



HOFFMANN EITLE

**D16A**

Translation of the Judgment issued by the Regional Court Dusseldorf, as pronounced on 19 November 2015

HE File: 184 570 / nlj

4c O 62/15

Pronounced on 19 November 2015  
Brassel, Chief Court Clerk  
as Registrar of the Court Registry

**Regional Court Dusseldorf**

**IN THE NAME OF THE PEOPLE**

**Judgment**

In the provisional injunction proceedings of

**AstraZeneca AB**, legally represented by the Vice President Mats Peter Berglund, 15185 Södertälje, Sweden,

- Petitioner -

Attorneys of Record: Attorney at Law Dr. Schüßler-Langeheine and the other attorneys at law of the law firm Hoffmann Eitle, Arabellastrasse 30, 81925 Munich, Germany,

versus

**Hexal AG**, legally represented by its Board Members Dr. Andreas Eberhorn, Ms. Sandrine Piret-Gérard, Mr. Wolfgang Späth, Mr. Matthias Weber and Mr. Dieter Ziebold, Industriestrasse 25, 83607 Holzkirchen, Germany,

- Respondent -

Attorneys of Record: Attorney at Law Tellmann-Schumacher and the other attorneys at law of the law firm Arnold Ruess, Königsallee 59A, 40215 Dusseldorf, Germany,

following the Hearing of 29 October 2015, the 4c Civil Chamber of Regional Court Dusseldorf, composed of the Presiding Judge at the Regional Court Klepsch, the Judge at the Regional Court Dr. Heidkamp-Borchers and the Judge at the Regional Court Dr. Büttner,

held:

- I. Petitioner's request for the issuance of a provisional injunction is rejected.
- II. The costs of the proceedings are to be borne by Petitioner.
- III. The Judgment is provisionally enforceable.

#### FACTS OF THE CASE

Petitioner is the registered and sole proprietor of the European patent EP 2 266 573 (hereinafter: "Injunction Patent") which was filed on 8 January 2001 claiming two British priorities of 10 January 2000 (GB 0000313) and 12 April 2000 (GB 0008837), and mention of grant of which was published on 17 June 2015. The Injunction Patent relates to a fulvestrant formulation.

Claim 1 of the Injunction Patent has the following wording:

"A pharmaceutical formulation for use in the treatment of breast cancer by intramuscular injection, wherein the pharmaceutical formulation comprises fulvestrant, a pharmaceutically-acceptable alcohol being a mixture of 10 % weight of ethanol per volume of formulation and 10 % weight of benzyl alcohol per volume of formulation, and the formulation contains 15 % weight of benzyl benzoate per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45 mgml<sup>-1</sup> of fulvestrant, wherein the ricinoleate vehicle is castor oil, and wherein the total volume of the formulation is 6 ml or less."

On 29 October 2015, Respondent lodged an opposition against the grant of the Injunction Patent and requested that the Injunction Patent be revoked in its entirety.

The Injunction Patent belongs to the same patent family as EP 1 250 138 which is the subject matter of the parallel proceedings 4c O 61/15 before the ruling Chamber. The Injunction Patent is a divisional application of the injunction patent of the parallel proceedings. Gedeon Richter Ltd. lodged an opposition against the injunction patent of the parallel proceedings. With the Decision of 27 November 2008, the Opposition Division rejected the opposition. Upon Opponent's appeal directed against this, the Board of Appeal of the European Patent Office reversed the contested decision, and referred the matter back to the Opposition Division for further handling. As grounds, the Board of Appeal stated (Exhibit AR 4) that various documents, *inter alia* McLeskey et al., "Tamoxifen-resistant fibroblast growth factor-transfected MCF-7 cells are cross-resistant *in vivo* to the antiestrogen ICI 182,780 and two aromatase inhibitors", Clinical Cancer Research, Volume 4, pages 697 to 711, March 1989 (Exhibit NiK10 of Exhibit HE 3, hereinafter referred to as D13 or McLeskey), had not yet been acknowledged by the Opposition Division since these were only introduced in the appeal proceedings. In its Summons to the oral proceedings of 7 November 2014, the Opposition Division stated that D13 could represent a bar to the novelty of the granted patent. On 30 December 2014, Opponent withdrew the opposition. With the Briefs of 2 January 2015 and 22 January 2015, Petitioner amended the claims. With the Brief of 26 January 2015 (Exhibit HE 26/26a), third-party observations were asserted against the patentability of the Injunction Patent also with regard to the amended claims. With the Decision of 11 February 2015 (Exhibit HE 2/2a), the injunction patent in the parallel proceedings was maintained in the restricted scope of the last filed requests. No oral proceedings were held.

Petitioner is part of the AstraZeneca group, a pharmaceutical company; Respondent is a company distributing generic medicaments.

With the letter of 26 August 2015, Respondent informed Petitioner that it intended to distribute a medicament with the designation "*Fulvestrant Hexal 250 ml Injektionslösung*" (hereinafter referred to as Contested Embodiment). In November 2015, the Contested Embodiment was supposed to be offered in the *Lauer-Taxe*. With the letter of 2 September 2015, Petitioner asked for more detailed information regarding the quantitative composition of the Contested Embodiment. Thereupon, Respondent specified

the composition with the letter of 3 September 2015. Subsequently, Petitioner issued a warning letter, dated 16 September 2015.

Respondent refused to issue a cease-and-desist declaration subject to penalty by referring to the lack of validity of the Injunction Patent. It is undisputed between the parties that the Contested Embodiment makes use of the teaching of the invention, as protected by patent claim 1 of the Injunction Patent.

With the Brief of 23 September 2015, as received by the Court on 24 September 2015, Petitioner requested the issuance of a provisional injunction.

Petitioner is of the opinion that there is both a claim for an injunction and a ground for an injunction. Petitioner also argues that the interests have to be weighed in its favor.

There is a claim for an injunction since the Contested Embodiment undisputedly makes use of the teaching according to the Injunction Patent.

In addition, the validity of the Injunction Patent is sufficiently established. The Injunction Patent was granted after extensive third-party observations. Another argument for the validity is that the injunction patent of the parallel proceedings was maintained – after a restriction – by the Opposition Division. Petitioner moreover stated that the objections raised by Respondent against the validity of the Injunction Patent are not likely to be successful. The Injunction Patent protects a specific use, for which there are no indications in the prior art.

Moreover, another argument for the issuance of a provisional injunction is that, in addition to the decision confirming the validity, this also constitutes an exceptional case within the terms of the “*Harnkatheterset*” case law that justifies the issuance of a provisional injunction. The reason for this is that what is presently at issue is the market entry of a generic medicament. There will be an irreversible decline in prices, and therefore Petitioner fears considerable damages.

Petitioner requests

- I. that Respondent be prohibited by way of the provisional injunction

from evidently preparing a pharmaceutical formulation comprising fulvestrant, a pharmaceutically acceptable alcohol being a mixture of 10% weight of ethanol per volume of formulation and 10% weight of benzyl alcohol per volume of formulation, and the formulation contains 15% weight of benzyl benzoate per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least  $45\text{mgml}^{-1}$  of fulvestrant, wherein the ricinoleate vehicle is castor oil, and wherein the total volume of the formulation is 6 ml or less, by recommending in the patient information leaflet the use in the treatment of breast cancer by intra-muscular injection,

and from offering, putting on the market or using or importing or possessing for the aforementioned purposes in the Federal Republic of Germany medicaments adapted in this manner.

- II. that Respondent be threatened as an execution measure for each instance of contravention of the court prohibition with a disciplinary fine of up to EUR 250,000.00 – alternatively detention – or detention of up to six months, and in the event of repeated contravention of up to a total of two years, to be executed on Respondent's legally authorized representative.

#### Respondent requests

that the request for issuance of a provisional injunction be rejected.

Respondent is of the opinion that there is no ground for an injunction. There is no decision confirming the validity. The decision of the Opposition Division relating to the injunction patent of the parallel proceedings does not support the validity of the Injunction Patent either. This decision was not issued in adversarial proceedings. The opposition had been withdrawn – undisputedly – before Petitioner amended the patent claims originally directed at a pharmaceutical composition into use claims. No oral proceedings were held regarding the amended claim version. Accordingly, the Injunction Patent will prove to be invalid in the nullity proceedings. The citations submitted by Respondent against the validity of the Injunction Patent either anticipate the subject matter of the invention or, in any case, constitute a bar to inventive step. Moreover, Respondent stated that the novelty of the invention according to the Injunction Patent is barred by the objection of prior public use. Dr. McLeskey and her team had been

provided with the composition according to the invention without confidentiality as regards the use thereof. However, Petitioner has refused for more than one year to participate in clarifying the facts. Moreover, all statements of Dr. McLeskey in the parallel US proceedings regarding these facts have been placed under a protective order. This persistent refusal to participate in clarifying the facts had to be considered in favor of Respondent when weighing the interests.

Petitioner disputes the submission.

With respect to the further circumstances of the case and status of the dispute, reference is made to the briefs exchanged between the parties and the enclosures thereof.

### GROUND FOR THE DECISION

The request for the issuance of a provisional injunction is admissible, but unfounded.

### I.

Petitioner has not been able to make a ground for an injunction credible.

1.

The invention relates to the use of 7-[9-(4, 4, 5, 5, 5-pentafluoropentylsulfinyl)nonyl]estra-1, 3, 5(10)-triene-3, 17 $\beta$ -diol in the preparation of a formulation for administration by intramuscular injection, containing the compound 7-[9-(4, 4, 5, 5, 5-pentafluoropentylsulfinyl)nonyl]estra-1, 3, 5(10)-triene-3, 17 $\beta$ -diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle, for the treatment of a benign or malignant disease of the breast or the reproductive tract.

The Injunction Patent states with regard to the background of the invention that oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract. In premenopausal women, this is achieved by the ablation of ovarian function through surgical, radiotherapeutic, or medical means, and, in postmenopausal women, by the use of aromatase inhibitors. An alternative approach is to antagonize oestrogens with antioestrogens. These are drugs that bind to and compete for oestrogen receptors (ER) present in the nuclei of oestrogen-responsive tissue.

Conventional nonsteroidal antioestrogens, such as tamoxifen, compete efficiently for ER binding but their effectiveness is often limited by the partial agonism they display, which results in an incomplete blockade of oestrogen-mediated activity.

It is further stated in the Injunction Patent that the potential for nonsteroidal antioestrogens to display agonistic properties prompted the search for novel compounds that would bind ER with high affinity without activating any of the normal transcriptional hormone responses and consequent manifestations of oestrogens. Such molecules would be “pure” antioestrogens, clearly distinguished from tamoxifen-like ligands and capable of eliciting complete ablation of the trophic effects of oestrogens. Such compounds are referred to as Estrogen Receptor-Downregulators (E.R.D.). Steroidal analogues of oestradiol, with an alkylsulphonyl side chain in the 7 position, provided the first examples of compounds devoid of oestrogenic activity. One of these, 7-[9-(4, 4, 5, 5, 5-pentafluoropentylsulfinyl)nonyl]estra-1, 3, 5(10)-triene-3, 17 $\beta$ -diol was selected on the basis of its pure oestrogen antagonist activity and exhibited significantly increased antioestrogenic potency over other available antioestrogens. *In vitro* findings and early clinical experience with 7-[9-(4, 4, 5, 5, 5-pentafluoropentylsulfinyl)nonyl]estra-1, 3, 5(10)-triene-3, 17 $\beta$ -diol have promoted interest in the development of the drug as a therapeutic agent for oestrogen-dependent indications such as breast cancer and certain benign gynaecological conditions.

7-[9-(4, 4, 5, 5, 5-pentafluoropentylsulfinyl)nonyl]estra-1, 3, 5(10)-triene-3, 17 $\beta$ -diol or ICI 182,780, has been allocated the international non-proprietary name fulvestrant, which is used hereinafter. Fulvestrant binds to ER with an affinity similar to that of oestradiol and completely blocks the growth stimulatory action of oestradiol on human breast cancer cells *in vitro*; it is more potent and more effective than tamoxifen in this respect. Fulvestrant blocks completely the uterotrophic action of oestradiol in rats, mice and monkeys, and also blocks the uterotrophic activity of tamoxifen. Because fulvestrant has none of the oestrogen-like stimulatory activity that is characteristic of clinically available antioestrogens such as tamoxifen or toremifene, it may offer improved therapeutic activity characterised by more rapid, complete, or longer-lasting tumour regression; a lower incidence or rate of development of resistance to treatment; and a reduction of tumour invasiveness.

Fulvestrant shows, along with other steroidal based compounds, certain physical properties which make formulation of these compounds difficult. Fulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds,

and its aqueous solubility is extremely low at around  $10 \text{ ngm}^{-1}$ . It is stated in the Injunction Patent that currently there are a number of sustained release injectable steroidal formulations which have been commercialised. Commonly these formulations use oil as a solvent and wherein additional excipients may be present. In Table 1 of the Injunction Patent, commercialised sustained release injectable formulations are listed, to which reference is made. Table 2, to which reference is also made, shows the solubility of fulvestrant in a number of different solvents. Thus, it was shown that fulvestrant is significantly more soluble in castor oil than any of the other oils tested. However, the Injunction Patent describes it as a disadvantage that even when using the best oil based solvent, castor oil, it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate. To achieve a therapeutically significant release rate the amount of fulvestrant needed would require the formulation volume to be large, at least 10 ml. This requires the doctor to inject an excessively large volume of formulation to administer a dose significantly high enough for human therapy. Guidelines recommend that no more than 5 ml of liquid is injected intramuscularly in a single injection. Pharmacologically active doses required for a 1 month long acting depot formulation of fulvestrant is around 250 mg. Therefore, when dissolved in just castor oil, fulvestrant would need to be administered in at least 10 ml of castor oil.

On this basis, the problem objectively underlying the Injunction Patent – which is not defined in the Injunction Patent – is to be seen in using fulvestrant in an advantageous formulation. According to the general consensus in case law and literature the definition of the object only depends on that which was actually, i.e. objectively invented. Therefore, the object must be directed at the results of the invention, which is why the starting point is that which was actually achieved over the prior art. Furthermore, it can only relate to those problems that are actually solved by the invention (established case law, cf. Federal Court of Justice judgment “*Fettsäurezusammensetzung*”, as published in GRUR 2010, at 607, with further references).

Consequently, it must be considered in the present case that the solution to the problem claimed according to the patent is directed at the use of fulvestrant in a pharmaceutical composition for the treatment of breast cancer or diseases of the reproductive tract. The achievement of the present invention consequently consists of having found a formulation that can be administered intramuscularly and that achieves a depot effect.

To solve this object, the Patent in Suit proposes a use having the following features in claim 1:

1. A pharmaceutical formulation
2. for use in the treatment
  - 2.1. of breast cancer
  - 2.2. by intra-muscular injection,
3. wherein the pharmaceutical formulation comprises
  - 3.1. fulvestrant,
  - 3.2. a pharmaceutically-acceptable alcohol being a mixture of
    - 3.2.1. 10% weight of ethanol per volume of formulation and
    - 3.2.2. 10 % weight of benzyl alcohol per volume of formulation,
  - 3.3. 15% weight of benzyl benzoate per volume of formulation, and
  - 3.4. a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45 mgml<sup>-1</sup> of fulvestrant,
    - 3.4.1. wherein the ricinoleate vehicle is castor oil,
4. and wherein the total volume of the formulation is 6 ml or less.

2.

It is established case law of the Higher Regional Court Dusseldorf (InstGE 9, 140 - "*Olanzapin*"; InstGE 12, 114 - "*Harnkatheterset*"; confirmed in: Higher Regional Court Dusseldorf, GRUR-RR 2011, 81 - "*Gleitsattelscheibenbremse II*") that the issuance of a provisional injunction, in particular for injunctive relief, is only possible if both the question of patent infringement and the validity of the Injunction Patent are to be answered so clearly in favor of the petitioner that an erroneous decision to be revised in potential subsequent main proceedings cannot be seriously expected (also: Higher Regional Court Karlsruhe, InstGE 11, 143 - "*VA-LVD-Fernseher*").

Accordingly, in patent infringement disputes, the existence of grounds for an injunction must be assessed particularly thoroughly. Particular difficulties generally arise when correctly assessing within a short period of time and without the proper written preparation that corresponds to main proceedings whether the IP right at issue is protectable or valid. The restricted possibilities particularly affect the respondent. While the petitioner, which does have to act quickly to enforce its rights so as not to lose the short period of time available to it, still generally has sufficient time also pursuant to the requirements of Sec. 940 German Code of Civil Procedure to thoroughly assess the

validity of the IP right prior to submitting a request for an injunction, the respondent is generally under considerable time pressure, even if a hearing is held, to build up its defense in the relatively short period of time until the hearing once the request for injunction has been served. Moreover, if a provisional injunction is issued, this generally greatly interferes in the commercial activities of the respondent and leads to the asserted claims being fulfilled during the time the injunction is in force (Higher Regional Court Dusseldorf judgments “*Olanzapin*”, as published in InstGE 9, at 140, 145; “*Harnkatheterset*”, as published in InstGE 12, at 114, 118 *et seq.*).

However, according to the case law of the Higher Regional Court Dusseldorf this does not mean that a provisional injunction on the grounds of patent infringement is generally not to be considered or only to be considered in particularly rare, exceptional cases. In order for a provisional injunction to be issued on the grounds of patent infringement, the requirement must however generally be met that the validity of the IP right at issue has been adequately established (Higher Regional Court Dusseldorf judgments “*Olanzapin*”, as published in InstGE 9, at 140, 146; “*Harnkatheterset*”, as published in InstGE 12, at 114, 119). Any doubts as to the patentability of the injunction patent that must in principle be respected can constitute a reason to deny there being grounds for an injunction. In this regard, the infringement court cannot simply rely on the fact that the patent was granted; rather, it must independently clarify whether, in view of the submission of the respondent, there are serious indications that the injunction patent might potentially not be valid. From the perspective of the infringement court, the destruction of said patent does not have to be the inevitable consequence of the respondent’s objections, and this does not have to be very likely either. However, in order for the infringement court to be able to refuse to issue a provisional injunction, the respondent’s arguments must be intrinsically conclusive, justifiable and ultimately undeniable (Higher Regional Court Dusseldorf judgment “*Harnkatheterset*”, as published in InstGE 12, at 114, 119).

In principle, a sufficient degree of validity of an injunction patent can therefore only be assumed if the injunction patent has already survived first-instance opposition or nullity proceedings (Higher Regional Court Dusseldorf judgments “*Olanzapin*”, as published in InstGE 9, at 140, 146; “*Harnkatheterset*”, as published in InstGE 12, at 114, 121; “*Gleitsattelscheibenbremse II*”, as published in GRUR-RR 2011, at 81). In order that an injunction patent may be the subject of provisional injunction proceedings, a positive decision by the technically competent courts responsible for the opposition and nullity proceedings is therefore essentially necessary.

The requirement of a validity decision in adversarial proceedings in favor of the petitioner can only be foregone in exceptional cases. Such exceptional cases may apply – without any claim to completeness – if the respondent has already participated with own objections in the grant proceedings so that the grant of the patent is substantively equal to a decision in *inter partes* opposition proceedings, or if validity proceedings have not been carried out since the injunction patent is generally acknowledged as patentable (which is reflected by renowned licensees or the like), or if the objections against the validity of the injunction patent have turned out to be untenable already in the summary examination inherent to proceedings for provisional legal protection, or if there are extraordinary circumstances (e.g. considering the market situation or disadvantages arising from the IP right infringement) so that, as an exception, it cannot be reasonably expected from the petitioner to wait for the outcome of the opposition proceedings or nullity proceedings (“*Harnkatheter*set”, as published in InstGE 12, at 114, 121).

In the present case, Petitioner asserted that the conditions of the “*Harnkatheter*set” case law are met since Petitioner can invoke that the market entry of a generics manufacturer is at issue here and that the grant proceedings were carried out like opposition proceedings with the participation of third parties. Moreover, Petitioner stated that the confirmation of validity of the injunction patent of the parallel proceedings also substantiates that the present Injunction Patent is sufficiently established since it is narrower. In the opinion of the Chamber, all of this does not result in that it can be assumed that the validity of the present Injunction Patent is sufficiently established.

It is correct that Petitioner can assert exceptional circumstances owing to the imminent distribution of the Contested Embodiment as generic medicament. However, even if an exceptional case with respect to the essential requirement of a decision confirming validity is given, this does not mean that it does not matter whether the validity is sufficiently established. In such an exceptional case, only the existence of a decision confirming validity is foregone. However, it still applies that the question of validity of the injunction patent is to be answered so clearly in favor of the petitioner that an erroneous decision to be revised in subsequent main proceedings cannot be seriously expected. This means that any doubts as to the patentability of the injunction patent that must in principle be respected can constitute a reason to deny there being grounds for an injunction. From the perspective of the infringement court, the destruction of the injunction patent may not be the inevitable consequence of the respondent’s objections, and this does not have to be very or sufficiently likely either. However, in order for the infringement court to be able to refuse to issue a provisional injunction, the respondent’s

arguments must be intrinsically conclusive, justifiable and ultimately undeniable. Thus, the exceptional circumstances stated by Petitioner do not allow the inevitable conclusion to be drawn that validity is sufficiently established, which would justify that a ground for an injunction exists without a detailed revision of the validity of the Injunction Patent.

The fact that the grant proceedings regarding the Injunction Patent were carried out with the participation of third parties with objections, i.e. that an exception is given, cannot lead to the assumption that the validity of the Injunction Patent is established. That stated above also applies in this regard. If the grant proceedings were carried out with the participation of third parties, the question of validity of the injunction patent still has to be answered so clearly in favor of the petitioner that an erroneous decision to be revised in subsequent main proceedings cannot be seriously expected. This means that any doubts as to the patentability of the injunction patent that must in principle be respected can constitute a reason to deny there being grounds for an injunction.

Finally, the decision of the Opposition Division confirming the validity of the injunction patent of the parallel proceedings does not result in that the question of validity of the present Injunction Patent is to be answered clearly in favor of Petitioner. With the interlocutory decision of 11 February 2015 (Exhibit HE 2), the Opposition Division of the European Patent Office confirmed the validity of the injunction patent of the parallel proceedings within the scope of the restricted claims so that the requirement of a decision confirming validity within the terms of the case law of the Higher Regional Court Dusseldorf is in principle fulfilled (cf. Higher Regional Court Dusseldorf decisions 2 U 47/12, as published in BeckRS 2013, at 13744; 2 U 95/11, as published in BeckRS 2012, at 21294; Higher Regional Court Dusseldorf judgment of 10 November 2011, 2 U 41/11; Higher Regional Court Dusseldorf judgment “*Gleitsattelscheibenbremse II*”, as published in GRUR-RR 2011, at 81). This decision issued by the responsible instance after a technically competent examination as regards the maintenance of the Injunction Patent is also to be accepted in principle. However, something else applies if the infringement court does not regard the line of arguments of the opposition instance or nullity instance to be tenable, or if the attack on the injunction patent by means of the appeal against the opposition decision or nullity decision is substantiated by (e.g. new) aspects promising success, which have not yet been considered or decided upon by the authorities dealing with the matter (cf. Ceppl/Voß/Voß, “ZPO”, Sec. 940, marginal no. 117, with further references). In contrast, it is not acceptable that the infringement court replaces a tenable assessment by the responsible opposition or nullity instance with its own assessment of the technical facts. Accordingly, validity is only then regarded as not established if the

infringement court regards the line of arguments of the responsible technical instance to be untenable or if the lodged appeal is based on (new) aspects promising success.

In the end, it can remain undecided whether the line of arguments of the Opposition Division is untenable. The reason for this is that in the present case it is also to be considered that the decision regarding the maintenance of the restricted patent claims was not made in *inter partes* proceedings, which is typical of an opposition. The reason for this is that the only opponent, Gedeon Richter Ltd., withdrew the opposition on 30 December 2014, i.e. at a time when the subject matter of the opposition proceedings was still the originally granted claim version directed at a formulation. With respect to this version, the Opposition Division stated the opinion in the Summons to the oral proceedings of 7 November 2014 (Exhibit AR 4) that said version is not novel. After the withdrawal of the opposition on 30 December 2014, Petitioner filed several different claim versions, and finally on 22 January 2015 a version directed at the use of a formulation. This claim version was regarded as patentable by the Opposition Division, as also stated in its decision of 11 February 2015. Thus, this claim version was not the subject matter of “normal” opposition proceedings with the participation of an opponent. The decision was taken only on the basis of the already stated objections which did not relate, however, to the claim directed at a use. It is also recognized that third-party observations were filed after submission of the new requests (Exhibit HE 26/26a). Said observations were also directed against the validity of the “new” claim version. However, what was asserted in this regard was not the lack of novelty against the background of the disclosure of D13, but lack of inventive step. Therefore, it is questionable whether the arguments constituting the subject matter of the present injunction proceedings and of the nullity action filed with the Federal Patent Court have also been considered by the Opposition Division in its decision. This is not apparent from the decision of 11 February 2015 (Exhibit HE 2/2a).

As stated by the Chamber in the judgment of the parallel proceedings 4c O 61/15, due to the described circumstances of the case, despite the existence of a decision confirming the validity of the Injunction Patent, sufficient establishment of validity cannot only be denied when the line of arguments by the technical instance confirming validity is untenable, but must already be denied when the destruction of the injunction patent seems possible owing to an intrinsically conclusive, justifiable and ultimately undeniable line of arguments by the respondent. The reason for this is that a decision taken by a responsible technical instance cannot simply be accepted if the opposition proceedings were ultimately not directed at the amended claim. In this regard, no consideration of

arguments by a third party calling the validity into doubt has taken place, and therefore it cannot be assumed that this is a decision confirming validity in adversarial proceedings. On the contrary, said circumstances of the case allow a comparison with grant proceedings carried out without the participation of third parties with objections, and in this regard the case law stipulates that – if an exceptional case is given – the validity of the injunction patent has to be so sufficiently established that (as stated above) an erroneous decision to be revised in subsequent main proceedings cannot be seriously expected. This means that any doubts as to the patentability of the injunction patent that must in principle be respected can constitute a reason to deny there being grounds for an injunction.

Since there is no decision confirming validity of the Injunction Patent in the present proceedings, it therefore applies that the question of validity of the injunction patent is to be answered so clearly in favor of the petitioner that an erroneous decision to be revised in subsequent main proceedings cannot be seriously expected. This means that any doubts as to the patentability of the injunction patent that must in principle be respected can constitute a reason to deny there being grounds for an injunction. From the perspective of the infringement court, the destruction of the injunction patent may not be the inevitable consequence of the respondent's objections, and this does not have to be very or sufficiently likely either. However, in order for the infringement court to be able to refuse to issue a provisional injunction, the respondent's arguments must be intrinsically conclusive, justifiable and ultimately undeniable. When applying the above-described parameter, there are doubts regarding the novelty or, in any case, the inventive step of the invention according to the Injunction Patent in view of the disclosure of D13 (McLeskey et al., "Tamoxifen-resistant fibroblast growth factor-transfected MCF-7 cells are cross-resistant *in vivo* to the antiestrogen ICI 182,780 and two aromatase inhibitors", Clinical Cancer Research, Volume 4, pages 697 to 711, March 1989 (Exhibit NiK10 of Exhibit HE 3)).

It is decisive for the assessment of whether the subject matter of a patent is anticipated by a previous publication which technical information is directly and clearly disclosed to the person skilled in the art in the entire content of the prior publication. It is a requirement of novelty of a medical indication that the use of the drug has not been described before as effective or at least promising in the way of its application or for the medical field where it is used and that it has not been previously used (cf. Federal Court of Justice judgment "*Memantin*", as published in GRUR 2011, at 999 marginal nos. 31, 33; Federal Patent

Court judgment of 01 July 2014 - court docket: 3 Ni 14/13, as published in BeckRS 2015, at09649; Schulte, “*PatG*”, 9th edition, Sec. 3 marginal nos. 93 to 96).

D13, a scientific article, reports on a study directed at clarifying a potential mechanism of tamoxifen resistance. It is described in the “Abstract” that after the successful treatment of patients with tamoxifen, these often exhibited tamoxifen resistance with responsive tumors, and that consequently only 30 to 50% [sic] of the patients have a positive response to second hormonal therapies. According to the authors, this lack of response can be explained by elucidating the mechanisms of tamoxifen resistance that bypass ER pathways completely. In this regard, it is further described that to elucidate the mechanism of tamoxifen resistance, ovariectomized tumor-bearing mice injected with fibroblast growth factor (FGF)-transfected MCF-7 breast carcinoma cells were treated with the steroidal antiestrogen ICI 182,780 (= fulvestrant) or one of two aromatase inhibitors, 4-OHA or letrozole. These treatments did not slow estrogen-independent growth or prevent metastasis of tumors produced by FGF-transfected MCF-7 cells in ovariectomized nude mice. FGF-transfected cells had diminished response to ICI 182,780 *in vitro*, suggesting – in the opinion of McLeskey et al. – that autocrine activity of the transfected FGF may be replacing estrogen as a mitogenic stimulus for tumor growth. The authors concluded that the altered hormonal responses are not due to the down-regulation of ER or to FGF-mediated activation of ER. Estrogen independence may be achieved through FGF signaling pathways independent of ER pathways. It is concluded from this that if this is the case, therapies directed at the operative mechanism might produce a therapeutic response or allow a response to a second course of antiestrogen treatment. Citation D13 discloses to the person skilled in the art the treatment of a benign or malignant disease of the breast. The person skilled in the art, i.e. a team of experts consisting of a pharmacist and a medical chemist each having experience in the field of development and use of pharmaceutical formulations as well as an oncologist, knows that tamoxifen as well as fulvestrant have an antiestrogenic effect and can be used for the treatment of breast cancer. In particular, it is known to the person skilled in the art that fulvestrant has been used as an active ingredient for the therapy of breast cancer since the beginning of the 1990s. Such an average person skilled in the art having the described knowledge gathers from the disclosure of D13 not only a basic research regarding the elucidation of a mechanism of tamoxifen resistance. The elucidation of such a mechanism also serves for the improved treatment of breast cancer patients exhibiting tamoxifen resistance after a first successful round of treatment with tamoxifen. Thus, the elucidation of the mechanism is inevitably also associated with treatment of breast cancer.

Moreover, already the Abstract of the citation mentions a therapy for estrogen receptor-positive breast cancer and that only 30 to 50% [sic] of the patients with breast cancer have a positive response to second hormonal therapies. In the introduction, a therapy of clinical breast cancer is also mentioned (page 3 of Exhibit HE 20). It is explicitly stated on page 4 that “only 30 to 40% of such patients have a positive response to a subsequent therapy with fulvestrant (= ICI 182,780) or aromatase inhibitors”. Thus, it can be gathered from the text passages given by way of example that the treatment of breast cancer is the subject matter of the study. The mechanism of tamoxifen resistance is supposed to be elucidated to make such a treatment possible or to improve it. Moreover, tests with the fulvestrant formulation were made with human breast cancer cells, and its effect on tumor growth was examined. Another argument for this is that e.g. in footnote 13 reference is made to a publication dealing with the treatment of breast cancer. The citation given in footnote 13 corresponds to Exhibit HE 22, i.e. an article by Howell et al., in *The Lancet*, “Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer”. Consequently, citation D13 describes the therapeutic use of a pharmaceutical formulation with fulvestrant for the treatment of breast cancer.

Contrary to the opinion of Petitioner, the citation also discloses the successful use of fulvestrant for the treatment of a benign or malignant disease of the breast. First of all, it can be stated that the formulation of fulvestrant used by McLeskey et al. corresponds to a formulation according to features 3.1 to 3.4. This is undisputed between the parties.

It was attempted to determine with the tests underlying D13 whether the selective antiestrogen fulvestrant inhibits the estrogen-independent growth of tumors of the FGF-transfected MCF-7 cells in ovariectomized animals. For this purpose, the fulvestrant formulation according to the invention was weekly administered subcutaneously to mice in a dose of 5 mg in 0.1 ml. It was found that the treatment of the breast cancer cell lines with the fulvestrant formulation did not slow estrogen-independent tumor growth or prevent the formation of metastases (Exhibit HE 20, end of page 2). As a control of the essential efficacy of the compounds used in addition to fulvestrant – i.e. aromatase inhibitors – a test was carried out, in which the active ingredient was administered in the same dosage and in the same way to reproductively intact female mice over a period of 2 weeks (Exhibit HE 20, page 17, second paragraph). It was found that fulvestrant as well as the further compounds showed activity although these had not shown efficacy in the tests regarding the elucidation of the mechanism of tamoxifen resistance. The corresponding activity was determined by a “uterus test” as also described in paragraph [0009] of the Injunction Patent. This is a scientifically acknowledged test for

the determination of the activity of chemical compounds (cf. Exhibit HE 23, Annex 3 of Exhibit AR 18, Exhibit HE 19). In contrast to Petitioner's opinion, there is no doubt that fulvestrant in the formulation according to the invention and the aromatase inhibitors were not [sic] used in the activity tests. On page 7 of D13, in the section "Drugs", the active ingredients used in the tests are stated. It is stated that ICI 182,780 (= fulvestrant) was donated by Zeneca Pharmaceuticals. It is further stated that for the experiment depicted in Fig. 1, powdered drug was first dissolved in 100% ethanol and spiked into warmed peanut oil to give a final concentration of 50 mg/ml. For the experiments depicted in Fig. 1, B and C, 50 mg/ml preformulated drug in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil, was used. This formulation was provided to Dr. McLeskey by an employee of Zeneca Pharmaceuticals and it is a formulation according to the invention. It is further stated that 4-OHA and letrozole, both of which are aromatase inhibitors, were provided by the University of Maryland and by Novartis, respectively. Tamoxifen was obtained from Innovative Research of America as sustained-release pellets.

These active ingredients were used in the tests for elucidating tamoxifen resistance. In these experiments it was found – as already stated – that estrogen-independent growth of tumors produced by FGF-transfected MCF-7 cells is not inhibited by treatment with a pure antiestrogen, i.e. fulvestrant, or with aromatase inhibitors (Exhibit HE 20, page 14, section "Results"). It is further described as part of the results that both FGF-1- and FGF-4-transfected MCF-7 cells from progressively growing tumors are formed in ovariectomized nude mice, as well as in similar mice treated with tamoxifen. Although ovariectomized mice could be expected to have substantially lower levels of estrogenic compounds than reproductively intact mice, some estrogens are synthesized at extraovarian sites. It is assumed that the transfected cells still possess ERs, because they respond to estrogen and tamoxifen administered to the mice, as well as to these compounds used in tissue culture. McLeskey et al. further stated that to test the hypothesis that growth of the FGF-transfected cells in ovariectomized or tamoxifen-treated nude mice is due to increased sensitivity to the small amounts of estrogens still present in ovariectomized nude mice, the ability of a pure antiestrogen (fulvestrant) and two aromatase inhibitors to inhibit the estrogen-independent tumor growth produced by these FGF-transfected cell lines was tested.

The corresponding tests showed that fulvestrant was not able to inhibit the estrogen-independent growth of the cell lines. The tests with the aromatase inhibitors had the same result. In order to prove by means of a control test that the inhibition inability was not to

due to the inactivity of the used compounds, fulvestrant and the two aromatase inhibitors were administered to productively intact female mice and showed effect, as described on page 17 of Exhibit HE 20. McLeskey et al. concluded from this on page 17 at the end of the second paragraph:

“Thus, these compounds retained activity, although they had no effect on tumor growth in our experiments.”

Although the specifically used compounds are not stated in this passage, it becomes apparent from the two sentences before the quote and the context of the statements under the heading “Results” and the list of active ingredients under “Drugs” that fulvestrant as well as the two aromatase inhibitors were subjected to the control test and showed efficacy there. There are no indications that both fulvestrant formulations were not subjected to the control test as well. The reason for this is that a control test would not make any sense if the used compounds were not subjected to this control test. Nothing to this effect can be gathered from the declaration by Dr. McLeskey of 1 October 2014 (Exhibit HE 24) either. She explained in marginal no. 6 of her declaration that the peanut oil and castor oil formulations were treated as interchangeable and no comparisons were drawn between the two formulations. However, if the two formulations were treated as interchangeable, this also allows the conclusion to be drawn that the two formulations were also used and subjected to the control test as well.

Thus, the citation discloses a successful treatment of breast cancer with fulvestrant. Moreover, a specific proof of efficacy is not necessary to prove a medical indication. Instead, it is sufficient that the prior art discloses the substance and its application in a medical method so clearly and completely to the person skilled in the art that he can successfully treat a specific disease (cf. Federal Patent Court, Judgment of 01 July 2014, *loc. cit.*), as directly shown by D13.

Where Petitioner objects with regard to the disclosure of the citation that the tests were only made with mice, i.e. that efficacy in humans had not been shown, this objection is not successful. The reason for this is that the same standards are to be applied with respect to the disclosure of a citation as with respect to the disclosure of a patent specification (cf. Federal Patent Court, Judgment of 01 July 2014, *loc. cit.*). The efficacy of fulvestrant is only substantiated by means of an animal model in the specification of the Injunction Patent, i.e. by means of the uterus test and the *in vivo* blood plasma tests in rabbits to which the pharmaceutical composition according to the invention was

administered by means of intramuscular injection. Moreover, the treatment is not limited to humans with the teaching according to the Injunction Patent.

Petitioner's further objection, i.e. that D13 does not disclose in which form the active ingredient fulvestrant was present in the pharmaceutical composition, namely as real solution, suspension or emulsion, is irrelevant since the Injunction Patent does not state anything in this regard in patent claim 1 either.

In contrast to Petitioner's opinion, D13 being detrimental to novelty is not called into question due to the fact that D13 does not disclose an intramuscular injection of the composition according to the invention. The reason for this is that an administration of the pharmaceutical composition of fulvestrant by means of intramuscular injection is disclosed to the person skilled in the art.

The assessment of whether the subject matter of a patent is anticipated by a previous publication demands that the overall content of the previous publication be ascertained. The decisive factor is the technical information disclosed to the person skilled in the art. The concept of disclosure in this context does not differ from that applied otherwise in patent law. What needs to be ascertained therefore is not in which form the skilled person, for instance with the help of his expertise, can reproduce a given teaching or how he can modify this teaching if necessary, but exclusively that which is directly and clearly apparent from the publication from the skilled perspective (cf. Federal Court of Justice judgment "*Olanzapin*", as published in GRUR 2009, at 382; Federal Court of Justice, judgment of 18 March 2014, court docket: X ZR 77/12). What is accordingly disclosed does not only include what is explicitly disclosed in the wording of the publication. Just as when the literal meaning of a patent claim is ascertained, the content and the meaning of the publication are decisive, i.e. the technical information the expert reader, based on his expertise, will find in the source (Federal Court of Justice judgment "*Olanzapin*", *loc. cit.*). This also includes modifications and additions that are so obvious to the skilled person from the overall context of the document that this is apparent to him when attentively reading the document, considering less the words than the recognizable meaning, such that he infers this as part of his thoughts even if he is not conscious of this (Federal Court of Justice judgment "*Elektrische Steckverbindung*", as published in GRUR 1995, at 330, 332). Considering such circumstances is not aimed at adding to the disclosure by the expertise, but grasping the entirety of the technical information apparent to the skilled person from a document. Modifications and further developments of this information are not a part of this disclosed content nor are such conclusions which the

skilled person, due to his expertise, may be able to draw from the technical information he receives (Federal Court of Justice judgment “*Olanzapin*”, *loc. cit.*). In the “*Proteintrennung*” decision, the Federal Court of Justice further stated that, if it is apparent to the skilled person from the description of a method for preparing a protein concentration suitable for therapeutic use that further method steps are necessary to bring about the therapeutic applicability, a measure that was the means generally used in practice on the priority date to achieve the objective is comprised by the disclosure.

On the basis of these principles, it is first of all apparent to the skilled person reading D13 that the subcutaneous injection in mice was inevitable owing to the small amount of muscle tissue, i.e. an intramuscular injection could not be considered. Thus, it was further apparent to the skilled person that when applied to humans or in other animal models with larger animals such as rabbits another form of application could also be considered. An intravenous injection was out of question since the skilled person knew owing to his general expertise that oily solutions cannot be administered intravenously since they are not miscible with the blood serum and due to the associated danger of pulmonary embolism. On the priority date of the invention, it was part of the general expertise that intramuscular administration was preferred in human patients over subcutaneous administration as regards the administration of lipophilic compositions, which can be gathered from the textbook excerpt from Sucker/Fuchs/Speiser, “*Pharmazeutische Technologie*”, 1978, page 612 (Exhibit NiK 13). Since the formulation according to the invention is lipophilic owing to its high content of castor oil, the skilled person would have regarded intramuscular administration as preferable when administered to humans. This is also evident from Table 1 in paragraph [0013] of the description of the Injunction Patent, according to which all oil-based steroid formulations stated therein, all of which are marketed, are administered intramuscularly. Even Petitioner’s employee, Mr. Gellert, assumed that a fulvestrant medicament had to be formulated with sustained release for intramuscular injection, and that given this objective the experienced formulator “would have appreciated that the traditional administration options to explore were intramuscular (IM) injection of a sustained release aqueous or oil suspension or an oil-based solution (depot)” (Exhibit HE 25a, section 12). Moreover, fulvestrant formulations had been administered intramuscularly without exception for almost 10 years before the priority date, as substantiated by the technical literature shown by Respondent. In this regard, reference is made to Exhibits HE 21 (D15), HE 22 (D18), HE 23 (D19), AR 23 (D21) and AR 19a. The intramuscular administration of fulvestrant as steroid-containing oily compound is thus the generally used type of administration, and therefore the skilled person infers this.

Where Petitioner objects in this regard that intramuscular injection is not the only option of alternative administration of a fulvestrant formulation, and therefore the case law regarding inference cannot be applied in the present case, the arguments and documents submitted in this context do not result in another conclusion. EP 0 346 014 (Exhibit NiK9 of Exhibit HE 3 / Exhibit AR 9) describes on page 5, line 26 *et seqq.*, both the subcutaneous and the intramuscular administration of an oily suspension of an antioestrogen. However, the intramuscular administration is described as preferred in the description on page 7, line 20 *et seqq.* The reference to the excerpt from Forth/Henschler/Rummel, "*Pharmakologie und Toxikologie*", 5th edition, page 37 (Exhibit HE 28), in which subcutaneous administration is described as preferred when a depot formulation is supposed to be achieved, does not lead to a another view. The reason for this is that this document does not deal with the administration of oily steroidal compounds. The same applies with regard to the references to Annices 6 and 8 of Exhibit AR 18. Annex 6, an excerpt from the textbook by Voigt, "*Pharmazeutische Technologie*", 7th edition, page 480 *et seqq.*, also deals with the injection of oily preparations. However, it is also illustrated (bottom of page 480) that the application is carried out intramuscularly, and more rarely subcutaneously. In Annex 8, an excerpt from the textbook by Pfeifer/Pflegel/Borchert, "*Biopharmazie*", 3rd edition, page 59 *et seqq.*, intramuscular application is also stated with more than 70%. Thus, the subcutaneous application may represent an alternative to intramuscular administration. However, it is clear from the literature cited by Respondent regarding the general application of oily compounds and the administration of fulvestrant formulations that intramuscular injection was the preferred type of administration, i.e. the generally used means within the terms of the case law of the Federal Court of Justice decision "*Proteintrennung*".

Even if one were to deny here that an intramuscular administration is "inferred", there would still be considerable doubts as to the inventive step of the invention according to the Injunction Patent. When considering the disclosure of D13 and the expertise of the skilled person together, an intramuscular administration would have been obvious in any case.

Where Petitioner further pointed out that no statements were made in D13 with regard to biocompatibility and toxicity, these are questions to be clarified in routine experiments, which do not include any inventive step (as regards routine tests, cf. Federal Court of Justice judgment "*Thrombozyten-Zählung*", as published in GRUR 1996, at 372). The Injunction Patent only makes few statements in this regard and is essentially limited to the test of the formulation according to the invention in the animal model.

**II.**

The decision on costs is based on Sec. 91 (1) German Code of Civil Procedure.

The decision regarding provisional enforceability arises from Sec. 708, no. 6, German Code of Civil Procedure.

The value in dispute of the proceedings is fixed at EUR 1,500,000.

Klepsch      Dr. Heidkamp-Borchers      Dr. Büttner