IN THE NAME OF THE KING

Judgment

COURT OF APPEAL OF THE HAGUE

Civil
Trade Team

Case no. Appeal : 200.325.249/01
Case no. First Instance : 625472/ HA ZA 22-183

Judgment of 14 January 2025

in the case of

Sandoz AG,
based in Basel, Switzerland, appellant,
Lawyer: Mr O.P. Swens, with office in Amsterdam,

versus

Astellas Pharma Inc, based in
Tokyo, Japan, the defendant,
Lawyer: F.W.E. Eijsvogels, with office in Amsterdam.

The Court of Appeal will hereinafter refer to the parties as Sandoz

and Astellas.

1. The case in brief

1.1 Astellas holds a European patent which, in short, protects the use of the compound mirabegron as an active ingredient for the treatment of overactive bladder. Sandoz claimed the nullification of the Dutch part of that patent in these proceedings, primarily for lack of novelty and inventive step on the application date and alternatively for lack of inventive step on the priority date. In this judgment, the court of appeal ruled that Astellas was correct that the patent was entitled to the priority date of an earlier patent application and that, based on that priority date, the patent was based on inventive step. The court of appeal thus joins the district court in rejecting the nullification claims.

2. Proceedings in appeal

2.1 The course of the appeal proceedings is evidenced by the following documents:
- the summons dated 22 February 2023 by which Sandoz appealed against the inter partes judgment of the District Court of The Hague of November 23, 2022;[1]

[1] ECLI:NL:RBDHA:2022:12463.

- Sandoz's statement of grounds, with exhibits;
- Astellas' statement of defence in appeal, with exhibits;
- the deed containing exhibits and containing a reply to Sandoz' auxiliary requests for the oral hearing referred to below;
- the deed containing a further exhibit by Astellas for the oral hearing referred to below;
- Sandoz' e-mail message dated 19 September 2024 stating that the parties have agreed that the legal costs will be € 150,000;
- the official report of the minutes of the oral hearing described below;
- Astellas' comment to that official report.

2.2 The court of appeal held an oral hearing on 27 September 2024, at which Sandoz was assisted by Mr Swens, Mr C. van der Beek, Mr M. Hendriks and D.E. Hesselink, patent attorney, and Astellas was assisted by Mr Eijsvogels, Mr T.M. Blomme, Mr N.C. Rodriguez Arigon and Dr J.H.J. Den Hartog, patent attorney. The lawyers pleaded the case by means of pleading notes which they submitted.

2.3 Sandoz brought statements into the proceedings from Prof P. Abrams (hereinafter Abrams) and Dr K.B. Thor. Astellas submitted statements into the proceedings from M.C. Michel (hereinafter Michel) and Dr C. Korstanje (hereinafter Korstanje). The court of appeal refers below to these statements with the author's name followed by the serial number.

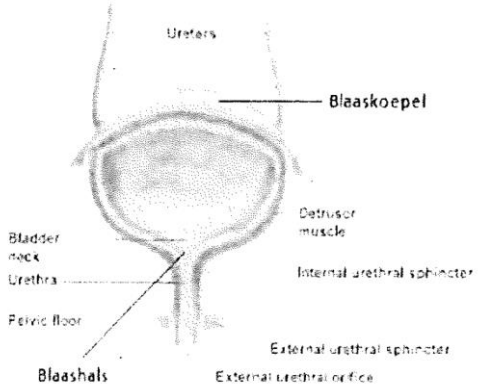
3. Factual background

Parties

3.1 The parties both belong to a pharmaceutical group.

The functioning of the bladder

3.2 The urinary bladder, together with the urethra, is part of the lower urinary tract. It is elastic organ whose function is: (i) store urine flowing from the kidneys through the ureters; and (ii) to discharge that urine into the urethra during urination. It is composed of muscle tissue, connective tissue and nerve fibres and consists of:
(i) the bladder dome, urine and consists largely of a smooth muscle called the detrusor; and
(ii) the bladder neck, where the exit to the urethra is located.



3.3 The closure mechanism from the bladder neck to the urethra consists of:
(i) the internal sphincter, which consists of so-called smooth muscle; and
(ii) the external sphincter, which consists of so-called transverse muscles.
In a normal urinary storage situation, both sphincter muscles are tightened.

3.3.1 Smooth muscles, such as the detrusor and the internal sphincter, cannot be consciously controlled, but regulated by the autonomic nervous system, the part of the peripheral nervous system that regulates a number of unconsciously occurring bodily functions and consists of a sympathetic and a parasympathetic part. That regulation takes place via transfer agents that bind to receptors on the cell surface of smooth muscle and have a reactive or blocking effect there.
Transfer agents that trigger a response at a receptor are referred to as agonists and transfer agents with a blocking effect as antagonists.

3.3.2 However, transverse muscles, such as the external sphincter, can be consciously controlled, which is done via the central nervous system.

3.4 The bladder can be in two states: the storage phase and the urinary phase.

3.4.1 To urine in the storage phase, the pressure in the bladder must remain low, while the pressure in the urethra must be higher. This is achieved in part because:
(i) the detrusor is relaxed, allowing the bladder wall to stretch and the bladder to fill; and
(ii) the internal and external sphincter muscles are tightened.
Relaxation of the detrusor and tightening of the internal sphincter are regulated by the sympathetic part of the autonomic nervous system by means of the transfer substance noradrenaline and receptors of this transfer substance, the adrenoreceptors. Several types of these adrenoreceptors exist, designated by the Greek letters α and β and subdivided by numbers. Noradrenaline is a non-selective adrenoreceptor agonist, that is, it can bind to any type of adrenoreceptor to a response there. For example, noradrenaline binds to the β_3-adrenoreceptors on the detrusor, causing it to relax, and to the α1-adrenoreceptors on the internal sphincter, causing it to contract.

3.4.2 When the amount of urine in the bladder exceeds a certain volume, an urge to urinate occurs. To enable urination, the pressure difference between the bladder and the urethra must be reversed. This is achieved by contraction of the detrusor and

simultaneous tightening of the internal and external sphincter muscle.
(i) For the contraction of the detrusor, the parasympathetic part of the autonomic nervous system releases the transfer substance acetylcholine into the bladder, where it binds to so-called muscarinic receptors on the detrusor, inducing a contraction of the detrusor.
(ii) It is believed that relaxation of the urethra is promoted by:
[a] the release of nitric oxide by the parasympathetic nerves; and
[b] the absence of noradrenaline, which prevents the internal sphincter from contracting.

3.4.3 The combination of:
(i) the release by the sympathetic nervous system of noradrenaline that binds to the β_3-adrenoreceptors on the detrusor, causing it to relax; and
(ii) the release by the parasympathetic nervous system of acetylcholine that binds to muscarinic receptors on the same muscle, causing it to contract,
is hereafter referred to as the detrusor's dual control mechanism.

The overactive bladder

3.5 Functional disorders of the lower urinary tract can be roughly divided into storage disorders and emptying disorders. The most common storage disorder is overactive bladder syndrome (the overactive bladder hereafter: OAB, and the related syndrome: OAB syndrome).

3.6 Until 2002, OAB syndrome was referred to in English as "overactive bladder syndrome", "'urge syndrome" and "'urgency-frequency syndrome", among others, and OAB as "bladder instability", "detrusor instability" or "overactive detrusor (function)".

3.7 In February 2002, the Subcommittee on Standardisation of the *International Continence Society* published in the journal *Neurourology and Urodynamics* a proposal for the standardisation of terminology for lower urinary tract complaints, including storage disorders (hereinafter, the 2002 ICS proposal). Section 1.7.2 of that proposal relates to *"Symptom syndromes suggestive of lower urinary tract dysfunction"* and discusses, among other things, the symptom syndrome *"Urgency"*. That section contains the following text in relation to "Urgency":[2]

"Urgency, with or without urge incontinence, usually with frequency and nocturia, can be described as the *overactive bladder syndrome, urge syndrome* or *urgency-frequency syndrome.*
These symptom combinations are suggestive of urodynamically demonstrable detrusor overactivity, but can be due to other forms of urethra-vesical dysfunction. These terms can be used if there is no proven infection or other obvious pathology."

The various components of this definition are defined in section 1.1 of the 2002 ICS proposal as follows (below in the order in which they are discussed above):

"Urgency is the complaint of a sudden compelling desire to pass urine, which is difficult to defer.
Urinary incontinence is the complaint of involuntary leakage accompanied by or

[2] Here and in the quotations from the 2002 ICS proposal that follow, the court of appeal will omit the designations "NEW" and "CHANGED" used in that proposal.

immediately preceded by urgency.
Increased daytime frequency is the complaint by the patient who considers that he/she voids too often by day. (...).
Nocturia is the complaint that the individual has to wake up at night one or more times to void."

The court of appeal hereinafter refers to these terms as urge to urinate, urge incontinence, diurnal frequency and nocturia respectively, the latter two together as frequency. In the 2002 ICS proposal, urge incontinence is of the broader concept of urinary incontinence (hereinafter: incontinence), which in addition includes two forms of incontinence that the court of appeal will refer to below as stress incontinence and mixed incontinence. These terms are defined in that proposal as follows:

*"**Urinary incontinence** is the complaint of any involuntary leakage of urine.*
***Stress urinary incontinence** is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.*
***Mixed urinary incontinence** is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing."*

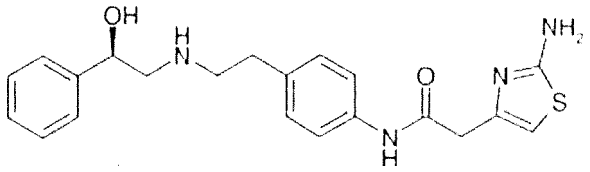
The 2002 ICS proposal was republished in January 2003, the journal *Urology*, which has a wider reach.

3.8 OAB syndrome is a so-called symptom syndrome, meaning that it consists of one or more symptoms, with no clear indication of their underlying cause.

The contested patent EP 427 and the contested SPC 599

3.9 Astellas is the holder of the Dutch part of European patent EP 1 559 427 (hereinafter EP 427) which, in brief, covers the use of the molecule mirabegron[3] as an active ingredient for the treatment of OAB. The (structural) formula of mirabegron is as follows:

(R)-2(aminothiazool-4-yl)-4'-[2-[(2-hydroxy-2-fenylethyl)amino]ethyl]azijnzuuranilide



3.10 EP 427 was applied for by (the legal predecessor of) Astellas through the PCT system on 4 November 2003, invoking the priority of its Japanese patent application JP 2002/323792 (hereinafter JP 792) dated 7 November (hereinafter priority date), and granted on 10 February 2011.

3.10.1 It contains the following six claims:

[3] "Mirabegron" is the neutral name assigned to this molecule. When the court of appeal below refers to mirabegron, it thereby refers also to salts thereof.

"l. A remedy for in the treatment of overactive bladder comprising [mirabegron, court of appeal] or a salt thereof as an active ingredient.
2. A remedy for use according to claim 1 comprising a free substance of [mirabegron, court of appeal] as an active ingredient.
3. A remedy for use according to claim 1 or claim 2, wherein it is a remedy for use in the treatment of overactive bladder as result of benign prostatic hyperplasia.
4. A remedy for use according to claim 1 or claim 2, wherein it is a remedy for use in the treatment of urinary urgency.
5. A remedy for use according to claim 1 or claim 2, wherein it is a remedy for use in the treatment of urinary incontinence.
6. A remedy for use according to claim 1 or claim 2, wherein it is a remedy for use in the treatment of pollakiuria."

A Dutch translation of these claims has been registered in the Dutch patent register.

3.10.2 The description of EP 427 - far as relevant here - includes the following:

"Technical Field
[0001] This invention relates to a remedy for use in the treatment of overactive bladder comprising [mirabegron, court of appeal] or a salt thereof as an active ingredient.
Background Art
[0002] Bladder of mammals is under a dual control of autonomic nerve and detrusor relaxes via an adrenaline β receptor by stimulation of sympathetic nerve upon urination while, upon excretion of urine, it contracts via a muscarinic receptor by stimulation of parasympathetic nerve. As a remedy for overactive bladder resulted when the dual control as such is unbalanced, anticholinergic agents such as propiverine hydrochloride and oxybutynin hydrochloride have been mostly used at present. However, there are intractable cases showing resistance to such compounds and there are side effects caused by anticholinergic agents such as urinary dysfunction and dry mouth, and, therefore, it is the current status that satisfactory clinical results are not always achieved.
(...)
[0004] The present inventors reported in Example 41 of a pamphlet of International Laid Open WO 99/20607 that [mirabegron, court of appeal] dihydrochloride has both promotion action for insulin secretion and enhancing action for insulin sensitivity and futiher has anti-obese and anti-hyperlipernic actions whereby it is a useful compound for the treatment of diabetes mellitus but there is neither suggestion nor disclosure for the therapeutic use for overactive bladder (refer to Patent Document 1).
(...)
[0012] WO02/0662 discloses β_3 adrenergic receptor agonists for the treatment of Overactive bladder, pollakiuria and urinary incontinence.
(...)

Disclosure of the lnvention
[0013] The present inventors have carried out intensive studies for finding new pharmacological effects of [mirabegron, court of appeal] or a salt thereof (hereinafter, referred to as "the active ingredient of the present invention") which is useful as a remedy for diabetes mellitus and, as a result, they have found that the active ingredient of the present invention is useful as a remedy particularly for use in the treatment of overactive bladder.

In the present invention as defined by the claims, overactive bladder is defined as a disease by which urinary urgency is frequently resulted. Although benign prostatic hyperplasia is exemplified as one of the causes for overactive bladder, there are many cases where the cause is ambiguous and they are called idiopathic overactive bladder. Although overactive bladder is sometimes accompanied by urinary frequency and urinary incontinence, it is not limited to the disease which is always accompanied by urinary frequency and urinary incontinence. Thus, in the case of mild overactive bladder, a patient is sensitive to the sense of wishing to urinate and frequently has a sense of wishing to urinate but, actually, he/she is able to hold his/her urine for a while. However, even in the case of a mild overactive bladder, its improvement has been strongly demanded in view of QOL (quality of life) of a patient. On the other hand, a severe overactive bladder is sometimes accompanied by urinary frequency and urinary incontinence. Urinary frequency is a state where number of times urination is more than the normal one and is said to be not less than about two times at night and not less than about 8 times during 24 hours. In urinary incontinence, there is an involuntary leakage of urine and that is defined as a state where there is a problem socially or hygienically and is classified into stress urinary incontinence which occurs when abdominal pressure is applied such as cough and sneeze, urinary urge incontinence where a desire to urinate suddenly occurs and urine leaks before arriving at the toilet and urinary incontinence of a mixed type where both stress urinary incontinence and urinary urge incontinence are present.

[0014] The characteristic feature of the present invention is that the active ingredient of the present invention mitigates especially the frequent occurrence of urinary urgency of a patient and number of times of urination and state of urination are made into a more normal state. It goes without saying that overactive bladder in the present invention includes not only that as a result of benign prostatic hyperplasia but also that accompanied with urinary urgency, urinary incontinence and pollakiuria.

[0015] In Patent Document 1 [WO 99/20607, court of appeal], the active ingredient of the present invention is useful, in addition to treatment of diabetes, as an agent for prevention and treatment of other diseases where an improvement in symptom is able to be achieved by reducing the symptom of obesity and hyperlipemia such as arteriosclerosis, ischemic cardiac disease such as cardiac infarction and angina pectoris, brain artery sclerosis such as cerebral infarction, aneurysm, etc. However, there is neither description nor suggestion at all to the that the active ingredient of the present invention is useful as a remedy for overactive bladder.

[0016] In Patent Document 2 [WO 98/07445, court of appeal], use for overactive bladder is not mentioned as well. In Patent Document 2, there is a description that only CGP-12, 177A has a relaxation action to bladder as a compound having a selective stimulating action to a β_3-adrenaline receptor. However, as compared with CGP-12, 177A, the active ingredient of the present invention has far stronger relaxation action for bladder. In addition, in Patent Document 2, there is no description for in vivo tests showing the usefulness for the treatment of overactive bladder such as "rat rhythmic bladder contraction measurement test" and "urination function measurement test on cyclophosphamide-induced overactive bladder model rat".

[0017] Further, use for overactive bladder is not mentioned in Patent Documents 3 to 5 as well. Compounds mentioned in Patent Documents 3 to 5 and the active ingreclient of the present invention are different in their fundamental structures in such respects that the compounds mentioned in the documents always have a phenol ring but have no thiazole ring and also have no amide bond. In addition, in Patent Documents 3 to 5, there is no description for in vivo tests showing the usefulness for the treatment of overactive bladder such as "rat rhythmic bladder contraction measurement test" and "urination

function measurement test on cyclophosphamide-induced overactive bladder model rat" (...).

Best Mode for Carrying Out the Invention

[0027] The present invention will now be specifically illustrated by way of the following Examples.

Example 1 (Isolated rat bladder smooth muscle relaxation test) Test Method

[0028] The test was conducted by referring to The Journal of Urology, 1999, volume 161, page 680.

[0029] Male rats of Wistar strain of 10 to 11 weeks age were sacrificed by depletion, whole bladder was isolated by laparotomy and bladder sections each being in a of about 3 x 10 mm were prepared in a nutrient solution (...). The section was hung in a Magnus tube (...), stabilised for 30 to 60 minutes with a load of 1g and 10^{-6} M carbachol (CCh) or 40 mM potassium chloride (KCl) was repeatedly applied thereto whereupon it was confirmed that reactivity to CCh or KCl became almost constant. After contraction by 10^{-6} M CCh or 40 mM KCl was induced and the generated tension was stabilised, a test drug (compound A or CGP-12, 177A) was cumulatively administered in 10-fold ratio with intervals of about 10 minutes and the relaxation reaction was observed. After completion of observation of relaxation reaction at maximum concentration of the test drug, 10^{-4} M papaverine was added to induce the maximum relaxation and a relaxation rate was calculated where the relaxation reaction was defined as 100%.

Results

[0030] As a result of the above test, the compound A which is the active ingredient of the present invention showed a strong relaxation action in antagonism test to contraction by carbachol and antagonism test to contraction by potassium chloride in an isolated rat bladder smooth muscle relaxation test. In addition, the compound A showed a significantly strong relaxation action as compared with CGP-12, 177A (control compound).

(…)

Table 1 EC_{50} and maximum relaxation rate of the test drug in the antagonism test to contraction by carbachol

Test drug	EC_{50} **(M)**	Maximum Relaxation Rate (%)
Compound A (Active Ingredient of the Present lnvention)	5.2×10^{-6}	94.0
CGP-12,177A (Control Compound)	$> 10^{-4}$	15.7

TabIe 2 Concentration comparison of the compound A expressing the maximum relaxation rate of CGP-12, 177A in antagonism test to contraction by carbachol

Test drug	Concentration (M)	Comparison of Action Strength*
Compound A (Active Ingredient of the Present lnvention)	3.7×10^{-7}	270
CGP-12, 177A (Control Compound)	10^{-4}	1
*: Compared in the concentration where the compound showed a relaxation rate of		

15.7%

Table 3 EC_{50} and maximum relaxation rate of the test drug in the antagonism test to contraction by potassium chloride

Test drug	EC_{50} (M)	Maximum Relaxation Rate (%)
Compound A (Active Ingredient of the Present Invention)	1.1×10^{-5}	69.1
CGP-12, 177A (Control Compound)	$> 10^{-4}$	17.4

TabIe 4 Concentration comparison of the compound A expressing the maximum relaxation rate of CGP-12,177A in antagonism test to contraction by potassium chloride

Test drug	Concentration (M)	Comparison of Action Strength*
Compound A (Active Ingredient of the Present Invention)	2.6×10^{-7}	383
CGP-12, 177A (Control Compound)	10^{-4}	1

Example 2 (Rat rhythmic bladder contraction measurement test) Test Method
(...)

Example 3 (Test for measurement of urination function of model rat suffering from overactive bladder induced by cyclophosphamide)
(...)

Example 4 (Formulation example)
(...)."

3.10.3 EP 427 includes the figures below showing schematically the results of Example 1 from the description, where "Compound A" is mirabegron.

FIG. 1

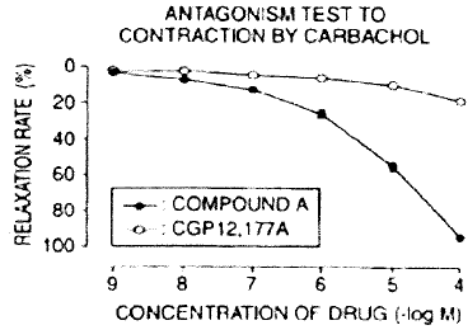
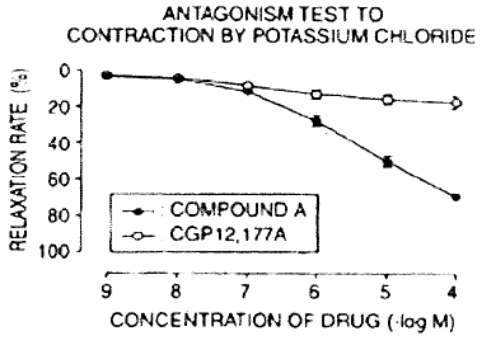


FIG. 2



3.11 A marketing authorisation for mirabegron was granted to Astellas in the European Union on 20 December 2012.

3.12 On the basis of EP 427, the supplementary protection certificate ABC 300599 (hereinafter SPC 599) was granted to Astellas for the Netherlands.

The priority document JP 792

3.13 In the (uncontested) English translation, the claims of JP 792, entitled "Agent for treating or preventing pollakiuria or urinary incontinence", read as follows:

"[claim 1] An agent for treating or preventing pollakiuria or urinary incontinence comprising [mirabegron, court of appeal] or a salt thereof as an active ingredient. [claim 2] An agent for treating or preventing pollakiuria or urinary incontinence comprising [mirabegron, court of appeal] as an active ingredient."

3.14 The description of JP 792 includes (in the uncontested English translation) the following:

"[0002) [Prior Art]
The present inventors reported in Example 41 of a pamphlet of International Laid-Open

WO 99/20607 that [mirabegron, court of appeal] dihydrochloride has both promotion action for insulin secretion and enhancing action for insulin sensitivity and further has anti-obese and anti-hyperlipaemic actions whereby it is a useful compound for the treatment of diabetes mellitus (...).
(...)
[0003] In the meantime, in a pamphlet of International Laid-Open WO 98/07445, as an agent for prevention and treatment of urinary frequency and urinary incontinence containing a drug having stimulating action to a β_3-adrenaline receptor as an active ingredient, there is described that CGP-12, 177A (...) has a relaxation action for bladder (...). CGP-12, 177A has been known as a selective drug having stimulating action to a β_3-adrenaline receptor (...).
(...)
[0006] [Problems that the Invention is to Solve]
Bladder of mammals is under a dual control of autonomic nerve and detrusor relaxes via an adrenaline preceptor by stimulation of sympathetic nerve upon urination while, upon excretion of urine, it contracts via a muscarinic receptor by stimulation of parasympathetic nerve. As a remedy for urinary frequency and urinaty incontinence resulted when the dual control as such is unbalanced, anticholinergic agents such as flavoxate hydrochloride and oxybutynin hydrochloride have been used at present. However, there are intractable cases showing resistance to such compounds and there are side effects caused by anticholinergic agents such as urinary dysfunction and dry mouth and, therefore, it is the current status that satisfactoty clinical results are not always achieved. Further, as a result of increase in population of aged people in recent years, numbers of patients suffering from urinary frequency and urinary incontinence are increasing year by year and, in view of QOL (quality of life) of patients, there has been a brisk demand for the development of new drugs.
[0007] [Means for Solving the Problems].
The present inventors have carried out intensive studies for finding new pharmacological effects of [mirabegron, court of appeal] or a salt thereof (hereinafter, referred to as "the active ingredient of the present invention") which is useful as a remedy for diabetes mellitus and, as a result, they have found that the active ingredient of the present invention is useful as an agent for prevention and treatment of urinary frequency and urinary incontinence.
In Patent Document 1, there is a description that the active ingredient of the present invention is useful, in addition to treatment of diabetes mellitus, as an agent for prevention and treatment of other diseases where an improvement in symptom is able to be achieved by reducing the symptom of obesity and hyperlipemia, such as arteriosclerosis, ischemic cardiac disease such as cardiac infarction and angina pectoris, brain artery sclerosis such as cerebral infarction, aneurysm, etc. However, there is neither description nor suggestion at all to the effect that the active ingredient of the present invention is useful as an agent for prevention and treatment of urinary frequency and urinary incontinence.
In Patent Document 2, there is a description that only CGP-12, 177A has a strong relaxation action to bladder as a compound having a selective stimulating action to a β_3-adrenaline receptor. However, as compared with CGP-12, 177A, the active ingredient of the present invention has far stronger relaxation action for bladder."

3.15 JP 792 further describes Example 1 as described in EP 427, and includes the tables and figures shown in connection with that example in EP 427.

The state of the art at the invoked priority date

3.16 At the priority date, 7 November 2002, the following documents, among others, were state-of-the-art.

3.16.1 On 6 May 1999, the Australian patent application AU 199889288 A1 (hereinafter AU 288) of (the legal predecessor of) Astellas was published. AU 288 relates to the use of amide derivatives according to a particular Markush formulation as active ingredients for the treatment of diabetes mellitus, with additional action against obesity and hyperlipidaemia. AU 288 describes the selective stimulation of β3-adrenoreceptors by β3-AR agonists for causing a therapeutic effect. A table lists six specific preferred compounds that can stimulate human β3- adrenoreceptors, including mirabegron. On the applicability of the described compounds, AU 288 includes the following (pp. 15- 18):

"The phenethanol derivative of the present invention represented by the formula or the salt thereof has both an insulin secretion promoting action and an insulin sensitivity potentiating action and also bas a selective β3 receptor stimulating action, so that it is useful as a therapeutic agent for diabetes mellitus.
(...) The β3-receptor stimulating action of the compound of the present invention is selective to β3-receptors in human being. lt has been known that the stimulation of β3-receptor stimulates decomposition of fat (decomposition of the fat tissue triglyceride into glycerol and free fatty acid), whereby a disappearance of fat mass is promoted. Therefore, the compound of the present invention has an anti-obesity act ion and an anti-hyperlipemia action (such as triglyceride lowering action, cholesterol lowering action and HDL cholesterol increasing action) and is useful as a preventive and therapeutic agent for obesity and hyperlipemia (such as hypertriglyceridernia, hypercholesterolemia and hypo HD-lipoproteinemia). Those diseases have been known as animus factors in diabetes mellitus, and amelioration of those diseases is useful for prevention and therapy of diabetes mellitus as well.
The compound of the present invention is also useful as a preventive and therapeutic agent for other diseases where the improvement of symptom can be achieved by reducing the symptoms of obesity and hyperlipemia, such as ischemic coronary diseases (for example, arteriosclerosis, myocardial infarction and angina pectoris), cerebral arteriosclerosis (for example, cerebral infarction) or aneurysm.
Further, the selective β3-receptor stimulating action of the compound of the present invention is useful for prevention and therapy of several diseases which have been reported to be improved by the stimulation of β3-receptor. Examples of those diseases are shown as follows.
It has been mentioned that the β3-receptor mediates the motility of non-sphincteral smooth muscle contraction, and because it is believed that the selective β3-receptor stimulating action assists the pharmacological control of intestinal motility without being accompanied by cardiovascular action, the compound of the present invention has a possibility of being useful in therapy of the diseases caused by abnormal intestinal motility such as various gastrointestinal diseases including irritable colon syndrome.
It is also useful as the therapy for peptic ulcer, esophagitis, gastritis and duodenitis (including that induced by Helicobacter pylori), enterelcosis (such as inflammatory intestinal diseases, ulcerative colitis, clonal disease and proctitis).
It is further shown that the β3-receptor affects the inhibition of release of neuropeptide of

some sensory fibres in lung. The sensory nerve plays an important role in neurogenic inflammation of respiratory tract including cough, and therefore, the specific β_3-agonist of the present invention is useful in the therapy of neurogenic inflammation and in addition, has little action to cardiopulmonary system.
Moreover, the β_3-adrenaline receptor is capable of resulting in a selective antidepressant action due to stimulation of the β_3-receptor in brain, and accordingly, the compound of the present invention has a possibility of being useful as an antidepressant.
The action of the compound of the present invention has been ascertained to be selective to β_3-receptors as a result of experiments using human cells, and the adverse action caused by other β_3-receptor stimulation is low or none.
Effects of the compound of the present invention have been ascertained by the following tests.
1. Hypoglycemic test in kk mice (insulin-resistant model; obesity and hyperglycemia):
(…)
2. Glucose tolerance test in normal rats:
(…)
3. Stimulating test to human β_3-, β_2- and β_1-receptors:
(…)"

3.16.2 In June 2002, the *abstract* of a study conducted by Y. Igawa and others (hereinafter: Igawa 2002) was published on the ICS website for the August 2002 ICS Congress. This publication describes the activity on the detrusor of the novel selective β_3-adrenoreceptor agonist KUC-7322. Among other things, Igawa 2002 discloses the following:

"Aims of Study

It is well known that the activation of the sympathetic nervous system contributes to urine storage by relaxing the detrusor via activation of beta-adrenoceptors (beta-ARs). It has been demonstrated that the relaxation of human detrusor, including the neurogenic detrusor, is mediated mainly via beta3-ARs [1-3]. However, the beta3-AR agonists previously used, such BRL37344A, CL316243 and CGP12177A, showed only a partial relaxing effect on human detrusor, though isoproterenol, a non-selective beta-AR agonist, completely relaxes it. In the present study, we investigated whether a novel selective beta3-AR agonist, KUC-7322, exhibits full agonistic activity on human detrusor. The effects of this beta3-AR agonist and other bladder relaxants on the contractile response induced by carbachol were also studied.

Methods

(…)

Results

Isoproterenol relaxed detrusor preparations in a concentration-dependent manner. Neither clenbuterol (beta2-AR agonist) nor tolterodine (anti-muscarinic drug) produced any significant relaxation at concentration up to $1X10^{-4}$ M. On the other hand, KUC-7322 significantly relaxed human detrusor in a concentration-dependent manner. The EC_{50} values of isoproterenol and KUC-7322 were $(5.8\pm2.1)X10^{-7}$ M and $(1.9\pm0.55)X10^{-6}$ M, respectively. The maximal relaxation obtained by isoproterenol, KUC-7322, clenbuterol

and tolterodine were 86.4±3.5%, 87.1±2.3%, 38.1±6.6% and 20.0±3.6%, respectively (Fig.1). Carbachol (3X 10-^{8} to 3X10-^{5} M) produced concentration-dependent contractions of human detrusor with EC_{50} value of (1.8±0.31)X10-^{6} M. Oxybutynin (1X10-^{6} M), tolterodine (1X10-^{6} M) and atropine (1X10-^{7} M) caused rightward shifts of the concentration-response curve for carbachol. Forskolin (1X10-^{5} M) slightly inhibited the maximal response of contraction. On the other hand, neither isoproterenol (1X10-^{8} to 1X10-^{4} M) nor KUC-7322 (1X10-^{8} to 1X10-^{4} M) affected the carbachol-induced bladder contraction.

(...)

Conclusions

KUC-7322, a selective beta3-AR agonist, showed full agonistic activity on human detrusor. Moreover, beta-AR agonists, including KUC-7322, did not affect the carbachol-induced contraction of human detrusor. These results suggest that novel selective beta3-AR agonists, such as KUC-7322, may be used for treatment of overactive bladder in patients, possibly without negative effects on voiding function."

3.16.3 In May 2002, an article by O. Yamaguchi was published in the journal *Urology*, entitled "β$_3$-Adrenoceptors in human detrusor muscle" (hereinafter Yamaguchi 2002). The *abstract* of this publication, as far as relevant here, reads as follows:

"The detrusor muscle contains β-adrenoceptors (β-AR), and 2 subtypes- β$_1$-AR and β$_2$-AR-have been identified in most species. Although β$_2$-AR has an important role in muscle relaxation (...), evidence suggests that a third subtype, β$_3$-AR (...) mediates relaxation of human detrusor muscle. There is a predominant expression of β$_3$-AR messenger RNA (mRNA) in human bladder tissue, with 97% of total β-AR mRNA being represented by the β$_3$-AR subtype and only 1.5% and 1.4% by the β$_1$-AR and β$_2$-AR subtypes, respectively. Functionally, selective β$_3$-AR agonists relax human isolated detrusor, whereas selective β$_1$-AR/β$_2$-AR agonists do not. lsoproterenol-induced relaxation is inhibited by selective β$_3$-AR antagonists but not by selective β$_1$-AR or β$_2$-AR antagonists. In anima! models, p3-AR agonists increase bladder capacity and have only weak cardiovascular side effects. Although this evidence points toward the clinical utility of β$_3$-AR agonists as therapy for overactive bladder, clinical trials of β$_3$-AR agonists identified in animal models as antiobesity agents indicate side effects of tremor and tachycardia. Development of compounds with high selectivity for the human β$_3$-AR, identified by screening techniques using cell lines transfected with the human β$_1$-AR, *β$_2$*-AR, and β$_3$-AR genes, may mitigate such problems. Together with the preliminary finding that 49% (21 of 43) of patients with idiopathic detrusor instability have a tryptophan 64 arginine mutation of the β$_3$-AR gene, which may be a useful genetic marker, evidence points towards β$_3$-AR being a therapeutic target for treatment of overactive bladder disorder."

The article itself includes the following section "Therapeutic potential for drugs acting at β$_3$-adrenoceptors":

"The in vivo effects of β$_3$-AR agonists on bladder function have been studied in animal models. Relaxation of rat detrusor muscle is known to be mediated by not only R2-AR, but also β$_3$-AR. [Description of experiments on rats, court of appeal]

Although these results are encouraging for the clinical development of β3-AR agonists for treatment of overactive bladder, β3-AR agonists have already been used clinically as antiobesity agents. Given that activation of β3-AR on adipocytes (fat cells) leads to lipolysis and an increase in energy utilisation, several rat β3-receptor-selective agonists that showed antiobesity effects in animal studies were studied in humans. Unfortunately, these studies revealed that any therapeutic benefits derived from these agents were complicated by side effects of tremor and tachycardia, probably mediated via R2-AR and β1-AR. These studies also indicated that pharmacologic differences existed between the rat and human β3-receptors. Indeed, all of the β3-AR agonists tested in the clinic to date are only weak partial agonists of the human β3-receptor and are not selective for the human β3-receptors.
Defining a treatment for the overactive bladder may therefore be dependent on the development of β3-AR agonists that show selectivity for the human β3-receptor. Others have used cell lines (...) to examine the selectivity of various compounds. [Reference to a comparative study on the action of isoproterenol, clenbuterol and substance L-755507 on β1-, β2-, and β3-adrenoreceptors, court of appeal]. As might be expected, isoproterenol shows no selectivity for the human β3-AR over β1-AR and β2-AR in binding assays and shows agonist activity at all 3 receptors. On the other hand (...) L-755,507 was shown to be a selective agonist for the human β3-AR with >1000-fold selectivity for activation of this receptor versus activation of the β1-AR receptor and no measurable β2-AR agonist activity.
Given the high selectivity of L-755,507 for the human β3-AR and its agonist activity at this site, we determined its activity on human isolated detrusor muscle precontracted with carbachol. L-755,507 dose dependently relaxed the human detrusor muscle with a potency comparable to that of isoproterenol (...). On the other hand, Clenbuterol, which has selectivity for human β2-AR (...), showed little propensity for relaxing human detrusor muscle (...). These results encourage the hope that a selective agonist of a human β3-AR subtype may be useful for the treatment of overactive bladder."

The conclusion of the article reads as follows:

"The human β3-AR appears to be a useful target for the therapy of overactive bladder and other disorders. Differentiating benveen compounds that have selectivity for human versus animal β3-AR is, however, an important consideration in the continued study of this receptor. The development of compounds that have high selectivity for the human β3-AR will not only aid in the production of new therapeutic modalities, but it will also help elucidate the mechanisms of detrusor instability."

4. First instance proceedings

4.1 Sandoz summoned Astellas and, in summary, sought the annulment of (i) the Dutch part of EP 427 and (ii) of SPC 599, ordering Astellas to pay the actual costs of the proceedings under section 1019h DCCP, with interest. To that end, it argued, primarily, that Astellas was not entitled to rely on the priority date of JP 792 and that EP 427 was neither novel nor inventive on the filing date of 4 November 2003 and, in the alternative, that EP 427 was not inventive on the priority date, in view of:
(i) AU 288 as the closest prior art document, in combination with Igawa 2002; or
(ii) Igawa 2002 as the closest prior art document, combined with AU 288.

4.2 The District Court dismissed the claims and ordered Sandoz to pay the legal costs. It held that the invention claimed in EP 427 was already directly and unambiguously disclosed in JP 792, allowing Astellas to invoke the priority of JP 792 over EP 427. Based on that priority date, the District Court ruled that EP 427 is inventive in relation to either prior art document chosen by Sandoz.

5. Claims in appeal

5.1 Sandoz has appealed this judgment and has requested that the court of appeal annul the Dutch part of EP 427 and SPC 599, ordering Astellas to pay the reasonable and proportionate costs of the proceedings as referred to in Section 1019h DCCP. Its objections to the judgment under appeal apply to all of the District court's considerations set out in the previous paragraph. In appeal, it has partly based its inventive step attack on the priority date on other prior art documents:
(i) Starting from AU 288:
Primary attack: in combination with common general knowledge, as, among others, known from Yamaguchi 2002;
In the alternative: in conjunction with lgawa 2002;
(ii) Starting from Yamaguchi 2002, in conjunction with AU288.
It dropped the arguments based on Igawa 2002.

6. Assessment in appeal

Competence

6.1 The Court of Appeal has international jurisdiction to the claim to annul the Dutch part of EP 427 and SPC 599 on the basis of Article 24 opening words and under 4 second and first paragraphs of Brussels *Ibis-Vo* respectively. Relative jurisdiction is based on Article 80(1)(a) DPA.

The average skilled person

6.2 The parties raised no objections to the determination of the average skilled person in para. 4.2 of the judgment under appeal. The court of appeal will therefore base its judgment on the combination of a molecular pharmacologist with knowledge of how nerve receptors work and a functional urologist, with or without the support of a biochemist.

Validity of JP 792 priority

6.3 According to Sandoz, JP 792 does not disclose the of mirabegron for the treatment of OAB. JP 792 only discloses the use of mirabegron for treating "pollakiuria or urinary incontinence", i.e. frequency and urinary incontinence, and not for treating urgency, which is the main symptom of OAB syndrome. While JP 792 refers to a dysfunction in the control mechanism of the detrusor and bladder closing muscles it cannot necessarily be inferred from this that mirabegron can also be used against urgency.

6.4 The court of appeal does not follow Sandoz in this objection. For the question of the possibility of relying on a priority document, it must be assessed whether in that document, considered as a whole, the invention for which protection is sought was directly and unambiguously disclosed to the average person skilled in the art, who, in reading it, made use of his/her common general knowledge.[4] In doing so, there may an implicit disclosure, namely when the invention, although not disclosed in so many words, was necessarily contained in the expressly disclosed, read in the light of the common general knowledge of the average person skilled in the art.[5]

6.5 Briefly, the invention protected by EP 427 is the use of mirabegron as an active ingredient for the treatment of OAB.

- Point [0002] of the description described both sides of the detrusor's dual control mechanism and described OAB as a consequence from an imbalance of that mechanism.
- Point [0013] of the description then defined OAB as: *'a disease by which urinary urgency* is *frequently resulted (...), sometimes accompanied by urinary frequency and urinary incontinence, [but, court of appeal] not limited to the disease which* is *always accompanied by urinary frequency and urinary incontinence*",

followed by:

(i) a definition of *urinary frequency* that briefly includes diurnal frequency and nocturia; and

(ii) A definition of *urinary incontinence* that refers to the occurrence of a social or hygiene problem and which includes urge, stress and mixed incontinence.

- With regard to OAB, point [0013] then explains that benign prostatic enlargement is mentioned as one of the causes of OAB, but that there are cases where the cause is unclear. That point also clarifies the relationship between urge to urinate, frequency and incontinence:

> *"[I]n the case of mild overactive bladder, a patient is sensitive to the sense of wishing to urinate and frequently has a sense of wishing to urinate but, actually, he/she is able to hold his/her urine for a white. (. ..) On the other hand, a severe overactive bladder is sometimes accompanied by urinary frequency and urinary incontinence.*

The same point also explains that, however, there is also a strong demand for the treatment of mild OAB for quality of life reasons.

- Item [0014] continues that the characteristic feature of the invention is that mirabegron in particular moderates the prevalence of urge to urinate, normalising the number of times of urination and the urination state, and that the OAB according to the invention includes not only the OAB resulting from benign prostate enlargement, but also those, associated with urge to urinate, incontinence and diurnal frequency.
- Example 1, with its accompanying tables and graphs, then describes an experiment in which strips of rat detrusor are placed in an *in* vitro environment mimicking the rat body, stretched with a weight, maximally tightened with carbachol or potassium chloride, and then disposed to increasing concentrations of mirabegron and CGP-12, 177A to compare its relaxation

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4 Supreme Court 14 April 2017, ECLl:NL:HR:2017:692 *(Sun/Novartis),* para 3.4.3, citing EBoA EPO 31 May 2001, case G 2/98, ECLl:EP:BA:2001:G000298.2001053 l.

5 TBoA EPO 28 January 1997, Case T 823/96, ECLI:EP:BA:l 997:T082396.l9970128; TBoA EPO 7 October 2009, Case T 1125/07, ECLI:EP:BA:2009:TI 12507.2009!007.

effects. That experiment therefore mimics an imbalance in the detrusor's dual control mechanism.
With that, EP 427 refers to the use of mirabegron to treat the symptoms resulting from that imbalance, with the frequent *("frequent")* symptom being urination, and sometimes frequency and incontinence.

6.6 Based on the party debate, the following is established when it comes the common general knowledge of the average skilled person at the time of the priority date:
- The detrusor is controlled by the dual control mechanism (Abrams 1, para 41, and Abrams 4, para 6). Abrams argues that the lower urinary tract is subject to a tripartite control, or at least tripartite nervous control, since, in addition to the two members described above, that control also occurs through the somatic nervous system, which drives the striated muscles of the internal sphincter and the pelvic floor (Abrams 1, paras 75, 76 and 88). This comment does not detract from the correctness of the finding that a dual control mechanism controls the detrusor, because it follows from Abrams' comment that by the three-member control he does not refer to the control of (only) the detrusor, but of the (entire) lower urinary tract.
- The syndrome now referred to as OAB syndrome is a relatively common symptom syndrome (Abrams 1, para 62).
- That syndrome was alternately referred to as "overactive bladder syndrome", "urge syndrome" and "urgency-frequency syndrome", and the underlying detrusor dysfunction as "bladder instability", "detrusor instability" or "overactive detrusor" prior to the publication of the 2002 ICS proposal in February (Abrams 1, para 17 and Michel 1, points 11 and 12).
- Detrusor overactivity was divided at the time into (i) a neurogenic variant in which such overactivity is caused by an identifiable nerve disorder and a (ii) idiopathic variant in which the cause is unknown (Abrams 1, para 51, and Abrams 4, para 6).
- The treatment of OAB syndrome at the time (following non-pharmaceutical interventions) consisted of anticholinergics, also referred to as antimuscarinics, such as oxybutynin, among others, which block its contraction due to their antagonistic action on the muscarinic receptors on the detrusor (Abrams 1, paras 58, 59 and 66, Abrams 4, para 6 and Abrams as a witness under oath in the parallel English procedure, para 6.2).
- These antimuscarinics were poorly selective for the bladder and showed significant side effects (Abrams 1, paragraphs 59, 61 and 62, and Abrams 4, paragraph 6).

6.7 Given this common general knowledge of the average skilled person on the priority date, JP 792 disclosed the following at the time.
- Item [0006] of the description first described the detrusor' dual control mechanism. The Court of Appeal ignores Abrams' comment that the average skilled person at the time would not have clearly understood what was meant by the term "dual control" (Abrams 1, para 76), because item [0006] contained an accurate description of the term, setting out the operation of both parts of the mechanism.
- Item [0006] continued by noting that an imbalance in that dual control mechanism leads to frequency and incontinence and that that imbalance was being treated with anticholinergics such as flavoxate and oxybutynin salts, but that there are cases of insurmountable resistance to those compounds and that anticholinergics have unpleasant side effects, with the result that satisfactory clinical

results were not always achieved at the time.
- The average skilled person at the time knew from his/her common general knowledge that the action of those anticholinergics is that they act on the muscarinic receptors on the detrusor to inhibit the contraction of that muscle, that is, to act on one of the two sides of the dual control mechanism of the detrusor described in paragraph [0006]. Abrams argues that flavoxate is not an anticholinergic, but a muscle relaxant (Abrams 1, para 89), but that is irrelevant to the present assessment because point [0006] only mentions flavoxate as an example of an anticholinergic agent, and continues in the following sentence with the side effects of anticholinergics. It was therefore clear that the description referred to the existing treatment of dual control mechanism imbalance by anticholinergics.
- In item [0003] of the description, JP 792 already described that the compound CGP-12, 177A has been previously described as a selective β_3-adrenoreceptor agonist with relaxing effects on the bladder.
- This is repeated in item [0007], with the addition that mirabegron has an even stronger relaxing effect on the bladder. Example 1 of JP 792, with accompanying tables and graphs, then described the same experiment as Example 1 of EP 427. In doing so, Astellas argues undisputed that the average skilled person knew at the priority date that carbachol, used in that experiment to contract the strips of rat detrusor stretched by a weight, is a cholinergic agonist and therefore active in the other member of the dual control mechanism.

6.8 Therefore, when reading JP 792, the average skilled person necessarily and immediately understood that fact:
(i) the consequences of an imbalance in the detrusor's dual control mechanism; and
(ii) the existing situation where anticholinergics had been tried to remedy those effects by the muscarinic receptors on the detrusor, but had not proved (fully) suitable for that purpose;
JP 792 teaches that those consequences can be remedied by intervening on the other side of that control mechanism, namely by eliciting a response to the β_3- adrenoreceptors on the detrusor with mirabegron, in order to relax it, even when it has been tightened by a cholinergic agonist, i.e. via the other side of the dual control mechanism.

6.9 Therefore, the average skilled person also necessarily and immediately understands that mirabegron according to JP 792 is used to remedy all the consequences of the described imbalance, which corresponds to the symptom syndrome that was at the time alternately referred to as OAB syndrome, "urge syndrome" and "'urgency-frequency syndrome" and which has as symptoms in addition to frequency and urge incontinence the overarching symptom urge to urinate. It also follows from the Venn diagrams on pp. 13 and 14 of Abrams 1 and the accompanying text that the cases of urge incontinence are a subset of the cases with urge to urinate, which means that urge incontinence always includes urge to urinate (but not vice versa). This is consistent with the invention that is protected by the patent.

6.10 That which Sandoz further argues against Astellas' reliance on the priority date of JP 792 cannot lead to a different outcome.

6.10.1 That the drafters of JP 792, contrary to those of EP 427, use neither the term "OAB" nor any of the preceding common *legacy designations*, nor the presupposed symptom of urge to urinate as proposed in the 2002 ICS proposal for OAB syndrome is understandable. This does not lead to a different understanding by the skilled person of the doctrine of JP 792. Indeed, Astellas correctly points out that there was no single scientifically accepted designation for OAB syndrome before 2002 and that the 2002 ICS proposal was only published in *Neurourology and Urodynamics* in February 2002, with the priority date already being 7 November 2002. Astellas also argues, without dispute, that the 2002 ICS proposal was republished in *Urology* in January 2003 to reach a broader public. Abrams said in his initial statement that *"there is always some delay in a term being used in the field"*. He nuanced that by continuing that *"it is safe to conclude that especially people working at the forefront of a particular aspect will adapt quickly and that is also what happened with the term OAB"*, but Astellas rightly points out that Abrams himself is the originator and proponent of the 2002 ICS proposal and that the common general knowledge of someone active at the forefront of a particular aspect of urology can precisely not be attributed to the average skilled person. Michel (first statement) and Korstanje (second statement) also explained that the term OAB syndrome was not yet commonly used by urologists on the priority date to refer to that syndrome. Michel is citing in this regard to case contemporaneous publications.
Abrams notes that Michel is not a urologist, but Michel responded by referring to an article on the rate of spread of specialist terms among medical specialists.

6.10.2 Contrary to Sandoz's sense, the person skilled in the art on the priority date could not think that the invention disclosed in JP 792 relates in part to the use of mirabegron for treatment of non-OAB-related incontinence or frequency, such as:
(i) incontinence or frequency due to drinking too much or bacterial infection;
(ii) stress incontinence; or
(iii) reflex incontinence, i.e. incontinence due to detrusor activity resulting from nerve damage, for example due brain haemorrhage, spinal cord injury or dementia.
Indeed, from points [0003], [0006] and [0007] of the description of JP 792 described above and the accompanying Example 1, with tables and graphs, it followed for the average person skilled in the art that the disclosed therein is only intended to remedy the (bundle of) symptoms that result (is) from detrusor overactivity caused by an idiopathic imbalance in the dual control mechanism. The skilled person would not mark Example 1 as relevant to an imbalance due to reflex incontinence, other types of tests were performed for that indication in the state of the art at the priority date, as Michel stated undisputed (Michel 4, para 5). Therefore, the average skilled person immediately understood on the basis of those points that mirabegron was presented in JP 792 as active substance to treat only the idiopathic variant of overactive detrusor, and not for non-disbalance-related incontinence or frequency.

6.10.3 Moreover, if a detrusor imbalance for the skilled person would be indicative not of OAB but also of reflex incontinence, as Sandoz has argued (only) on appeal, JP 792 directly and unambiguously discloses two indications. That an overactive detrusor could therefore also indicate

reflex incontinence, also does not benefit Sandoz for this reason.

6.10.4 For the same reason, it is irrelevant that:
(i) Example 1 from JP 792 closely resembles experiments conducted before the priority date to prove the usefulness of an active substance in the treatment of a variety of diseases and conditions that may benefit from relaxation of smooth muscle in humans, including non-bladder-related conditions;
(ii) Example 1 may also be illustrative of those other conditions; and
(iii) it is not possible to demonstrate with an *in vitro* test on rat detrusor strips that mirabegron is suitable for eliminating the urge to urinate associated with OAB syndrome in humans.
The key throughout is that Example 1 illustrates the action of mirabegron as a β_3-adrenoreceptor agonist in the (cholinergic muscarinic agonist) tightened rat detrusor, and thereby, having described the dual control mechanism of the detrusor and of the imbalance therein, makes it plausible that mirabegron can also remedy that imbalance in humans.

6.10.5 For the same reason, it is also irrelevant that oxybutynin and flavoxate, to the extent they are prescribed by urologists, were not specifically or solely prescribed to treat OAB.

6.10.6 Sandoz's reliance on the *fingolimod* [6] case cannot help it either.
- That case involved the application of Article 123(2) European Patent Convention, which deals with added matter. Under those provisions, amendments to a patent application are allowed only within the limits of what was disclosed in the original application. This often implicates application of the same test as the one that applies to reliance on a priority date (see above under 6.4).
- Briefly, the patent attacked in that case related to a dosage regimen for the use of the molecule fingolimod as an active substance for treatment of a certain form of multiple sclerosis (hereinafter RRMS). At the priority date, it was already known to the average person skilled in the art that daily oral administration of fingolimod at a dose of 1.25 mg provided clinical benefit for that treatment.
- The application included a description of a 'prophetic' (not yet performed) clinical trial involving the administration of fingolimod at daily oral doses of 0.5, 1.25 or 2.5 mg. During the grant procedure, the application was amended and claim 1 of the patent covered (after the grant of the patent) the use of fingolimod by oral administration for treatment of RRMS, at a daily dose of 0.5 mg.
- This court of appeal held that in such a medical-indication claim, the achievement of a therapeutic effect of the claimed dosage regimen is considered a functional technical feature, and that the original application in that therefore had to directly and unambiguously disclose to the average skilled person that that therapeutic effect in the treatment of RRMS is achieved with a daily orally administered dose of 0.5 mg fingolimod. According to this court of appeal, that was not the case, because the application, in its description, contained only a reference to a not yet

[6] Court of Appeal of The Hague 18 October 2022, ECLI:NL:GHDHA:2022:2079; Conclusion AG Van Peursem 19 January 2024, ECLI:NL:PHR:2024:77; HR 8 March 2024, ECLl:NL:HR:2024:341 *(Novartis/Mylan).*

conducted clinical trial with daily doses of 0.5, 1.25 or 2.5 mg, while at the priority date it was known to the average skilled person that daily oral administration of fingolimod at a dose of 1.25 mg provided clinical benefit.

- Again, this is a medical-indication claim. Unlike in the *fingolimod* case, however, JP 792 discloses, as stated above, a substantiation with a first study result that directly and unambiguously describes to the average skilled person that mirabegron has therapeutic effect in the treatment of OAB syndrome. Example 1 in JP 792 is not a prophetic study. On the contrary, in the fingolimod *case*, the skilled person learned from the description of the prophetic study that there was no information yet on the efficacy of the low dose claimed in the patent. Contrary to Sandoz's argument, for the disclosure test, the mere statement in the priority document is sufficient that the therapeutic effect in question will occur, and it does not have to be demonstrated or made plausible that this effect will actually occur: the latter is only relevant for the sufficiency of disclosure test.[7]
- For the same reasons, Sandoz does not benefit from its reference to the decision of the Technical Board of Appeal of the European Patent Office (hereinafter: TBoA and EPO) in case T-2842/18.

6.10.7 For the above reasons, it is irrelevant that the description of JP 792 differs in points from that of EP 427.

6.11 Because Astellas rightly relies on the priority of JP 792, Sandoz's novelty and inventive step attacks based on documents of later date than the priority date can be without discussion. Remaining are the two inventive step attacks described above under 5.1.

Inventive step

Legal test

6.12 According to Article 56 of the European Patent Convention, there is an inventive step if an invention does not follow from the prior art in an obvious manner for a person skilled in the art. Sandoz uncontestedly uses the problem-solution approach (PSA) used by the EPO for this assessment. According to the EPO's Examination Guidelines[8], the PSA consists of three steps:

- determining the closest state of the art;
- determining, on that basis, what the objective technical problem to be solved is; and
- assessing whether the solution for which protection is sought is for the average skilled person would have obvious, assuming the state of the art.

6.12.1 The closest prior is that document which discloses in a single piece the combination of features that provides the most promising starting point for a development leading to the invention. That starting point must be directed to the same

[7] See paragraph 5.18 of this court of appeal's judgment cited in the previous footnote.
[8] Version March 2024, Part G Patentability, Chapter VII Inventive step, Section 5 PSA and Section 8 "Ex post facto" analysis. The four sub-paragraphs below are also taken from these chapters.

effect or purpose as the invention or at least relate to the same or a closely related part the technique. In practice, the prior art is that document which provides a similar use and requires the smallest structural or functional changes to arrive at the invention. In some cases, several equally valid starting points can be found, for example when the average person skilled in the art has a choice between workable solutions starting from different documents to get to the invention. In that case, it may be necessary to apply the PSA with respect to each of these starting points.

6.12.2 the objective technical problem to be requires the determination of the distinguishing features between the patent and the closest prior art (hereinafter: distinguishing features), determining the technical effect of these distinguishing features and formulating the technical problem. If the closest prior art is found to be different as described by the applicant, this may mean that the objective technical problem has to be adapted from the description of the problem in the application. The objective technical problem should be worded as specifically as possible, but should not contain any indications of the technical solution, as this would necessarily result in the inventive step being assessed with hindsight.

6.12.3 In the third step, it must be whether the entire state of the art teaches something that would have induced the average person skilled in the art faced with the objective technical problem to adapt the closest prior art in order to arrive at the invention. It is not important whether the average person skilled in the art could have arrived at the invention that way, but whether he/she would have arrived at it because the prior art provided an incentive to do so, with the prospect of some improvement or some advantage.

6.12.4 In doing so, the court of appeal should, as far as possible, avoid hindsight with what is now known.

6.13 Sandoz complains that although the District Court described AU 288 in paragraph 2.23.2 of the judgment under appeal, it did not reiterate its content in the assessment of the inventive step. That complaint cannot in itself lead to annulment, as the court of appeal is reassessing that question on appeal. Moreover, it follows from the assessment of inventive step in question that the District Court did have the content and scope of AU 288 well in mind when making that assessment.

AU 288, in combination with (i) the common general knowledge, as known, inter alia, from Yamaguchi 2002, or (ii) Igawa 2002

6.14 According to Sandoz, AU 288 provides a suitable starting point as the closest prior art. AU 288 relates to the use of amide derivatives according to a particular Markush formulation as active ingredients for treatment of diabetes mellitus, with additional action against obesity and hyperlipidaemia. AU 288 teaches that there are six preferred compounds, including mirabegron, which:
(i) Are synthesized;
(ii) exhibit activity as a β_3-adrenoreceptor agonist in humans;
(iii) are also selective for those β_3-adrenoreceptors in humans, in the sense that they are not

effective on human β_1- and β_2-adrenoreceptors;
(iv) have been tested on rats, including by oral administration, showing that the toxicity of the compounds is limited and that they are bioavailable after administration.
The distinguishing features in view of EP 427 are the use of [a] specifically mirabegron [b] for the treatment of OAB instead of diabetes mellitus. The effect of these distinguishing features is a further use of mirabegron. Based on this, the objective technical problem to be solved can be formulated as providing further use of the six β_3-adrenoreceptor agonists disclosed as preferred compounds in AU 288. Contrary to the District court's ruling, that problem does not include that those β_3-adrenoreceptor agonists must induce very strong detrusor relaxation, but rather the problem must be limited to the six compounds disclosed in AU 288. At the priority date, common general knowledge included that β_3-adrenoreceptors are also present in the human bladder wall, that certain disorders in humans are mediated by β_3- adrenoreceptors, and that those disorders can be treated by β_3- adrenoreceptor agonists in which, unlike in rats, it is important that these agonists are selective with respect to human β_1- and β_2- adrenoreceptors, in that they should not elicit a response on these receptors, since stimulation of these receptors leads to cardiac arrhythmias and tremor. Yamaguchi 2002 is a review article in the journal *Urology*, which is authoritative for urologists. In it, Yamaguchi extensively describes the role of β_3-adrenoreceptors in the bladder wall and the possibilities of treating OAB with β_3-adrenoreceptor agonists. In doing so, Yamaguchi concluded that the β_3-adrenoreceptor in humans appears to be a useful target for the treatment of OAB and other conditions, provided that a compound that is not only active but also selective as a β_3- adrenoreceptor agonist in humans is used. Igawa, who investigated the use for the treatment of OAB of β_3-adrenoreceptor agonists that had already been developed for the treatment of other β_3-mediated conditions, such as diabetes and obesity, published in Igawa 2002 the results of studies on the action of the selective β_3-adrenoreceptor agonist KUC-7322 on the human detrusor. KUC-7322 had a good relaxing effect on the detrusor, which, according to Igawa, indicated efficacy of selective β_3-adrenoreceptor agonists in the treatment of OAB. Instead of synthesising and testing new β_3-adrenoreceptor agonists, it was obvious to start from existing synthesised and evaluated compounds. Michel also proceeded that way in arriving at a similar patent. Although that patent dates from after the priority date, Michel's course of action shows how the average person skilled in the art proceeded in solving the objective technical problem. Because the average person skilled in the art knew on the priority date that there was a great need for new drugs for the treatment of OAB, it was obvious on that date to try the six selective β_3- adrenoreceptor agonists disclosed in AU 288 in humans, including mirabegron, for treatment of OAB, Sandoz still argues.

6.15 The court of appeal does not follow Sandoz in this attack because, in its opinion, AU 288 cannot be considered a real starting point for research, and therefore does not constitute the closest prior art within the meaning of the PSA.

6.16 The question of whether mirabegron can serve as a real starting point for investigation should not be asked from the perspective of investigating a possible second medical indication for the six preferred connections disclosed in AU 288.

Indeed, in that case those preferred compounds would be designated as research starting points on the basis of hindsight, whereas the invention is precisely about choosing one of them, namely mirabegron, for the treatment of OAB.[9]

6.17 The decision of the TBoA of 6 October 2023 in case T 1165/20 referred to by Sandoz does not alter this. Specifically, Sandoz points to a paragraph explaining that the determination of the closest prior art in the case of a second medical indication is not limited to the prior art in relation to the treatment of that second indication, but may also consist of a document disclosing the use of the same active ingredient for the treatment of the first indication. However, Sandoz thereby failed to clarify that in that paragraph, the TBoA merely reflects the position of the opponent concerned and then only presumptively follows that position, in favour of the opposant, in order to then reject the opposition. Sandoz did not give an example during the oral hearing, after being requested to, of another decision in which the TBoA ruled (other than presumptively) that, in the case of a second medical indication invention, the disclosure of the compound in question as an active ingredient to treat the first medical indication can be the closest prior art.

6.18 If the question of the suitability of mirabegron as a research starting point is posed from the perspective of research for a β_3-adrenoreceptor agonist as an active compound for the treatment of OAB, mirabegron must be a real starting point, in the sense that the average skilled person would actually consider this compound to be a good starting point for research on the priority date based on his/her common general knowledge and the state of the art.[10] In the court of appeal's opinion, this is not the case.

6.19 AU 288 mentioned nothing about the use of the amide derivatives disclosed therein, including mirabegron, for the treatment of OAB or detrusor control. AU 288 relates to the treatment of diabetes mellitus, obesity and hyperlipidaemia and in its description in passing also mentions (i) other conditions whose symptoms can be remedied by the symptoms of obesity and hyperlipidaemia; and (ii) a multitude of β_3- adrenoreceptor-mediated conditions, but neither OAB nor any other urological condition (see above under 3.16.1).

6.20 AU 288 also contained no pointers for the average skilled person as to the successful use of mirabegron as an active ingredient for treatment of OAB. The fact that the six preferred compounds, including mirabegron, as Sandoz argues: (i) have been synthesised; (ii) show activity and: (iii) are selective as β_3-adrenoreceptors in humans: and (iv) have been tested in rats, including by oral administration, does not alter this for the following reasons.

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[9] Cf. the judgment of the Bundesgerichtshof in the parallel German case, in which it provided a similar reasoning with regard to determining the objective technical problem: Bundesgerichtshof 25 June 2024, ECLI:DE:BGH:2024:250624UXZR92.23.0 *(mirabegron),* paragraphs 15 to 17.

[10] Court of Appeal The Hague l 8 August 2020, ECLI:NL:GHDHA:2020: l 62 l *(Shire-NPS/Accord, cinacalcet),* para. 4.12.

6.20.1 Astellas argues in that connection that although it had been disclosed in the prior art, including in Yamaguchi 2002 and Igawa 2002, that β_3-adrenoreceptor agonists could potentially be used as an active ingredient for the treatment of OAB, research into the treatment of OAB up to and including the priority date focused on improving muscarinic antagonists, i.e. treating via the other side of the dual control mechanism of the detrusor. Astellas correctly points out in that context that although Yamaguchi's article from 2002, which has been chosen by Sandoz as the closest prior art in its second attack, and has been indicated as authoritative by Sandoz because it is a review article published in *Urology*, writes in the general conclusion of that article: "The human β_3-AR appears to be a useful target for the therapy of overactive bladder and other disorders", but in its conclusion to the section relevant here, "Therapeutic potential for drugs acting at β_3- adrenoceptors", gets no further than: "These results encourage the hope that a selective agonist of a human β_3-AR subtype may be useful for the treatment of overactive bladder". Encouraging a hope is not in itself sufficient for a real research premise. On top of this, Yamaguchi 2002 describes an experiment with L-755.507, a very different compound from mirabegron.

6.20.2 In addition, Astellas has argued undisputedly that there are many thousands of β_3-adrenoreceptor agonists, that even if the average skilled person were to limit itself to actually synthesised compounds, thousands remain, and that the structural diversity within the group of known β_3-adrenoreceptor agonists is big, whereby relatively small structural differences can cause potentially large effects in efficacy. Subsequently, Astellas has also argued, uncontested, that within the group of known synthesised β_3-adrenoreceptor agonists, there is still a plethora of compounds that have been identified as selective in the prior art.

6.20.3 It is also established between the parties that efficacy in humans requires activity in addition to selectivity, and that there are different types of β_3-adrenoreceptors in humans, whereby the efficacy of a β_3-agonist on one such says nothing about its efficacy on another type. This too was common general knowledge at the priority date.

6.20.4 Astellas also rightly points out that although AU 288 states that the six disclosed compounds are active and selective in humans, it does not contain absolute values for mirabegron with regard to selectivity as well as activity in humans. The Court of Appeal does not follow Sandoz in its assertion that those absolute values are not necessary for the average person skilled in the art to think that the six synthesised compounds disclosed in AU 288 can serve as a starting point: after all, without those values, the suitability a compound as a research starting point among the many other synthesised and selective compounds remains guesswork for the person skilled in the art, even if these have been tested in rats by oral administration.

6.21 Astellas has also disputed, with reasons, that Michel followed the path described by Sandoz in arriving at his invention.

6.22 The present case is also distinct from the case that led to the judgment

of the District Court of The Hague on 11 April 2018[11] which Sandoz referred to during the oral hearing, because the invention in that case did not relate to a particular compound, but to a particular formulation of a compound that was already known to have therapeutic effect for the same indication as that of the patent. Also in that decision, a document disclosing the same compound for a different indication was not considered a real starting point for the PSA, nor was a document in which the identical formulation had already been disclosed assessed as the closest prior art, because it did not relate to the problem described in the patent and did not relate to the same application.[12] It should also be noted that the District Court's inventive step assessment that contained the considerations relied on by Sandoz was overturned in this court of appeal's subsequent assessment[13].

6.23 This first attack fails already for this reason, without the need to assess the next steps of the PSA. Sandoz therefore no has an interest in its grounds directed at those next steps.

Attack starting from Yamaguchi 2002, combined with AU 288

6.24 In this second attack, Sandoz relies on Yamaguchi 2002, whose review article discloses the use of β_3-adrenoreceptor agonists for the treatment of OAB. Based on the distinguishing feature of identifying mirabegron as a suitable β_3-adrenoreceptor agonist, the objective technical problem, according to Sandoz, is finding a human selective β_3-adrenoreceptor agonist for the treatment of OAB. Given that problem, mirabegron was the obvious choice based on the disclosure in AU 288, Sandoz argues, because the average skilled person searching for such a human-selective β_3-adrenoreceptor agonist stumbles upon the six synthesised, human-selective and active compounds orally tested in rats disclosed in AU 288. This is also exactly the route Michel took to arrive at WO 666. The average skilled person will then test these six preferred compounds for suitability to treat OAB with a reasonable expectation of success.

6.25 This attack also fails. First, Astellas argues that Yamaguchi 2002 discloses a different potential therapy and that this information should be involved in the formulation of the problem. For this reason, according to Astellas, Yamaguchi 2002 is not the closest prior to the invention of the patent. In addition, if Yamaguchi 2002 does qualify as the closest prior art, application of the next steps of the problem-and-solution approach should rely on the compound L- 755.507 described therein as the leading compound. On the first question, the Court of Appeal finds that Yamaguchi 2002 must be regarded at least as one the closest prior art documents, as it describes the use of β_3-adrenoreceptor agonists for the possible treatment of OAB, among others. The answer to the second question can be left in the middle, because even if Yamaguchi 2002 were to encourage in general terms the finding of an effective selective β_3-adrenoreceptor agonist for the treatment of OAB in humans, it is not certain that the average skilled person – based on that

[11] ECLI:NL:RBDHA:2018:4127 *(Sandoz/AstraZeneca, fulvestrant),* paras 4.21 and 4.28.
[12] See para. 4.14.
[13] The Hague Court of Appeal 27 November 7018, ECLI:NL:GHDHA:2018:3954.

problem formulation and who would start from Yamaguchi 2002 with a reasonable expectation of success - would combine with AU 288 and explore mirabegron as one of the six compounds disclosed therein.

6.26 In the assessment of that reasonable expectation of success, the Court of Appeal follows the standard applied by the Bundesgerichtshof in the parallel German case: this requires consideration of all the relevant circumstances of the case, including the field of technology involved, the degree of research incentive, the effort required to formulate and pursue a research design, and the alternatives that may be present, with their respective advantages and disadvantages.[14]

6.27 For the reasons described above at 6.18 ff, the Court of Appeal considers that AU 288 would provide no incentive for the average skilled person on the priority date to explore the compounds disclosed therein with a reasonable expectation of success for the treatment of OAB. In particular, this is because AU 288 does not mention any urological conditions at all, let alone OAB, and discloses six different β_3-agonists. Furthermore, at the priority date, it is not dispute, thousands of β_3-agonists were known. The skilled person was also aware that the human selectivity of β_3-agonists and activity in one organ had little predictive value for action in another organ. Sandoz has not been able to explain why, at this state of affairs, the skilled person would start investigating precisely mirabegron with a reasonable expectation of success.

Final words and litigation costs

6.28 Sandoz's appeal fails. The Court of Appeal will therefore uphold the contested judgment and order Sandoz, as the unsuccessful party, to pay the legal costs of the appeal proceedings. Astellas claimed that Sandoz should be ordered to pay its actual legal costs pursuant to Section 1019h DCCP. Since the parties have agreed that the reasonable and proportionate costs of proceedings within the meaning of this provision in this case are €150,000, the court will award that amount.

7. Decision

The court:

Ratifies the judgment of the District Court of The Hague of 23 November 2023 rendered between the parties;

orders Sandoz to pay the costs of the appeal proceedings, fixed at €783 for court registry fees and € 150,000 for lawyer's fees on the part of Astellas;

stipulates that if Sandoz has not complied with this cost order within fourteen days of notice and Astellas subsequently serves this judgment on it, Sandoz must pay the costs of such service, plus additional post-service costs of

[14] Bundesgerichtshof 25 June 2024, ECLI:DE:BGH:2024:250624UXZR92.23.0 *(mirabegron).* para 83.

€ 92,-;

declares this order for costs to be provisionally enforceable.

This judgment has been delivered by H.M.H. Speyart van Woerden, M.Y. Bonneur and F.M. Bus and was pronounced in public on 14 January 2025 in the presence of the Registrar.

Voor grosse aan:
Uitgegeven aan mr.
Advocaat van/ appellant.
De Griffier van het Gerechtshof
te Den Haag

F.W.E. Eijsvoogels