IN THE NAME OF THE KING

D25A

JUDGMENT

DISTRICT COURT OF THE HAGUE

Commercial law team
The Hague location

Case number / cause-list number: C/09/513437 / KG ZA 16-779

Judgment in provisional relief proceedings of 27 July 2016

in the matter of:

ASTRAZENECA AB,
a company incorporated according to foreign law,
with its registered office in Södertälje (Sweden),
the Claimant in the original proceedings,
the Defendant in the counterclaim proceedings,
Lawyer: W.A. Hoyng, practising in Amsterdam,

v.

SANDOZ B.V.,
a private limited company,
with its registered office in Almere, the Netherlands,
the Defendant in the original proceedings,
the Claimant in the counterclaim proceedings,
Lawyer: O.P. Swens, practising in Amsterdam.

The parties are hereinafter referred to as AstraZeneca and Sandoz.

AstraZeneca was also assisted in the proceedings by T.M. Blomme and J.M.J.A. Krens and Sandoz by R. Dijkstra and T.D. Stigterman, all lawyers practising in Amsterdam.

1. The proceedings

1.1. The course of the proceedings is shown by:
- the Summons of 27 June 2016, with exhibits 1-7;
- Sandoz's Statement of Defence in provisional relief proceedings, Statement of Claim in the counterclaim proceedings, and Statement submitting exhibits 1 to 20;
- AstraZeneca's Statement submitting additional exhibits, with exhibits 8 -21, with a later addition to exhibits 14 and 15;
- Sandoz's Statement submitting additional exhibits 21-22;
- AstraZeneca's Statement submitting further additional exhibits, with exhibits 22 – 23;
- the court hearing held on 6 July 2016;
- AstraZeneca's pleading notes;
- Sandoz's pleading notes;

- the shortened record of the court hearing.

1.2. After the court hearing was closed, an injunction against infringement was imposed on Sandoz for the duration of the provisional relief proceedings, as stated in the shortened record that was drawn up of the court hearing.

1.3. Judgment was scheduled for today.

2. Procedural decisions

Admissibility of exhibits

2.1. Given the brevity of the period leading up to the hearing, the Provisional Relief Judge determined that AstraZeneca's exhibits were to be submitted by 27 June 2016, and Sandoz's exhibits by 1 July 2016. Nevertheless, both parties also submitted further exhibits at later dates. Neither of the parties objected to this. The Provisional Relief Judge then stated at the hearing that the deadlines had been set partly in order to enable him to prepare the hearing properly. The parties were informed that exhibits would be refused *ex officio* if it turned out that they were relevant but had been insufficiently discussed at the hearing due to having been submitted late. This proved not to be the case, however, so all exhibits have been admitted.

Injunction against disclosure

2.2. Prior to the court hearing, AstraZeneca requested that Dr. Gellert's opinion, which it had submitted, be heard behind closed doors in view of the confidential nature of the information set out in that opinion. It also requested that an injunction against disclosure be imposed on Sandoz with regard to the opinion and the proceedings in that regard at the hearing. At the hearing, AstraZeneca stated that it no longer considered the hearing behind closed doors necessary.

2.3. Sandoz did not oppose AstraZeneca's request for an injunction to be imposed on it against disclosing the content of Dr. Gellert's opinion (with appendices), submitted by AstraZeneca, and anything stated by AstraZeneca in that regard at the hearing. Furthermore, having studied that opinion, the Provisional Relief Judge realises that its contents must be regarded as confidential and that it could be damaging to AstraZeneca's interests if third parties learn of it. The requested injunction will therefore be imposed on Sandoz, with the application of Article 29(1)(b) DCCP.[1]

3. The facts

3.1. AstraZeneca is an international pharmaceutical company that researches, develops and markets pharmaceutical products, in particular oncological products.

3.2. Among other things, AstraZeneca markets the drug FASLODEX. This drug is used for the treatment of oestrogen-dependent types of breast cancer. FASLODEX contains fulvestrant as the active ingredient. The effect of this substance is to prevent oestrogen from reaching cancer cells, thus inhibiting or even stopping their growth.

3.3. AstraZeneca owns the European Patent EP 1 250 138 B2 (hereinafter also referred to as: EP 138 or the patent), which relates to a *Fulvestrant formulation*. The application for the patent, which invoked the priority dates 10 January 2000 and 12 April 2000 on the basis of two English patent

[1] Dutch Code of Civil Procedure.

applications, was filed on 8 January 2001. The grant of the patent was published on 19 October 2005.

3.4. After the patent was granted, opposition proceedings were filed with the European Patent Office. The Opposition Division initially maintained the patent without alteration. That decision was appealed. After the technical board of appeal referred the matter back to the Opposition Division, the opposition was withdrawn. AstraZeneca then amended its claims. In a decision of 11 February 2015, the Opposition Division once again maintained the patent, in that altered form, taking account of the publications from the prior art which are discussed below.

3.5. Claim 1 of the patent reads, in the authentic English version:

> *1. Use of fulvestrant in the preparation of a pharmaceutical formulation for the treatment of a benign or malignant disease of the breast or reproductive tract by intra-muscular administration, wherein the formulation comprises fulvestrant in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol, and wherein the formulation is adapted for attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.*

3.6. The undisputed Dutch translation of claim 1 reads as follows:

> *Toepassing van fulvestrant bij de bereiding van een farmaceutische formulering voor de behandeling van een benigne of maligne ziekte van de borst of voortplantingstractus door intramusculaire toediening waarbij de formulering fulvestrant in een ricinoleaatmedium, een farmaceutisch aanvaardbaar niet-waterig esteroplosmiddel en een farmaceutisch aanvaardbare alcohol omvat, waarbij de formulering aangepast is voor het verkrijgen van een therapeutisch significante bloedplasmaconcentratie aan fulvestrant gedurende ten minste 2 weken.*

3.7. The following publications form part of the prior art of the patent:

3.7.1. Howell et al., *Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer*, British Journal of Cancer, [1996] 74, pp. 300-308 (hereinafter: Howell), is a study of the effects of ICI 182,780 (another name for fulvestrant) in the treatment of breast cancer patients who have developed a resistance to the drug tamoxifen. The article concludes that ICI 182,780 is tolerated well in long-term treatment and is active against tumours. The article also states: *ICI 182780 was administered as a long-acting formulation contained in a castor oil[2]-based vehicle by monthly i.m.[3] injection (5 ml) into the buttock.*

3.7.2. 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, Vol. 4, March 1998, pp. 697-711 (hereinafter: McLeskey), states the following on pages 697, 698, 700 and 701 (highlighting added by this Provisional Relief Judge):

---

[2] A ricinoleate, as understood by the District Court.
[3] intramuscular.

Tamoxifen-resistant Fibroblast Growth Factor-transfected MCF-7 Cells Are Cross-Resistant *in Vivo* to the Antiestrogen ICI 182,780 and Two Aromatase Inhibitors[1]

Sandra W. McLeskey, Lurong Zhang, Dorraya El-Ashry, Bruce J. Trock, Cecilia A. Lopez, Samir Kharbanda, Christopher A. Tobias, Lori A. Lorant, Rachel S. Hannum, Robert B. Dickson, and Francis G. Kern[2]

Lombardi Cancer Center [S. W. M., L. Z., B. J. T., C. A. L., S. K., C. A. T., R. S. H., D. E-A., R. B. D., F. G. K.], Departments of Biochemistry and Molecular Biology [D. E-A., F. G. K.], Cell Biology [R. B. D., L. Z.], Medicine [B. J. T.], and Pharmacology [S. W. M.], and the School of Nursing [S. W. M.], Georgetown University Medical Center, Washington, D. C. 20007

ABSTRACT

Although the antiestrogen tamoxifen has been the mainstay of therapy for estrogen receptor (ER)-positive breast cancer, successful treatment of responsive tumors is often followed by the acquisition of tamoxifen resistance. Subsequently, only 30–40% of patients have a positive response to second hormonal therapies. This lack of response might be explained by mechanisms for tamoxifen resistance that sensitize ER pathways to small amounts of estrogenic activity present in tamoxifen or that bypass ER pathways completely. To elucidate one possible mechanism of tamoxifen resistance, we treated ovariectomized tumor-bearing mice injected with fibroblast growth factor (FGF)-transfected MCF-7 breast carcinoma cells with the steroidal antiestrogen ICI 182,780 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 responses to ICI 182,780 *in vitro*, suggesting that autocrine activity of the transfected FGF may be replacing estrogen as a mitogenic stimulus for tumor growth. ER levels in FGF transfectants were not down-regulated, and basal levels of transcripts for estrogen-induced genes or of ER-mediated transcription of estrogen response element (ERE) luciferase reporter constructs in the FGF expressing cells were not higher than parental cells, implying that altered hormonal responses are not due to down-regulation of ER or to FGF-mediated activation of ER. These studies indicate that estrogen independence may be achieved through FGF signaling pathways independent of ER pathways. If so, therapies directed at the operative mechanism might produce a therapeutic response or allow a response to a second course of antiestrogen treatment.

INTRODUCTION

Because conventional therapy is not usually curative in clinical breast cancer, development of tamoxifen resistance, in which breast tumors previously growth-inhibited by tamoxifen become refractory, represents an important therapeutic dilemma. However, the development of tamoxifen resistance is not necessarily associated with progression to an ER[3]-negative phenotype. In many cases of clinical tamoxifen resistance, ER expression may be retained (1–4), implying that the resistance is due an alteration in activity of the tamoxifen/ER complex. Tamoxifen resistance in such a case could result from three possible mechanisms that, according to present knowledge, would not preclude successful treatment with an alternative hormonal therapy. First, alterations in the ER could arise, which might diminish or extinguish inhibitory responses to tamoxifen, leaving only its partial agonist effects to predominate (5–8). Second, tamoxifen resistance arising in the setting of an intact ER could be a result of altered intratumoral tamoxifen metabolism, which might produce more estrogenic metabolites locally (7, 9–11). Third, available tamoxifen could be sequestered by an increase in antiestrogen binding sites not associated with ERs (12). As mentioned, in each of these three instances, substitution of a hormonal therapy different from tamoxifen might result in a clinical response. Two such alternative therapies used in this report are steroidal estrogen antagonists, such as ICI 182,780, which lack the partial agonist activity of tamoxifen, and aromatase inhibitors, which inhibit endogenous estrogen production by all tissues, depriving the ER of its ligand.

Although the mechanisms of tamoxifen resistance de-

Received 7/3/97; revised 11/26/97; accepted 12/10/97.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] This work was supported by NIH Grants CA50376 (to F. G. K.), CA09218 (to F. G. K. and S. W. M.), CA53185 (to F. G. K. and R. B. D.), CA66154 (to S. W. M.), CA71465 (to D. E-A.), and Cancer Center Grant CA51008, American Cancer Society Grant IRG-193 (to S. W. M.), U.S. Army Medical Research and Material Command Grants DAMD 17-94-4172 (to D. E-A.) and DAMD 17-94-J-4173 (to S. W. M.), and a Susan Komen Foundation Fellowship (to L. Z.).

[2] To whom requests for reprints should be addressed, at Southern Research Institute, P. O. Box 55305, 2000 Ninth Avenue South, Birmingham, AL 35255-5305. Phone: (205) 581-2480; Fax: (205) 581-2877; E-mail: kern@sri.org.

[3] The abbreviations used are: ER, estrogen receptor; FGF, fibroblast growth factor; IMEM, improved minimal essential medium; X-gal, 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside; FBS, fetal bovine serum; 4-OHA, 4-hydroxyandrostenedione; NK, natural killer; CCS, charcoal-stripped calf serum; ERE, estrogen response element; CAT, chloramphenicol acetyltransferase; RT, reverse transcription.

scribed above should be amenable to alternative hormonal therapy, early results for small numbers of tamoxifen-resistant patients have shown that only about 30–40% of such patients have a positive response to subsequent ICI 182,780 or aromatase inhibitor therapy (13–20). These data imply alternative mechanisms for tamoxifen resistance. Constitutive production of autocrine growth factor(s) or growth factor receptors by tumor cells has been proposed as a mechanism for tamoxifen resistance that may or may not involve ER pathways. Evidence supporting this hypothesis is gained from the acquisition of estrogen-independent growth in tumor models, including the one used in this report, in which growth factors or growth factor receptors have been overexpressed in estrogen-dependent breast carcinoma cell lines (21–26). In addition, recent clinical data showing decreased efficacy of tamoxifen in treating tumors overexpressing *c-erbB2* (27) supports a role for growth factor signaling in clinical tamoxifen resistance. Because some growth factor signaling pathways, including the ERB-B pathway, have been shown to interact with ER signaling pathways (25, 28–32), increased growth factor signaling could be one mechanism by which cells could become sensitive to previously ineffective amounts of estrogenic stimulation produced by the partial agonist activity of tamoxifen itself or its estrogenic metabolites, above. In cases in which such interactions have been demonstrated, the growth factor and ER pathways may act collaboratively (25), making the final outcome susceptible to pharmacological manipulations of either pathway and implying that second line hormonal therapies might have an effect. However, increased autocrine or intracrine growth factor signaling might also bypass the need for ER-mediated growth stimulation in tumor cells or affect stromal components of the tumor, such as endothelial or immune cells (33–36), to alter the tumor environment in ways conducive to tumor growth. In either case, alternative hormonal therapies might not be effective.

Recently, cell-specific coactivators and corepressors have been identified for steroid hormone receptors, including the ER, which may influence steroid receptor-induced transcription positively or negatively (37, 38). Thus, the activity of tamoxifen in inhibiting or even stimulating tumor growth might depend on the relative expression of various stimulatory or inhibitory cofactors in a particular tumor (39, 40). However, transient transfection experiments suggest that tamoxifen-resistant tumors produced by such mechanisms should still be sensitive to pure antiestrogens (40).

FGFs and their receptors have been shown to be present with high frequency in breast cancer specimens (41–50). Evidence for a possible role for FGF signaling in the estrogen-independent growth of breast tumors is gained from study of clonal and polyclonal FGF-transfected MCF-7 cell lines, which are capable of forming large, progressively growing tumors in ovariectomized or tamoxifen-treated nude mice. Moreover, the FGF-transfected cells are metastatic, forming micrometastases in lymph nodes, lungs, and other organs (21, 22, 51). The estrogen-independent and tamoxifen-resistant growth of FGF-transfected MCF-7 cells suggests an interaction between FGF signaling pathways and ER-activated pathways that could occur at the level of the ER itself or at the end point of both pathways, where they impinge on growth mechanisms. If FGF-mediated growth pathways bypass the ER pathway to affect growth directly, we would expect that growth would be unaffected by hormonal treatments devoid of agonist activity. We therefore sought to determine the sensitivity of the estrogen-independent tumor growth of FGF-transfected MCF-7 cells to ICI 182,780 or aromatase inhibitors. In contrast to what was seen with ERB-B signaling pathways, we report that FGF-mediated pathways appear to provide an alternative growth stimulatory signal that is not dependent on ER activation.

MATERIALS AND METHODS

Cell Lines. FGF-transfected MCF-7 cell lines have been described previously (21, 22, 51, 52). Briefly, the ML-20 clonal cell line is a MCF-7-derived cell line that is stably transfected with a *lacZ* expression vector. The *in vitro* and *in vivo* growth characteristics of ML-20 cells are indistinguishable from wild-type MCF-7 cells (51), and >90% of the cells routinely stain positive for β-galactosidase expression by X-gal staining (52). MKL-F (FGF-4-transfected; Ref. 52) and FGF-1 clone 18 (FGF-1-transfected) cells (22) resulted from the stable transfection of the ML-20 clonal cell line with expression vectors for FGF-4 (also known as hst-1/K-FGF) and FGF-1 (also known as acidic FGF or aFGF), respectively. Both cell lines continue to stably express β-galactosidase, allowing effects of FGF overexpression on metastatic capability to be assessed by X-gal staining of organs and tissues of tumor-bearing mice. The MKL-4 cell line was derived by transfecting wild-type MCF-7 cells (of similar passage number used for the ML-20 transfection) with an expression vector for FGF-4, which produced the clonal MKS-1 cells (21). These cells were then retransfected with an expression vector for *lacZ*, yielding MKL-4 cells (51). Cells were maintained in IMEM (Biofluids, Rockville, MD) supplemented with 5% FBS in a humidified, 37°C, 5% CO_2 incubator in routine culture until used for tumor cell injection.

Drugs. ICI 182,780 was kindly donated by Dr. Alan Wakeling of Zeneca Pharmaceuticals (Macclesfield, England), and was administered s.c. at a dose of 5 mg in 0.1 ml of vehicle every week. For the experiment depicted in Fig. 1, powdered drug was first dissolved in 100% ethanol and spiked into warmed peanut oil (Eastman Kodak, Rochester, NY) 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 supplied by B. M. Vose (Zeneca Pharmaceuticals). 4-OHA was donated by Angela Brodie (University of Maryland, Baltimore, MD) and was administered s.c. at a dose of 1 mg/mouse/day 6 days of the week in a vehicle of 0.3% hydroxypropylcellulose. Letrozole was donated by Dr. Ajay Bhalnagar (Novartis, Ltd., Basil, Switzerland) and was administered via gavage at a dose of 1 mg/mouse/day 6 days of the week in a vehicle of 0.3% hydroxypropylcellulose. Sustained-release (60 day) pellets containing 5 mg of tamoxifen were obtained from Innovative Research of America (Sarasota, FL) and implanted s.c. in the interscapular area at the time of tumor cell injection.

Tumor Cell Injection. The procedure for tumor cell injection has been described previously (21). Briefly, tumor cells were scraped into their normal growth medium, and viable cells were quantified using trypan blue exclusion. The cells were

Cycle analyses using RNA from ML-20, estradiol-treated cells (the highest expressors of progesterone receptor) revealed that amplification remained logarithmic at 35 cycles for the GAPDH reaction and 40 cycles for the progesterone receptor reaction, making these assays semiquantitative. The GAPDH PCR reaction was performed using standard reagent conditions recommended by the manufacturer and cycles of 95°C for 45 s and 50°C for 45 s for 35 cycles. For the progesterone receptor PCR reaction, final $MgCl_2$ concentrations were adjusted to 1.25 mM, and 0.25 M acetamide was included. Cycles were of 95°C for 45 s and 50°C for 45 s for 40 cycles. GAPDH and progesterone receptor reaction products were first visualized by ethidium bromide staining following electrophoresis in a 2% agarose gel. Products were then electrophoresed on a 4–20% acrylamide gel that was subjected to both autoradiography and PhosphorImager quantitation as described above.

Transient Transfection, Luciferase, and CAT Reporter Assays. ML-20 and clone 18 cells were plated in 6-well plates, allowed to attach overnight, and stripped of estrogens in a procedure similar to that for the growth assays (see above). Following stripping, cells were transfected by the calcium phosphate, low-CO_2 method (58). The luciferase plasmids pGLB-MERE or pGLB-MNON were obtained by inserting an approximately 1.48-kb fragment containing a glucocorticoid response element-deleted mouse mammary tumor virus promoter with either a substituted double consensus ERE (MERE) or the same sequence with the ERE palindromes scrambled (MNON) (59) into the *Hin*dIII site of pGLB (Promega, Madison, WI). Each dish received 2.5 μg of either pGLB-MERE or pGLB-MNON and 1.0 μg pCMV-CAT, which directs constitutive expression of CAT, cotransfected as a control for transfection efficiency. Following transfection, each well was washed twice with PBS and incubated for 48 h in medium containing vehicle (0.01% ethanol), 10^{-9} M estradiol, 10^{-7} M ICI 182,780, a combination of E_2 and ICI, 10 ng/ml FGF-1 plus 10 μg/ml heparin, or a combination of FGF, heparin, and ICI 182,780. (Duplicate samples of each treatment were used.) Cells were lysed and assayed for luciferase activity using the Luciferase Reporter Gene Assay (Boehringer Mannheim, Indianapolis, IN) according to the manufacturer's instructions. Luciferase values, expressed as relative light units, for each sample were corrected for background by subtracting the value of lysates of untransfected cells prepared in parallel. CAT expression was assayed using the CAT ELISA (Boehringer Mannheim, Indianapolis, IN) according to the manufacturer's instructions. Protein content of the lysates was determined using the BCA Protein Assay Reagent (Pierce, Rockford, IL). Luciferase and CAT values, normalized for protein, were used to calculate mean specific relative light units/ng CAT.

Statistical Analyses. Statistical methods used for tumor growth have been described previously (53, 60). For Figs. 1 and 2, only mice surviving at the end of the experiment were included in the analysis. When no tumor developed from a particular injection, tumor volume was recorded as zero. The repeated measures ANOVA (60) was used to compare tumor volumes among the treatment groups using measurements taken over the entire time course of the experiment. In addition, final tumor volumes for weights in the case of clone 18) were compared among treatment groups at the end of each experiment using ANOVA. For analysis of metastasis in Table 1, for each transfectant, analysis of covariance was used to compare the effects of treatment on total metastases, total distant metastases (lung metastases plus other metastases), lymph node metastases, lung metastases, and other metastases. The analyses were all conducted with final tumor volume (or weight for the clone 18 cells) included in the model as a covariate. The analyses considered the effects of all treatments simultaneously, as well as the effects of individual treatment comparisons (which were adjusted for multiple comparisons using Dunnett's method). For each transfectant, the effect of final tumor volume (or weight for clone 18) on the number of metastases was evaluated using linear regression (for each of the categories of metastasis described above). In Fig. 3, paired *t* tests were performed comparing control and transfected cells under different conditions of treatment. For the anchorage-dependent growth assays depicted in Fig. 4, we examined the effect of treatment on the rate of cell growth, using linear regression with an interaction between time and treatment. To compare cell growth rates and doubling times among the cell lines under specific treatment conditions, nested linear regression models were used. For Fig. 6, ANOVA was used to determine significant differences in ER binding among cell lines.

RESULTS

Estrogen-Independent Growth of Tumors Produced by FGF-transfected MCF-7 Cells Is Not Inhibited by Treatment with a Pure Antiestrogen or with Aromatase Inhibitors. We have previously shown that both FGF-1- and FGF-4-transfected MCF-7 cells form progressively growing tumors in ovariectomized nude mice, as well as in similar mice treated with tamoxifen (21, 22, 53). 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, such as adrenal gland, liver, fat, or possibly the tumor itself. The transfected cells evidently still possess ERs, because they respond to estrogen and tamoxifen administered to the mice, as well as to these compounds used in tissue culture (21, 22). 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, we tested the ability of a pure antiestrogen, ICI 182,780, and two aromatase inhibitors, 4-OHA and letrozole, to inhibit the estrogen-independent tumor growth produced by these FGF-transfected cell lines.

In a first experiment to test the above hypothesis, FGF-4-transfected MKL-4 cells were injected as before, and the mice were treated with vehicle, tamoxifen, or ICI 182,780. There were no significant differences in tumor volume among the treatment groups considered over the entire time course of the experiment ($P = 0.72$) or at the final time point (Fig. 1A, $P = 0.72$). Treatment with ICI 182,780 did not inhibit tumor growth below that achieved in vehicle-treated mice ($P = 0.675$). Thus, the failure of ICI 182,780 to inhibit the estrogen-independent growth exhibited by this cell line supports the hypothesis that such growth does not result from small amounts of estrogenic

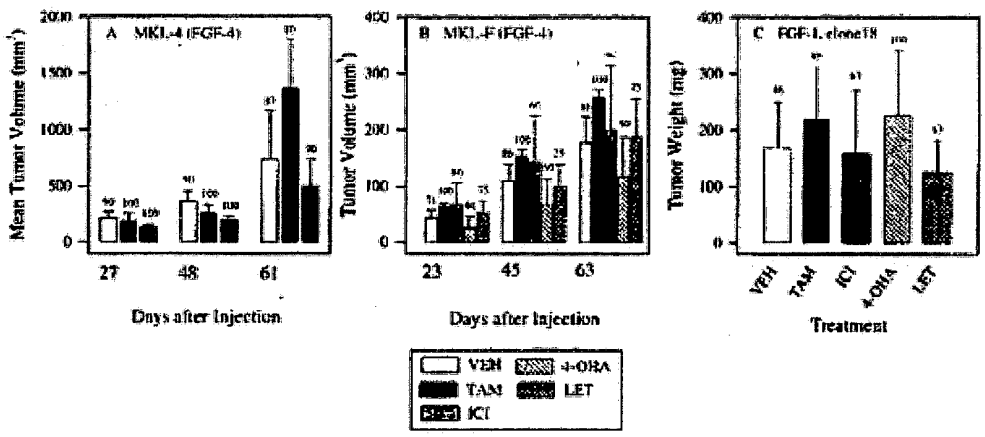

Fig. 1 Growth of FGF-transfected MCF-7 cells in ovariectomized nude mice is not inhibited by treatment with ICI 182,780, 4-OHA, or letrozole. Ten million cells from the indicated cell lines were injected into the mammary fat pads of ovariectomized nude mice treated with vehicle (*VEH*); a 5-mg, 60-day-release tamoxifen pellet (*TAM*); ICI 182,780, 5 mg s.c. every week (*ICI*); 1 mg of 4-OHA s.c. per day 6 days of the week (*4-OHA*); or 1 mg of letrozole per day via gavage 6 days of the week (*LET*). *Columns*, group mean; *bars* SE. *Numbers* above each column are the percentages of injections resulting in measurable tumors at that time point. *A*, volumes of tumors produced by one clonal FGF-4-transfected MCF-7 cell line, MKL-4, at the indicated number of days following tumor cell injection. *B*, volumes of tumors produced by a second clonal FGF-4-transfected MCF-7 cell line, MKL-F, at the indicated number of days following tumor cell injection. *C*, weights of tumors produced by a clonal FGF-1-transfected MCF-7 cell line, FGF-1, clone 18, weighed after sacrifice of the animals 28 days after tumor cell injection. (Because the FGF-1 producing MCF-7 cells may form fluid-filled sacs around the tumor, confounding tumor measurements before sacrifice, only postmortem weights are presented here.)

growth stimulation achieved by extraovarian estrogen production.

We wished to assess the effect of ICI 182,780 on metastasis as well as on tumor growth. In spite of its retention of the transfected *lacZ* expression plasmid, the MKL-4 cell line becomes heterogeneous over time with respect to β-galactosidase expression, such that a few cells have high expression, but most are negative (52). We therefore used a second clonal FGF-4-transfected MCF-7 cell line, MKL-F, the β-galactosidase expression of which is stable, for a subsequent experiment involving FGF-4-transfected MCF-7 cells. Because FGF-1 has also been shown to produce estrogen-independent *in vivo* growth when transfected into MCF-7 cells (22), we also included a clone of FGF-1-transfected cells designated clone 18, the β-galactosidase expression of which is also stable. For these experiments, two aromatase inhibitors, 4-OHA (61, 62) and letrozole (63), were also used to inhibit extraovarian synthesis of estrogens.

In agreement with the experiment using MKL-4 cells depicted in Fig. 1*A*, when the FGF-4-transfected MKL-F cells were used, there were no differences in tumor volume among treatment groups over all time points ($P = 0.382$), and ICI 182,780 did not decrease tumor growth below that obtained in vehicle-treated animals (Fig. 1*B*; $P = 0.837$ for the last time point). In addition, neither 4-OHA nor letrozole decreased tumor growth below vehicle-treated levels ($P = 0.571$ and 0.931 for the last time point, respectively).

FGF-1-transfected clone 18 cells form tumors that are sometimes surrounded by a fluid-filled sac (22, 53), preventing accurate tumor volume measurements during the course of the experiment. Consequently, when these cells were used (Fig. 1*C*), only terminal tumor weights were analyzed with ANOVA. As with the MKL-4 and MKL-F cells, ICI 182,780 did not inhibit estrogen-independent tumor growth in the clone 18 cells ($P = 0.977$). Administration of ICI 182,780 to animals injected with ML-20 cells, a clonal line of β-galactosidase-transfected wild-type MCF-7 cells (51), also produced no effect when compared with vehicle-treated animals [*i.e.*, no progressively growing tumors were obtained in either case (data not shown)]. In other, separate experiments, a polyclonal population of control vector-transfected ML-20 cells that forms progressively growing tumors in estrogen-supplemented mice (22) did not form tumors in either untreated or ICI 182,780-treated animals.[5] Thus, the continued progressive *in vivo* growth of FGF-transfected cells in ovariectomized animals treated with either a pure antiestrogen or aromatase inhibitors demonstrates that the estrogen-independent growth of these cells in untreated ovariectomized nude mice is not due to estrogenic activity produced at extraovarian sites.

Because ICI 182,780, 4-OHA, and letrozole were without effect in the experiments described above, we injected reproductively intact female mice for 2 weeks with these compounds at the same doses used in the above experiments to observe for activity in preventing effects of endogenous estrogens on the

[5] Unpublished results.

3.8. Sandoz also operates in the pharmaceuticals market. On 6 October 2015, Sandoz obtained a marketing authorisation for a fulvestrant formulation entitled "Fulvestrant Sandoz 50 mg/ml, solution for injection in a prefilled syringe" (hereinafter also referred to as: Fulvestrant Sandoz). Sandoz's generic fulvestrant formulation infringes (in any case) claim 1 of the patent.

3.9. On 21 June 2016, Sandoz had Fulvestrant Sandoz included in the "G-Standard". AstraZeneca then wrote to Sandoz, after which Sandoz promised to cease marketing Fulvestrant Sandoz in the Netherlands up to and including the day of the court hearing of the provisional relief proceedings (6 July 2016).

3.10. In Germany, AstraZeneca claimed provisional relief against Hexal AG, an affiliate of Sandoz, for infringement of the patent. The defence disputed the validity of the patent. In a decision on appeal of 19 February 2016 the *Oberlandesgericht* (Higher Regional Court) Düsseldorf, having considered Howell, McLeskey and other studies, issued the provisional finding that the patent was valid. Proceedings are also pending in Switzerland and Spain in relation to the infringement and/or validity of EP 138.

4. The dispute in the original proceedings

4.1. Alleging that Sandoz is threatening to infringe, inter alia, claim 1 of the patent by putting the directly obtained product of the method on the market in the Netherlands, AstraZeneca has claimed that the Provisional Relief Judge:

> A. issue judgment in provisional relief proceedings, with immediate enforceability:
> 1. prohibiting Sandoz from having any (direct and/or indirect) involvement in the Netherlands with the infringement of the European patent EP (NL) 1 250 138 B2, *inter alia* by being involved in putting into circulation, selling on, supplying or otherwise trading in, or, with regard to all of this, offering (or further offering) generic "Fulvestrant Sandoz 50 mg/ml, solution for injection in a prefilled syringe" or any other fulvestrant formulations that come under the scope of protection of the patent, on pain of a penalty of EUR 50,000 for each violation of this provisional injunction, or, at the discretion of AstraZeneca, of EUR 25,000 for each product concerned or for each day, with part of a day counting as a whole day, that Sandoz's involvement with the direct or indirect infringement of the patent continues after the provisional judgment is served, up to a maximum of EUR 1,000,000, with this provisional injunction remaining valid for the remainder of the proceedings and, in any case, until judgment is issued in them;
> 2. ordering Sandoz to pay the costs of the proceedings with regard to the provisional relief, with due observance of the provisions of Article 1019h DCCP;
>
> B. also issue judgment in provisional relief proceedings, with immediate enforceability:
> 1. prohibiting Sandoz from having any (direct and/or indirect) involvement in the Netherlands with the infringement of the European patent EP (NL) 1 250 138 B2, *inter alia* by being involved in putting into circulation, selling on, supplying or otherwise trading in, or, with regard to all of this, offering (or further offering) generic "Fulvestrant Sandoz 50 mg/ml, solution for injection in a prefilled syringe" or any other fulvestrant formulations that come under the scope of protection of the patent;
> 2. ordering Sandoz to remove (or give instructions to remove) "Fulvestrant Sandoz 50 mg/ml, solution for injection in a prefilled syringe", registered under number RVG 115994, as soon as this is reasonably possible, from the G-Standard;
> 3. ordering Sandoz to place an advertisement in the next issue of the *Pharmaceutisch Weekblad*, in accordance with the outline given in the Summons;
> 4. ordering Sandoz to provide AstraZeneca, within two weeks after the service of the judgment, with a list in writing of all the customers to whom Sandoz has sold, delivered and/or offered products that come under the scope of protection of the patent;
> 5. ordering Sandoz to send a registered letter the content of which is determined by AstraZeneca (i.e. recalling the delivered products) to all the customers referred to in 4.,

within two weeks after the service of the judgment, with the obligation that it simultaneously provides AstraZeneca with copies of all the letters to be sent;

6. ordering Sandoz to pay a penalty to AstraZeneca in the amount of EUR 50,000 for every violation of the injunction referred to in 1. and for every failure to comply (fully and properly) with the orders set out in 2., 3., 4 and/or 5., or, at the discretion of AstraZeneca, to pay a penalty of EUR 25,000 to AstraZeneca for each product concerned or for each day, with part of a day counting as a whole day, that Sandoz's involvement with the direct or indirect infringement of the patent continues after the provisional judgment is served, or that the orders referred to in 2., 3., 4 and/or 5. are not fully and properly complied with after the judgment is served, with these penalties being owed for any injunction or order that is not (fully and properly) complied with;

7. ordering Sandoz to pay the costs of these proceedings, with due observance of the provisions of Article 1019h DCCP.

4.2. Sandoz takes the position that the relief applied for by AstraZeneca should be rejected because there is a serious, real chance that the Dutch designation of EP 138 would be invalidated in proceedings on the merits. Its defence comprises, put briefly, in particular, the following.

Novelty

4.2.1. Claim 1 of EP 138 is not novel in the light of McLeskey. McLeskey discloses a formulation containing fulvestrant, which is to be injected, in a concentration of 50 mg/ml, 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol and given volume with ricin oil.

4.2.2. The skilled person would immediately understand that this formulation is suitable for treating breast cancer because it had long been known that fulvestrant was effective in this regard. McLeskey discloses the fact that fulvestrant acts as an alternative hormonal therapy in the treatment of breast cancer in patients who have become resistant to tamoxifen. The activity of the fulvestrant formulation is also confirmed by the uterus test, described by McLeskey, which shows that the fulvestrant formulation has an oestrogen-inhibiting effect which, in the clinical studies to which McLeskey refers, leads to the treatment of breast cancer.

4.2.3. The skilled person would also know that, as a rule, injections in mice are administered subcutaneously given the animal's tiny muscles, but that a formulation in castor oil is generally administered intramuscularly to human beings because only a small volume can be injected subcutaneously. When reading McLeskey, the skilled person would therefore understand that administration is to be performed intramuscularly.

4.2.4. Finally, on the basis of his general professional knowledge the skilled person would expect this formulation to be effective in obtaining a therapeutically significant blood plasma concentration of fulvestrant for the treatment of breast cancer for at least two weeks. The fact is that McLeskey describes this formulation as an alternative to tamoxifen, and it states that it is a pre-formulation obtained from Zeneca (AstraZeneca's legal predecessor). The skilled person would assume that this formulation is intended for sustained release.

Conditional: replicability

4.2.5. To the extent that AstraZeneca submits that McLeskey only carried out tests on mice and does not, therefore, demonstrate that the described formulation is effective in the treatment of human beings for at least two weeks, Sandoz invokes the non-replicability of

the claims of EP 138. In EP 138, too, the formulation was only tested on rabbits and the blood plasma concentration was measured over a period of just five days.

Inventive step

4.2.6. Claim 1 of EP 138 lacks an inventive step, assuming Howell as the closest prior art. Howell discloses the therapeutic effect of fulvestrant in the treatment of patients with breast cancer. The formulation used contains fulvestrant in a concentration of 50 mg/ml in castor oil. It does not disclose any other excipients. The dose of fulvestrant is 250 mg per month.

4.2.7. The only difference with the second medical use claim in EP 138 is the disclosure of the exact formulation, including the other excipients. The problem to be solved can be formulated as follows: *providing a formulation for fulvestrant for the (intramuscular) treatment of a benign or malignant disease of*[4] *the breast or reproductive tract.*

4.2.8. The average formulator searching for a solution to this problem would carry out (or commission) a search in the literature focusing on articles and publications on fulvestrant / ICI 182,870. This search would lead to McLeskey. On the basis of McLeskey, the formulator would then arrive at the formulation claimed in claim 1 of EP 138 because he would have a reasonable expectation of the formulation being successful i.e. suitable for the treatment of breast cancer. Any doubts or concerns that the skilled person might have would mean that this search lacks an inventive step as long as there is no bias, which is not the case.

4.2.9. McLeskey can also be assumed to be the closest prior art. On that basis, no objective technical problem can be formulated because there is no difference between McLeskey and the wording of claim 1 of EP 138. Alternatively, to the extent that it is found that EP 138 states more explicitly that the formulation can be used for the treatment of breast cancer, the problem to be formulated lies in the fact that it provides the skilled person with greater certainty about the application of the specific formulation of fulvestrant for the treatment of breast cancer.[5] Proceeding from McLeskey the skilled person would conclude, without doing any inventive work, that there is a reasonable chance that the formulation used by her can be successfully used in treating people with breast cancer, particularly after consulting Howell, to whom McLeskey refers in footnote 19.

4.2.10. Claims 2 – 31 are also invalid given the lack of novelty or an inventive step.

4.3. AstraZeneca has disputed Sandoz's submissions, with reasons given. To the extent relevant, these submissions are discussed below.

5. The dispute in the counterclaim proceedings

5.1. Sandoz has claimed that the Provisional Relief Judge issue judgment, with immediate enforceability:

---

[4] In its pleading notes Sandoz uses the word "for" here (erroneously, this Provisional Relief judge assumes) rather than "of".

[5] When putting forward its oral arguments Sandoz referred to an alternative problem: finding an intramuscular use for fulvestrant.

A. ordering AstraZeneca to permit and tolerate the fact that Sandoz performs the acts exclusively reserved to it under section 53 of the Dutch Patents Act[6] with regard to the product Fulvestrant Sandoz;
B. ordering AstraZeneca to restrain from carrying out the following legal or factual acts that may damage the sale of the product Fulvestrant Sandoz until the court ruling on the merits in the present dispute has issued its final judgment:
i. levying (prejudgment) attachment (or having (prejudgment) attachment levied), against Sandoz itself or against third parties, on stocks of the product Fulvestrant Sandoz;
ii. sending demand letters to resellers of the product Fulvestrant Sandoz without referring to the decision to be handed down by Your Honour and enclosing a copy thereof;
iii. taking legal measures by requesting a ban on sales against resellers of the product Fulvestrant Sandoz or by threatening to do so;
C. ordering AstraZeneca to pay a penalty of EUR 100,000.00, which is not subject to mitigation by the court, for each violation of the injunctions and orders set out under A and B, as well as a penalty of EUR 50,000.00 for every day, with part of a day being regarded as a whole day, that a violation of the injunctions and/or orders to be issued continues;
D. ordering AstraZeneca to pay the costs of the proceedings under Article 1019h DCCP.

5.2. Sandoz has invoked the invalidity of EP 138 in the counterclaim proceedings as well. Put briefly, Sandoz submits that if the court rules in its favour in the original proceedings, AstraZeneca might wish to use two related patents (EP 1 669 073 and NL 1017075) against Fulvestrant Sandoz. According to Sandoz, these two patents are also invalid. However, AstraZeneca has refused to confirm that it will not invoke these two patents. Sandoz submits that it therefore has an urgent interest in its claims in the counterclaim proceedings.

6. The assessment in the original proceedings and in the counterclaim proceedings

Jurisdiction

6.1. On the basis of Articles 4(1) and 24(4) of the Recast Brussels I Regulation[7], this Court has international jurisdiction to hear the main action. Therefore, it also has jurisdiction to order the provisional relief claimed by AstraZeneca. This Court's jurisdiction in the counterclaim proceedings is based on, *inter alia,* Articles 7(2) and 24(4) of the Recast Brussels I Regulation.

Urgent interest

6.2. Having regard to the threat of infringement against its patent, AstraZeneca has an urgent interest in its claims.

Novelty

6.3. In *Material and methods, Drugs* McLeskey discloses two formulations of ICI 182,780 (fulvestrant), one of which based on peanut oil was used for the experiment shown in figure 1[8] and

---

[6] *Rijksoctrooiwet 1995.*
[7] Regulation (EU) No 1215/2012 of the European Parliament and of the Council of 12 December 2012 on jurisdiction and the recognition and enforcement of judgments in civil and commercial matters.
[8] According to the District Court's conclusion from the follow-up of the article, this should probably be 1A; see the penultimate paragraph on page 700.

the other based on castor oil (hereinafter: the castor oil formulation) for the experiments shown in figures 1B and 1C. In each of these experiments, three different cell lines were used (MKL-4, MKL-F and FGF-1 clone 18). The experiments were performed on ovariectomised mice which therefore produced much less estrogen. The parties agree that the components of the castor oil formulation are the same as those referred to in claim 1 of the patent.

6.4. McLeskey also describes an experiment with mice whose ovaries had not been removed. These mice were also injected with, inter alia, ICI 182,780 to test the inhibiting activity of ICI 182,780 on the effect of oestrogen (referred to as anti-oestrogenic activity). Oestrogen has an effect on endometrial growth. The parties refer to this test as the uterus test. The anti-oestrogenic activity of fulvestrant had been known about for some time. As Sandoz argues,[9] the uterus test was an accepted test for measuring anti-oestrogenic activity.

6.5. McLeskey is a study of the mechanisms that lead to tamoxifen resistance. Although it refers to ICI 182,780 as an alternative therapy for the treatment of breast cancer,[10] in this study it is used as an anti-oestrogen to test the effect of oestrogen (which is not produced by the ovaries but rather in other parts of the mouse's body) on the growth of the tumour (*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 amount of estrogens still present in ovariectomized nude mice, we tested the ability of a pure antiestrogen, ICI 182,780, and two aromatase inhibitors, 4-OHA and letrozole, to inhibit the estrogen-independent tumor growth produced by these FGF-transfected cell lines*).[11] In that study, treatment with ICI 182,780 did not reduce tumour growth. McLeskey thus concludes that tumour growth is not caused by oestrogen produced outside the ovaries.[12]

6.6. Any therapeutic effect of ICI 182,780 (the castor oil formulation) in the treatment of a benign or malignant disease (which, according to the parties, must be understood to mean cancer) of the breast or reproductive tract cannot be deduced from McLeskey. Rather, it leads to the conclusion that ICI 182,780 has no such therapeutic effect. For the present, this Provisional Relief Judge is not convinced that the skilled person (hereinafter: the skilled person) would consider the effectiveness of the castor oil formulation to be a plausible treatment for cancer on the basis of the uterus test, which is used to test anti-oestrogenic activity. Sandoz submits that, for the skilled person, this test demonstrates the oestrogen-inhibiting activity of the formulation used, but AstraZeneca disputes the fact that the skilled person would consider the therapeutic effect against cancer plausible on the basis of the test, and Sandoz has not demonstrated this plausibility,[13] meaning that it cannot be assumed.

6.7. In addition, the castor oil formulation used by McLeskey was apparently not modified to obtain a therapeutically significant blood plasma concentration of fulvestrant for at least two weeks. Any conclusion that can be drawn regarding the sustained-release properties of the castor oil formulation in McLeskey points in a different direction. The fact is that, in the test performed by McLeskey, the mice were injected with ICI 182,780 on a weekly basis. According to Sandoz, on the basis of his general professional knowledge the skilled person would expect McLeskey's castor oil formulation to be effective in obtaining a therapeutically significant blood plasma concentration of fulvestrant for at least two weeks. However, Sandoz has not made it clear why the skilled person's professional knowledge would lead him to expect this.

---

[9] Para. 44 of the pleading notes.
[10] Page 697, right-hand column.
[11] Page 700, right-hand column.
[12] Page 701, penultimate paragraph.
[13] The opinion of Dr. H. Vromans, submitted by Sandoz, says nothing about this.

6.8. Given the foregoing, it must be concluded for the present that McLeskey does not destroy the novelty of the patent.

Inventive step

6.9. The parties agree that a formulation consisting solely of fulvestrant in castor oil, as disclosed in Howell, cannot be used and that the formulation used by Howell has to contain other excipients as well. Proceeding from Howell, and given the differences with the subject-matter of claim 1 of the patent, this Provisional Relief Judge concurs with the objective technical problem formulated by Sandoz.[14]

6.10. The question to start with is whether, in conducting a search in the literature, the skilled person (according to Sandoz comprising a team of an oncologist and a formulator, with the possible addition of a pharmacologist) would happen upon McLeskey, since the study reported in it does not focus on the use of fulvestrant, formulations of fulvestrant or formulations of whatever else, but rather on mechanisms that lead to tamoxifen resistance. For the present, the report of a simulated search in the literature in the Medline database filed by Sandoz is not convincing. Although this search identifies McLeskey as one of the six refined search results, one possible factor in this is that it is a lot easier to search for something that has already been found. Having regard to the subject-matter dealt with by McLeskey, in which the castor oil formulation (in addition to the formulation based on peanut oil) is used as an anti-oestrogen and is only discussed in passing (not in the summary or the introduction but solely in the text itself), this Provisional Relief Judge moreover considers it doubtful, as does the Opposition Division, whether the skilled person would combine the two documents.

6.11. If the skilled person were to combine Howell and McLeskey, that would still not lead to the features of claim 1. The skilled person would have to carry out further study, in any case, in order to determine whether McLeskey's castor oil formulation has the desired therapeutic effect when administered intramuscularly to human beings. Referring to the opinion of the expert Dr. H. Vromans, Sandoz submits that he considers that this would have a reasonable chance of success. In this regard this opinion states the following about the castor oil formulation used in McLeskey:

[14] Therefore, unlike the Opposition Division and the German court, this Provisional Relief Judge does not assume a desired alternative formulation but rather, actually, a fulvestrant formulation.

65. This preformulated formulation supplied by Zeneca would have been of great interest to any formulator, for the following reasons:

a) The formulation has the desired concentration of fulvestrant;

b) The formulation is a castor oil-based vehicle, just as the formulation administered to breast cancer patients in the Howell study;

c) The formulation was supplied *preformulated*, which indicates that the formulation is used or supplied in some frequency;

d) The formulation was supplied by an employee of Zeneca, the company that was developing fulvestrant;

e) The formulation appears to have been thoroughly elaborated with regard to the specific relative concentrations of the substances used;

f) The combination of the excipients ethanol, benzyl benzoate and benzyl alcohol was well known and was used in (castor) oil based parenteral formulations for human patients already for quite some time.

66. I would have assumed that this was a formulation designed for human use that McLeskey happened to use in mice in her research. I would actually have assumed that the formulation was in fact the formulation that was administered to patients in the Howell study. After all, the amount of fulvestrant in the formulation, 50 mg/ml, is exactly the same amount as the amount in the formulation used in breast cancer patients in the Howell study.

6.12. This opinion then discusses a number of circumstances that could possibly affect the skilled person's expectation of success, after which it concludes, put briefly, that these circumstances would not reduce the expectation of success. Conversely Dr. K. Schaupp and Prof. D.J.A. Crommelin, the experts consulted by AstraZeneca, consider that the skilled person would not have any expectation of success.

6.13. What seems to be of prime importance in the opinion of the expert Vromans is that he assumes that the skilled person would presume that the formulation used by McLeskey is the same as that used in Howell's study. The relevant issue is, however, whether on the basis of his technical knowledge the skilled person had reason to expect that he could successfully use McLeskey's anti-oestrogenic castor oil formulation for the desired application against cancer. The skilled person would have to base that expectation on the circumstances listed under a), b) and f) above.

6.14. Although this Provisional Relief Judge is willing to assume that the skilled person's interest would be piqued if he encountered McLeskey's castor oil formulation, the opinion submitted by Sandoz, of the expert Vromans, is not yet convincing on this point. In particular, the following circumstances, referred to by AstraZeneca's experts and not rebutted by Sandoz, raise doubts about the skilled person's expectation of success.

6.15. The skilled person was aware that studies, such as the one by McLeskey, can examine formulations that are intended solely for trials on animals, such as the tamoxifen pellets used by McLeskey that were to be administered subcutaneously to mice. The skilled person should therefore take account of the fact that the castor oil formulation used by McLeskey is not automatically suitable for treating cancer in human beings, particularly since McLeskey's study does not focus on that. It also follows from that study that, in relation to the weight of the mouse, the dosage of fulvestrant used by McLeskey is far higher (by a factor of 70) than that used by Howell in his study on human beings. Sandoz has also affirmed that McLeskey's castor oil formulation contains an unusually high concentration of alcohols (10% ethanol and 10% benzyl alcohol). According to Sandoz's expert, the toxicity of this concentration is not such that the skilled person would therefore consider that the formulation could not be used on human beings, but it would certainly temper his expectation of success.

6.16. Given the foregoing there is too much doubt that, in proceedings on the merits, the subject-matter of claim 1 of the patent would be regarded as lacking an inventive step when proceeding from Howell as the closest prior art, in combination with McLeskey.

6.17. This Provisional Relief Judge also considers, as does the Opposition Division, McLeskey to be a further removed starting point because, as found above, the focus of that study is entirely different from that of the patent. McLeskey does not disclose the therapeutic effect of the castor oil formulation used as an anti-oestrogen in the treatment of cancer. If the skilled person looking for a (further) therapeutic use were even to consult Howell, then, as found above, it cannot be considered, for the present, that he would have a reasonable expectation that McLeskey's anti-oestrogenic castor oil formulation could be used successfully in the treatment of cancer/breast cancer.

Replicability

6.18. The replicability of the patent does not need to be investigated because the requirement that Sandoz attached to this objection has not been satisfied met.

Conclusion

6.19. Since Sandoz has not contested the fact that there is a threat of infringement against, in any case, claim 1 of the patent and for the present there is insufficient reason to assume that the patent would be invalidated in proceedings on the merits, the injunction claimed in the original proceedings should be allowed.

6.20. No evidence has emerged of any unlawful involvement in infringement or indirect infringement (or any threat thereof), so that the injunction set out below will be limited. Sandoz has also challenged the submission that AstraZeneca has an urgent interest in the claims set out under 3, 4 and 5 because it, Sandoz, has not carried out any reserved acts so far.

AstraZeneca did not provide any further explanation of its urgent interest in this, so that these claims will be dismissed.

6.21. To preclude any enforcement disputes, the penalty amount to be determined will be different from what has been claimed.

6.22. The parties have reached agreement on the costs of the proceedings (EUR 175,000, 5% of which are to be allocated to the dispute in the counterclaim proceedings). The costs of the proceedings will be determined in accordance with this agreement and, as the largely unsuccessful party, Sandoz will be ordered to pay them.

6.23. Leaving aside the validity or invalidity of EP 1 669 073 and NL 1017075, the claims in the counterclaim proceedings cannot be allowed, given the provisional findings in the original proceedings about the validity of EP 138. The fact is that AstraZeneca cannot be prohibited from using, in any case, EP 138 against Fulvestrant Sandoz. The claims in the counterclaim proceedings should therefore be dismissed, with Sandoz, as the largely unsuccessful party, being ordered to pay the costs of the proceedings.

7. The decision in the original proceedings

This Provisional Relief Judge:

7.1. prohibits Sandoz from infringing the Dutch designation of European patent EP 1 250 138, *inter alia* by putting into circulation, selling, supplying or otherwise trading in, or, with regard to all of this, offering generic "Fulvestrant Sandoz 50 mg/ml, solution for injection in a prefilled syringe".

7.2. orders Sandoz to remove (or give instructions to remove) "Fulvestrant Sandoz 50 mg/ml, solution for injection in a prefilled syringe", registered under number RVG 115994, as soon as this is reasonably possible, from the G-Standard;

7.3. orders Sandoz, in the event of any violation of the injunction referred to in 7.1 or failure to comply with the order referred to in 7.2, to pay a penalty to AstraZeneca in the amount of EUR 25,000 for each product concerned or, at AstraZeneca's discretion, for each day, with part of a day counting as a whole day, that such a violation continues, up to a maximum of EUR 10,000,000.

7.4. orders Sandoz to pay the costs of the proceedings, including the costs of the proceedings with regard to the provisional relief, set up to today's date on AstraZeneca's part at EUR 166,250;

7.5. declares this judgment immediately enforceable to this extent;

7.6. dismisses any additional or other claims;

7.7. sets the period referred to in Article 1019i DCCP at six months after today's date;

8. The decision in the counterclaim proceedings

This Provisional Relief Judge:

8.1. dismisses the claims;

8.2. orders Sandoz to pay the costs of the proceedings, set up to today's date on AstraZeneca's part at EUR 8,750;

8.3. declares this order for costs immediately enforceable.

This judgment was issued by P.G.J. de Heij and pronounced in open court on 27 July 2016.

[signed]