certified electronic copy

FEDERAL PATENT COURT

JUDGMENT IN THE NAME OF

THE PEOPLE

3 Ni 20/23 (EP)

(reference number)

In the patent nullity case

1. Hexal AG, Industriestr. 25, 83607 Holzkirchen,

Plaintiff re 1,

Attorneys of record: df-mp Dörries Frank-Molnia & Pohlmann Patentanwälte Rechtsanwälte PartG mbB, Theatinerstraße 16, 80333 Munich,

2. Accord Healthcare GmbH, Hansastrasse 32, 80686 Munich,

Plaintiff re 2,

Attorneys of record: Ter Meer Steinmeister & Partner Patentanwälte mbB, Nymphenburger Straße 4, 80335 Munich,

3. Synthon B.V., 6545 CM Nijmegen (Netherlands),

Plaintiff re 3,

Attorney of record: Bonabry Partnerschaft von Rechtsanwälten mbB,
Luise-Ullrich-Straße 14, 80636 Munich,

4. STADA Arzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel,

Plaintiff re 4,

Attorneys of record: Hamm & Wittkopp Patentanwälte PartmbB,
Jungfernstieg 38, 20354 Hamburg,

g o v e r

The Regents of the University of California, Oakland, 94607 California (USA),

Defendant,

Attorneys of record: Hoffmann Eitle Patent- und Rechtsanwälte PartmbB,
Arabellastraße 30, 81925 Munich,

Intervener/intervener of the defendant:

Astellas Pharma Inc, Tokyo 103-8411 (Japan),

Attorneys of record: Hoffmann Eitle Patent- und Rechtsanwälte PartmbB,
Arabellastraße 30, 81925 Munich,

relating to European patent 1 893 196

(DE 60 2006 027 175)

and

the supplementary protection certificate DE 12 2013 000 155

the 3rd Senate (Nullity Senate) of the Federal Patent Court on the basis of the oral hearing of April 8, 2025 by Judge Berner as Chairwoman, Judges Dipl.-Chem. Univ. Dr. Münzberg and Dorn, Judge Dipl.-Chem. Univ. Dr. Freudenreich and Judge Dipl.-Chem. Univ.
Dr. Wagner

found to be right:

I. The claims are dismissed.
II. The plaintiffs 1 to 4 shall each bear 25 % of the costs of the legal dispute, including the costs incurred by the intervening parties.
III. The judgment is provisionally enforceable against provision of security amounting to 120% of the amount to be enforced in each case.

Facts of the case

The defendant is the proprietor of the European patent 1 893 196 (patent in dispute) , filed in English on March 29, 2006 and also granted with effect for the Federal Republic of Germany, with the designation "DIARYLHYDANTOIN COMPOUND" (in the German translation: DIARYLHYDANTOIN-VERBINDUNG). The patent in suit originates from an international application with of the application number PCT/US2006/011417

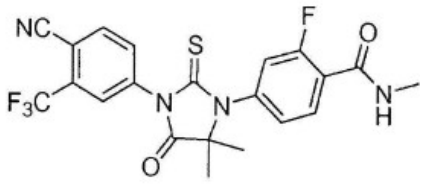
and the disclosure document WO 2006/124118 from and takes the priorities of three US-American applications US 680835 P of May 13, 2005, US 750351 P dated December 15, 2005 and US 756552 P dated January 6, 2006. It is registered at the German Patent and Trademark Office under file number 60 2006 027 175.1.

The patent in suit received its current version following opposition proceedings by a final decision of the Opposition Division of the European Patent Office, which was published on July 29, 2015 as EP 1 893 196 B2.

The patent in suit relates to a diarylhydantoin compound and its use in the treatment of hormone-refractory prostate cancer. In the limited version, it comprises 18 patent claims relating to the structurally defined compound RD162', a pharmaceutical composition comprising it and their respective uses. According to paragraph [0001] of the description of the patent in suit, the invention also relates to the synthesis of the compound, which, however, is no longer claimed.

The applicable claims 1 to 18 in the limited maintenance version of the patent in suit read as follows in the language of the proceedings English:

1. A compound having the formula



[RD162']

or a pharmaceutically acceptable salt thereof.

2. A compound according to D claim 1 or a pharmaceutically acceptable salt thereof for use in lhe treatment of lhe human or animal body by therapy

3. A compound acoording to daim 1 or a pharmaceutically acceptable salt thereof for use in a method of Creating a hyperproJifera|ive disorder.

4. A pharmaceutical composition comprising a fherapeuiically effective amount of a compound according to claim 1 or a pharmaceutically acceptable sall thereof, and a pharmaceutically acceptable carrier or diluenL

5. A pharmaceutical com position according to claim 4 for use in the treatment of the human of animal body by therapy.

6. A pharmaceutical composition according to la claim 4, for use in a method for treading a hyperproliferative disorder.

7. The composition of claim 6, wherein fh0 compasi\ion iS administered at a dosage of the compound in the range of

(a) from about 0.001 mg per kg body weight per day b aboul 1D0 mg per kg body weight per day. or
(b) from about 0.01 mg per kg body weight per day to about 100 mg per kg body weight per day, or
(c) from about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day.

8. The composition of claim 6, wherein the composition is administered at a dosage of lie compound Of aboul 1 mg per kg body weight per day.

0. the compound of claim 3 or a pharmaceutically acceptable salt thereof or ihe comp€isition of claim 6, wherein the hyperpraliferafive disorder is hormone refractory prostate cancer.

10. The compound of claim 3 or a pharmaceutically acceplabie salt thereof or the composition oi claim 6, wherein the hyperprolifelative disorder is prostate cancer.

11. The composition of claim 6, wherein the composition is administered by intravenous injection, by injection into lissue, intraperitoneally, orally, or nasally.

12. The composition of r.laim G, wherein the compasi\ion has a form Selected from the group consisting of a solution, dispersion, suspension, powder, capsule, lablet. pill, time release capsule, time release tablet, and time release pil|,

13. A composition according to any one of claims 4 to 6, wherein the carrier is a liquid and the compound is dissolved in the liquid.

14. A composition according to any one of claims 4 0 6, wherein the carrier is a solvent.

15. Use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition as defined in any one of claims 4, 7, 8 or 11 to 14 in the manufacture of a medicament for use in a method of treating a hyperproliferative disorder.

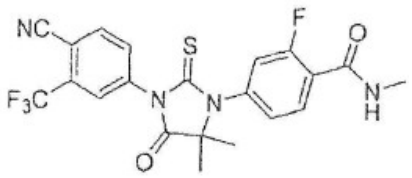
16. Use according to claim 15, wherein the hyperproliferative disorder is prostate cancer.

17. Use according to claim 15, wherein the hyperproliferative disorder is hormone refractory prostate cancer.

18. Use according to claim 15, wherein the hyperproliferative disorder is hormone sensitive prostate cancer.

In German they read:

1. Verbindung mit der folgenden Formel



[RD162']

oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon zur Verwendung bei der Behandlung des menschlichen oder tierischen Körpers durch Therapie.

3. Verbindung nach Anspruch i oder ein pharmazeutisch verträgliches Salz davon zur Verwendung bei einem Verfahren zur Behandlung einer hyperproliferativen Störung.

4. Pharmazeutische Zusammensetzung umfassend eine therapeutisch wirksame Menge einer Verbindung nach Anspruch 1 oder eines pharmazeutisch verträglichen Salzes davon und einen pharmazeutisch verträglichen Träger oder ein Verdünnungsmittel.

5. Pharmazeutische Zusammensetzung nach Anspruch 4 zur Verwendung bei der Behandlung des menschlichen oder tierischen Körpers durch Therapie.

6. Pharmazeutische Zusammensetzung nach Anspruch 4 zur Verwendung bei einem Verfahren zur Behandlung einer hyperproliferativen Störung.

7. Zusammensetzung nach Anspruch 6, wobei die Zusammensetzung in einer Dosierung der Verbindung im Bereich

(a) von etwa 0,001 mg pro kg Körpergewicht pro Tag bis etwa 100 mg pro kg Körpergewicht pro Tag, oder
(b) von etwa 0.01 mg pro kg Körpergewicht pro Tag bis etwa 100 mg pro kg Körpergewicht pro Tag, oder
(c)von etwa 0,1 mg pro kg Körpergewicht pro Tag bis etwa 10 mg pro kg Körpergewicht pro Tag verabreicht wird.

8. Zusammensetzung nach Anspruch 6, wobei die Zusammensetzung in einer Dosierung der Verbindung im Bereich von etwa 1 mg pro kg Körpergewicht pro Tag verabreicht wird.

9. Verbindung nach Anspruch 3 oder ein pharmazeutisch verträgliches Salz davon oder die Zusammensetzung nach Anspruch 6, wobei die hyperproliferative Störung hormonresistenter Prostatakrebs ist.

10. Verbindung nach Anspruch 3 oder ein pharmazeutisch verträgliches Salz davon oder die Zusammensetzung nach Anspruch 6, wobei die hyperproliferative Störung Prostatakrebs ist.

11. Zusammensetzung nach Anspruch 6, wobei die Zusammensetzung durch intravenöse Injektion, durch Injektion in Gewebe, intraperitoneal, oral oder nasal verabreicht wird.

12. Zusammensetzung nach Anspruch 6, wobei die Zusammensetzung eine Form besitzt, die aus der Gruppe ausgewählt ist, bestehend aus einer Lösung, Dispersion, Suspension, Pulver, Kapsel, Tablette, Pille, Retardkapsel, Retardtablette und Retardpille.

13. Zusammensetzung nach einem der Ansprüche 4 bis 6, wobei der Träger eine Flüssigkeit ist und die Verbindung in der Flüssigkeit gelöst ist.

14. Zusammensetzung nach einem der Ansprüche 4 bis 6, wobei der Träger ein Lösungsmittel ist.

15. Verwendung einer Verbindung nach Anspruch I oder eines pharmazeutisch verträglichen Salzes davon oder einer pharmazeutischen Zusammensetzung nach einem der Ansprüche 4, 7, 8 oder 11 bis 14 bei der Herstellung eines Medikaments zur Verwendung bei einem Verfahren zur Behandlung einer hyperproliferativen Störung.

16. Verwendung nach Anspruch 15, wobei die hyperproliferative Störung Prostatakrebs ist.

17. Verwendung nach Anspruch 15, wobei die hyperproliferative Störung hormonresistenter Prostatakrebs ist.

18. Verwendung nach Anspruch 15, wobei die hyperproliferative Störung hormonempfindlicher Prostatakrebs ist.

Furthermore, the defendant is the owner of the supplementary protection certificate DE 12 2013 000 155, which was granted by the German Patent and Trade Mark Office upon its application of December 16, 2013 on the basis of the patent in dispute and the European authorization EU/1/13/846 of June 21, 2013 relating to the product
"Enzalutamide or a pharmaceutically acceptable salt thereof" (marketed under the name "Xtandi"), with a term from March 30, 2026 until
June 25, 2028.

With its action of July 7, 2023, the plaintiff re 1 seeks the full declaration of invalidity of the patent in dispute, relying on the grounds of invalidity of lack of patentability in the form of lack of inventive step and lack of practicability. It is also seeking a declaration of invalidity of the supplementary protection certificate on the grounds of invalidity of the patent in dispute.

In the course of the proceedings, the plaintiffs re 2, 3 and 4 submitted written pleadings dated
July 28, 2023 (plaintiff no. 2), December 18, 2023 (plaintiff no. 3) and December 20, 2023 (plaintiff no. 4) each declared their intervention in the action or actions, citing the same grounds for nullity as plaintiff no. 1. Plaintiffs 1, 2 and 3 have consented to the joinder of the plaintiff or plaintiffs following them in time.

By letter dated December 21, 2023, the intervener of the defendant, as the holder of an exclusive sublicense relating to the territory of the Federal Republic of Germany for the subject matter of the patent in dispute, declared its accession as an intervening party on the side of the defendant. None of the parties objected to the joining of the intervener.

In support of their respective submissions, the plaintiffs introduced the following documents, among others, into the proceedings:

NK2 EP 1 893 196 B2 (patent in suit) and translation of the description and drawings according to the statement of the plaintiff 1 dated March 01, 2024.

NK3.1 US 60680835 dated May 13, 2005

NK3.2 US 60750351 dated December 15, 2005

NK3.3 US 60756552 dated January 6, 2006

NK8 TEUTSCH, G. et al, J. Steroid Biochem. Molec. Biol. 48(1), 1994, S. 111-119

NK9 SINGH, S.M. et al, Current Medicinal Chemistry 7, 2000, pp. 211-247

NK13 CHEN, .D.C. et al, Nature Medicine 10(1), 2004, pp. 33-39

NK14 SAWYERS, C.L., Presentation at the Prostate Foundation Scientific Retreat, Scottsdale Arizona, September 29-October 1, 2005, undated, unnumbered, 18 pages,

NK17 OUK, S. et al, poster, undated, one page

NK19 LANGER, T.L., University of Vienna, expert opinion dated June 24, 2023, 14 pages

NK26 KIER, L.B. et al, Chemistry & Biodiversity (1), 2004, pp. 138-151.

NK27 GMEINER, P., Friedrich-Alexander-Universität Erlangen Nürnberg, Expert opinion dated December 4, 2023, 14 pages

NK33 MACKAY, S., expert opinion dated April 29, 2024, 10 pages NK34 MACKAY, S., expert opinion dated October 31, 2024, 3 pages

NK41 MEIER, J. et al [eds], Biopharmazie Theorie und Praxis der Pharmakokinetik, Thieme Verlag, Stuttgart New York 1981, pp. 152-155.

The plaintiffs argue that the prior art documents NK14 and NK17 had well-matched disclosure contents and, individually or in combination, possibly taking into account the general knowledge of the art, such as on bioisosterism, provided the skilled person with the information that suggested to him to search for alternative thiohydantoin-

active substances for the treatment of hormone-resistant prostate cancer.

The plaintiffs 1 to 4 apply in unison,

> declare the European **patent** 1 893 196 invalid with effect for the territory of the Federal Republic of Germany and declare the supplementary **protection certificate** 12 2013 000 155 invalid.

The defendant and the intervening party request that the

> claims be dismissed.

They do not agree with the interventions of the plaintiffs 2 to 4. In their opinion, these interventions or actions are deemed not to have been filed due to the lack of payment of fees and are otherwise inadmissible. The defendant defends the patent in suit in its current version.

In their argumentation, the defendant and the intervening party refer, among other things, to the expert opinion

> HE15 CARREIRA, E.M., Expert opinion dated August 9, 2024, 22 pages and 40 pages of appendix.

They are of the opinion that the subject-matter of the patent in suit is executably disclosed and is based on an inventive step. The documents NK14 and NK17 were not publicly available and, independently of this and supported by HE15, show a clear teaching which does not lead the skilled person away from the cyclobutyl structure in the 5-position of the thiohydantoin ring. The plaintiffs' attempts to reverse or negate this teaching did not constitute evidence of a corresponding suggestion.

Reasons for the decision

The admissible actions are unfounded with regard to both the patent in suit NK2 and the contested supplementary protection certificate.

I.

1. There is a majority of plaintiffs, as the declared joinder of plaintiffs 2, 3 and 4 is effective and admissible as a subjective accumulation of claims.

a) Contrary to the opinion of the defendant and the intervening party, the interventions are not invalid because the plaintiffs 2 to 4 have not paid any court fees. The legal consequence provided for in § 6 para. 2 PatKostG cannot occur because the court fee is only payable once even if an additional plaintiff or additional plaintiffs join the action. There is no statutory provision in this respect. This is because the PatKostG and the schedule of fees under Section 2 (1) PatKostG - in contrast to interventions in opposition proceedings (see Section 3 (1) sentence 2 no. 3, Section 8 (1) no. 2 lit. c)
PatKostG; fee 313 600 in the list of fees under Section 2 (1) PatKostG) - there is no separate charging of fees for interventions in nullity proceedings before the Federal Patent Court.

Against this background, the general principle of cost law remains that only one court fee is incurred for a uniform subject matter of the legal dispute even if several plaintiffs are involved (see BGH, judgment of September 17, 2020, X ZR 147/18 - Signalumsetzung, juris para. 49). The plaintiffs are not represented by a joint attorney of record. However, this has no bearing on the issue,

whether there is a single subject matter of the legal dispute. In contrast to the facts on which the aforementioned decision of the BGH is based, the plaintiffs 1 to 4 have not filed a joint action in the present case, so there is no subjective accumulation of actions from the outset. Even in the latter case, a subsequent termination of a joint power of attorney does not lead to the accrual of a further court fee (see BGH loc. cit., para. 58). This must apply a fortiori in the case of a subsequent joining, especially since a joint power of attorney by the four plaintiffs may also not be appropriate due to the different interests of the plaintiffs or may not be in accordance with the professional code of conduct.

b) The interventions of the plaintiffs 2 to 4 are admissible.

The plaintiffs 1 to 4 are interveners within the meaning of Sec. 99 (1) PatG in conjunction with Sec. 99 (1) PatG.
§ Section 60 ZPO, as they assert similar claims in fact and in law.

The plaintiffs 1, 2 and 3 have agreed to the accessions of the plaintiff following them in time.

The interventions are also expedient within the meaning of Sec. 99 (1) PatG in conjunction with Sec. 263 ZPO in order to avoid new independent nullity actions by plaintiffs 2, 3 and 4 with the additional costs incurred as a result. The submissions on which the interventions of plaintiffs 2 to 4 are based are each based on the same grounds for nullity as the action brought by plaintiff 1. In addition, the claims of all plaintiffs are identical. The consent of the defendants is not required at first instance (see Thomas/Putzo/Hüßtege, ZPO, 43rd ed., Vorb § 50 para. 15 and 25; Zöller/Greger,
ZPO, 34th ed. § 263 para. 27).

2. The intervening party is admissible because the intervening party, as the licensee of the patent in dispute, has the necessary legal interest in the defendant prevailing as a supported party in the present proceedings (Section 99 (1) PatG in conjunction with Section 66 ZPO).

II.

The patent in suit is valid in its defended version because the asserted grounds for invalidity of lack of patentability and lack of practicability are not present (Art. II Sec. 6 (1) No. 1 and No. 2 IntPatÜG, Art. 138 (1) (a) in conjunction with Art. 52, 54, 56, Art. 138 (1) (b) EPC).

1. In the technical field of combating prostate cancer, the androgen receptor (AR) - which stimulates the growth of tumor cells - plays an essential role, according to the introductory remarks of the patent in suit NK2, whereby it is necessary to reduce its activity. In the advanced stage of the disease, this is achieved by castration and/or androgen deprivation therapy, whereby the AR is competitively blocked by antiandrogens. However, these treatment methods quickly lose their effect and the cancer becomes hormone-resistant (NK2, [0002]). The NK13 study identified and validated overexpression of the AR as the cause of hormone-resistant prostate cancer. This is sufficient to cause progression from hormone-sensitive to hormone-resistant prostate cancer, suggesting that better AR inhibitors than current drugs could slow the progression of prostate cancer. The AR and its ligand binding have been shown to be necessary for the growth of hormone-refractory prostate cancer, suggesting that the AR remains a target for this disease. It has also been shown that overexpression of the

AR antiandrogens convert from antagonists to agonists in hormone-resistant prostate cancer (an AR antagonist inhibits AR activity and an AR agonist stimulates AR activity). The data from this work explained why castration and antiandrogens could not prevent the progression of prostate cancer (NK2, [0003]).

Bicalutamide is the most commonly used antiandrogen and has an inhibitory effect on AR in hormone-sensitive prostate cancer, but cannot suppress AR when the cancer becomes hormone-resistant. Currently known antiandrogens do not prevent the progression of prostate cancer from the hormone-sensitive to the hormone-resistant stage and its treatment because they show only weak antagonistic activities, but strong agonistic activities when the AR is overexpressed in hormone-resistant prostate cancer. Therefore, better AR inhibitors with stronger antagonistic activities and minimal agonistic activities are needed (NK2, [0004]).

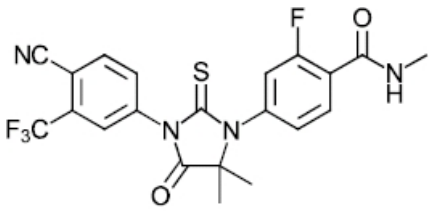
Non-steroidal antiandrogens described in many patents, such as bicalutamide, are preferred to steroidal compounds in prostate cancer because they are more selective and have fewer side effects (NK2, [0005] and [0006]).

Since the mechanism of hormone-refractory prostate cancer was not known, there was no biological system to test the compounds described in these patents for their effect on hormone-refractory prostate cancer. In particular, the ability of AR overexpression in hormone-refractory prostate cancer to convert inhibitors from antagonists to agonists was not recognized. An international PCT application presents a method for identifying androgen receptor antagonist and agonist properties of compounds , at which for each produced compound of the

time-consuming process of determining the antagonist and agonist properties of a compound. There is no method with which the properties relevant for the treatment of prostate cancer can be accurately predicted based solely on the chemical structure of a compound (NK2, [0007]).

2. According to the patent in suit, on the other hand, there is a need for new thiohydantoin compounds with desirable pharmacological properties. Since the activities responded to small structural changes, one compound could be effective in the treatment of prostate cancer, whereas a second compound could be ineffective, even if it differed only slightly from the first compound, for example by replacing a single substituent (NK2, [0008]). The identification of compounds that exhibited high potency to antagonize androgen activity and minimal agonistic activity should overcome hormone-resistant prostate cancer (HRPC) and prevent or slow the progression of hormone-sensitive prostate cancer (HSPC). Therefore, there is a need for selective modulators of the androgen receptor, such as those that are non-steroidal, non-toxic and tissue-specific (NK2, [0009]).

3. The problem of the patent in suit is solved according to patent claim 1 by the compound RD162' with the structure shown below and a pharmaceutically acceptable salt thereof (INN name "Enzalutamid", trade name "Xtandi"), according to patent claim 4 likewise by a composition comprising a therapeutically effective amount of RD162':



RD162'

Claims 2, 3, 5 to 11 and 15 to 18 relate to specific medical indications of RD162' alone or as a component of a composition according to claim 4, which are described in more detail in claims 12 to 14.

4. Because of the stated structural formula for the compound RD162', patent claim 1 does not require an in-depth interpretation of the compound according to patent claim 1, the compound as a component of a composition or the stated medical indications from the point of view of the competent team of medical chemists and pharmaceutical technologists and/or a physician working in the relevant field of drug development. There is also no dispute between the parties on this point.

5. The plaintiffs' assumption, based on any argumentation on the part of the defendant, that the patent in suit lacks sufficient disclosure is irrelevant.

For even if the defendant were to claim that the therapeutic applicability of the compound RD162 described in NK14 and NK17 does not follow from these documents, which would then also have to apply to the claimed compound RD162', because the patent in suit NK2 falls short of the experiments in NK14 or NK17, it must be stated that the invention is so clearly and completely disclosed that a person skilled in the art can carry it out.

Thus, according to the case law of the Federal Court of Justice, a sufficient disclosure exists if the information contained in the patent specification provides the skilled reader with sufficient technical information to enable him to successfully carry out the invention with his technical knowledge and skill. It is not necessary for at least one practically useful embodiment to be directly and unambiguously disclosed as such (BGH, judgment of July 13, 2010, Xa ZR 126/07, Ls. - Klammernahtgerät). After the grant of the patent, which can no longer be contested by means of an opposition, sufficient disclosure must also be assumed until the contrary is proven (BGH, judgment of 11 May 2010, X ZR 51/06, para. 31 - Polymerizable cement mixture).

The plaintiffs do not dispute that the patent in suit in the section "Ranking of Compounds in Tiers" classifies the compounds into different activity tiers, whereby Tier 1 on the one hand (NK2, pp. 64-67; "Tier 1") shows "much better" compounds than bicalutamide (NK2 [0243] "Tier 1 compounds (see Table 5) were judged to be much better than bicalutamide for treating prostate cancer"; similarly [0246]) and RD162 and RD162' are listed next to each other under "Tier 1" (NK2, p. 67, line 2 of the table). On the other hand, Figures 21A and 21B list activity data for these compounds, according to which the PSA value ("Prostate Specific Antigen") falls with increasing dose for both compounds (NK2, [0245]), whereby the antagonistic activity is also expressed in figures. Insofar as the plaintiffs assess the activities of RD162 and RD162' in the same concentrations as comparable, they confirm the claimed efficacy according to the invention and thus the feasibility.

6. The diphenylthiohydantoin RD162' or a pharmaceutically acceptable salt thereof claimed in valid patent claim 1 according to NK2 proves to be patentable.

a) The subject matter of the current patent claim 1 is new.

To the extent that the applicants addressed a high structural similarity of the two compounds RD162' and RD162 in the context of the novelty of RD162' at the hearing, their submission is not to be assessed as an attack on the novelty of the compound RD162'.

The novelty of the compound RD162' remains undisputed by the plaintiffs. It is also new because none of the documents submitted to substantiate the lack of patentability and to be assessed as prior art show the chemical structure of RD162' or an equivalent chemical nomenclature.

b) The subject matter of valid patent claim 1 is also based on an inventive step.

aa) With regard to the objective task of the patent in suit, the defendant's objection that the thiohydantoin structure already forms part of the solution even in view of the task stated in the patent in suit and that the objective task is rather the provision of a further androgen receptor antagonist cannot prevail.

This is because the patent in suit asserts a need for new thiohydantoin compounds - with desirable pharmacological properties - and for synthesis methods for their preparation in the field of the invention compared to the compounds used for this purpose to date (NK2, [0008]). These compounds should be non-steroidal, non-toxic and tissue-specific (NK2, [0009]).

In fact, androgen receptor antagonists with a thiohydantoin structure were already known in the prior art as an effective class of active compounds before the effective date of the patent in suit (NK8, p. 113, Fig. 1 No. 5; NK9, p. 236, Tab. 8 Nos. 117-119). The fact that the patent in suit is limited to a specific lead structure known from the literature and attempts to arrive at further effective compounds on this basis does not justify a broader task.

Against this background, the objective task for the specialist team is to provide a further thiohydantoin derivative as an androgen receptor antagonist. These derivatives are inherently non-steroidal, while the toxic and tissue-specific effects can only be determined after these compounds have been provided. In this respect, claim 1 also claims only one compound and its salts.

bb) Contrary to the defendant's view that the documents NK14 and NK17 did not constitute prior art within the meaning of Art. 56 sentence 1 in conjunction with Art. 54 para. 2 EPC. in conjunction with Art. 54(2) EPC, this question, as well as the question of whether the patent in suit effectively claimed the priorities of the three US applications NK3.1, NK3.2 and NK3.3, can be left open.

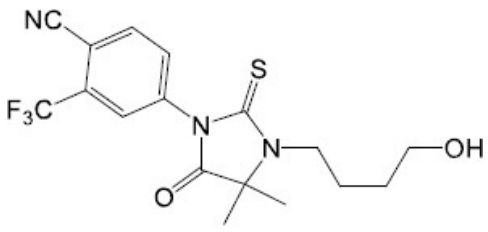
This is because the subject matter of claim 1 is not obvious from documents NK14 and NK17.

According to supreme court case law, the choice of starting point requires justification. In order for the skilled person to be able to develop the solution according to the invention, he must - decisively - be stimulated by the state of the art to follow the path of the invention; this generally requires additional impulses, suggestions, hints or other reasons beyond the recognizability of the technical problem to seek the solution to the technical problem by way of the invention (BGH, judgment of
November 6, 2018, X ZR 13/17 - Installation of supply lines; BGH, judgment of December 12, 2012 - X ZR 134/11, para. 27 - Polymer composition; BGH, judgment of April 30, 2009, Xa ZR 92/05, Ls. - Operation of a safety device).

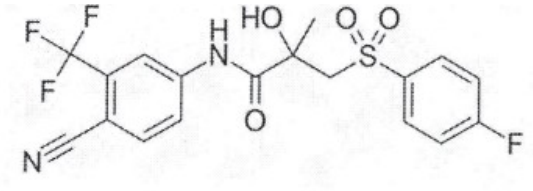
It is a question of the individual case to what extent and with what concretization the skilled person needs suggestions in the prior art in order to be able to make a

to further develop a known solution in a certain way. In this respect, peculiarities of the technical field in question [...] can also play a role (BGH, judgment of December 20, 2011, X ZB 6/19, Ls. - Installiereinrichtung II).

The documents NK14 (presentation) and NK17 (poster), which were presented according to the plaintiffs' presentation at the "Prostate Cancer Foundation Scientific Retreat" from September 29 to October 1, 2005 in Scottsdale, Arizona, USA, are documents which attract the interest and attention of the skilled person. This is because, like the patent in suit NK2, they follow the plan to find compounds which, like the known active substance RU59063, show a high AR affinity (NK8, p. 111, Abstr.) and act as AR antagonists, but do not have an agonistic effect (NK2, [0004]), as is the case with RU59063 (NK14, p. 8
"But with agonistic affinity") or the active substance bicalutamide mentioned in NK2 (NK13, p. 33 and 34).

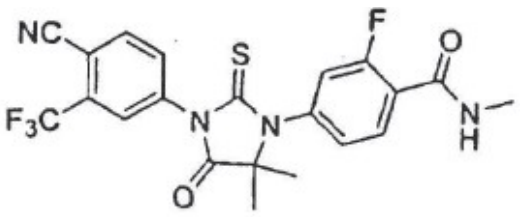


RU 59063

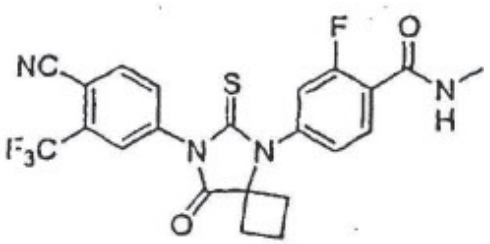


Bicalutamid (Casodex®)

The compound RD162' according to the patent in suit (NK2 [0011] and claim 1) and the compound RD162 presented in documents NK14 and NK17 (see also NK2, [0017]) differ only in the replacement of the cyclobutyl group by a 2-propyl group in the 5-position of the thiohydantoin ring.



[RD162']



[RD162]

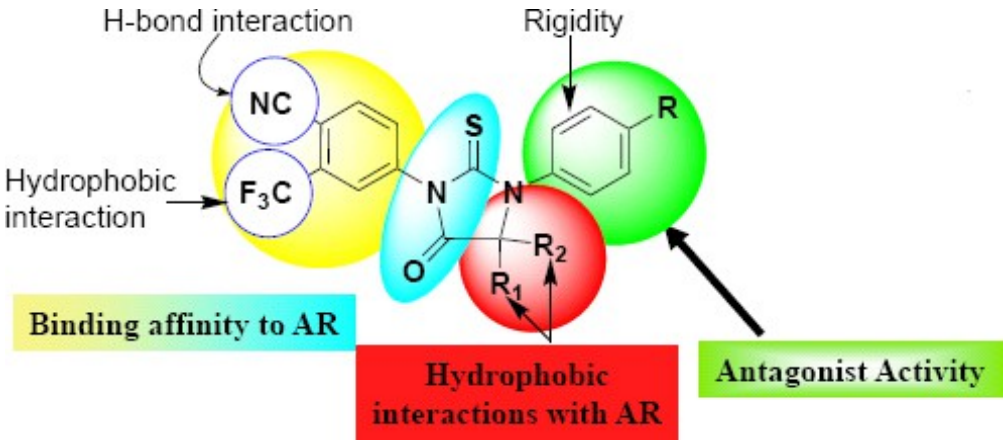
For the assessment of inventive step in the development of the compound RD162', the primary question is therefore whether, in the overall consideration of all relevant factual elements in documents NK14 or NK17, if necessary with the involvement of the technical skill and knowledge attributable to the technical team, indications or suggestions can be found to make precisely this replacement.

cc) Insofar as the plaintiffs rely on a technical understanding of the teaching of NK14 and, based on this document, consider the connection RD162' in accordance with the patent in dispute to be obvious in combination with the general technical knowledge, their submission is not convincing.

Neither document NK14 nor document NK17 directly or explicitly indicate that replacing the cyclobutyl group in RD162 with a 2-propyl group in the 5-position of the thiohydantoin ring could lead to an active ingredient with the advantageous activity profile and degradation behavior found in the patent in suit.

In detail, presentation NK14 shows that new antiandrogens solve the problem of the conversion of antagonists into agonists and have a stronger antagonistic effect than bicalutamide and this with minimal agonistic effect (NK14, sheets 4, 5, 11 and 14).

The formula picture of the new substance class with the representation of the interactions between active substance and receptor forms a core point of their teaching (NK14, p. 8).



When evaluating the formula, the skilled team is aware that the molecule as a whole interacts with the AR receptor and that it is therefore not possible to selectively distinguish between parts of the molecule and their interaction with the AR. This is also addressed by the patent in suit in paragraph [0008] to the effect that one compound may be effective in the treatment of prostate cancer, but another compound may not, even if it differs only slightly from the first compound, for example by the substitution of a single substituent. This known circumstance therefore makes it impossible to link a substituent exchange on a specific part of the molecule to a defined change in the effect of the compound. Consequently, the subdivision made can only be seen as a "working model" of the authors in the light of the structure-activity studies (SAR studies) carried out in NK14.

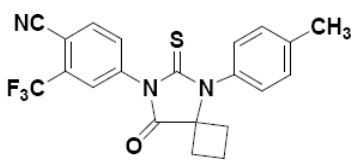
The fact that the "left phenyl ring" remains unchanged in the formula image and also in the derivatives investigated in NK14 with regard to its substituents can be explained by the fact that the known active substances bicalutamide and RU59063 have such a

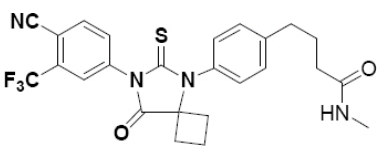
substitution on the left "phenyl ring" and have a high binding affinity with it (NK14, sheet 16, Table). In this context, however, NK14 also clarifies that the binding affinity is not necessarily important, since the compound RU59063 is described therein as an attractive lead structure despite its high binding affinity without the addition that attention must be paid to the retention of the left phenyl ring (NK14, sheet 18, substr. 3).

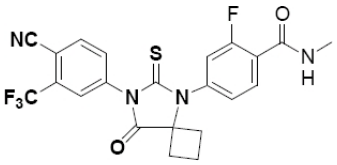
Not disregarding the known interaction of the entire molecule with the AR, the formula also assigns a "hydrophobic interaction" with the AR not only to the "left phenyl ring", but also to the thiohydantoin ring via its substituents in the 5-position, generically designated R_1 and R_2. NK14 makes no further statement on the nature of this interaction in terms of how it can be advantageously influenced. The generically formulated residues in the formula also do nothing to answer this question in that no examples of these residues are given.

Finally, the "right-hand phenyl ring", to which the antagonistic activity is assigned, is also substituted with a generic residue R in the para position (p or 4 position) of the phenyl ring, the choice of which is left to the expertise of the specialist team. This may indicate that this type of substitution co-determines the antagonistic effect.

The formula according to NK14 thus provides the promising lead structure of $^{(1)}$N, ^{3}N- diphenylthiohydantoins, under which the three compounds investigated below with the abbreviations RD37, RD131 and RD162 can be structurally subsumed.







RD37 RD131 RD162

Overall, the formula does not indicate which type of substitution on the "left phenyl ring", the thiohydantoin ring and the "right phenyl ring" could be advantageous (due to the identical representation of these compounds in NK14 and NK17, the simplifying terms "left phenyl ring" and "right phenyl ring" are used).
"right phenyl ring" retained in the following).

Presentation NK14 presents examples and test results for the three compounds mentioned, primarily for compound RD37, on the sheets following the formula image, which follow the structure-activity investigation undertaken there.

According to this study, RD37 has a more active antagonistic effect against hormone-sensitive cancer cells than bicalutamide (Bic) or RU59063 (NK14, Bl. 9).
"step-like" decrease in the relative PSA level ("Prostate Specific Antigen"). Furthermore, in two assays (NK14, sheet 11 "Reporter assay" and "PSA assay") it shows no agonistic effect, has a binding affinity like bicalutamide (NK14, sheet 13 "comparable binding affinity") and, compared to bicalutamide, noticeably inhibits tumor growth in a living organism, namely an *in vivo mouse model* for hormone-resistant prostate cancer (NK14, sheet 14).

In contrast, the stability of RD37 in the organism (*in vivo*) is low (NK14, sheets 15 and 16), as the serum concentration drops to zero after 6 hours, whereas it is still noticeably present in the case of compound RD131. Compound RD162 shows the best *in vivo stability* among the three compounds investigated, namely 10 µM over 15 hours. All three newly introduced compounds RD37, RD131 and RD162 act as antagonists (NK14, sheet 17).

The plaintiffs' submission based on the formula image and the test results of NK14 and their evaluation by various experts (NK19, NK27, NK33 and NK34), according to which NK14 proves the "left phenyl ring" to be well suited for binding affinity, the expert proves the antagonistically acting
"right phenyl ring" in the course of the balancing act between antagonism effect and desired biostability according to the model of the biostable compound RD162 and only the 5-position of the thiohydantoin ring remains for modification, to which the compound RU 59063, together with expert knowledge of bioisostery, provides inspiration and leads to the compound RD162', cannot be accepted.

This is because the formula image on sheet 8 of NK14 opens up a wide range of possible variations for the provision of new diphenylthiohydantoins, both for the substituents in the 5-position of the thiohydantoin ring, namely any selection of common and predominantly hydrophobically interacting residues, as well as an arbitrary selection for the substitution of the "right phenyl ring" determining the antagonist activity and finally also for the electron-withdrawing residues on the "left phenyl ring" known to him, all this also under the condition of bioisostery, i.e. the often biologically comparable effect of different, but spatially and electronically comparable substituents on a lead structure, which provides corresponding leads for modification (NK26, esp. p. 139, para. 4 and para. p. 144/145 with Tab. 4). Restrictions in the range of variation for the substituents on the phenyl rings or for the substitution pattern (possibly more in the para position) therefore do not result from the formula picture for both phenyl rings.

But even if the expert team were to limit itself to the experiments carried out in NK14 with three compounds as the basis for a variation of the compound RD162, without there being any reason to do so, the findings shown there do not point the way to the compound RD162'.

The assay on sheet 17 of NK14 clearly demonstrates a pronounced antagonistic effect of the compounds RD37, RD131 and RD162 compared to the reference substances DMSO or bicalutamide (Bic). Common to all the presentations in NK14 is that bicalutamide, as was already known, has no antagonist effect. An individual assessment of the specific numerical values for the respective dose-response relationship, for which error ranges or test figures are missing, is therefore not relevant, since even without this information the compound RD131 tends to have the best effect. For the evaluation and development of derivatives prior to further studies, the expert team also relies on figures without statistical errors as in NK14, as *in vivo* studies (NK14, sheet 14) require a great deal of work and time.

Because NK14 does not state why the compounds RD37, RD131 and RD162 (NK14, p. 16) derived from bicalutamide or RU59063 (NK14, p. 9) are always substituted with a cyclobutyl group in the 5-position of the thiohydantoin ring (NK14, p. 16), nor does it explain why the antagonistically active derivatives were obtained exclusively by substituent variation on the "right-hand phenyl ring" (NK14, p. 16). 16), and also does not explain why the antagonistically active derivatives were obtained exclusively by substituent variation on the "right phenyl ring", these circumstances lead the expert team to leave the substitution on the thiohydantoin ring unchanged. This should also apply to the "left phenyl ring", which is considered "established", even though the above-mentioned concept of bioisostery puts suitable alternatives within the reach of the expert team for the substituents shown there.

There is also an expectation of success for the described procedure in the further development of diphenylthiohydantoins, which is supported by further data in NK14. For example, NK14 specifically examines the agonistic effect of such (thio)hydantoin derivatives, which is relevant to the patent in dispute and must be taken into account: Sheet 11 of NK14 compares the agonistic effect of bicalutamide, RU59063 and RD37 and shows that the first two compounds, as is well known in the art, develop a noticeable agonism, while this is less pronounced in the case of RD37.

is very low. This is underlined by sheet 14 of NK14, as RD37 causes a significant slowdown in tumor growth *in vivo* compared to bicalutamide.

When comparing the molecular structure of RU59063 and RD37, the team of experts realized that both compounds differ in the majority of the molecular structure ("left phenyl ring" and "thiohydantoin ring") only by the 2-propyl or the cyclobutyl group. Both compounds "fit" into the AR, so that the few experimental results in NK14 on agonism and the fact that the formula image on page 8 does not provide any information on agonism lead to the assumption that the agonist activity is associated with the 2-propyl substitution on the thiohydantoin ring, possibly in conjunction with the "left phenyl ring".

Finally, presentation NK14 on sheet 16 compares the plasma or serum concentration (PK) as an indicator of the biostability of RD37, RD131 and RD162 *in* vivo. A higher bioavailability is advantageous as it prevents frequent re-dosing of the active substance in patients, which can be associated with undesirable side effects. The graph on sheet 16 shows that compound RD37 is highly susceptible to degradation, followed by RD131. Compound RD162 shows the least degradation.

The expert team keeps an eye on both parameters in the balancing act between biostability and the desired antagonistic effect of the active substance. It may give priority to the positive results on the biostability of the compound RD162 despite the lower antagonist effect compared to RD37 and RD131. However, this cannot motivate the replacement of the cyclobutyl group with a 2-isopropyl group in compound RD162, because the expert team had to fear an agonistic effect in this derivative.

However, even if the expert team would prefer the compounds RD37 and RD131 as a starting point for a modification due to their probably better antagonistic effect in the collective of the three compounds investigated, it is informed by the *in vivo investigation* on sheet 16 of NK14 about the higher susceptibility to degradation of these two substances, which, however, does not appear to hinder the desired antagonistic effect.

The fact that the degradation of exogenous substances in the organism takes place according to certain mechanisms and that benzylic hydrogen atoms, as they occur in these compounds (RD37 with "right *H-CH2-phenyl* group", RD131 with right "*p-N-methylamidoethyl-CH2-group*"), are relatively easily oxidized (NK41, p. 153 para. 2), is a fact known to the specialist team. In order to avoid this oxidation, it will replace the oxidation-sensitive p-substituents with non-oxidation-sensitive substituents, using its knowledge of bioisosterism to its advantage. However, even this approach does not lead the team of experts to replace the cyclobutyl group in RD37 or RD131 with a 2-propyl group, especially as there is no indication of the type of substituents on the "right phenyl ring".

As a result, the evaluative consideration of presentation NK14 does not lead the specialist team to be able to provide RD162' without inventive intervention.

dd) No other assessment of the inventive step in providing the compound RD162' arises if the skilled team starts from the teaching of poster NK17, even if it applies specialized knowledge, such as on bioisostery, and is consequently not limited to the collective of individual compounds described therein or to the substituents present on these compounds.

Poster NK17 was the almost sole subject of consideration and discussion at the hearing and shows a structure-activity relationship between the

Optimization starting from the compound RD2, which was derived from a rational drug design based on RU59063 and nilutamide and differs from the former compound by the replacement of the hydroxybutyl group by an azidobutyl group at ^{1}N. Furthermore, it can be seen that in the course of optimization the 2-propyl group in the 5-position of the thiohydantoin ring (RD2, RD6, RD7) was replaced by a cyclobutyl (RD37) or by a cyclopentyl group (RD54) and that the azidobutyl group in RD2 was replaced by a para-substituted phenyl group, where p-azido (RD6), p-methyl (RD7, RD37), p-cyano (RD54), p-N-methyl butyramide (RD131) and p-N-methyl carboxamide (RD161) were selected as substituents. Finally, an m-fluoro substituent was introduced into the "right phenyl group" of RD161, leading to the compound RD162 already discussed in NK14.

The left part of the poster essentially shows the degradation behavior of the compounds RD37, RD131 and RD162 in the organism, as already discussed for NK14. All diphenylthiohydantoins RD6, RD7 (2-isopropyl in 5-position of thiohyantoin), RD37 (cyclobutyl in 5-position of thiohyantoin) and RD54 (cyclopentyl in 5-position of thiohyantoin) newly investigated in comparison to NK14 show a noticeable antagonist effect (NK17, bottom right graph). Unlike NK14 (op. cit., sheet 11), NK17 does not list any special assays to determine the agonistic effect.

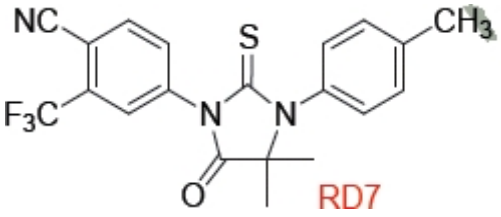
Insofar as the plaintiffs argue that RD162' is not inventive compared to NK17 because all diphenylthiohydantoins investigated there showed comparable antagonistic effects, which shows the hydrophobic substitution at the 5-position of the thiohydantoin ring to be meaningless, and further, that all the compounds were promising candidates for further modification, that the team of experts was developing these further along the lines of the pharmacokinetic optimization on the left-hand side of the poster and in doing so easily arrived at the compound RD162', their arguments cannot be accepted.

The comparison of the teaching according to NK14 with that according to poster NK17 provides a larger collective of new thiohydantoin derivatives (3 derivatives according to NK14 and 8 derivatives according to NK17), which were provided and tested for an antagonistic effect.

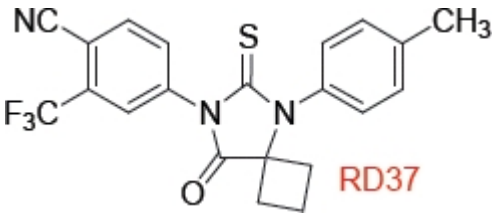
With regard to the compounds RD131, RD37 and RD162, due to the identical graphs in NK14 and NK17 on biostability and the conclusions to be drawn from them (NK17, left half, in comparison with NK14, p. 16), reference is made to the comments on NK14. 16), reference is made to the comments on NK14, as well as to the significance of the specific figures in the structure-activity studies according to NK17 in the graph at the top ("Antagonist assay on Hormone Sensitive PC") and bottom right ("Antagonist assay on Hormone refractory PC").

As already explained for the smaller collective with three compounds according to NK14, the compound RD131 also appears to be the most active in the larger collective of eight thiohydantoins with regard to the antagonistic effect (NK17, bottom right graph) and therefore forms a promising starting point for the search for a derivative that is less easily degradable in the organism. This makes the selection of this compound for the optimization of biostability plausible (NK17, bottom left "PK-DM optimization"). As explained, on the path from RD131 via RD161 to RD162, the poorer antagonist effect of the compound RD161 did not prevent the discovery of the compound RD162. This circumstance, in turn, did not cause the 5-cyclobutyl substitution to be abandoned.

In view of the fact that neither NK14 nor NK17 refer to bioisosterics and in view of their noticeable antagonistic activity, the skilled team may pay attention to the structurally similar compounds RD7 and RD37 examined in NK17. However, even their consideration does not lead to the teaching according to the patent in suit.



RD7



RD37

RD7 and RD37 are the only diphenylthiohydantoins presented in NK17 that differ only in the 5-position of the thiohydantoin ring. They exhibit a comparable antagonistic effect (NK17, bottom right graph). As far as the agonistic effect that can be inferred from the reduction in tumor growth is concerned, RD7 and RD37 outperform bicalutamide according to the *in vivo assay* (NK17, graph right p. center; cf. NK14, sheet 14 left without information on the structure of RD7).

However, the comparison of the two compounds with each other indicates a higher activity for RD37 over a longer period of time. Without having to make further considerations about the significance of these differences, the expert team considers the information content of this graph and is not motivated to abandon the cyclobutyl ring, which has already been proven to be advantageous in terms of biostability. In addition, RD7 and RD37 are two compounds with methyl substituents in the p-position on the "right-hand phenyl ring", which differ significantly from the differently substituted compounds RD131 to RD162 in the "right-hand phenyl ring". Transferability of the test results is therefore not to be expected.

In sum, the evaluation of all graphs in NK17 concerning RD7 and RD37 cannot stimulate the replacement of cyclobutyl with 2-propyl. This also applies to the compound RU59063 (NK17, graph in the center and top right). As has been explained, RU59063 has an agonistic effect, but is not a stimulant with regard to the

"left phenyl ring" and the thiohydantoin ring is identical to RD7, but, like the compound RD7, differs significantly from RD162 in the "right" part

of the molecule. This means that NK17 lacks any information that would justify an expectation of success with regard to the physiological effect of replacing cyclobutyl with 2-isopropyl in RD162.

ee) For the reasons mentioned above and because of the limited information on agonism provided by NK14 and NK17, there is no different assessment if these documents are used as starting points in combination with each other, possibly in combination with the specialist knowledge.

ff) The further printed matter introduced by the plaintiffs in the proceedings, which has not been taken into account in the present case, is still further away, has not been taken up by the plaintiffs and is also not to be taken into account in other respects (see BGH, judgment of November 28, 2023, X ZR 83/21, para. 36 - Tretkurbeleinheit).

7. The subsidiary patent claims directed to a composition comprising the compound RD162' according to patent claim 1 and their respective medical indications and the patent claims 2 to 18 referring back to these are characterized by the patentable teaching of patent claim 1 and are valid with this.

III.

Since the patent in suit NK2 on which the contested protection certificate DE 12 2013 000 155 is based is valid for the territory of the Federal Republic of Germany, the application for a declaration of invalidity based on Article 15(1)(c) of Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152, 16 June 2009, p. 1) is also unfounded.

IV.

The decision on costs is based on Section 84 (2) sentence 2 PatG in conjunction with Sections 91 (1), 100 (1), 101 (1) ZPO.

The decision on provisional enforceability follows from Section 99 (1) PatG in conjunction with Section 709 sentence 1 and sentence 2 ZPO.

Information on legal remedies

An appeal may be l o d g e d against this judgment.

The appeal must be lodged in writing or in electronic form with the Federal Court of Justice, Herrenstr. 45 a, 76133 Karlsruhe, by a lawyer or patent attorney licensed in the Federal Republic of Germany as an authorized representative within one month of service of the judgment in full form, but at the latest within one month of the expiry of five months after pronouncement.

Bernese	Dr. Münzberg (also for the judge who was unable to sign due to illness) Berner).	Mandrel	Dr. Freudenreich	Dr. Wagner

Federal Patent Court

3 Ni 20/23 (EP)

(reference number)

Announced on

8. April 2025

Köglsperger Inspector
of Justice
as clerk of the registry

Certified Köglsperger
Inspector of Justice
as clerk of the registry