Deckblatt Übersetzung

Daten der Übersetzung:

Court/Gericht:	Bundesgerichtshof
Date of Decision / Datum der Entscheidung:	2014-11-11
Docket Number / Aktenzeichen:	X ZR 128/09
Name of Decision / Name der Entscheidung:	Repaglinid

FEDERAL COURT OF JUSTICE

IN THE NAME OF THE PEOPLE

JUDGMENT

X ZR 128/09

Pronounced on:
11 November 2014
Wermes
Judicial Secretary as
Clerk of the court
registry

in the matter

Repaglinid

EPC Art. 56; Patent Act Sec. 4

a) Advantages of the invention to which the skilled person would not have directed his efforts for further development of the prior art, because they have only been shown to be attainable by the invention, cannot determine the technical problem (the task of the invention) underlying the invention.

b) Depending on the circumstances of the technical field and the circumstances of the individual case, it may be obvious to follow any one of several different paths to solve the problem.

Federal Court of Justice, judgment of 11 November 2014 - X ZR 128/09 –
Federal Patent Court

The X. Civil Senate of the Federal Court of Justice, following the oral hearing on 11 November 2014, attended by the presiding judge Prof. Dr. Meier-Beck, the judges Gröning and Dr. Bacher as well as the judges Schuster and Dr. Kober-Dehm

ruled that:

The appeal against the judgment of the 3. Senate (Nullity Senate) of the Federal Patent Court, pronounced on 30 June 2009, is dismissed at the expense of the defendant.

By operation of law

Facts of the case:

1 The defendant was the owner of European patent 589 874 (patent in suit), filed on 21 June 1991 and granted with effect for the territory of the Federal Republic of Germany, the term of protection of which expired during the appeal proceedings, as did that of the protection certificate granted to the defendant (17 August 2013). The patent in suit comprises 7 claims, the first of which reads in the language of the proceedings:

"Use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid as an active ingredient or a physiologically acceptable salt thereof for the preparation of a long-term antidiabetic agent, characterized in, that in comparison with the double single dose in a racemate application unnecessarily high and long-lasting substance loads are avoided, whereby substantially lower active substance plasma levels occur which go beyond the normal advantage of the dose halving in the enantiomer application. "

2 The plaintiffs challenged the patent-in-suit in its entirety in their nullity actions, claiming that its subject matter was not patentable. The defendant

opposed the claims and, in the alternative, defended the patent-in-suit in two limited versions.

3 The Patent Court declared the patent in suit null as requested. In its appeal, which the plaintiffs request to be dismissed, the defendant continues to pursue its motion to dismiss the actions.

4 On behalf of the Senate, Prof. Dr. H. W. , ... , prepared a written expert opinion which she explained and supplemented during the oral proceedings. The parties submitted expert opinions, namely the defendant by Prof. Dr. E. V. (B12, B21, B24), Prof. Dr. S. B. (B13), Prof. Dr. B. T. (B14, B14a) and Prof. Dr. T. L. (B22), the plaintiffs re 1 and 2 by Prof. Dr. O. R. (NiK13) and Prof. Dr. A. B. (NiK14) and the plaintiff re 3 by Prof. Dr. R. W. H. (HBP1, HBP2).

Grounds of the decision:

5 I. The patent in suit concerns the use of the (S)-enantiomer of 2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]-benzoic acid (international non-proprietary name: repaglinide, hereinafter only: repaglinide).

6 1. According to the description of the patent in suit, European patent specification 147 850 (BM5) discloses, inter alia, the racemate of this benzoic acid (code no.: AG-EE 388 ZW, hereinafter also: AG-EE 388) and European patent specification 207 331 (NiK8) discloses two further polymorphic compounds of this racemate. These compounds and their physiologically tolerable salts would have valuable pharmacological properties and act on intermediary metabolism, in particular they would have blood sugar lowering activity.

7 Both enantiomers of this compound, repaglinide (also designated by the code no. AG-EE 323 ZW) and (R)(-)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]benzoic acid (code no. AG-EE 624 ZW, hereinafter only: the (R) enantiomer) had been tested in female rats for their

blood sugar-lowering effect. Repaglinide was found to be the active enantiomer and its effect lasted longer than 6 hours in rats. In humans, the possibility of dose halving compared with the racemate and a relatively long duration of action were confirmed. The human studies also revealed surprising pharmacokinetic properties and therapeutic advantages of repaglinide that were not expected compared with the racemate. Even at the same absolute dose, the levels of repaglinide fell to zero more rapidly than those of the racemate, and in relation to the reduction in blood glucose, the plasma levels of repaglinide were significantly lower than would have been expected if the dose of the racemate had been halved. In addition, the blood glucose-lowering effect occurred more rapidly after administration of repaglinide than with the racemate.

8 The difference between the two enantiomers is that repaglinide is eliminated more rapidly than the (R)-enantiomer despite a relatively long duration of action. After racemate administration, the (R)-enantiomer is therefore not only unnecessary ballast in the same high plasma concentration as repaglinide, but is also present in higher maximum and continuous levels. The rapid onset of blood glucose lowering with repaglinide relative to the racemate is particularly advantageous for diabetics because optimal control of the disease is possible and unnecessarily high and prolonged drug-induced stress on the body can be avoided.

9 2. In the description of the patent in suit a task is not formulated. The defendant sees this in proposing a (long-term) diabetes therapeutic agent with advantageous pharmacological properties compared to the state of the art, in particular with a special pharmacokinetic profile characterized by a rapid onset of action, a low plasma level in relation to the lowering of blood sugar and rapid elimination of the active substance from the blood. This task definition cannot be accepted. There might be no objection to it if it were established beyond doubt that the skilled person had directed his efforts on the filing date specifically and exclusively to the parameters mentioned. However, this is not the case. According to the description, it was only during the inventors' efforts to advance the prior art that repaglinide was found to have the advantageous pharmacokinetic properties mentioned. The determination of the technical problem serves to locate the starting point of the skilled person's efforts to enrich

the state of the art without knowledge of the invention, in order to evaluate, in the subsequent and separable examination for patentability, whether or not the solution proposed for it was suggested by the state of the art. Elements which belong to the patentable solution or which have become apparent during its elaboration are therefore not to be taken into account in determining the technical problem (Federal Court of Justice, judgment of 22 May 1990 - X ZR 124/88, GRUR 1991, 811, 814 - Falzmaschine; judgment of 30 July 2009 - Xa ZR 22/06, GRUR 2010, 44 marginal no. 14 - Dreinahtschlauchfolienbeutel). Accordingly, the patent in suit is based on the problem of providing a (long-term) diabetes therapeutic with improved effect.

10 3. To this end, patent claim 1 proposes:

1. Use of (S)(+)-2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-3-methyl-1-butyl]aminocarbonylmethyl]benzoic acid or a physiologically acceptable salt thereof

2. as active ingredient for the preparation of a long-term antidiabetic agent,

3. wherein, in comparison with the double single dose in a racemate application

- unnecessarily high and long-lasting substance loads are avoided,

- resulting in substantially lower drug plasma levels beyond the normal dose halving advantage of enantiomeric application.

11 By auxiliary claim I, the compound is claimed according to feature 1 in an optical purity of at least ee = 98% and is claimed according to auxiliary claim II with the further addition in feature 2 as a long-term antidiabetic agent in human medicine in the form of tablets with a single dose of 0.5, 1.0 or 2.0 mg; feature 3 is omitted according to this auxiliary claim.

12 II. The Patent Court left open whether the subject matter of claim 1 is new compared to the citations BM5 and NiK8 discussed in the patent

specification in suit, and assumed that it had been suggested to the skilled person by the prior art in all defended versions. It essentially reasoned as follows.

13 On the filing date, the skilled person, an experienced organic or pharmaceutical chemist who was part of a team, had indeed been offered several documents disclosing benzoic acid derivatives with a blood sugar lowering effect. However, in BM5 - in addition to 2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-1-butyl]aminocarbonylmethyl]-benzoic acid (claim 5, compound B of the composition, description column 12) - the racemate of the compound protected by the patent in suit was highlighted by a separate claim (claim 6). Moreover, in BM5, the activity of the S-(+)-enantiomer of compound B was shown (compound E, description p. 12). In addition, NiK8 showed that the high-melting form B of AG-EE 388 in animal experiments under the test conditions of BM5 (column 12, lines 45 to 63) already caused a sustained high reduction of the blood glucose level for at least four hours with a substance application of only 0.1 mg/kg (NiK8, p. 6, lines 22 to p. 7, line 15). No other compound had shown a comparably favorable, consistently high and long-lasting blood glucose-lowering effect in animal studies, taking toxicity and other side effects into account.

14 In the selection of AG-EE 388 and its enantiomers for further investigations guided by this, the skilled person is supported by the studies documented in the paper "Evidence for more than One Binding Site for Sulfonylureas in Insulin-secreting Cells" by Verspohl et al, J. Pharmacol. 1990, 230 ff. (BM9), which dealt with the binding sites in insulin-secreting cells for blood-sugar-lowering sulfonylureas in comparison with other blood-sugar-lowering benzoic acid derivatives, including AG-EE 388 (as compound I, see BM9 p. 230 and "Abstract"). There, not only the inclusion of the benzoic acid derivatives in the study documented in BM9 is justified by the availability of enantiomers of these benzoic acid derivatives (BM9 p. 230 left column fourth last line to right column line 5); the studies in BM9 also showed that the (+)-enantiomer of compound II, which is structurally close to AG-EE 388, causes the lowering of blood glucose. In addition, it is clear from this that AG-EE 388 is not only superior to the sulfonylureas, but in particular also to the racemic mixture of compound II (BM9 p. 232 right column last paragraph in conjunction

with p. 233 Table I and p. 233 Table II). p. 233 Table I and p. 231 left column, paragraph 1). On the basis of these indications, repaglinide had to be subjected to further preclinical and clinical investigation from the skilled person's point of view as the most likely effective enantiomer of the racemate claimed in claim 6 of BM5.

15 From the experimental report (BM5a) submitted in the examination proceedings of BM5 before the European Patent Office, there was nothing that could have prevented, from a technical point of view, the selection of the compound of claim 6 in BM5 as the active ingredient for the development of a long-term antidiabetic agent.

16 By choosing BM5 as the starting point for the skilled person's development considerations and the starting point for the assessment of the inventive step, this document was not given any unjustifiable priority over other documents to be considered. Rather, the selection of repaglinide and its inclusion in clinical trials for the skilled person resulted solely from the particular constellation of the state of the art. No other benzoic acid derivative is in the field of vision of the skilled person with regard to its blood sugar lowering effect as AG-EE 388 and thus also its (+)-enantiomer.

17 The additionally found advantage of the substantially lower active substance plasma level, which goes beyond the normal advantage of halving the dose when using only the one active enantiomer in relation to the use of the mixture, does not put the question of inventive step in a different light, because this additional effect occurs by itself in the course of the investigations suggested by the state of the art.

18 The subclaims referring back to patent claim 1 were also not capable of being maintained. Specifying the individual dose required for the therapy between 0.25 and 5 mg or concrete individual doses of 0.5, 1.0 or 2.0 mg did not require inventive step, especially since BM5 (column 13 lines 40 to 42) and NiK8 (p. 8 lines 7 to 9) had specified a dose range or the order of magnitude.

19 The application of the (+)-enantiomer in a purity of at least ee = 95% or at least ee = 98% was also not inventive, especially since a synthesis or

purification in the respective purification step from the racemic mixture could be carried out without further ado by means of the data in BM5, as shown by the embodiments of the patent in suit, in which exactly these usual working methods were applied (cf. BM5 claim 11, column 39 lines 25 to 30 in connection with column 31 example 15). column 31 example 15).

20 III. The appeal attacks this assessment without success.

21 1. The Patent Court did not err in law in assuming that the compound according to claim 6 of BM5, i.e. AG-EE 388, had to appear to the skilled person, who according to the findings in the judgment under appeal and the expert opinion of the court experts could, if necessary, draw on the knowledge of pharmacists, biologists and physicians experienced in drug research, as a particularly suitable starting point in the search for an improved long-term antidiabetic agent.

22 Admittedly, as the defendant argues with regard to several documents introduced in the proceedings (European patent applications 58 779, 208 200, 239 815 and 305 845, German published application 37 18 638, experimental report BM5a), but the Patent Court also considered, not only AG-EE 388 may have been considered as a starting point for further investigations. However, the decision in favor of this compound as a starting point is not an expression of inventive activity, but represents a selection from a generally manageable number of alternatives which, for the reasons pointed out by the patent court, were particularly suitable for further investigations and from which AG-EE 388 again stood out.

23 a) According to the test report on BM5 (BM5a), no other substance investigated exhibits a stronger effect than AG-EE 388 (there: compound F2) when comparing the effects of a dose of 0.5 mg/kg over the investigated duration of four hours. If, as can be seen from the table below, NiK8 also shows that an only insignificantly lower effect can be achieved with one fifth of the dose, this indicates, as the Patent Court rightly assumed, a potency that gave the skilled person reason to take a closer look at the compound:

24

Blood sugar lowering effect	1	2	3	4 Hours
Dose according to BM5a (0.5 mg/kg)	-45 %	-44 %	-47 %	-43 %
Dose according to NiK8 (0.1 mg/kg)	-38 %	-44 %	-41 %	-40 %

25 The fact that comparable measurements for other compounds at a dosage of 0.1 mg/kg are not known does not call into question the choice of this compound as the starting point for further investigations. Due to the good values in BM5 and NiK8, the skilled person could easily be sure to have found a promising candidate in AG-EE 388. This applies all the more as this compound had also performed well in terms of quality in test B9 (there as compound I).

26 b) Contrary to the view of the defendant, it cannot be assumed that the skilled person working on the filing date of the patent in suit would not have considered the property of the sustained high blood sugar-lowering effect of a compound over four hours to be worthy of preference. It is true that this is not entirely consistent with the requirement profile of a medicinal product with a meal-appropriate effect. For a meal-appropriate effect, the effect of the antidiabetic drug taken preprandially should start as quickly as possible, but to avoid hypoglycemic states, it should subside in unison with the blood glucose level normalizing postprandially. From this perspective, compounds such as C1, D1, E and J1 in the table of BM5a or compounds K to N from European patent application 208 200 (BR41, p. 35) may well have been plausible candidates. However, the oral proceedings did not show, nor is it otherwise evident, that the skilled person's search grid was already oriented to this understanding of a meal-appropriate medication on the filing date of the patent in suit. This is evidently based - the oral hearing did not reveal any findings to the contrary - on the fact that the skilled person's search at that time was still determined by the pharmacokinetics of the sulfonylureas commonly prescribed until the

approval of repaglinide in 1997, which, as long-acting drugs, were generally taken only once or twice a day (Mark, B1 p. 3 marginal no. 9, see also Bornstein, B13 p. 5 sub 2.2). The patent in suit is also characterized by this orientation, as can be seen from the fact that the effect of the (S)-enantiomer (AG-EE 623 ZW) lasting longer than 6 hours on the rat is emphasized as an advantage (description para. 3).

27 That this basic orientation would have been overcome on the filing date of the patent in suit is not apparent from the US patent specification 4 873 080 (RWH3) submitted. There it is indeed articulated as a problem that with oral antidiabetics the substance effect starts too late, the maximum effect is often only reached when the blood glucose values already drop after food intake even without medication, and the effect lasts even when the blood glucose has already reached the initial value again. However, the document seeks solutions at the level of an improved release profile through essentially galenic measures, without questioning the compounds used, for example, because of the course of their action as such and considering their replacement by substances with a more favorable action curve.

28 c) From a skilled person's point of view, BM5 and NiK8 are not questionable as a starting point for further investigations because the results there were based solely on experiments in rats.

29 For reasons of medical ethics alone, the testing of drug candidates begins with their experimental use in animals. Prof. T. (B14 p. 7 = B14a p. 8 f.) describes the rat as the most suitable laboratory animal for this purpose. The objection that these tests merely represent exclusion filters for ineffective compounds (see also Verspohl, B12 p. 13, Mark, B1 p. 4 para. 13) falls short. According to the entire content of the negotiations and the taking of evidence (Sec. 286 Code of Civil Procedure), it must rather be assumed that the skilled person sees reason for further tests in the case of compounds that prove to be effective in the rat test, even if these tests do not allow any predictions to be made about the pharmacokinetics in humans (suffering from diabetes). As Prof. B. (NiK14 p. 4) convincingly explained, the data obtained in a professionally accepted study model, such as the animal model with rats in this case, have, from a skilled person's point of view, a certain informative value for the possibility

of developing a drug suitable for use in humans. This was confirmed by the hearing of the court experts, and the defendant also does not demonstrate a criterion for the selection of promising active ingredient candidates that is superior or even equivalent to the proof of blood sugar-lowering efficacy in rats. Rather, the patent in suit also assumes the significance of the results of corresponding animal experiments when it is stated in its description that, on the basis of the findings obtained in the rat, the exclusive use of repaglinide for humans appears to be advisable (para. 4). Although this assessment refers to the solution proposed by the patent in suit, it confirms the general significance and potential informative value of rat experiments even before the filing date.

30 2. The Patent Court also rightly assumed that the skilled person had sufficient concrete reason on the filing date to turn to the enantiomers of AG-EE 388 on the basis of BM5 and NiK8.

31 Contrary to the view of the defendant, not every other skilled person's decision than the one to further develop AG-EE 388 into a drug that can be approved can be dismissed as an "unrealistic scenario". Advancing the approval of AG-EE 388 to a marketable drug may have been favorable, especially for skilled persons from a company which, like the applicant of the patent in suit, had already investigated this compound and had patent protection for it (BM6, NiK8). However, the group of skilled persons to be considered is not limited to this. Furthermore, the search for analogous compounds, galenic development possibilities or combinations with known antidiabetics discussed by the defendant in another context or the search for active compounds with deviating side chains mentioned by the co-inventor Dr. M. (B1 p. 5 no. 16) may have been worth considering. However, it is not necessarily always the case that only one alternative course of action within the meaning of Art. 56 EPC and Sec. 4 Patent Act is obvious. Rather, depending on the circumstances of the field of technology concerned, various possibilities for further action may present themselves to the skilled person, and accordingly it is recognized in the case law of the Federal Court of Justice that taking different paths may be obvious (Federal Court of Justice, judgment of 22 May 2007 - X ZR 56/03, GRUR 2008, 56 marginal no. 24 - Injizierbarer Mikroschaum; judgment of 6 March2012 X ZR 50/09, juris marginal no. 19, both with further references). In the case in dispute,

the obvious measures included in any case dealing with the enantiomers of AG-EE 388.

32 a) On the filing date of the patent in suit, according to the expert opinion of the court experts and the statements of the experts commissioned by the parties, it was known, among other things, that enantiomers differ in their interaction and pharmacokinetics, since they interact differently with the body's own receptors, that one enantiomer of an active ingredient known as a racemate has a better effect and that the other enantiomer can have opposite or even toxic effects. This is consistent with the findings of the Senate in a legal dispute in which the relevant priority date of the enantiomer protected there was around three years (14 June 1988) before the filing date of the patent in suit (Federal Court of Justice, judgment of 10 September 2009 Xa ZR 130/07, GRUR 2010, 123, marginal no. 38 Escitalopram).

33 b) In addition, a study of sulfonamides that are structurally related to benzoic acid derivatives and have blood glucose-lowering activity was known, according to which the (S)-enantiomer was significantly more active than the (R)-enantiomer in the compounds studied there and in which in this respect a 30-fold dose difference for achieving the same effect in mice/rats was reported (Rufer et al., Blood Glucose Lowering Sulfonamides with Asymmetric Carbon Atoms, J. Med. Chem. 1974, 708 ff). In a follow-up article, these results were supplemented and the example of a higher blood glucose-lowering effect of an S- versus an R-configured benzoic acid was also presented (Rufer et al., Blood Glucose Lowering Sulfonamides with Asymmetric Carbon Atoms, Related N-Substituted Carbomoylbenzoic Acids, J. Med. Chem. 1979, 750 ff.).

34 On the filing date, enantiomers of benzoic acid derivatives were particularly suitable for further development because the latter had become an alternative to the second-generation sulfonylureas available at that time (cf. Verspohl, B12 p. 3). The derivative AZ-DF 265 had caused hypoglycemia in rats with broadly the same efficacy as the most potent hypoglycemic sulfonylurea glibenclamide, which "was the standard in the early 1990s and against which every oral antidiabetic had to be measured" (Verspohl, loc. cit., p. 3). The study by Garrino and Henquin (Highly potent and stereoselective effects of the benzoic acid derivate AZ-DF 265 on pancreatic β-cells, Br. J. Pharmacol. 1988,

61 ff.) ties in with these findings, which were first presented at a congress by, among others, the co-inventor of the patent in suit G. (abstract NiK15 = RWH2). Thereby, as also mentioned above and confirmed by the forensic expert, as a result of the experiments conducted there, the (-)-AZ-DF-265 enantiomer is assigned a significantly higher efficacy than the other enantiomer. As can be seen from RWH3, there have also been human trials for AZ-DF 265, albeit to a lesser extent.

35 In BM9, where in addition to AG-EE 388 (as compound I) the closely related AG-EE 86 and its two enantiomers were investigated (compound II), it was found that the (+)-enantiomer had a significantly more favorable effect with regard to blood glucose lowering than the racemate, while the ()-enantiomer had proved to be comparatively ineffective.

36 c) The doubts of the court expert as to whether the skilled person on the filing date could have been prepared to rely on the potential of an enantiomerically pure active ingredient to solve the problem are, as she explained in more detail at the oral hearing, essentially based on her assessment of the scientific discussion documented by the parties. This, however, reveals a controversial and detailed debate of the pros and cons of the use of racemates or their enantiomers already some time before the filing date of the patent in suit. The publications of a pronounced advocate of the exclusive use of the latter, Ariëns, date from 1984 and 1986 (Stereochemistry, a Basis for Sophisticated Nonsense in Pharmacokinetics and Clinical Pharmacology, Eur. J. Clin. Pharmacol. 1984, 663 ff. = NiK5; Chirality in bioactive agents and its pitfalls, TIPS 1986, 200 ff. = NiK4). T. considered this to be an oversimplification which ran the risk of not doing justice to the complexity of the respective subject matter (Chirality aspects of drug metabolism, TIPS 1986, 60 ff.) and advocated the testing of enantiomers for their specific suitability in individual cases (in this sense also T. , B14 p. 13 f. = B14a p. 16). However, this position presupposes a closer examination of the properties of the enantiomers and the racemate in the individual case before a decision is made on the pros and cons of using an enantiomer or the racemate. As far as the forensic expert referred to a strong increase in scientific publications (only) in 1991, this refers to the stereoselective synthesis of

enantiomers, i.e. it only concerns a new form of enantiomer extraction.

37 The fact that the technical awareness of the development possibilities associated with the use of enantiomers was already pronounced well before the filing date of the patent in suit is also indicated by the fact that the guidelines of the U.S. Food and Drug Administration published in 1987 (NiK9) contain the recommendation to separate asymmetric active ingredients into their stereoisomers and to investigate them. This is also consistent with the enantiomer policy approved by Dr. Karl Thomae GmbH in 1989 ("enantiomer policy", HBP3 para. 260), which is based on the assessment that racemates will in future be regarded by regulatory authorities as 50:50 mixtures of biologically different substances to be characterized in terms of their efficacy and safety, and that a forced movement towards the development of enantiomerically pure active substances results from the necessary minimization of development time and costs as well as in order to comply with the current state of the art. Although this assessment is only internal to the company, it confirms that there was already reason to deal with enantiomers in the technical field of the patent in suit before the filing date, also with a view to the approval of an active ingredient under pharmaceutical law.

38 d) The fact that the favorable blood sugar lowering values were essentially verified (only) for the rat did not call into question the skilled person's sufficient expectation of success with regard to the possible uses of the enantiomers of AG-EE 388 in diabetes therapy (on the criterion of sufficient expectation of success cf. Federal Court of Justice, judgment of 15 May 2012 X ZR 98/09, GRUR 2012, 803 marginal no. 46 Calcipotriol monohydrate), but caused him to continue on the intended and usual path up to the marketable and approved drug (see in this regard, for example, T. , B14 p. 3 et seq. = B14a p. 4 et seq.). For the reasons already explained (above para. 28 f.), favorable results found in rats gave reason to strive for use in humans (cf. description of the patent in suit, para. 4) as long as no obstacles or other circumstances arose as a result of these experiments which, from a technical point of view, made it no longer advisable to continue along the path taken. The defendant is not able to show such obstacles and circumstances, and they are also not otherwise evident.

39 aa) Setbacks with other benzoic acid compounds (the development of AZ-DF 265 into a marketable drug ultimately failed due to its lack of bioavailability in humans, and compound II investigated in BM9 later proved to be teratogenic and for this reason unsuitable for use as a human drug) did not deter the skilled person from addressing the enantiomers of AG-EE 388, if only in view of the possibility, of which he was aware, that small structural differences can have large effects (expert opinion p. 12).

40 bb) From an expert point of view, there was also no reason to turn away from the enantiomers of compound AG-EE 388 because the experiments documented in B5 had shown essentially identical values for the (R)-enantiomer (compound E) of AGEE 388 - structurally very similar - compound B and for compound B itself when administered at 0.5 mg/kg each (BM5 p. 7 f.). The controversial scientific statements of Prof. V. and Prof. H. on this finding show that this measurement result on two compounds can be interpreted differently. The fact that the view represented by Prof. V. would have prevented the skilled person from turning to the enantiomers of AG-EE 388, especially since in B9 the (+)-enantiomer of a compound which is structurally also closely related to AG-EE 388 is found, differing only by the absence of an ethoxy and a methyl group, although later found to be teratogenic, had proven to be very active and effective in comparison to the racemate and the (-)-enantiomer and the skilled person was aware, as already explained, that even small structural deviations can trigger significantly different effects.

41 cc) The fact that the Federal Court of Justice did not consider the provision of an enantiomer to be obvious in a special case (Federal Court of Justice, GRUR 2010, 123 marginal no. 42 et seq. Escitalopram) does not give rise to a different assessment of the dispute. This was based on the fact that there was no obvious way for the skilled person to get hold of the enantiomers of citalopram on the filing date there. Such or comparable difficulties are not at issue for repaglinide. It is true, as the expert witness correctly pointed out, that enantioselective synthesis was still in an early phase of development at the time. However, Prof. R. has pointed out that such an enantioselective synthesis was not necessary for the production of the enantiomers of AG-EE 388, because - as the forensic expert also assumes (expert opinion p. 13 below) - other

techniques were established for this purpose, such as recrystallization with an enantiomerically pure auxiliary such as phenylethylamine (cf. iE NiK13 p. 6 f.). Other documents also suggest that the preparation of the enantiomers of AG-EE 388 did not present serious difficulties to the skilled person at the filing date. The enantiomers of AZ-DF 265 studied by Garrino and Henquin had been synthesized by the co-inventor of BM5 Dr. Hurnaus for Dr. Karl Thomae GmbH (BM8, p. 62 l. sp. below). This company had also provided V. et al. with the enantiomers of compound II there (2-ethoxy-4-[N-[1-(2-piperidino-phenyl)-1-butyl]aminocarbonylmethyl]-benzoic acid [AG-EE 86]) (BM9, p. 231 above). The co-inventor of the patent in suit, Dr. M., reported that after a search for a licensee for the racemate of repaglinide had begun in late 1989 or early 1990, both enantiomers of this compound had been synthesized (B1, p. 6 at n. 20). In this respect, there is no mention of significant difficulties in the production.

42 dd) Finally, it cannot be assumed that the skilled person would have allowed himself to be deterred from a closer examination of the enantiomers of a compound such as AG-EE 388, which is so promising with regard to its blood sugar-lowering effect in animal experiments, by the prospect of ultimately having to develop an enantiomer-specific bioassay (ELISA test) for investigating the stability of the enantiomer in human patients, especially since it cannot be assumed that the development of such an immunological method would have required inventive activity. The co-inventor Dr. M. only states that the development took approximately one year (B1, p. 7 para. 22; similarly Prof. T. , B14 p. 20 = B14a p. 23); expert opinion L. only emphasizes the difficulties ("failure was possible", B22, p. 6).

43 e) The subject matter of claim 1 is not patentable because the exposed activity of just the (S)-enantiomer was recognized. In view of the fact that in general one of the two enantiomers is more active than the other (expert opinion p. 12; cf. also EPO T 296/87, OJ EPO 1990, 195, 209 [insofar not published in GRUR Int. 1990, 851] - Enantiomers/HOECHST) and in view of, in particular, the findings published in BM7 and BM8 as well as NiK15 (= RWH2), there were clear indications that the blood sugar lowering effect of the (S)-enantiomer could be (significantly) stronger than that of the (R)-enantiomer, which is why the court expert convincingly stated that the higher effect of

repaglinide compared to its (R)-enantiomer was not a surprise based on the previously published data (expert opinion p. 12).

44 f) Repaglinide's rapid onset of action and rapid excretion from the plasma also do not qualify it for patentability. These are additional, albeit unexpected and surprising effects which, according to the case law of the Federal Court of Justice, cannot in themselves justify the assumption of inventive achievement (see Federal Court of Justice, judgment of 12 February 2002 - X ZR 68/99, GRUR 2003, 317, 320 Kosmetisches Sonnenschutzmittel I; BGH, GRUR 2010, 123 marginal no. 41 Escitalopram).

45 IV. The patentability of patent claim 1 in the version of the auxiliary requests is to be denied for the reasons of the Patent Court judgment, which the appeal does not challenge with substantial objections.

46 V. The decision on costs is based on Sec. 121(2) sentence 2 Patent Act in conjunction with Sec. 97(1) Code of Civil Procedure.

Meier-Beck Gröning Bacher

Schuster Kober-Dehm

Previous instance:

Federal Patent Court, judgment of 30 June 2009 – 3 Ni 28/07 (EU) –