only conceivable in cases where the provisional positive decision granting a preliminary injunction or decision on legal validity of the injunction patent no longer serves as a reliable basis for the preliminary injunction proceedings, because its content can be expected to be amended with sufficient certainty in further European or subsequent national instances because revoking or nullity findings on the technical facts in question have already been issued there (Kühnen, loc. cit., Chapter G para. 100). 59

However, findings detrimental to the patent proprietor (e.g. of foreign infringement courts) which do not meet these special institutional requirements constitute indications as technically expert statements which the infringement court, although without any binding effect, must nevertheless seriously consider as part of its examination as to whether or not it considers the decision to grant or the decision upholding the validity of the right to injunctive relief to be justifiable (and therefore follows it) (Senate, GRUR-RS 2019, 33227 - MS-Therapie). The more extensive the experience of the foreign instance in dealing with questions of legal validity and the greater the technical expertise available to the foreign decision-maker in his assessment, the higher its indicative value tends to be (Senate, GRUR-RR 2021, 400 - MS-Therapie II). 60

This differentiation - and only this differentiation - ensures effective interim legal protection in favor of the patent proprietor, which is indispensable in the field of generics. Of course, it is conceivable and also realistic that the legal status of a patent will ultimately be assessed differently in different jurisdictions, and this primarily concerns the dispute about the inventive step, which raises a question that has to be weighed up and which can be answered in one direction or the other with equally good reasons in individual cases. Because this is the case, the patent proprietor cannot be denied provisional enforcement of his property right despite a decision to grant or maintain it having been obtained by him, with reference to the fact that a patent office or court elsewhere has reached a (perhaps equally justifiable) contrary result (Kühnen, loc. cit., Chapter G para. 102). 61

New attacks against the legal status not yet dealt with by the granting appeal instance are - as in the case of an opposition or nullity decision upheld at first instance - subject to the proviso that the citation is closer to the invention in comparison with that examined by the appeal instance or, if the attack in question is made for the first time, offers a sufficient prospect of success in itself from the point of view of the infringement court. 62

2.

On the basis of these principles, the legal validity of the injunction patent is not secured to a sufficient extent for the issuance of a preliminary injunction. In retrospect, new findings have emerged from the state of the art which were not yet available to the Board of Appeal at the time of its decision and which give rise to serious doubts as to whether the injunction patent will withstand the oppositions against its grant. 63

a) 64

For the legal assessment, it is of no decisive importance whether the state of the art of the injunction plaintiff 's presentation submitted as Annex FBD 15, the associated press release submitted as Annex FBD 14, the publication by *H et al.* (Annex FBD 22) 65

or the publication by *I et al* (Annex FBD 26), because all statements have the same disclosure content relevant for the assessment of the legal status.

aa) 66

The presentation according to Annex FBD 15 from 2005 reports on the results of a Phase-II-Study with RRMS patients under daily oral treatment with 1.25 mg or 5 mg F (see slides 11 and 15) as well as the announcement of a further arm in the next planned Phase-III-Study with a reduced dose of 0.5 mg F (slide 26). According to the content of the presentation, the daily doses of 1.25 mg and 5 mg F administered showed a significant reduction in the number of Gd^+ lesions compared to the use of a placebo (slide 15), whereby the therapeutic efficacy of the doses mentioned is summarized on slide 24 to the effect that the higher 5 mg dose appears to cause an increase in undesirable side effects (see slides 23 and 24). Slide 24 states in German translation: 67

[...] *Keine offensichtlichen Unterschiede zwischen den Dosierungen in Bezug auf die Wirksamkeit, wobei einige unerwünschte Ereignisse bei höheren Dosierungen häufiger auftreten* [...]“. 68
"[...] *No obvious differences between doses in terms of efficacy, with some adverse events occurring more frequently at higher doses* [...]".

bb) 69

Nothing else is stated in the press release of April 6, 2006 (Annex FBD 14) (acknowledged in the granting procedure). It also reports the same in two groups of patients who were treated daily with F doses of 1.25 mg and 5 mg over a period of 18 months. The press release states the therapeutic efficacy as follows (page 1, 2nd paragraph): 70

"*Data presented at the American Neurological Association (AAN) meeting showed that both groups of patients taking G (1.25 mg and 5 mg) who experienced a greater than 50% reduction in annualized relapse rate compared to placebo during the first six months of the study maintained this low relapse rate during the subsequent 12-month extension period.*" 71

In addition, it is stated that after 12 months of use, the patient group receiving the 5 mg dose was switched to the lower dose of 1.25 mg because it was found that both doses were equally effective, but that the higher dose of 5 mg F led to more severe side effects (p. 1, last paragraph): 72

"[...] *All patients in the extension study will now continue with the 1.25 mg dose, as both the 5 mg dose, which had a higher rate of adverse events, and the 1.25 mg dose were equally effective in reducing disease activity."* 73

A further study arm is announced for the planned Phase-III-Study, which is to be based on a daily dose of 0.5 mg F (p. 2, 2nd paragraph): 74

"*E has started its first Phase-III-Approval-Study named "..." (...) has started. [...] Study participants will be randomized equally to receive either 1.25 mg or 0.5 mg G or placebo once daily for up to 24 months."* 75

The only additional information that can be taken from the (later, from April 2006) press release (Annex FBD 14) in comparison with the (earlier) presentation according to Annex FBD 15 is that the prospective study arm has already started in various European countries. 76

cc) 77

The disclosure content of the citation by *H et al.* (Annex FBD 22) does not go beyond the described information content of Annexes FBD 14 and 15. The document deals with the announced Phase-III-Study, stating the parameters under which the study is to be conducted. In particular, the F doses of 1.25 mg and 0.5 mg planned for administration are emphasized. The penultimate paragraph of Annex FBD 22 expressly informs the expert in this context that no results are yet available for the doses mentioned ("*Results are expected in 2009")* and that the study has accordingly been initiated to investigate efficacy ("*A large randomized, double-blind, placebo-controlled Phase-III-Study (Protocol 2301) has been initiated to further evaluate efficacy and safety of f in patients with RR-MS*."). 78

dd) 79

I et al. (Annex FBD 26) also deal with the Phase-II-Study on study participants suffering from RRMS ("80 *relapsing MS*") who were administered F in daily doses of 1.25 mg or 5 mg. In the conclusion, further studies with lower doses are recommended ("*These data support exploring potentially lower doses of G in future MS studies*."). A daily dose of 0.5 mg is not explicitly mentioned ("*lower doses*"). 80

b) 81

On the basis of the above-mentioned state of knowledge on the priority date (June 27, 2007), it cannot be assumed - as the Regional Court correctly decided following the decision of the Board of Appeal - that the technical teaching of the patent in suit was already disclosed to the expert in a manner prejudicial to novelty, namely directly and unambiguously. Since the invention consists - for a specific purpose - in using the F active ingredient orally in a daily dose of 0.5 mg *for the treatment of RRMS,* and since the Phase-III clinical studies announced in the prior art were only intended to provide certainty as to whether the additional dosage regimen to be investigated can actually bring about the therapeutic success contemplated, it was not part of the knowledge of the expert on the priority date that RRMS can be treated promisingly with an oral daily dose of F of 0.5 mg. 82

c) 83

The published results of the Phase-II-Study have, however, given the specialist - subject to special circumstances? to be discussed later under d)? - have in principle given sufficient reason to consider whether a lower daily dose of 1.25 mg F than the one to be administered orally, which has already proven to be therapeutically effective in the Phase-II-Study, is suitable for the treatment of RRMS. 84

aa) 85

86

The fundamental reason for the search for a lower dosage than that already successfully investigated is already explained by the fact that there is generally an obvious connection between the amount of active ingredient and any side effects of its administration in such a way that a larger dose of active ingredient is often associated with stronger and/or more extensive side effects, so that the expert consideration is suggested to favorably influence the undesirable side effects by a lower (but therapeutically nevertheless or equally useful) dose of active ingredient (Senate, GRUR-RS 2023, 5166 - Fumarsäureester). The fact that the 1.25 mg daily dose in the Phase-II-Study already proved to have only minor side effects does not eliminate the said motivation, because the comparative consideration of the side effect profile of the 5 mg dose justifies the expectation for the expert that a further reduction of the dosage to a value below 1.25 mg will also further reduce the remaining (already minor) side effects and probably eliminate them completely. In the field of MS treatment, this is of considerable importance because patients affected by RRMS have to take medication over extraordinarily long periods of time, possibly even decades, until the end of their lives (Senate, GRUR-RS 2023, 5166 - Fumarsäureester), which also reveals further advantages of a lower dosage of active ingredients beyond a minimal or complete absence of side effects for countless affected RRMS patients. As discussed at the hearing, these are that a patient would have to take less medication per day as a result of a noticeably reduced amount of active ingredient (which in case of doubt makes medication easier under everyday conditions), and that he can also benefit from a lower dose in view of the metabolization of the drug that takes place. 84

bb) 87

Thanks to the Phase-II-Study, the efficacy of a daily F dose of 1.25 mg was proven; however, there was no indication that *this* amount - by chance - was the lowest significantly effective dosage of F found. On the contrary, there was a certain expectation of success simply because it would have been a real stroke of luck if the first and lowest therapeutically effective dose had been found by chance with the minimum daily dose of 1.25 mg F tested. From a technical and scientific point of view, there was therefore considerable reason to assume that the efficacy limit had not yet been determined with the study, but that it was still awaiting clarification (Senate, GRUR-RS 2023, 5166 - Fumarsäureester). In this context, it is not a question of including a further dosage in an extraordinarily extensive, lengthy and costly Phase-III-Study, but rather of obtaining certainty, e.g. in a more cost-effective Phase-II-Study, as to whether and which dose of active ingredient below 1.25 mg is therapeutically effective and less burdensome for the patient (Senate, GRUR-RS 2023, 5166 - Fumarsäureester). This does not change the fact that - as the injunction plaintiff emphasized at the hearing - the earliest possible approval and provision of an effective F-therapy for RRMS patients was an important concern, which made it urgent to continue the clinical studies in the next phase instead of remaining in Phase-II with a new dosage. Apart from the fact that both measures are not mutually exclusive, but can even be carried out by the same company alongside each other in a meaningful way, the specific concerns of the injunction plaintiff, who had already successfully tested the 1.25 mg daily dose in a Phase-II-Study and was in a clinical trial series, are not relevant for the legal assessment, but rather what would have 88

been a possible course of action for any expert. The expert would have had at disposal all conceivable information options that could have provided insights into the therapeutic efficacy of a lower F dose.

It was all the more obvious for the expert to try a 0.5 mg dose in the present case because the various reports on the results of the Phase-II-Study on RRMS patients (Annexes FBD 14, 15, 22) conclude - even for the subsequent, cost-intensive Phase-III-Study with 1,000 (!) subjects - that an F daily dose of 0.5 mg should be included in this study, thus expressly pointing the expert in the direction that was already obvious to him from general pharmaceutical considerations. 89

d) 90

For the question of obviousness, it is therefore decisive whether there were reliable indications for the expert with the knowledge of the priority date that an F daily dose of only 0.5 mg cannot prove to be therapeutically effective, so that attempts to this effect (which would have had to be considered in principle) are superfluous. 91

aa) 92

The mere lack of a reasonable expectation of success is not sufficient, because the "try and see" approach is recognized in the case law of the European Patent Office. It states that a lack of reasonable expectation of success does not lead to the affirmation of an inventive step if, in view of the circumstances of the individual case, the expert would prefer to check whether the possible solution devised by him would work instead of abandoning the project from the outset with the consideration that its success is not certain (Case Law of the Boards of Appeal of the EPO, loc. cit, Section I. D. 7.2 "try and see" situation with reference, inter alia, to T 333/97, T 377/95 of April 24, 2001, T 1045/98, T 1396/06, T 2168/11). In view of this, the affirmation of an inventive step therefore requires a situation in which the attempt must appear to the expert to be futile. 93

bb) 94

The Technical Board of Appeal of the EPO accepted this - without, however, expressly addressing the "try and see" problem - because the state of the art had provided the expert with the knowledge that at least 70% of the lymphocytes circulating in the lymph nodes had to be eliminated for effective treatment of RRMS and that this rate could not be achieved with a daily F-dose of (only) 0.5 mg, which is why the state of knowledge on the priority date "taught away" from the technical teaching of the patent in suit. 95

(1) 96

The first-mentioned circumstance, according to which a threshold value for the reduction of the lymphocyte count by at least 70 % is required for successful therapeutic treatment of RRMS, was taken by the Board of Appeal from the publication by *J et al.* (Annex FBD 16). The Board of Appeal considered the publications by *M et al.* (Annex FBD 17) and *K et al.* (Annex FBD 18) in conjunction with the publication by *N to* justify the expert finding that the required lymphocyte reduction value cannot be achieved with a daily F dose of 0.5 mg. 97

(2) 98

In its assumption in this regard, the Board of Appeal did not overlook, but expressly acknowledged that the initiators of the Phase-II-Study were apparently not driven by the doubts about the potential therapeutic benefit of a 0.5 mg daily dose, because they announced the inclusion of exactly such a daily dose (of 0.5 mg F) for the - even significantly more extensive and costly – Phase-III-Study with a total of 1,000 subjects without hesitation. 99

(a) 100

Nonetheless, the actual design of the Phase-III-Study is a very important indication of the expert's view at the time as to the usefulness of the planned extension of the study design, because the heads of a pharmaceutical study are also technically knowledgeable, pharmaceutical companies that commission and finance such studies do not traditionally invest their money in foreseeably hopeless "research", and the medical treatment of patients suffering from RRMS as part of a Phase-III-Study with a dosage (of 0.5 mg) which - unlike the daily dose of 1.25 mg, which has already been confirmed as therapeutically effective - is clearly not able to achieve anything, would not be ethically justifiable if - as in this case - it is to be given in addition to a placebo group already planned for the study. 101

Under these circumstances, an indicative effect exists all the more as the extension of the daily doses to be examined in the study by 0.5 mg, which was undertaken by the injunction plaintiff and which, according to its current argumentation, was therapeutically foreseeably pointless, was undertaken without any discussion of the problem (which would have been to be expected from the technical point of view of the Board of Appeal) and thus as a matter of course. 102

(b) 103

To the extent that the injunction plaintiff invoked in its pleadings and at the hearing that an amount of active ingredient of only 0.5 mg, reduced by 60 % compared to the 1.25 mg daily dose, was without any prospect of therapeutic success, but was included to speed up the official approval procedure for the 1.25 mg dose in order to clarify the dose-response profile of F, which is important for the drug approval, there are no viable indications for *this* motivation according to the contents of the file. 104

First of all, the one - the facilitation of the desired drug approval for a safely therapeutically effective dosage of 1.25 mg - by no means excludes the other - the gaining of new knowledge about the possible therapeutic usefulness of an (also significantly) reduced daily dosage of 0.5 mg. According to the guidelines of the US Food and Drug Regulatory Authority cited by the injunction plaintiff, Phase-III-Studies not only serve to confirm the findings of the previous studies with regard to efficacy and safety on a broader data basis, but can also have the additional purpose of further clarifying the dose-response relationship or investigating whether there is a treatment potential for other population groups, other disease stages or in combination with other drugs. Even if the Phase-III-Studies were therefore indeed primarily concerned with a rapid drug approval for the 1.25 mg daily dose (for which objective evidence - such as 105

correspondence with the regulatory authority, authentic internal file notes or the like - has not been provided), this does not negate the additional meaningful purpose of discovering a further application for the therapeutic treatment of RRMS by including the 0.5 mg dose in the study.

In addition, as already mentioned, it would be ethically irresponsible to provide hundreds of other sick patients within a Phase-III-Study - in addition to the already planned placebo group - with a dose of active ingredient which - as the injunction plaintiff claimed at the hearing - was certainly known to have no therapeutic effect and which is therefore said to have served the sole purpose of documenting a failure for the regulatory authority. Such a motivational situation must also be ruled out because meaningful findings on the dose-effect relationship of a drug cannot be obtained if a dose that is certainly foreseeably ineffective is tested, but are only conceivable if such a lower dosage is chosen that it is associated with the prospect and chance of a therapeutic benefit. Only under this condition can it be demonstrated to the regulatory authority that the (higher) dose of active substance envisaged for approval (here: 1.25 mg) is therapeutically necessary and can therefore be expected of the patient. For this purpose, in order to exclude the possibility that a therapeutic benefit is also achieved below the amount of active ingredient intended for authorization, it is absolutely essential to test one (or possibly even several) dosage(s) from which the expert can still legitimately expect therapeutic efficacy, because only in this way is it plausible that the amount intended for authorization (here: 1.25 mg) is actually the dose of active ingredient required for treatment. From this perspective, the dose of 0.5 mg is a considerable distance from the 1.25 mg dose successfully tested in Study-II. However, in the absence of any other reasonable explanation that could be considered instead, the expert will nevertheless conclude that the dose in question is associated with a justified expectation of success, which makes it reasonable to include the 0.5 mg dose (without further intermediate doses of e.g. 0.75 mg, 1 mg) in the Phase-III-Study to clarify the question of whether a dose below 1.25 mg is of therapeutic benefit. 106

(c) 107

The actual expansion of the study design, which includes the daily dose of 0.5 mg, nevertheless represents only one (albeit weighty) indication, which means that it must ultimately depend on the assessment of the legal status to be attested to the injunction patent by the Senate, whether a necessarily layman's technical assessment of the circumstances, which is possible for an infringement court alone without a technical expert, raises such doubts about the Board of Appeal's argumentation that the issuance of an injunction is also justified under Art. 50(1) TRIPS and Article 9(1) of the Enforcement Directive, the courts' obligation to effectively enforce intellectual property rights on a provisional basis cannot be justified. 108

It should be borne in mind that the injunction patent can only be revoked if a statutory ground for revocation can be positively established to the satisfaction of the responsible legal instance (which will probably be the Technical Board of Appeal of the EPO within the European instance procedure), so that any remaining doubts that lead to the question of inventive step remaining unresolved are in favor of the patent proprietor and his injunction patent, that, however, if - as here - the invention is generally assumed to 109

be obvious because the expert in principle had reason to search for a lower therapeutically effective dose, and this reason is *exceptionally* said not to exist because the prior art is said to have conveyed to the expert the futility of such an undertaking, the burden of presentation and proof for this lies with the patent proprietor.

bb) 110

The appeal submissions reveal new circumstances not yet taken into account in the decision to grant, which make the considerations of the Board of Appeal no longer appear justifiable and instead lead to the revocation of the injunction patent. They show that on the priority date there was a reasonable prospect that an oral daily F-dose of significantly less than 1.25 mg could prove to be therapeutically useful, so that the announced Phase-III clinical studies with a dose of 0.5 mg do not, from the perspective of an expert, merely represent an undertaking undertaken in the forlorn hope of success, but an attempt which, although not associated with a guarantee of success, is certainly associated with a realistic prospect of success. 111

The new scientific findings are the results of a study financed by the group of companies of the injunction plaintiff, on which *L et al.* (Annex TW 18 in proceedings I-2 U 49/23) report in a specialist publication from 2005. The document is more recent than the publication by *J et al.* from 2004 (Annex FBD 16) used by the Board of Appeal for the allegedly required lymphocyte loss rate of at least 70 % and its content can provide a plausible explanation as to why the injunction plaintiff, after the course of the Phase-II-Study with oral daily F doses of 1.25 mg and 5 mg, included a daily dose of 0.5 mg as a promising alternative in the upcoming Phase-III-Study without further discussion. 112

(1) 113

The publication by *J et al.* referred to by the Board of Appeal is based on experimental model studies carried out with F (*G)* on SJL mice with established relapsing-remitting autoimmune encephalitis (EAE). Without documenting detailed study results, e.g. in tabular or graphical form, the authors record the following findings relevant to the dispute (note: underlining added): 114

"It was originally assumed that ... one effect of in vivo treatment with G (...) was profound lymphopenia [1] in the peripheral blood, with lymphocyte counts falling to 5-10% of control levels at therapeutic doses of the drug. ... It now appears that at least one of the mechanisms by which G achieves its effects in vivo is by sequestering circulating lymphocytes in the peripheral lymph nodes (...)." 115

"As previously reported, during treatment with G ... a dose-dependent and reversible lymphopenia was observed. This reached a maximum reduction of about 70 - 80 % at the highest doses used." 116

117

"In dose-response experiments, we found that a threshold of approximately 70% of peripheral lymphocytes was required to achieve an effect and that the dose-response relationship between clinical benefit and lymphopenia was very steep. Despite these observations, we found an interrupted relationship between lymphopenia and clinical outcomes. ... At the beginning of administration to sick animals, we observed a rapid clinical improvement that occurred before the onset of a significant degree of lymphopenia. After discontinuation of the preparation, there was a delay of 1 - 2 days before the clinical signs began to intensify. ... The correlation between lymphopenia and clinical efficacy is therefore imperfect, and although lymphopenia is a biomarker that correlates with clinical efficacy and may be a mechanism contributing to that efficacy, other mechanisms may also be involved in achieving the overall therapeutic benefit observed in models of transplantation and autoimmune disease."

Although *J et al.* themselves point out that the relationship between the reduction in peripheral blood lymphocyte count and the therapeutic efficacy of F is not an absolute strict one, the Board of Appeal decision does not address this very limitation and the consequences for the practitioner's expectation of success with respect to lower than maximum dosing. 118

In connection with the discussion of the inventive step (clause 7.10), the Board of Appeal decision merely states apodictically that the prior art according to *J et al.*, *M et al.*, *K et al*. and *N* provided the expert with the knowledge that the required lymphopenia (lymphocyte loss of at least 70%) cannot be achieved with a daily oral F dose of 0.5 mg. The more detailed content of the documents is not discussed; instead, the decision refers to the preceding clauses 5.4 (b) to 5.4 (d), which, however, only deal with the question of whether the prior art has made it plausible for the expert that an oral F daily dose of 0.5 mg can be therapeutically effective in the treatment of RRMS, so that the plausibility of a therapeutic benefit does not have to be inferred from the patent application itself. However, it is two fundamentally different things whether the prior art makes it plausible for the expert that a particular dosage regimen can be therapeutically effective, or whether the same prior art gives him the message that a particular dosage regimen is therapeutically doomed to failure with such certainty that it is sensible not even to attempt it. 119

Similar deficits in reasoning exist with regard to the other publications by *M et al.* and *K et al.* dealt with by the Board of Appeal decision. 120

(2) 121

M et al. report on 23 kidney transplant patients who were administered F (*G*) in oral daily doses of 0.25 mg, 0.5 mg, 1 mg and 2.5 mg and in whom "*G was shown to cause a dose-dependent increase in the mean percentage reduction in peripheral lymphocyte counts (...)."* It goes on to say (note: underlining added): 122

"When using lymphopenia as a G-PD surrogate marker, high percentage reductions (approximately 80%) of peripheral lymphocytes are required to achieve the best efficacy in preventing acute graft rejection." 123

The following Fig. 7A of the publication shows the lymphocyte reduction (in %) as a function of the F dose administered. 124

[...]

The detailed evaluation shows that the presumed threshold value of 70 % lymphocyte reduction is reached at a daily F dose of around 1.7 mg, while the lymphocyte loss rate at a dose of 1.25 mg F confirmed as therapeutically effective by the Phase-II-Study is not at least 70 %, but only slightly more than 60 %. A dose of 0.5 mg still shows a lymphocyte reduction of around 45 %.

125

The Board of Appeal does not explain why it should follow from this disclosure - the dose-dependent loss rate of lymphocytes and the finding that the optimal ("best") therapeutic effect is achieved at a loss rate of about 80 % - that below a lymphocyte loss of 70 % and therefore also at a loss rate of e.g. 45 % no useful clinical benefit can be achieved in the treatment of RRMS. This would have been necessary above all because the injunction plaintiff 's own Phase-II-Study showed the efficacy of a 1.25 mg dose and, according to the study findings of *M et al.* for this (therapeutically effective) dose, the allegedly necessary threshold value of a lymphocyte loss of 70 % is not reached, but is missed by a considerable margin.

(3) 126

Finally, the publication by *K et al*. also describes a Phase-I-Study with a total of 61 kidney transplant patients who received daily oral F doses of 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg, 2.5 mg or 5 mg over a period of 28 days. From the graphic below 127

128

[...]

the authors conclude that "*G doses of greater than or equal to 1.0 mg/day led to a significant reduction in peripheral blood lymphocyte counts of up to 85%, which was reversed within 3 days after discontinuation of the study medication."* It also states: 129

"Pharmacokinetic measurements showed that G exhibits linear relationships between doses and concentrations over a wide range ...". 130

The figure below impressively confirms the finding from the study by *M et al.* that a daily F dose of 0.5 mg (open triangles) results in a lymphocyte reduction of between 40 and 50 %. 131

If one takes the documents discussed so far together, the Senate is unable to recognize from what exactly it should have emerged with the necessary reliability on the priority date that an oral daily F dose of 0.5 mg is unsuitable for a meaningful RRMS treatment. 132

(4) 133

However, there is no longer any room for this assumption if the publication by *L et al.* is taken into account, which has not yet been submitted to the Board of Appeal. 134

It is particularly important because it is the evaluation of a comprehensive Phase-II-Dose-finding-Study in which 167 kidney transplant patients were treated with *G at* a dose of 0.25 mg, 0.5 mg, 1.0 mg or 2.5 mg over a period of 3 months. Since the treatment groups of the study (0.25 mg: 43; 0.5 mg: 43; 1.0 mg: 40; 2.5 mg: 41) - with a treatment duration of several months - were significantly larger than those of the other studies on which the Board of Appeal is based, it is not necessary to interpret nominal differences between the groups with caution due to the broad data basis - as is the case with small-scale studies. 135

As a result of the investigations carried out, the paper by *L et al.* states: 136

"The immunosuppressive efficacy of anti-lymphocyte agents is well known; however, the mode of action of G differs in many respects. The apparent decrease in peripheral lymphocytes with G is not related to lymphocyte death, but to increased sequestration during homing to the lymph nodes and Peyer's patches, where the cells are fully active and responsive to immune stimuli. After administration of G, the rapid recovery of a normal lymphocyte count reflects the pharmacology of the drug, and the recovery of all lymphocyte subsets is also complete. 137

... 138

Although depletion of peripheral lymphocytes appears to be a necessary prerequisite for the efficacy of G, these results suggest that the immunomodulatory effect of G is not exclusively mediated by its pharmacodynamic effect on circulating lymphocytes." 139

The subsequent conclusions go on to say (note: underlining added): 140

"G is the first S1P-R agonist to modulate lymphocyte 141 *homing and prevent allograft rejection in preclinical models. In de novo kidney transplant recipients, this study demonstrated that this novel drug at a dose of 1.0 or 2.5 mg/day in combination with a standard dose of CsA has equivalent efficacy to MMF-based therapy for the prevention of acute rejection. ... The trend toward improved rejection prevention in patients treated with G at 2.5 mg/day without increasing the risk of infection or side effects suggests that of the doses examined in this study, G at 2.5 mg/day provides the best balance of safety and efficacy."* 141

The last sentence clearly does not imply that all doses other than 2.5 mg are therapeutically ineffective. With regard to the daily dose of 1 mg, this is already clear from its explicit recommendation in the text quoted above. As far as the even lower doses of 0.25 mg and 0.5 mg are concerned, the publication only refers to them by stating that the "*efficacy parameters of G at doses of 1.0 and 2.5 mg compared to 0.25 and 0.5 mg indicate that the efficacy is dose-dependent*", which also does not mean that the low doses in question certainly lack a therapeutic effect. In order to obtain more detailed information on the open comment regarding efficacy and its actual dependence on the F dose, the expert will therefore refer to Figure 2 of the publication - shown below - which relates to the mean change in the absolute lymphocyte count for all dosing regimens examined. 142

[...]

If the expert compares the loss rate for the 1.0 mg dosage expressly recommended in the publication (triangles) with the loss rate recorded for the 0.5 mg dosage (circles), he will find that the values do not differ significantly. It does not matter that the graphic shows the absolute lymphocyte losses, because regardless of the chosen method of presentation, it is still possible to make a representative statement about the extent to which lymphopenia has occurred under treatment with certain F doses - whether approximately the same or very different. In this respect, Figure 2 shows that although the 0.25 mg dose performs significantly worse in the loss rate (diamond) than all others, this does not apply to the 0.5 mg dose in comparison to the 1.0 mg dose. For this reason alone, it is not clear why it should have seemed hopeless for the expert to at least try an F dose of 0.5 mg. 143

This is particularly true in light of the fact that *L et al.,* with the extensive study they conducted, substantiated the erroneous conclusion already addressed by *J et al. that* the mechanism of action of F is not - as assumed by experts and also taken as a basis by the Board of Appeal decision - essentially based on the loss of lymphocytes, but that other causalities must also be taken into account. However, as long as - as is the case for the priority date - the real connections behind the clinical benefit of F were not reliably clarified and known, the fact that a daily oral F dose of 0.5 mg may not achieve a lymphocyte loss of at least 70% could not lead to the reliable conclusion that a daily 144

dose of 0.5 mg is futile for RRMS treatment. dose of 0.5 mg is futile for RRMS treatment. The expert had to take into account as a serious possibility that the loss rate of lymphocytes is only *one* of several causes for the therapeutic efficacy of F and that the actual mechanism of action, which had not yet been fully discovered at the time, is one that also comes into play at a dose of 0.5 mg.

This possibility was supported by the results of the Phase-II-Study conducted by the injunction plaintiff itself, which had shown that - as cited above (p. 16) - the F doses of 1.25 mg and 5 mg were equally effective in the therapeutic treatment of RRMS. 16) - that the F doses of 1.25 mg and 5 mg proved to be equally effective in the therapeutic treatment of RRMS, which could either call into question the assumption of a linear dose dependency of the efficacy of F or lead to the conclusion that a maximum activity plateau had already been reached with the 1.25 mg dose or - which was not dispelled by anything - with an even lower dose, from which a further amount of active substance would no longer bring any additional therapeutic benefit. In the latter case, however, it is not clear why a dosage (possibly also significantly) below 1.25 mg should no longer be reliably foreseeable as having any meaningful clinical efficacy. 145

Accordingly, *I* as one of the study authors also recommends in a publication prior to the priority date (Annex FBD 26), which was also not submitted to the Board of Appeal, that the "*data* collected with the Phase-II-Study on drug doses of 1.25 mg and 5 mg *speak in favor of exploring potentially lower doses of F in future MS studies.*" When reading this recommendation, it is clear to the expert that a "*lower dosage*" can only meaningfully refer to a dosage that is characterized by a significantly and not just minimally lower amount of active substance. Typically, only under this condition can a noticeable reduction in the side effects and metabolic activities associated with the administration of the active substance and a significant increase in comfort for the patient when taking the medication be expected. 146

(5) 147

Taking into account all sources of knowledge available on the priority date (which were not available to the Board of Appeal at the time of its decision), it can be summarized that there was considerable doubt that the efficacy of F was actually based on a lymphocyte loss of at least 70%, which meant that the exact mechanism of action was open to the expert. The trial with a significantly lower dose of active ingredient than 1.25 mg was therefore not associated with any guarantee of success; however, this is not necessary for an obviousness. Rather, it is sufficient that the uncovered lack of clarity about the cause-effect relationships for the use of a low F-dose justified the chance of a therapeutic effect, which made it worth a try. According to life experience, there is much to suggest that the injunction plaintiff did not assess the situation differently than described above, knowing the dose-finding study by *L et al.* financed by her group and the findings obtained in the study. It is obvious that this is precisely why - firstly - it saw no obstacles to trying an F daily dose of 0.5 mg in the upcoming Phase-III-Study and - secondly - did not even see any need for further explanation of the planned extension of the dosage regimen in its announcement in this regard. 148

III.

The decision on costs is based on Section 91 (1) sentence 1 Code of Civil Procedure (ZPO). 149

There is no need for a ruling on provisional enforceability because this judgment, as a second-instance decision in preliminary injunction proceedings, is no longer subject to appeal (Section 542 (2) sentence 1 Code of Civil Procedure (ZPO)) and is finally enforceable without a specific ruling. 150

Prof. Dr. A	Dr. B	Dr. C	151

---

[1] = unphysiological reduction of the lymphocyte count. 152