Estudios clínicos y patentes: el difícil equilibrio entre la divulgación y la protección de la invención

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Lunes de Patentes - Centre de Patents UB

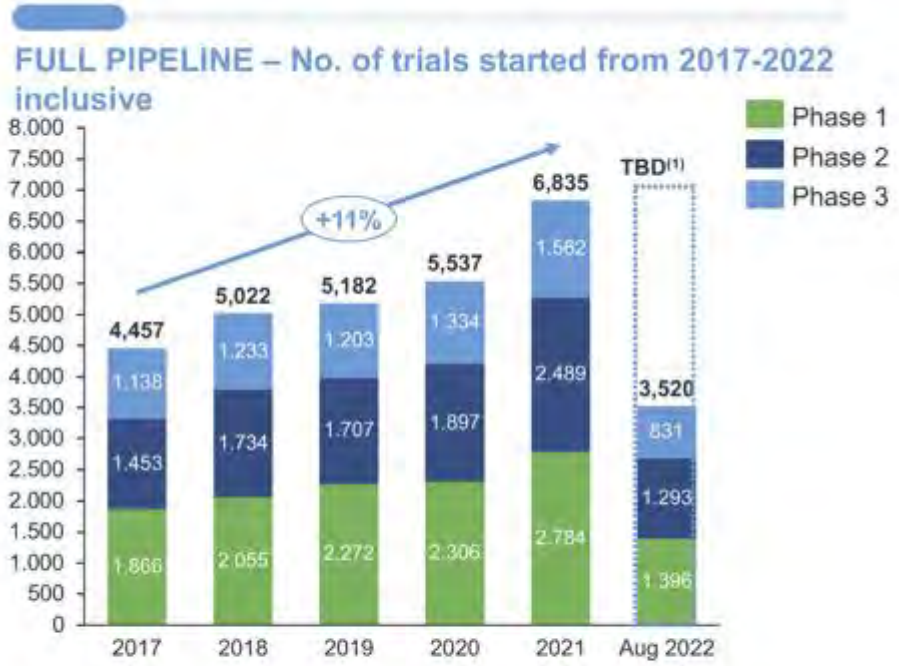
30 Septiembre 2024

Molecule List	RIVAROXABAN			
Region	Country	Sum of 2021_USD MNF	Sum of 2022_USD MNF	Sum of 2023_USD MNF
EU	FRANCE	394,505,840	365,563,493	384,599,092
	GERMANY	875,359,772	813,330,281	859,085,150
	ITALY	321,814,566	310,024,557	335,191,499
	SPAIN	147,120,321	133,980,572	138,637,432
	UK	349,509,160	316,079,487	301,485,550
EU Total		**2,088,309,659**	**1,938,978,390**	**2,018,998,723**
Grand Total		**2,088,309,659**	**1,938,978,390**	**2,018,998,723**

Molecule List	CABAZITAXEL			
Region	Country	Sum of 2021_USD MNF	Sum of 2022_USD MNF	Sum of 2023_USD MNF
EU	FRANCE	62,297,713	37,201,122	22,578,758
	GERMANY	11,298,507	3,585,959	3,229,577
	ITALY	23,222,644	18,036,386	16,885,651
	SPAIN	22,189,370	12,800,179	14,890,008
	UK	24,664,525	17,438,916	16,569,659
EU Total		**143,672,759**	**89,062,562**	**74,153,653**
Grand Total		**143,672,759**	**89,062,562**	**74,153,653**

Molecule List	EDOXABAN			
Region	Country	Sum of 2021_USD MNF	Sum of 2022_USD MNF	Sum of 2023_USD MNF
EU	GERMANY	418,717,569	406,012,810	437,347,308
	ITALY	184,029,324	202,165,812	255,594,943
	SPAIN	94,509,364	101,290,626	122,063,080
	UK	152,617,738	180,047,975	284,597,792
EU Total		**849,873,995**	**889,517,223**	**1,099,603,123**
Grand Total		**849,873,995**	**889,517,223**	**1,099,603,123**

Clinical Trials



Since 2017, the **volume of pipeline activity has increased steadily year-on-year**, with new records reached in 2021 with the resumption of clinical activity following the COVID-19 pandemic

Oncology dominates the pipeline, representing approximately 26% of ongoing trials

https://www.efpia.eu/more-than-medicine/turning-science-into-new-medicines/

Regulatory Framework - EU

Art. 6 Directive 2001/83/EC as amended
No medicinal product may be placed on the market of a Member State unless a **marketing authorisation** has been issued by the competent authorities of that Member State in accordance **with this Directive** or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, **read in conjunction** with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on **medicinal products for paediatric use** (2) and Regulation (EC) No 1394/2007

Art. 8(3) The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:
(i) Results of:
- pharmaceutical (physico-chemical, biological or microbiological) tests,
- **pre-clinical (toxicological and pharmacological) tests,**
- **clinical trials.**

Art. 10.1
[...] no generic can be filed before 8 years and the generic product cannot be placed on the market until 10 years of the initial marketing authorisation.

The ten-year period **can be extended to 11**, if during the first 8 years a new indication bringing significant therapeutic benefit over existing therapies is approved.

Art.10. Derogation of Art. 8(3)(i)- Generic applications no clinical trial data required.

Pediatric Regulation

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

Article 7

1. An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a **medicinal product for human use which is not authorised in the Community** at the time of entry into force of this Regulation shall be regarded as valid only if it includes, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:

(a) the results of all studies performed and details of all information collected in compliance with an agreed **paediatric investigation plan**;

(b) a decision of the Agency granting a product-specific waiver;

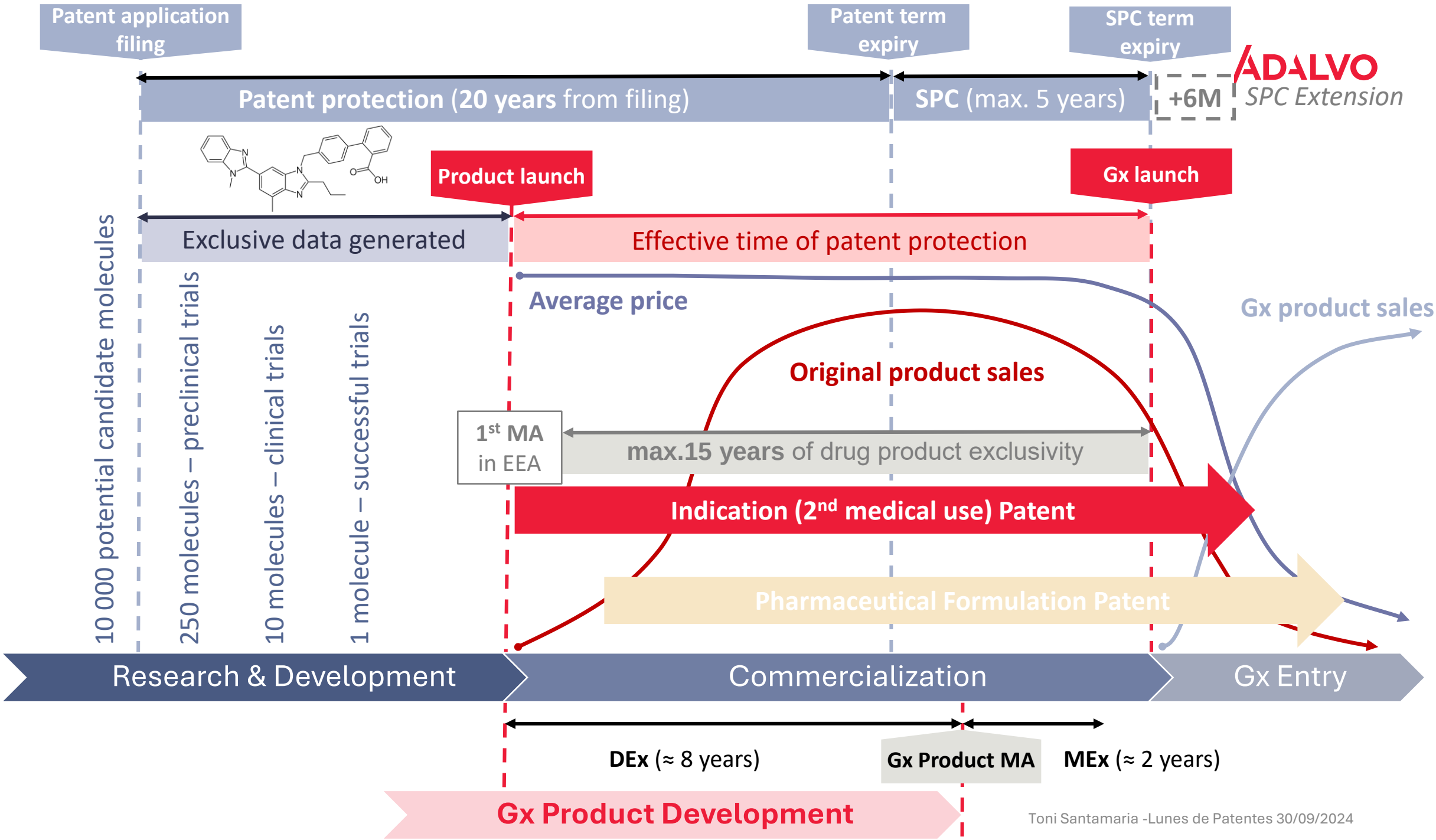
(c) a decision of the Agency granting a class waiver pursuant to Article 11;

(d) a decision of the Agency granting a deferral.

For the purposes of point (a), the decision of the Agency agreeing the paediatric investigation plan concerned shall also be included in the application.

Article 8

In the case of **authorised medicinal products** which are protected either by a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate, Article 7 of this Regulation shall apply to applications for authorisation of new indications, including paediatric indications, new pharmaceutical forms and new routes of administration.


Patent application filing
Patent term expiry
SPC term expiry
ADALVO
SPC Extension
Patent protection (20 years from filing)
SPC (max. 5 years)
+6M
Product launch
Gx launch
Exclusive data generated
Effective time of patent protection
Average price
Gx product sales
Original product sales
10 000 potential candidate molecules
250 molecules – preclinical trials
10 molecules – clinical trials
1 molecule – successful trials
1st MA in EEA
max.15 years of drug product exclusivity
Indication (2nd medical use) Patent
Pharmaceutical Formulation Patent
Research & Development
Commercialization
Gx Entry
DEx (≈ 8 years)
Gx Product MA
MEx (≈ 2 years)
Gx Product Development

Scope of clinical research

- New dosage forms
- New indications - Repurposing
- Sub populations
- Paediatric studies
- Drug-drug interaction
- Food effects

Some data on clinical trials

- Clinical trials are studies intended to discover or verify the effects of one or more **investigational medicines**.
- The regulation of clinical trials aims to ensure that the rights, safety and well-being of **trial participants** are protected and the results of clinical trials are credible.
- Regardless of where they are conducted, all clinical trials included in applications for marketing authorisation for human medicines in the European Union (EU) / European Economic Area (EEA) must have been carried out in accordance with the requirements set out in Annex 1 of Directive 2001/83/EC.
- This means that:
  - clinical trials conducted in the EU / EEA have to comply with EU clinical trial legislation;
  - clinical trials conducted outside the EU / EEA have to comply with **ethical principles** equivalent to those set out in the EEA, including adhering to international good clinical practice and the Declaration of Helsinki.
- In the EU / EEA, approximately 2,800 clinical trials are authorised each year.
- Approximately 60% of clinical trials are sponsored by the **pharmaceutical industry** and 40% by non-commercial sponsors, mainly **academia**.

https://www.ema.europa.eu/en/human-regulatory-overview/research-development/clinical-trials-human-medicines

EMA Good clinical Practices

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected and that clinical-trial data are credible

https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-clinical-practice

Declaration of Helsinki (Medical research involving human subjects)

World Medical Association's policy
First version adopted in 1964

- Research ethics committees
- Informed consent
- Use of placebo

https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/

Clinical trials in EU

- A clinical trial is a study performed to investigate the safety or efficacy of a medicine. For medicines intended for human use, these studies are carried out in people who volunteer.

- Clinical trials in the EU and EEA are governed by the **Clinical Trials Regulation** (Regulation (EU) No 536/2014) which came into application on 31 January 2022. It is part of a broad initiative to transform the EU/EEA clinical trials environment in support of large clinical trials in multiple European countries, to the benefit of medical innovation and patients.

- The regulation of clinical trials aims to ensure that the rights, safety and well-being of clinical trial participants are protected and the results of clinical trials are reliable and informative.

https://euclinicaltrials.eu/about-this-website/

Publication. Why?

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

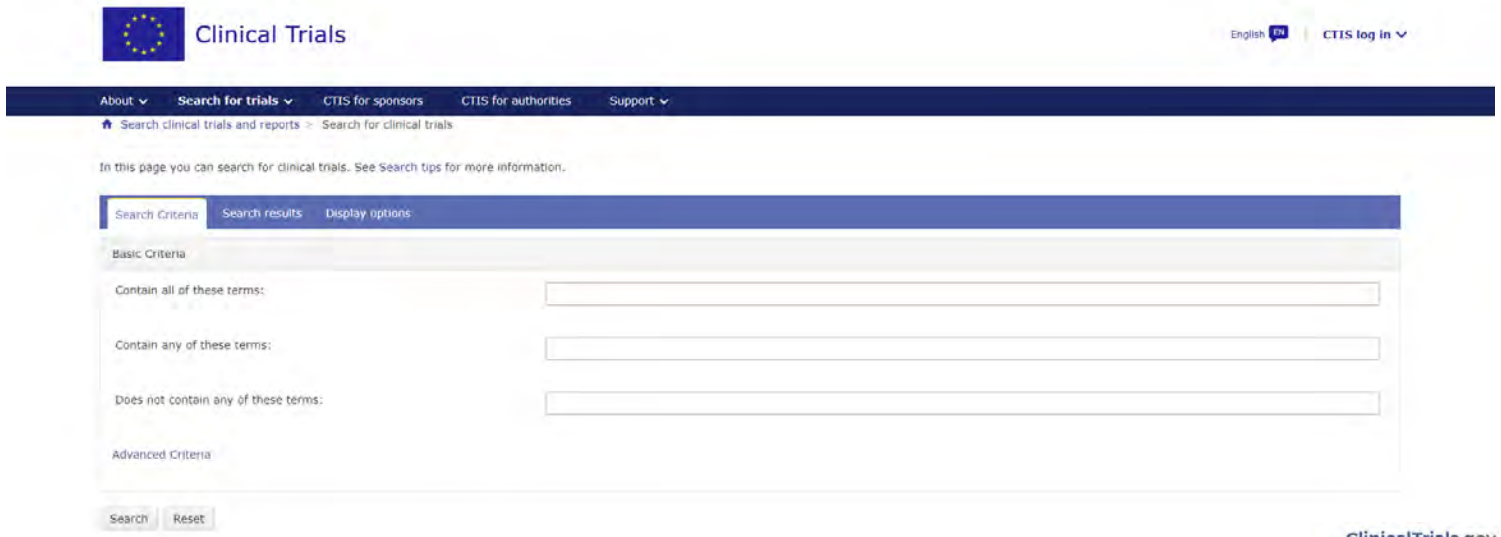
Transparency

25) In order to increase **transparency in the area of clinical trials**, data from a clinical trial should only be submitted in support of a clinical trial application if that clinical trial has been recorded in **a publicly accessible and free of charge database** which is a primary or partner registry of, or a data provider to, the international clinical trials registry platform of the World Health Organization (WHO ICTRP). Data providers to the WHO ICTRP create and manage clinical trial records in a manner that is consistent with the WHO registry criteria. Specific provision should be made for data from clinical trials started before the date of application of this Regulation.

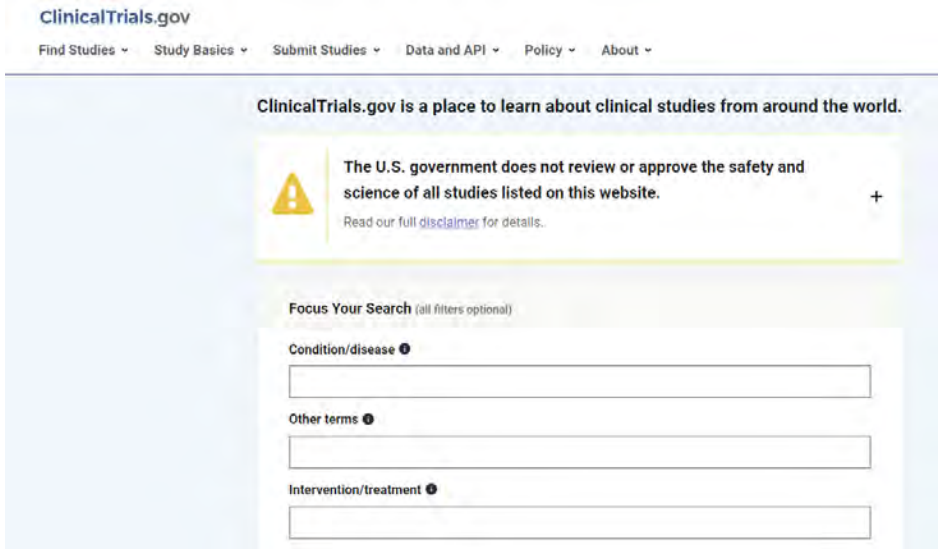
Patient – informed consent in writing

(27) Human dignity and the right to the integrity of the person are recognised in the Charter of Fundamental Rights of the European Union (the 'Charter'). In particular, the Charter requires that any intervention in the field of biology and medicine **cannot be performed without free and informed consent of the person concerned.** Directive 2001/20/EC contains an extensive set of rules for the protection of subjects. These rules should be upheld. Regarding the rules concerning the determination of the legally designated representatives of incapacitated persons and minors, those rules diverge in Member States. It should therefore be left to Member States to determine the legally designated representatives of incapacitated persons and minors. Incapacitated subjects, minors, pregnant women and breastfeeding women require specific protection measures.

https://euclinicaltrials.eu/



https://clinicaltrials.gov/



CTIS information published

You can view the information below on each clinical trial when available:

- EU clinical trial number
- Name and address of researcher or company carrying out the trial
- Outcome of the application and date of decision
- Start and end dates of the trial
- Start and end dates of participant recruitment
- Background information on the principal investigator

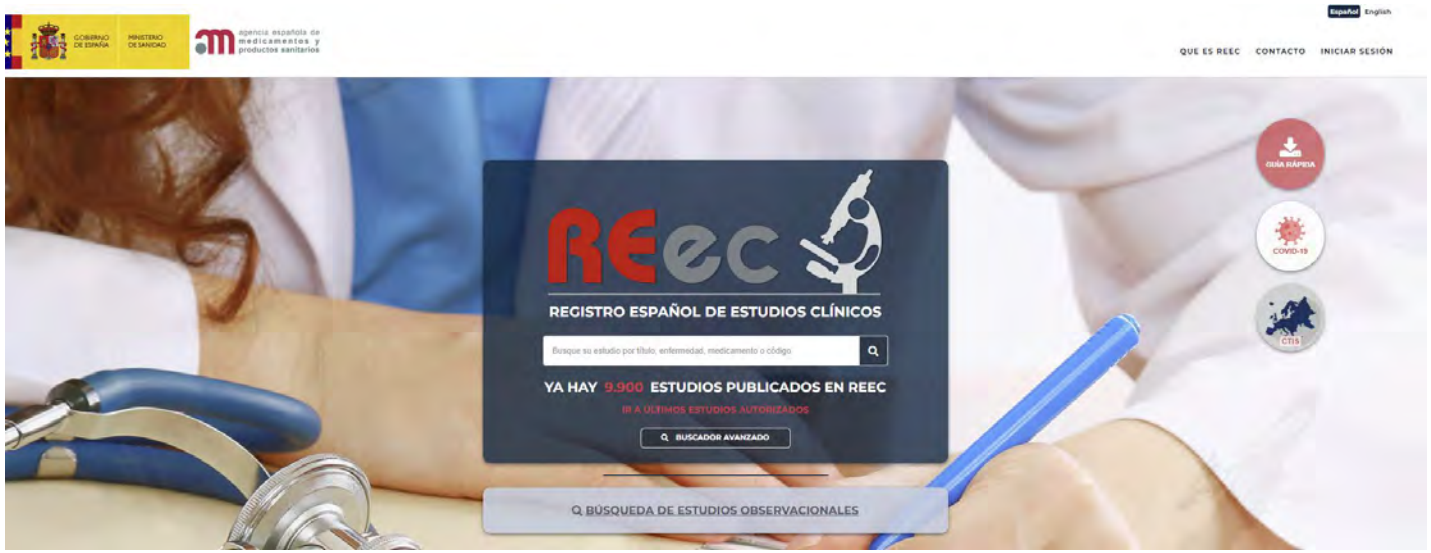
Further information is also available on trials:

- Name of the trial
- Identity of the investigational medicine
- Trial design, therapeutic intent and protocol code
- Objectives and endpoints
- Participant inclusion and exclusion criteria
- Details of treatment arms
- Trial results

Excluded from publication:

- Personal data
- Commercial confidential information
- Communications with EU Regulators during assessment

https://euclinicaltrials.eu/search-clinical-trials-reports/



PARA QUE SIRVE

•Para garantizar que las decisiones relacionadas con la salud y cuidados médicos se toman con el aval de datos científicos públicos y por tanto, reconocidos

•Para garantizar que se ponen a disposición de la sociedad datos y resultados tanto positivos como negativos de los estudios clínicos realizados.

•Para que los sujetos participantes en dichos estudios tengan información previa de calidad.

•Para evitar estudios repetitivos o no aceptables, especialmente en niños, ancianos y otras poblaciones vulnerables, potencialmente desfavorecidas o con dificultades para poder tomar una decisión por sí mismos.

•Para detectar aspectos científicos poco investigados y ayudar a cubrir esas carencias.

•Para facilitar la participación en estudios clínicos recién autorizados o en marcha y poder así alcanzar resultados fiables.

https://reec.aemps.es/reec/public/web.html

Patentability of medical uses - EPC

Art. 53 EPC – Exceptions to Patentability

(c)methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.

Art. 54 EPC- Novelty

4) Paragraphs 2 and 3 shall not exclude the patentability of any **substance or composition**, comprised in the state of the art, **for use in a method** referred to in Article 53(c), provided that its use for any such method is not comprised in the state of the art.

(5) Paragraphs 2 and 3 shall also not exclude the patentability of any **substance or composition** referred to in paragraph 4 for any specific **use in a method** referred to in Article 53(c), provided that such use is not comprised in the state of the art.

Drug Approval Phases and Clinical trials

Pre-approval

Post-approval

Pre-Clinical

Phase I

Researchers test a drug or treatment in a small group of people (20–80) for the first time. The purpose is to study the drug or treatment to learn about **safety and identify side effects.**

Phase II

The new drug or treatment is given to a larger group of people (100–300) to determine its **effectiveness** and to further study its safety.

Phase III

The new drug or treatment is given to large groups of people (1,000–3,000) to confirm its **effectiveness, monitor side effects, compare it with standard or similar treatments**, and collect information that will allow the new drug or treatment to be used safely.

Phase IV

After a drug is approved by the FDA and made available to the public, researchers track its safety in the general population, seeking more information about a drug or treatment's benefits, and optimal use.

https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics

Drug Approval Phases and Clinical trials

Stage	Purpose	Participants	Length	Next phase
Phase I	Safety and dosage	20 to 100 healthy volunteers or people with the disease condition	Several months	**Aprox 70%** of drugs move to the next phase
Phase II	Efficacy and side effects	Up to several hundred people with the disease/condition	Several months to 2 years	**Aprox 33%** of drugs move to the next phase
Phase III	Efficacy and monitoring of adverse reactions	300 to 3000 volunteers who have the disease or condition	1 to 4 years	**Aprox 25-30 %** of drugs move to the next phase
Phase IV	Safety and efficacy	Several thousands of volunteers who have the disease/Condition	--	Post approval

https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#Clinical_Research_Phase_Studies

Blind trials vs Open Label

A **double-blind** trial is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received

In an **open-label** trial the identity of treatment is known to all

Patent filing, when?

- **Late filing**

- Maximise protection – prolong lifecycle management
- Risk of Public disclosure
  - Mandatory publications
  - Congress, scientific articles
  - Press Release, Investors
  - SEC filings (US)

- **Early filing**

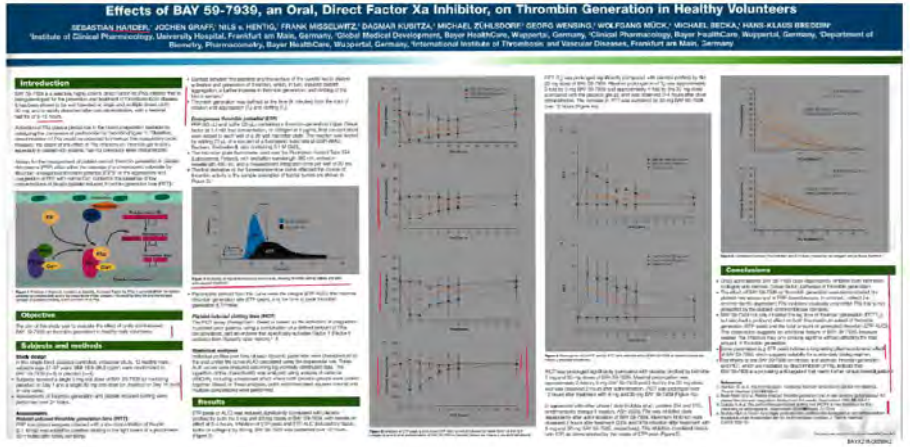
- Shorter protection
- Lack of data – sufficiency of disclosure / Plausibility
- Reduced risk of disclosure

Lilly

January 7, 2013

Boehringer Ingelheim and Eli Lilly and Company announce positive top-line pivotal Phase III data results for empagliflozin

INGELHEIM, Germany, Jan. 7, 2013 /PRNewswire/ -- Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) today announced top-line results for four completed Phase III clinical trials for empagliflozin, an investigational sodium glucose co-transporter-2 (SGLT-2) inhibitor being studied for treatment of patients with type 2 diabetes (T2D). In all four studies, the primary efficacy endpoint, defined as significant change in HbA1c from baseline compared to placebo, was met with empagliflozin (10 and 25 mg) taken once daily.



When to apply for patent?

Pre-approval

Post-approval

Pre-Clinical

Phase I

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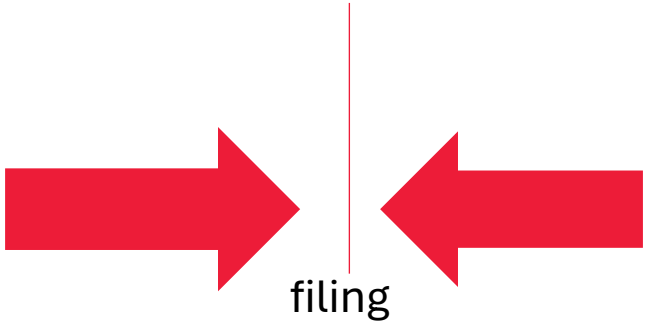


https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics

Protection of Data from Clinical trials

- **Data / Market exclusivity**
  - 8+2 years
  - +1 new indication – significant clinical benefit
  - Orphan Exclusivity 10y (+ 2y)

- **Patent protection**
- SPC PED 6M
- Carve-out – Art 11 Directive 2001/83/EC
  - Parts of SmPC referring to indications or dosage forms covered under patent need not to be included

EPO decisions

Novelty (I.C.4.1) – Therapeutic effect –Technical feature of the claim

- **T 1941/21 (TAUROURSODEOXYCHOLIC ACID (TUDCA) FOR USE IN THE TREATMENT OF NEURODEGENERATIVE DISORDERS/Bruschettini S.r.l.) 05-06-2024**

As a general rule, a claim to the use of a known compound for a particular purpose or to a product for use in a particular medical purpose, which is aimed at obtaining a technical effect described in the patent, should be interpreted as including **that purpose as a functional technical feature**, and is accordingly not open to objection under Article 54(1) EPC provided that such technical feature has not previously been made available to the public.

- **T 0715/03 (Use of ziprasidone for treating Tourette's syndrome/PFIZER) 16-01-2006)**

Additionally, contrary to the examining division's opinion, it cannot be seen that the skilled person would conclude that "some beneficial effects are present" (cf. point 6 of the decision) just because the clinical trials are "nearing completion". Indeed, since they are **double blind trials the skilled person only knows after the completion of the trials and evaluation of the results whether this is the case.**

Case Law of the Boards of Appeal, 10th Ed.

- According to decision T 158/96, the **information in a citation that a medicament was undergoing a clinical phase evaluation for a specific therapeutic application was not prejudicial to the novelty of a claim** directed to the same therapeutic application of the same medicament, if such information was plausibly contradicted by the circumstances, and if the content of said **citation did not allow any conclusion to be drawn with regard to the actual existence of a therapeutic effect or any pharmacological effect** which directly and unambiguously underlay the claimed therapeutic application (see also T 385/07, T 715/03, T 1859/08).

- a mere statement that a combination therapy was being explored did not amount to a novelty-destroying disclosure. The "currently being explored" situation, where no clinical benefit was disclosed, fell within the rationale of decisions T 158/96 and T 715/03.

- According to these decisions, **if a prior art document disclosed clinical investigations such as phase I, II or III studies** (or stated that these investigations were ongoing), **but failed to disclose the final result of these studies, it was not novelty-destroying**. The board concluded that there was no description in the prior art documents of the treatment of a human patient, nor any disclosure of the biological effect. Therefore, the claims satisfied the requirements of Art. 54 EPC.

Novelty – Therapeutic effect must be shown

T 0158/96 (Obsessive-compulsive-disorder/PFIZER) 28-10-1998

- Prior art: table 4 of document (5), which showed that in 1989 sertraline was undergoing clinical phase II trials for obsessive-compulsive disorder.

- 3.4 For this reason the skilled person, reading in table 4 that **sertraline was undergoing phase II trials for OCD, had no means of concluding from this information, reliably and beyond mere speculation, that the drug finally proved, during this phase, any therapeutic effect potentially useful in the treatment of OCD.** In fact, as the appellant reiterated, and as a matter of common general knowledge, many candidate drugs submitted to phase I and II evaluation do not proceed to phase III studies at all.

- 3.5.1. [...]This is also confirmed by the fact that, according to the Code of Federal Regulations, phase I is not necessarily conducted on patients, but may be conducted on normal volunteers. Therefore, the reader of (5) could not conclude that a therapeutic effect had already been proven or observed during phase I investigation.

- At the priority date of the European application, sertraline was known to be a selective serotonin re-uptake inhibitor. [...] No evidence is on record showing that, before the priority date of the European application, a clear and accepted relationship between these physiological activities and the many psychiatric disorders and diseases (ranging from depression to anxiety) allegedly affected by the potentiation or the depression of the serotoninergic neurotransmission had finally been established. **Thus, the skilled reader of (5) had no means of concluding with the required certainty that any evidence of a therapeutic effect in relation to OCD could have been produced by the results of the pharmacological studies carried out in clinical phase I.**

Novelty – Therapeutic effect must be disclosed

- **T 1457/09 (CTL epitopes of WT-1/GANYMED PHARMACEUTICALS) 17-01-2014**
- 36. Pursuant to established case law, a disclosure destroys novelty only if the teaching it contains is reproducible, in other words if it can be carried out by the person skilled in the art [...] For the requirement of reproducibility to be considered as fulfilled in relation to a medical use it is necessary - following the principles developed by the case law in the framework of the evaluation of Article 83 EPC in the case of a second medical use claim (see decision T 609/02 of 27 October 2004, reasons point 9) - **that the disclosure in the prior art document is such as to make it credible that the therapeutic effect on which the disclosed treatment relies can be achieved. Thus, in the present case a prior art document is novelty-destroying only if it discloses not only the product referred to in the claim - here RMFPNAPYL - for the claimed therapeutic application - here treatment of cancer - but also that the claimed product is indeed suitable for the claimed therapeutic application.**

- **T 1859/08 (Anti-ErbB2 antibodies/GENENTECH, INC.) 05-06-2012**
- 13. However, **a mere statement that a combination therapy is being explored does not amount to a novelty-destroying disclosure** of what is claimed in claim 1, because claim 1 is a medical use claim which includes, as a technical feature of the claim, the achievement of a clinical benefit in breast cancer patients as measured by an increased time to disease progression.
- The present "currently being explored" situation, where **no clinical benefit is disclosed**, falls within the rationale of decisions T 158/96 and T 715/03. According to these decisions, **if a prior art document discloses clinical investigations such as phase I, II or III studies (or states that these investigations are ongoing), but the document fails to disclose the final result of these studies, this document is not novelty-destroying.**

Novelty – Therapeutic effect must be disclosed

- **T 1437/21 (Empagliflozin/BOEHRINGER INGELHEIM) 09-02-2024**
- 3.1 Claim 1 as granted (see point I above) defines empagliflozin for a specific use in therapeutic treatment in the format of Article 54(5) EPC. Accordingly, the therapeutic efficacy of empagliflozin in the defined treatment represents a functional feature of the defined subject-matter.
- 3.2 Documents D22/D29, which are press releases from Boehringer Ingelheim and Eli Lilly and Company with essentially identical technical content, announced results for four completed Phase III clinical trials involving empagliflozin for treatment of T2DM patients as follows[...]
- 3.3 The Board considers that in accordance with the precise wording of the press releases in documents D22/D29 the announced efficacy of treatment with the 25 mg dose of empagliflozin in Study 1245.36 may well be understood as relating to the patient population having mild, moderate or severe renal impairment as a whole. **Therefore, from these press releases the skilled person cannot directly and unambiguously derive the information that the treatment is effective in each of the subgroups of patients defined by the mentioned levels of renal impairment.**

Lilly

January 7, 2013

Boehringer Ingelheim and Eli Lilly and Company announce positive top-line pivotal Phase III data results for empagliflozin

INGELHEIM, Germany, Jan. 7, 2013 /PRNewswire/ -- Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) today announced top-line results for four completed Phase III clinical trials for empagliflozin, an investigational sodium glucose co-transporter-2 (SGLT-2) inhibitor being studied for treatment of patients with type 2 diabetes (T2D). In all four studies, the primary efficacy endpoint, defined as significant change in HbA1c from baseline compared to placebo, was met with empagliflozin (10 and 25 mg) taken once daily.

Prior Disclosure – Samples not returned

- **T 0007/07 (Ethinylestradiol and drospirenone for use as a contraceptive/BAYER PHARMA AG) 07-07-2011**
- 3.3 The respondent did not contest that clinical trials were carried out prior to the priority date and that the principal **investigators but not the participants entered into confidentiality agreements**. The participants were informed about the active agents of the contraceptive, but were not told that the drospirenone was present in micronised form. Nor did the respondent contest that the oral contraceptive used for the study comprised all the features of the subject-matter according to claim 1.
- It is established board of appeal case law that if a **single member of the public, who is not under an obligation to maintain secrecy**, has the theoretical possibility to access particular information, this **information is considered as being available to the public** within the meaning of Article 54(2) EPC.
- Such trials are to be distinguished from trials where a large number of patients are given tablets to take home with them and for use over a longer period of time. It has been acknowledged by the US court that not all of the unused study drugs were returned. Therefore, it appears that after having handed out the **drugs the respondent effectively lost control** over them as the participants in the clinical trials were in no way barred from disposing of the drugs as they wanted.

- **Difference tablets vs implanted devices**
- 3.3 The board does not agree with the respondent's interpretation of the case law. Both decisions cited by the respondent (T 0152/03 of 22 April 2004 and T 0906/01 of 28 September 2004) concern prototype devices that were to be implanted in a small number of patients. **Therefore, even if the patients did not sign a confidentiality agreement, they would not have been in a position to pass the prototypes on or even inspect them themselves.**

Prior Disclosure – Samples not returned

- **T 0670/20 (Pharmaceutical composition/SANKYO) 02-12-2022** (Edoxaban)
- 4.3 Documents D29 and D30 represent the clinical trial protocols for the studies disclosed respectively in documents D19 and D20. According to document D29 (see sections 4.5.4 and 4.7.2.3) and document D30 (see sections 3.10 and sections 5.1 and 5.5**) the investigators in the trials of documents D19 and D20 were instructed to ensure drug accountability and to monitor treatment compliance by taking account of the unused medication returned by the patients discharged from hospital**.
- As further pointed out by the respondent and not contested by the appellants the clinical trials of documents D19 and D20 were carried out **in accordance with the EMEA Guidelines for Good Clinical Practice** (document D33). These guidelines explicitly require adherence to the prescribed protocol (see D33, sections 2.6 and 2.12) and assurance of drug accountability (see D33, sections 4.6.1, 4.6.5 and 4.6.6).
- 4.5 The appellants further argued that the patients may have been requested to return unused tablets, but that in the absence of any legal sanction no parallel to a confidentiality agreement could be assumed on such basis, especially as full compliance by all patients would not be likely.
- The Board notes, however, that the **patients' agreement to use the provided medication according to instruction or to return the unused medication** obliges the patients irrespectively of any sanction on non-compliance and therefore **disqualifies the patients as members of the public** with respect to the medication provided to them.
- 4.6 **In T 7/07** the competent board concluded on the basis of the available information that apparently **the sponsor of the trial had effectively lost control over the drugs** after these had been handed out to the participants of the trial as members of the public who were not bound to secrecy (see section 3.3, pages 17-18, bridging paragraph, and section 3.6, page 22, lines lines 5-11). In view of the explanations in sections 4.3-4.5 above the Board considers that **in the present case the tablets were not provided to the participants of the trial as members of the public**, which distinguishes the circumstances of the trials of documents D19 and D20 from the circumstances of the trial considered in T 7/07.

Prior Disclosure – members of the public

- **T 0239/16 (Zoledronic acid/NOVARTIS) 13-09-2017**
- Document (55) is entitled "Information for the patient concerning the study 42446 02 041". It consists of six pages numbered 1/6 to 6/6. In the introductory lines the following is stated: "Dear Madam, We would like to ask you to read the following information so that you understand the study you are asked to participate in and so that you may decide whether or not to participate... You were diagnosed with a reduced density of the bone. The medical term for this is Osteoporosis." [...] Finally, page 6/6 can be summarised as representing the patient consent form, comprising statements of the patient and the physician and their signatures.
- From the information that is directly obtainable from document (55) it can thus be derived that it was addressed to a number of patients suffering from osteoporosis who were asked to participate in study 42446 02 041.
- Of particular importance in this context is Prof. Verbruggen's affidavit (document (57)). In point 6, he stated that he had explained the contents of LV-1 to his patients and told them that, before signing the form, they **should openly discuss the treatment referred to in the document with anyone**, including their family and family doctor. Then he stated: "Indeed, I encouraged my patients to do so. That is without any obligation of confidentiality."
- The board agrees with the principle that information cannot be regarded as made available to the public for the purpose of Article 54(2) EPC and that the recipient of that information cannot be regarded as a member of the public if at the time of receipt of the information he is in some special relationship to the donor of the information (cf. T 1081/01, Reasons 7, and T 1057/09, Reasons 5.13). However, each case has to be assessed on its own facts, and in the circumstances of the present case the board does not acknowledge the existence of such a special relationship.
- It is established case law that if a single member of the public who is not under an obligation to maintain secrecy has the possibility to access particular information, this information is considered as being available to the public within the meaning of Article 54(2) EPC. In view of the fact that document (55) (or its respective country/language version, see "LV1" of document (57)) **was handed out to people who were encouraged to discuss its contents with anyone, the board comes to the conclusion that the contents of document (55) have been made available to persons neither being bound by any confidentiality agreement nor being in a special relationship to the study sponsor who are thus to be classified as members of the public.**

Support to the application

- **T 0966/18 (Synucleinopathic disease/PROTHENA BIOSCIENCES) 10-11-2020**
- According to the relevant case law, see for example T 609/02, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported. Yet, this does not mean that a simple verbal statement in a patent specification is enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical.
- In that decision the board also stated that the patent has to provide some information, for example in the form of experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent.

- The board explained in decision T 609/02 that:
- i) **A mere assertion that compound X is suitable for treating disease Y is not sufficient** on its own to render the invention plausible (Reasons 9).
- ii) The disclosure of the patent specification does not have to be definitely predictive of the efficacy of the invention: in vitro tests which may well not be reproducible in humans or animals may suffice (Reasons 10 and 11).
- iii) The patent should provide some information to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, an example of adequate support being experimental tests (Reasons 9).
- iv) Ultimately the purpose of the **requirement of sufficiency is to place the reader in possession of the invention without imposing undue burden on them by way of further investigation or research** (Reasons 10).

10. At the heart of the present case lies the question whether or not the skilled person, having regard to the disclosure of the patent and the common general knowledge at the relevant date of the application, would have considered that the compounds referred to in the claim were suitable to achieve the therapeutical effect (see decision T 609/02, point 9). Or, in other words, whether it was plausible (or, in yet other words, whether it was credible) that the therapeutic effect could be achieved by the claimed composition.

Support to the application

- T 1437/07 (Botulinum toxin for treating smooth muscle spasm/ALLERGAN) 26-10-2009

- 26. In accordance with the principles developed by the case law in the framework of the evaluation of the requirements of Article 83 EPC in the case of a medical use, the skilled person should not only be able to carry out the teaching of document R21, but it should also be credible that the effect at issue - here relief of pain - has been achieved. [...[As a consequence, **under Article 83 EPC, unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application.**"

Support to the application

- T609/02 (AP-1 complex/SALK INSTITUTE) 27-10-2004

- It is a well-known fact that proving the suitability of a given compound as an active ingredient in a pharmaceutical composition might require years and very high developmental costs which will only be borne by the industry if it has some form of protective rights. Nonetheless, variously formulated claims to pharmaceutical products have been granted under the EPC, all through the years. The patent system takes account of the intrinsic difficulties for a compound to be officially certified as a drug by not requiring an absolute proof that the compound is approved as a drug before it may be claimed as such. The boards of appeal have accepted that for a sufficient disclosure of a therapeutic application, **it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported.**

- Yet, this does not mean that **a simple verbal statement** in a patent specification that compound X may be used to treat disease Y **is enough to ensure sufficiency of disclosure** in relation to a claim to a pharmaceutical. It is required that the patent provides some **information in the form** of, for example, **experimental tests**, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se. Showing a pharmaceutical effect in vitro may be sufficient if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application (T 241/95, OJ EPO 2001, 103, point 4.1.2 of the reasons, see also T 158/96 of 28 October 1998, point 3.5.2 of the reasons) or, as decision T 158/96 also put it, if there is a "clear and accepted established relationship" between the shown physiological activities and the disease (loc. cit.). **Once this evidence is available from the patent application, then post-published** (so-called) expert evidence (if any) **may be taken into account, but only to back-up the findings in the patent application** in relation to the use of the ingredient as a pharmaceutical, and not to establish sufficiency of disclosure on their own.

Clinical trials as closest Prior art

Case Law of the Boards of Appeal, 10th Ed.

- According to established case law (see for example **T 2057/12**, **T 1148/15**, **T 96/20**, **T 2443/18**), a central consideration in selecting the closest prior art is that it must be directed to the same purpose or effect as the invention, otherwise it cannot lead the skilled person in an obvious way to the claimed invention.

- **T 1123/16 (Eosinophilic bronchitis/GLAXO) 13-04-2021**

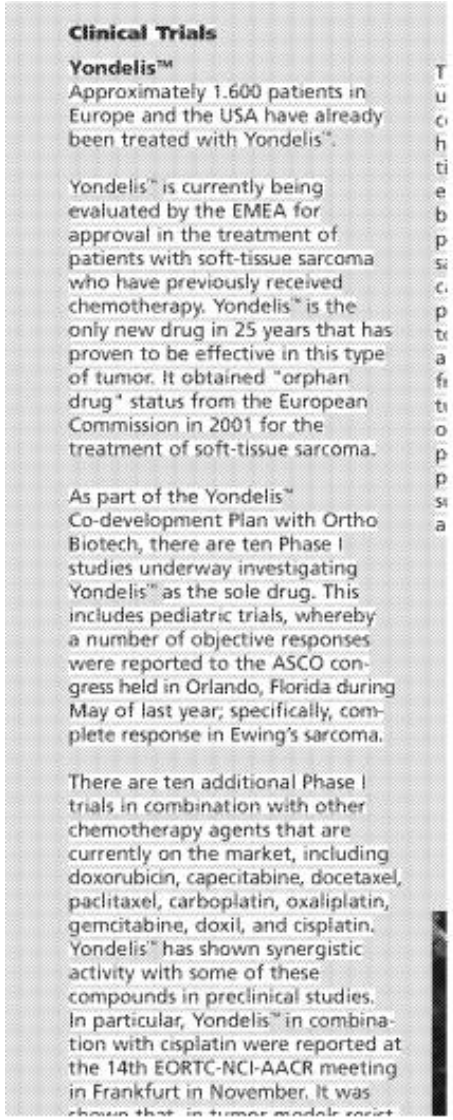
- 5. Like the opposition division and the parties, the board considers **the disclosure of this phase II clinical trial to constitute an appropriate starting point for assessing whether the claimed subject-matter involves an inventive step**. Indeed, it concerns the treatment of patients with the **same medical condition** (i.e. steroid-dependent EB) using the **same substance** (i.e. a humanised antibody to IL-5) with the **same objective** (i.e. a reduction in prednisone administration).

- **T 0096/20 (Treatment of myasthenia gravis/ALEXION) 22-04-2021**

- 4. According to established jurisprudence of the boards of appeal, the **closest prior art should be a teaching directed to the same purpose or effect as the claimed invention** (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, I.D.3.2.). The board therefore holds that **actual therapies** for treatment of MG in humans, such as therapies with immunosuppressants including prednisone, methotrexate, cyclosporine and cyclophosphamide, also disclosed in document D4 (page 1), **represent the closest prior art, rather than the clinical trial protocol which is also disclosed there**.

Disclosure of Clinical trials as closest Prior art

- **T2506/12- (PEGYLATED LIPOSOMAL DOXORUBICIN/Pharmamar) 04/10/2016**
- D1: Zeltia Group Annual Report 2002
- D2: Zeltia Junta General de Accionistas 2003
- Therapeutic application as defined in claim 1 and 2 not disclosed. (Novelty)
- 3.2 The parties have regarded documents D1 or D2 (without particular preference) as the closest prior art. The board has no reason to select a different starting point for the assessment of inventive step.
- 3.3 The relevant information content of both documents is very similar. As already mentioned, both documents disclose that the combination of ET-743 and PLD was being tested in a clinical phase I study for the treatment of cancer.



Clinical Trials

Yondelis™
Approximately 1.600 patients in Europe and the USA have already been treated with Yondelis™.

Yondelis™ is currently being evaluated by the EMEA for approval in the treatment of patients with soft-tissue sarcoma who have previously received chemotherapy. Yondelis™ is the only new drug in 25 years that has proven to be effective in this type of tumor. It obtained "orphan drug" status from the European Commission in 2001 for the treatment of soft-tissue sarcoma.

As part of the Yondelis™ Co-development Plan with Ortho Biotech, there are ten Phase I studies underway investigating Yondelis™ as the sole drug. This includes pediatric trials, whereby a number of objective responses were reported to the ASCO congress held in Orlando, Florida during May of last year; specifically, complete response in Ewing's sarcoma.

There are ten additional Phase I trials in combination with other chemotherapy agents that are currently on the market, including doxorubicin, capecitabine, docetaxel, paclitaxel, carboplatin, oxaliplatin, gemcitabine, doxil, and cisplatin. Yondelis™ has shown synergistic activity with some of these compounds in preclinical studies. In particular, Yondelis™ in combination with cisplatin were reported at the 14th EORTC-NCI-AACR meeting in Frankfurt in November. It was

Clinical trials as closest Prior art

- **T 0239/16 (Zoledronic acid/NOVARTIS) 13-09-2017**
- (55) Information for the patient concerning the clinical study 42446 02 041, pages 1/6-6/6
- document (55), after an introduction identifying the disease as osteoporosis and the active agent as "Zoledronate", the objective of the study is set out: "The objective of this study is to check if Zoledronate is an effective product in the prevention of bone loss in patients with post-menopausal Osteoporosis. Five different doses of Zoledronate shall be compared and it shall be determined what dose delivers the best result" (page 1/6, "Objective of the study"). The study is performed double-blindly, including a placebo arm in addition to the five study arms.
- document (55) does not directly and unambiguously disclose the effective treatment of osteoporosis as defined in the independent claims of the main request.
- 6.2 A possible starting point for the assessment of inventive step is document (55). The content of document (55) is discussed in detail in point 5.2 above. The **five study arms are presented** in the same manner. Each can be seen as a valid starting point. In the present case, the board considers the last study arm pertaining to once-yearly administration as the most promising starting point for the assessment of inventive step.

Clinical trials as closest Prior art

- **T 2154/14 (Daptomycin II/CUBIST PHARMACEUTICALS) 29-03-2017**
- D1 Baltz R.H., in W.R. Strohl (Editor) Biotechnology of Antibiotics, Second Edition, Marcel Dekker, Inc., New York 1997, pages 415 to 435.
- D8 Cubist Press release (1 March 1999).

- D8 – CPA in opposition

- 38. Thus, while document **D1 reviews the results of completed clinical trials in humans** which had shown that the treatment of bacterial infections with daptomycin was effective, document **D8 does not report on the outcome of the clinical studies** it describes.
- 39. Therefore, the board takes the view that document **D1 represents the more promising springboard than document D8,** and accepts that the clinical study reported in document D1, wherein 3 mg/kg daptomycin administered every 12 hours was used to treat bacterial infections, represents the closest state of the art for the purpose of the assessment of inventive step of the subject-matter of claim 1.

Clinical trials as closest Prior art

T 2963/19 (Liposomal irinotecan/IPSEN) 18-03-2022

D15b: "Study of MM-398 With or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer", Clinical Trials Identifier: NCT01494506 (25 January 2013)

Patent revoked. Inventive step denied starting from D15b (Phase III)

Appellant (patentee) contested use of D15b as CPA – do not disclose effective treatment and suggests another document as CPA.

4.1.2 The Board recalls that the problem solution approach implies that in case an inventive step can be recognized starting from a particular item of prior art which is convincingly identified as most promising starting point and thus represents the closest prior art, attempts to argue a lack of inventive step starting from less promising starting points are bound to fail. However, in case an inventive step is denied starting from a realistic particular item of prior art, the mere argument that the claimed subject-matter nevertheless involves an inventive step in view of an allegedly closer prior art, may not be persuasive, because in such case the allegedly closest prior art may well represent a starting point that is in fact not more promising.

- In view of the fact that the patent itself does not present experimental results specifically demonstrating the therapeutic effect of the claimed triple dosage regimen involving administration once every two weeks the Board considers that the **disclosure of the triple dosage regimen in document D15b cannot be disqualified as a realistic starting point in the prior art on the ground that it does not report results of the described treatment**. The facts of the present case differ in this respect from the facts in decisions T 2154/14 and T 96/20, in which the original disclosure did present experimental results specifically demonstrating the therapeutical effect of the defined treatment. The Board further observes that in decisions T 239/16 and T 2506/12 protocols for clinical trials without disclosure of results were regarded as suitable starting points in the prior art. In view of the considerations in section 4.1.2 above the Board finds the applicant's argument, that in contrast to the present case in T 239/16 and T 2506/12 no further starting points were under consideration, not persuasive.

Obviousness

- **T 1806/18 (Nilotinib for treating chronic myeloid leukemia / NOVARTIS) 21-10-2021**
- Prior art. D1: EMA Paediatric investigation plan
- 6.6 The clinical study [...] involves the use of the following three nilotinib formulations [...]:
- **(b) mixture of the content of a Tasigna capsule with apple sauce ("nilotinib/apple sauce formulation")**
- 6.7 It is undisputed that the nilotinib/apple sauce formulation is a dispersion of nilotinib in apple sauce in accordance with claim 1.
- This formulation is to be administered to healthy adult volunteers instead of CML patients (see table of section C). Hence, the disclosure of study 1 of the PIP of document D1 **does not anticipate the subject-matter of claim 1**.

- **Obviousness**
- D1 – Closest prior art.
- 7.2 The claimed subject-matter differs from D1 in that the claimed dispersion of nilotinib in apple sauce **is administered to patients with CML instead of healthy volunteers.**
- 7.52 However, as set out under point 7.21 above, **whether the announcement of a clinical study in a prior-art disclosure leads to a reasonable expectation of success depends on the facts and circumstances of the case**. In the case at issue, the respondents did not explain why the clinicians of the PIP applicant - **despite being aware of the known unpredictability of the food effect of apple sauce on nilotinib - would still have had a reasonable expectation that the nilotinib/apple sauce formulation would exhibit an oral nilotinib bioavailability in healthy human adults comparable to that of the Tasigna capsule formulation**. Absent any such explanation, the respondents' argument cannot convince the board.

Carve-out

2.7. Can I submit my generic/hybrid application even if some parts of the product information of the reference medicinal product are covered by usage patents?

Companies use patent law to obtain further protection for an innovative medicine in some or all Member States. This protection applies e.g. to new uses of the medicine, such as new indications and pharmaceutical forms. While this 'usage patent' protection is in place, a generic/hybrid medicine cannot be marketed for the protected indication or pharmaceutical form, even if the period of data and market exclusivity of the reference medicine has expired.

Applications for marketing authorisation for generic/hybrid medicinal products can however be submitted and authorised even if some parts of the product information of the reference medicinal product are covered by patent law.

Article 11 of Directive 2001/83/EC and Article 3.3(b) of Regulation No 726/2004 allow applicants/Marketing Authorisation Holders to exclude from their proposed product information those parts of the SPC of the reference medicinal product referring to indications or dosage forms still covered by patent law.

2.9. If a therapeutic indication is covered by patent law which sections of the SPC can be deleted in connection with the patented indication?

Information directly related to the patented indication can be deleted from sections 4.1. therapeutic indications, 4.2. posology and method administration and 5.1. pharmacodynamic properties of the summary of product characteristics.

For public health reasons, safety related information in sections 4.3 to 4.8. of the SPC should be maintained.

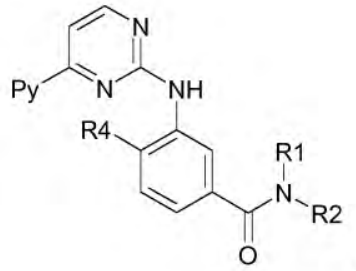
If the applicant wishes to omit other information than the one mentioned above directly related to the patented indication, this must be properly justified.

https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/generic-hybrid-medicines/generic-hybrid-applications

EP2501384 B1

Claims

1. A pyrimidylaminobenzamide of formula (I)



(I),

wherein

Py denotes 3-pyridyl,
R_1 represents hydrogen,
R_2 represents 5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)-phenyl; and
R_4 represents methyl;
or a pharmaceutically acceptable salt thereof, for use in the treatment of chronic myeloid leukemia (CML), wherein the compound of formula (I) or a pharmaceutically acceptable salt thereof and, optionally, pharmaceutically acceptable carriers, is orally administered dispersed in apple sauce.

Tasigna

4.2. Posología y forma de administración

Forma de administración

Tasigna debe tomarse dos veces al día con aproximadamente unas 12 horas entre las dos administraciones y no debe tomarse junto con la comida. Las cápsulas duras deben tragarse enteras, con agua. No se debe ingerir alimentos durante las dos horas previas a la administración de la dosis ni durante, al menos, una hora después.

Para pacientes que no puedan tragar las cápsulas duras, el contenido de cada cápsula dura puede dispersarse en una cucharadita de compota de manzana (puré de manzana) y debe tomarse inmediatamente. No debe utilizarse más de una cucharadita de compota de manzana ni ningún otro alimento aparte de compota de manzana (ver secciones 4.4 y 5.2).

4.4. Advertencias y precauciones especiales de empleo

Efecto de los alimentos

La biodisponibilidad de nilotinib aumenta con los alimentos. Tasigna no se debe tomar junto con la comida (ver las secciones 4.2 y 4.5) sino que se debe tomar 2 horas después de una comida. No se debe ingerir ningún alimento durante al menos una hora después de tomar el medicamento. Debe evitarse tomar zumo de pomelo y otros alimentos que se sabe que son inhibidores de CYP3A4. Para pacientes que no puedan tragar las cápsulas duras, el contenido de cada cápsula dura puede dispersarse en una cucharadita de compota de manzana y debe tomarse inmediatamente. No debe utilizarse más de una cucharadita de compota de manzana ni otro alimento aparte de la compota de manzana (ver sección 5.2).

Nilotinib Genérico

4.2. Posología y forma de administración

Forma de administración

Nilotinib debe tomarse dos veces al día con aproximadamente unas 12 horas entre las dos administraciones y no debe tomarse junto con la comida. Las cápsulas duras deben tragarse enteras, con agua. No se debe ingerir alimentos durante las dos horas previas a la administración de la dosis ni durante, al menos, una hora después.

Para pacientes con dificultad para tragar, incluyendo pacientes pediátricos que no puedan tragar las cápsulas duras, **deben utilizar otros medicamentos con nilotinib** en lugar de Nilotinib

4.4. Advertencias y precauciones especiales de empleo

Efecto de los alimentos

La biodisponibilidad de nilotinib aumenta con los alimentos. Nilotinib no se debe tomar junto con la comida (ver las secciones 4.2 y 4.5) sino que se debe tomar 2 horas después de una comida. No se debe ingerir ningún alimento durante al menos una hora después de tomar el medicamento. Debe evitarse tomar zumo de pomelo y otros alimentos que se sabe que son inhibidores de CYP3A4.

Para pacientes con dificultad para tragar, incluyendo pacientes pediátricos que no puedan tragar las cápsulas duras, **deben utilizar otros medicamentos con nilotinib** en lugar de Nilotinit

Obviousness – Expectation of success

- **T 1941/21 (TAUROURSODEOXYCHOLIC ACID (TUDCA) FOR USE IN THE TREATMENT OF NEURODEGENERATIVE DISORDERS/Bruschettini S.r.l.) 05-06-2024**

1.5 Clinical trials are usually initiated on the basis of encouraging results from preclinical experiments. Thus, the announcement of a phase II clinical trial protocol for a particular therapeutic agent and a disease **may provide the skilled person with a reasonable expectation of success. Such reasonable expectation of success is, however, to be denied in a situation where a skilled person would have been discouraged from carrying out the clinical trials**, such as when the state of the art provides the skilled person with reasons for not pursuing the solution envisaged in the clinical trial or provides the skilled person with an expectation of failure. **Consequently, "a reasonable expectation of success" is linked with the specific circumstances of the case and requires a case-by-case evaluation of all the facts at hand at the priority date of the contested patent.**

- **T 1123/16 (Eosinophilic bronchitis/GLAXO) 13-04-2021**
- 4. Document **D1 describes a phase II clinical** trial entitled "The prednisone-sparing effect of anti-IL-5 antibody (SB-240563)".
- 5. Like the opposition division and the parties, the board considers the disclosure of this phase II clinical trial to constitute an appropriate starting point for assessing whether the claimed subject-matter involves an inventive step. Indeed, it concerns the treatment of patients with the same medical condition (i.e. steroid-dependent EB) using the same substance (i.e. a humanised antibody to IL-5) with the same objective (i.e. a reduction in prednisone administration).

11. In the board's view, **the disclosure of a clinical trial with the same substance for the treatment of the same medical condition,** [...], **provides the skilled person with an expectation of success for the treatment** (see also decision T 2506/12, Reasons 3.10 and decision T 239/16, Reasons 6.5). It was therefore obvious for the skilled person to conduct the treatment in document D1 with a reasonable expectation of success, unless the state of the art provided the skilled person with reasons for not pursuing the solution envisaged in the clinical trial or, in other words, **unless the state of the art provided the skilled person with an expectation of failure** (see also decision T 2506/12, Reasons 3.11 and decision T 239/16, Reasons 6.5, second paragraph).

Obviousness – Expectation of success

- **T 2963/19 (Liposomal irinotecan/IPSEN) 18-03-2022**
- D15b CPA – Phase III study
- 4.3.1 As explained in document D23 (see D23, page 5, section 27), the development of therapy of gemcitabine refractory pancreatic cancer represents a particular challenge taking account of the poor prognosis and low success rates of clinical trials (see documents D23A and D23B). Documents D37 and D38 confirm in this context that **the approval of a clinical study depends on the assessment of the foreseeable risks in relation to the anticipated benefit in terms of relevance of the findings, which does not necessarily imply an expected positive outcome** and does not represent a scientific advice on the development programme of the investigational product tested ([...]). **The Board is therefore not convinced that the mere fact that document D15b reports the testing of the dosage regimen in a Phase 3 clinical trial already by itself provided the skilled person with a reasonable expectation that the treatment under investigation would be safe and effective**. [...]
- 4.3.2 **However, the presentation of the triple dosage regimen in document D15b is not to be considered by itself, because the publication of document D15b was preceded by reports of beneficial triple treatment** of gemcitabine refractory pancreatic cancer patients involving non-liposomal irinotecan with 5-FU and leucovorin, the FOLFIRI regimen, in Phase 2 studies (see documents D2-D6) as well as the report of benefits from treatment of such patients with liposomal irinotecan with or without 5-FU and leucovorin in Phase 1 investigations (see documents D12 and D13).
- In this context the Board takes the view that in as far as the patent proposes the claimed dosage regimen to be safe and effective **in view of considerations based on information which was essentially already available**, the same considerations apply in the assessment whether following the presentation of the clinical trial in document D15b **a positive outcome for the described triple therapy could reasonably be expected.**

Obviousness - Expectation of success vs hope to succeed

- T209/22 (Umeclidinium, Vilanterol) 21/03/2024
- 6.20 [...] Still according to the appellants, the person skilled in the art would have derived a reasonable expectation of success for the claimed combination product from the combined disclosures of D3 and D5, which at least disclosed favourable preclinical data for both compounds. While success was never guaranteed in pharmaceutical development, positive results at one stage of clinical testing would necessarily have given the skilled person a reasonable expectation of success for the next stage absent any prejudice or disincentive to proceed.
- 6.21 The board is not convinced by the appellants' arguments, for the following reasons.
- 6.21.1 The question to be answered with regard to obviousness is whether, at the effective date, there was a direct route that would have led to the development of the claimed combination with a reasonable expectation of success.
- 6.21.2 At the relevant date, both vilanterol and umeclidinium were still in early stages of their pharmaceutical development. **While the basis for proceeding with the pharmaceutical development of a compound is favourable preclinical data, this does not necessarily give rise to a well-founded expectation of success,** even less in the case of a combination product when neither combination partner has, as yet, progressed to the clinical stage of development.
- 6.21.5 The board is, therefore, of the view that the information derivable from D3 and D5 might, at best, have provided the person skilled in the art with the **hope to succeed**, but that this **does not amount to a reasonable expectation of success**. Neither agent had been established for the treatment of patients. Each agent's efficacy and safety as well as the duration of action was still to be established. Thus, a high level of uncertainty regarding the potential for successful dual therapy with both agents would have been involved.

Expectation of success – approval for clinical trials not sufficient

- **T 1437/21 (Empagliflozin/BOEHRINGER INGELHEIM) 09-02-2024**
- 4.3.1 The prior disclosure that an investigational product for use in the treatment of a particular condition is undergoing clinical trials may in accordance with established jurisprudence preclude that a subsequently claimed invention involving this product for use in the treatment of that specific condition is considered to involve an inventive step, even where the results of the trial have not been made available to the public (see T 2506/12, reasons 3.10 and 3.15; T 239/16, reasons 6.5 and 6.6; T 1123/16, reasons 11; T 2963/19, reasons 4.3.1).

- However, as explained in T 2963/19, **the approval of a clinical study depends on the assessment of the foreseeable risks to the participants in relation to the anticipated benefit in terms of the relevance of the findings. The approval of a clinical trial does therefore not, by way of a heuristic, imply an expected positive outcome of the treatment.** Furthermore, as underlined in point 4.3.1 of T 2963/19 by reference to the "Communication from the Commission 2010/c 82/01", the authorisation of a clinical trial does not represent a scientific advice on the development programme of the investigational product tested. The considerations in T 2506/12, T 239/16 and T 1123/16 regarding the expectation of success in view of the disclosure of clinical trials are, as in T 2963/19, evidently linked to the further circumstances of the cases decided therein, in particular the nature of the investigational product and of the condition to be treated and the absence of information suggestive of failure of the trial.
- The crucial issue in the assessment of inventive step starting from the teaching in documents D22/D29, in particular the reported results from Study 1245.36, thus remains whether in view of the available information in the prior art, including the information in documents D22/D29, the skilled person had a reasonable expectation that empagliflozin would be effective in treatment of diabetic patients having moderate renal impairment.

Expectation of success

- **T-2506/12(PEGYLATED LIPOSOMAL DOXORUBICIN/Pharmamar) 04-10-2016**

- 3.12.1 The patent proprietors argued in this respect that the success rate in oncology trials was generally very low, at about 5% (as disclosed in the expert declaration D50: page 2), and it was therefore surprising that the studies they had conducted showed that the combination treatment could be carried out successfully at safe dosage levels.
- 3.12.2 The board observes that the statement in document D50 cited by the patent proprietors regarding low success rates of oncology drugs refers to tests carried out on individual new drugs rather than to combination treatments with known anti-cancer drugs.
- In any case, the patent proprietors' argument cannot succeed, since the general consideration that any clinical trial might fail does not throw additional doubt on the particular combination treatment envisaged and is therefore not sufficient to establish an inventive step. **The reason why clinical studies are carried out at all is that they have uncertain outcomes. But they are routine tests and the fact that their outcome is uncertain does not in itself turn their results into an invention,**

- **T-96/20 (Treatment of myasthenia gravis/ALEXION) 22-04-2021**

- 7. Document D4 discloses a protocol of a safety and efficacy clinical trial of eculizumab in patients with refractory generalised MG. The results of this clinical trial are not disclosed. [...]
- 9. Thus, **the board considers that the announcement of a detailed safety and efficacy clinical trial protocol for a particular therapeutic and disease provided the skilled person with a reasonable expectation of the success of this particular therapeutic, unless there was evidence to the contrary in the state of the art**. In the case in hand, the board holds that no such evidence to the contrary has been brought forward by the appellant.
- 10. The appellant has submitted that the disclosure of the clinical trial protocol of document D4 constituted, at most, an invitation for the skilled person to try the treatment of MG with eculizumab. Indeed, MG was particularly difficult to treat in humans, as was evident from document D7 which disclosed that no therapy for generalised MG had been approved in more than 60 years.
- 11. **The board however fails to see how the mere fact that no MG therapy has been approved for a long time would have diminished the expectation of success for the specific clinical trial disclosed in document D4**.

Expectation of success. Routine testing

- **T 0237/15 (SAHA/Sloan) 28-01-2019**

4. Inventive step

The patent in suit relates to the use of histone deacetylase (HDAC) inhibitors, especially suberoylanilide hydroxamic acid (SAHA), for inducing terminal differentiation of neoplastic cells and thereby aiding in the treatment of tumours in patients. The invention aims to provide suitable dosages and dosing schedules of these compounds and develop formulations, preferably oral formulations, which give rise to steady, therapeutically effective blood levels of the active compounds over an extended period of time (e.g. paragraphs [0001] and [0017]).

4.6.1 The step from pre-clinical animal studies to clinical studies involving human patients is an unavoidable step when developing a new medicament. In the present case, the skilled person, aware of the complete disclosure of document (2), would take this step with a reasonable expectation of success. This expectation of success is based on the teaching of page 200, right-hand column, first paragraph, which discloses that SAHA was successfully used in the treatment of solid tumours in human patients (administered intravenously). Consequently, a skilled person, in the knowledge that SAHA is bioavailable when given orally in animal studies and having been given the information that SAHA achieves effective treatment in humans when introduced directly into the blood stream, would expect an effective treatment also for oral administration in human patients.

The determination of the optimum dosage regimen required to achieve the therapeutic effect in the (human) patient is a matter of routine experimentation for the skilled person. Such routine tests do not require inventive skill and can consequently not establish an inventive step.

Expectation of success. Routine testing

- **T 0799/16 Methods of Using Sustained Release Aminopyridine Compositions (Acorda) 04-09-2019**

- Routine testing
- 6.7 The respondents contended that determining the appropriate dosage of a known drug, let alone merely confirming the efficacy of the 10 mg bid dosage regime envisaged in C27, would not have required inventive skill, for the following reasons (points 6.7.1 to 6.7.4).
- 6.7.1 The person skilled in the art would have routinely sought to identify the lowest effective dose in order to minimise the risk of adverse effects.

- 6.8.2 However, presumably due to the high intra-patient and inter-patient variability of disease symptoms (here walking speed) in the case of MS and the relatively high proportion of non-responders to 4-aminopyridine, **it actually turned out to be exceptionally difficult in this case to provide the required proof of efficacy** – [...].
- (e) These data support the appellant's argument that it was not straightforward, even with data obtained in an adequately powered dose-finding study, to demonstrate and compare the efficacy of the three dosage regimes. Using conventional methods, the person skilled in the art would have thus failed to appreciate the utility of the 10 mg bid dosage regime.
- 6.8.4 **Only by developing, post hoc, a new statistical technique** (the "responder analysis") [...] was the appellant able to prove that the 10 mg bid dosage regime has efficacy in increasing walking speed
- 6.8.6 Thus, the respondents' arguments failed to convince the board that the person skilled in the art would have been able, without difficulty and without resorting to the novel responder analysis based on consistency of response, to confirm the efficacy of the 10 mg bid dosage regime.
- 6.9 As a consequence, the subject-matter of independent claims 1 and 5 would not have been obvious starting from the disclosure of document C27.

G2/21- Headnote

- I. Evidence submitted by a patent applicant or proprietor to prove a technical effect relied upon for acknowledgement of inventive step of the claimed subject-matter may not be disregarded solely on the ground that such evidence, on which the effect rests, had not been public before the filing date of the patent in suit and was filed after that date.

- II. A patent applicant or proprietor may rely upon a technical effect for inventive step if the skilled person, having the common general knowledge in mind, and based on the application as originally filed, would derive said effect as being encompassed by the technical teaching and embodied by the same originally disclosed invention.

G2/21 – Sufficiency of disclosure

- Considerations concerning the jurisprudence regarding **sufficiency of disclosure**
- 73 As noted in points 11 and 12 above, the referred questions do not require an answer to the issue of sufficiency of disclosure and Article 83 EPC. However, as the terminological notion of plausibility relied upon by the referring board in questions 2 and 3 of the referral and the reasons for it is mainly to be found in the case law of the boards of appeal with regard to the patentability requirement of sufficiency of disclosure, the Enlarged Board accepts the appropriateness of a comparative analysis and comparative considerations in this regard.
- 74 While the issues of sufficiency of disclosure (Article 83 EPC) and inventive step (Article 56 EPC) and their assessment are clearly to be treated separately and on their own, as correctly pointed out by the referring board in point 13.3.1 of the Reasons of the referring decision, the Enlarged Board is aware of the case law in particular concerning second medical use claims where the notion of "plausibility" has been used. For such claims, the issue of reliance on post-published evidence for a purported technical effect arises in particular in the context of sufficiency of disclosure.
- Indeed, a **technical effect, which in the case of for example a second medical use claim is usually a therapeutic effect, is a feature of the claim**, so that the issue of whether it has been shown that this effect is achieved is a question of sufficiency of disclosure under Article 83 EPC.
- Hence, because the subject-matter of second medical use claims is commonly limited to a known therapeutic agent for use in a new therapeutic application, **it is necessary that the patent at the date of its filing renders it credible that the known therapeutic agent, i.e. the product, is suitable for the claimed therapeutic application**. The Enlarged Board explained the legal and historical background to the patentability of further medical uses in its decision G 2/08.

G2/21 – Sufficiency of disclosure

- 77 The reasoned findings of the boards of appeal in the decisions referred to above make clear that the scope of reliance on post published evidence is much narrower under sufficiency of disclosure (Article 83 EPC) compared to the situation under inventive step (Article 56 EPC). In order to meet the requirement that the disclosure of the invention be sufficiently clear and complete for it to be carried out by the person skilled in the art, **the proof of a claimed therapeutic effect has to be provided in the application as filed, in particular if, in the absence of experimental data in the application as filed, it would not be credible to the skilled person that the therapeutic effect is achieved. A lack in this respect cannot be remedied by post-published evidence.**

Rivaroxaban (Xarelto®, Bayer)

Rivaroxaban (Xarelto®, Bayer)

EP1261606 – compound patent. PED SPC 01/04/2024
EP1845961 – Dosage. Exp 19/01/2026
Grant: 22/04/2015
Opposition:
- Feb 2018

Appeal
- OP 27/10/2021
- Decision 16/05/2022

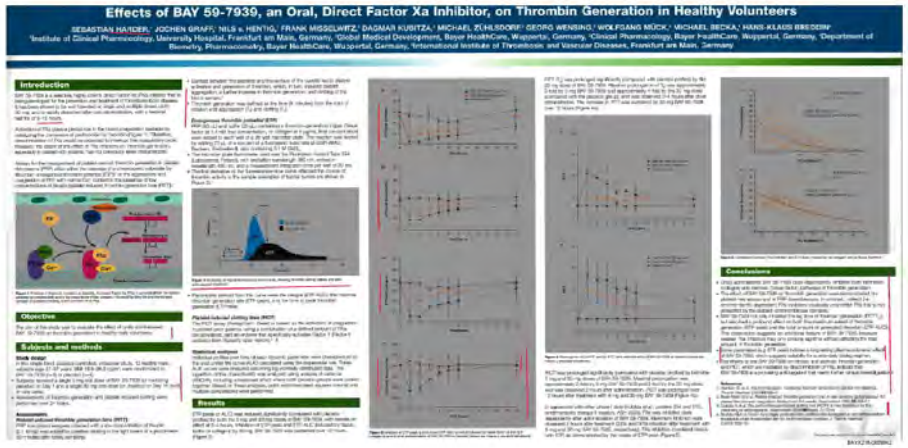
Prior Art – Phase I clinical trials in healthy volunteers
- Kubitza Phase I- posters and abstracts
- Harder Study – posters and abstracts

EP1845961

Claims

1. The use of a rapid-release tablet of the compound 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide for the manufacture of a medicament for the treatment of a thromboembolic disorder administered no more than once daily for at least five consecutive days, wherein said compound has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

2. The use as claimed in Claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.


Effects of BAY 59-7939, an Oral, Direct Factor Xa Inhibitor, on Thrombin Generation in Healthy Volunteers

Rivaroxaban (Xarelto®, Bayer)

T1732/18

5.9.1 The mere assumption that tablets may well have been used in the study of D2/D11 does not meet the standard of direct and unambiguous disclosure in the prior art.

5.9.2 The clinical study described in D2/D11 was a preliminary phase I study carried out with healthy subjects. It was not designed to test the efficacy and safety of a specific dosage regimen in subjects requiring prophylactic or therapeutic anticoagulant treatment.

Clinical efficacy is only determined in phase II and phase III studies. A phase I study limited to the initial testing of a range of doses on healthy subjects to obtain certain base parameters cannot establish the clinical efficacy of a dosage regimen for treating patients with pathology.

9.20 The issue to be decided under obviousness is whether the skilled person would have had an incentive and reasonable expectation of clinical success regarding the specific regimen defined in claim 1, i.e. once-daily dosing of rapid-release rivaroxaban for at least five consecutive days, in patients, i.e. subjects at heightened risk for thromboembolism.

9.22. At the effective date of the patent in suit, it had not been shown that rivaroxaban was safe and effective in patients, i.e. subjects requiring therapeutic or prophylactic anticoagulant treatment (see also point 5.9.2 above). Neither had this been shown for the class of direct-acting oral factor Xa inhibitors in general.

9.22.2 **Due to ethical and safety concerns, the person skilled in the art would have adopted a cautious attitude regarding the set-up of first-time dose-ranging clinical studies of a novel anticoagulant in patients since the risk of both bleeding and thrombosis was expected to be high**.
Participants in phase I anticoagulant studies are selected to exclude susceptibilities to and potential causes of bleeding. The fact that no bleeding complications had been observed with rivaroxaban in healthy volunteers did not permit drawing the conclusion that the drug would be safe in patients with pathology.

Rivaroxaban (Xarelto®, Bayer)

T1732/18

9.22.4 **In summary, the serious concerns about safety in the case of a new anticoagulant did not warrant a "try-and-see" attitude for the dosage regimen, and the known, relatively short, half-life of rivaroxaban would not have supported an expectation of success with regard to once-daily dosing of rapid-release rivaroxaban.**

9.24.4 All of these post-published documents contain statements made by their authors with hindsight, after the clinical success of rivaroxaban had been proven. In this context, it appeared plausible that the thrombin generation data from the study of D15/D17 was consistent with the general concept of once-daily administration. As these documents (and the larger context they were based on) were not available to the person skilled in the art before the priority date, it is not permissible to use them to interpret the statements and data provided in the abstracts D15/D17.

9.24.5 For these reasons, the skilled person could not have derived a teaching or expectation of success from the data reported in D15/D17 that would have provided them with the specific motivation to explore once-daily dosing of a rapid-release form of rivaroxaban in subsequent phase II studies in patients.

Rivaroxaban (Xarelto®, Bayer) [2024] EWHC 796 (Pat) 12/04/2024

240. The key criterion in the assessment of inventive step in the present case, at least as it would be in the real world, is **whether the skilled team would have sought the approval of the relevant external ethics committee for a phase II study including a once daily regimen, based on the phase I** data contained in Harder and the Kubitza posters, and whether the committee would have given its approval. The difficulty is that there was no direct evidence as to how such a committee would go about its decision, in particular on a scale between complete intolerance of anything with a chance of causing harm to a patient down to something very much less stringent than that.

243. I think two matters which were in evidence provided an idea of what this would mean. First, data from a phase I trial can never be predictive of what may happen in a phase II trial. In the case of a study involving a drug for treating thromboembolic disorders a phase I trial of the type disclosed in Harder and the Kubitza posters can only test anticoagulant activity ex vivo. That is not the same thing as, and need not necessarily correlate closely with, antithrombotic activity. The results of the trial do not strictly prove anything with regard to antithrombotic activity. A highly risk averse approach would mean that phase II trials would seldom if ever be conducted. That would not be in the public interest and is clearly not the approach adopted in the real world.

248. As I have found**, the skilled team in this case would have had been aware of the clinical advantages of a once daily tablet and the financial potential of marketing the first available once daily tablet** for the treatment and prevention of thromboembolic disorders should that prove possible. It would certainly have been secondary to their safety concerns. But even if that awareness would not have been at the forefront of the skilled team's thinking before reading the prior art, where the prior art raised the possibility of a phase II trial including a once daily regimen, that possibility would have been given serious consideration.

257. Therefore I think that the combined evidence of Professors Hirsh and Wilkins was correct in taking the position that the skilled team would have believed that **conducting a phase II trial which included a 30 mg once daily regimen would not have caused an unacceptable level of risk**.

258. It follows that the skilled team would have found it obvious to conduct a phase II trial which included such a regimen.

Rivaroxaban (Xarelto®, Bayer)

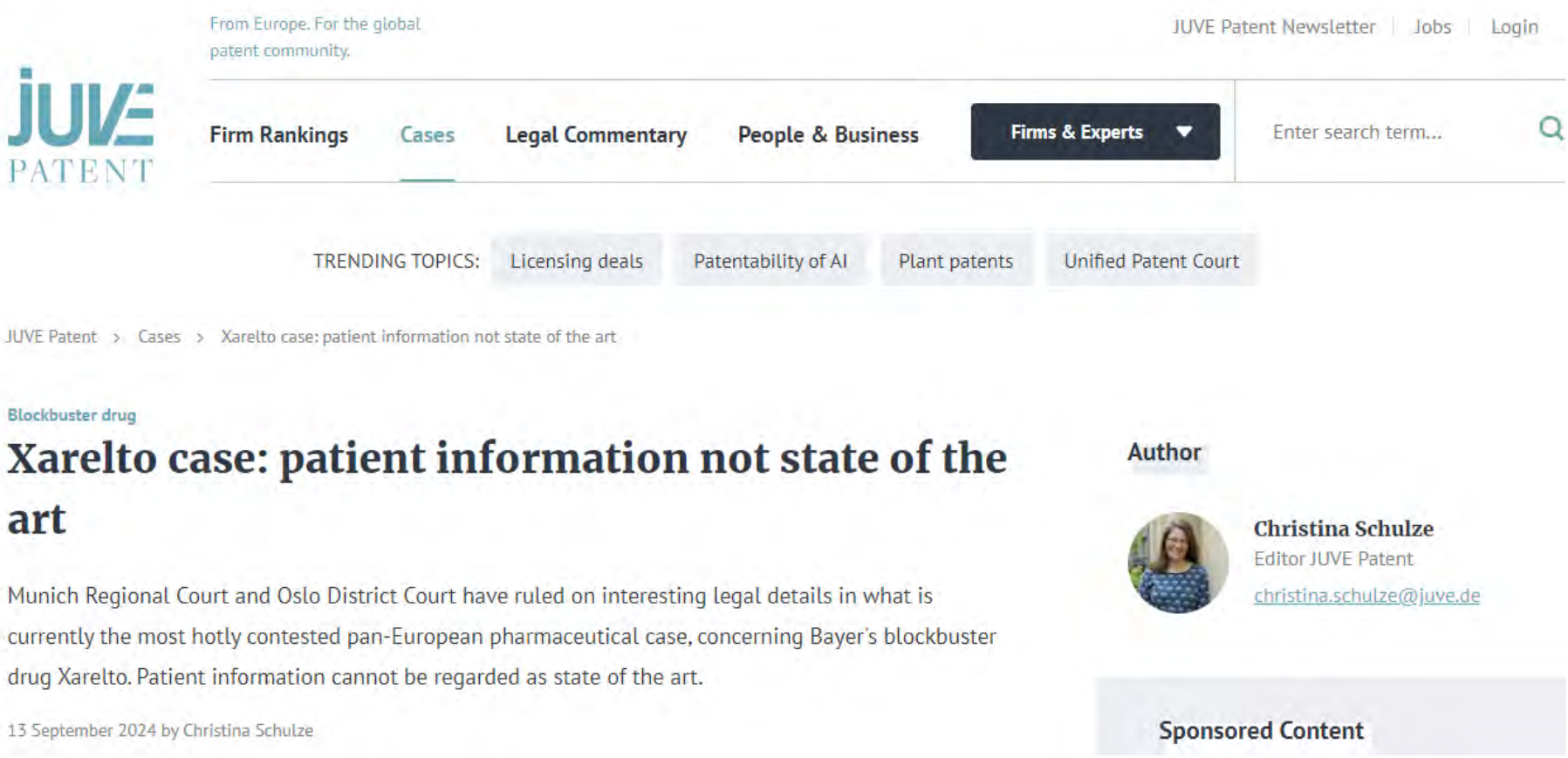
EPO T1732/18

9.26.2 Also, the skilled person setting up a phase II clinical trial of a new anticoagulant was not in a routine "try-and-see" situation. Without a reasonable expectation of success with regard to clinical efficacy and safety, the mere wish for patient convenience would not have been sufficient as an incentive for testing an od regimen of a rapid-release form of the drug.

UK Court

248. As I have found, the skilled team in this case would have had been aware of the clinical advantages of a once daily tablet and the financial potential of marketing the first available once daily tablet for the treatment and prevention of thromboembolic disorders should that prove possible. It would certainly have been secondary to their safety concerns. But even if that awareness would not have been at the forefront of the skilled team's thinking before reading the prior art, where the prior art raised the possibility of a phase II trial including a once daily regimen, that possibility would have been given serious consideration.

Rivaroxaban (Xarelto®, Bayer)... Continuation



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JUVE Patent > Cases > Xarelto case: patient information not state of the art

Blockbuster drug

Xarelto case: patient information not state of the art

Munich Regional Court and Oslo District Court have ruled on interesting legal details in what is currently the most hotly contested pan-European pharmaceutical case, concerning Bayer's blockbuster drug Xarelto. Patient information cannot be regarded as state of the art.

13 September 2024 by Christina Schulze

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https://www.juve-patent.com/cases/bayer-xarelto-case-patient-information-not-state-of-the-art/

Rivaroxaban (Xarelto®, Bayer)... Continuation

The Einstein DVT Study:

- December 2004 – December 2005
- 543 patients in 79 different locations in many countries
- Phase II

OSLO DISTRICT COURT

[redacted]

Handed down:	02.09.2024 in Oslo District Court, courthouse
Case no.:	24-093228TVI-TOSL/08 and 24-104702TVI-TOSI/08
Judge:	District Court Judge Helge Johannessen
The case	Temporary injunction patent

The study was conducted in accordance with the Declaration of Helsinki.

In the case, patient consent forms, information letters and/or patient brochures from before the priority date of 31 January 2005 have been submitted. Central to the case is whether these were generally known and whether the invention could be read out of the papers and exercised and, if so, whether the documents prevent inventive step. Here is an overview of the documents that are relevant related to the Einstein DVT study.

Traducción automática Google translate

Rivaroxaban (Xarelto®, Bayer) – Oslo District Court

The question of whether the information provided in the patient information forms, leaflets and consent forms, related to prior phase II studies is known, i.e. generally available before priority date.

- phase II prior to the priority date. This applies to Einstein DVT, ODIXa-OD-HIP and ODIXa-HIP1.
- results of these studies, also from 2002- 2003, not known at the time of priority, but there were certain documents, examples of which have been documented in this case. Reference is made to the review of the documents above.
- Patients not bound to confidentiality – can discuss with doctors and family etc.
- Large number of patients enrolled in many different locations.
- Patients knew number of daily doses and the intended indication.
- Other people involved, except patients, bound to confidentiality.
- Essential element of the invention is that the regime is effective and secure.
- Indirectly indicated due to ethical committee approval.
- Information regarded as not publicly available.

Cabazitaxel (Jevtana®, Sanofi)

Cabazitaxel (Jevtana®, Sanofi)

EP081779 – 1996. Compound patent
Marketing Authorisation;17/03/2011
Generic Entry possible: March 2021

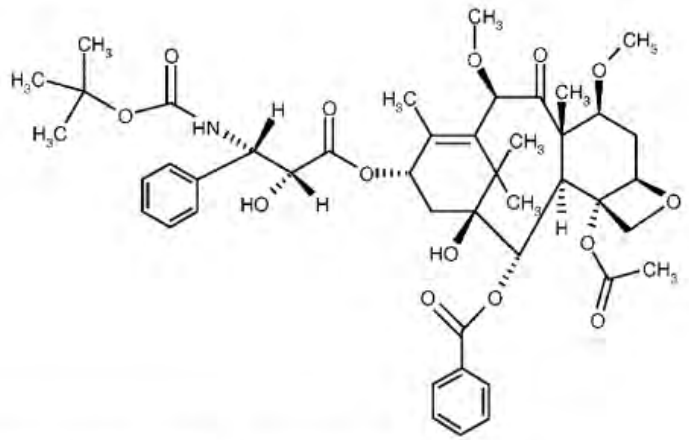
EP2493466 – 27/10/2010 – Co-administration – Drug/Drug interaction
Patent granted: 10/03/2021
Opposition filed. 10/03/2021

Prior art – TROPIC clinical trial (Phase III)
No prior Phase II

EP2493466

Claims

1. Compound of formula



which may be in base form or in the form of a hydrate or a solvate,
in combination with prednisone or prednisolone,
for use in treating prostate cancer,
in patients with castration resistant metastatic prostate cancer who have been previously treated with docetaxel based regimen and have prostate cancer that progressed during or after said treatment.

Cabazitaxel (Jevtana®, Sanofi)

EPO – Opposition Division

6.8 The first consideration concerns the explicit teaching provided by the disclosure of an ongoing clinical trial and the view is taken that the document lacks any anticipation of a preliminary positive or negative outcome of the reported trial (see reasons 3.4[1]). The same conclusion is to be drawn in the present case, since, even though concerned with a phase 3 trial, neither of the cited documents D1, D2 or D6 provides any indications as to interim results or the final outcome thereof. Thus**, the mere report of the phase 3 clinical study being under way fails to provide explicit disclosure of the results thereof**.

[1]T158/96

Cabazitaxel (Jevtana®, Sanofi)

EPO (Opposition division) – Prior use

6.14 In Os' view the protocol of the TROPIC trial as disclosed in D1, D2 and D6, since it was open-label and, thus, rendered accessible to patients the medication, was evidence of a prior use resulting in the claimed therapeutic effect as shown by the positive trial outcome disclosed in the patent.

6.15 It appears undisputed that on **an individual basis patients enrolled in the TROPIC trial were informed about the drug given** and their disease parameters such as PSA levels or tumour progression as determined by CT or MRI. It appears accepted as well that by contrast to medical staff involved in the trial **patients were not bound by a confidentiality agreement** that would have prevented them from sharing these clinical parameters with their relatives.

6.16 Nevertheless, it cannot be assumed that the patients were in a position to share the knowledge about their own clinical state to such extent that a single person could gain insight into the clinical parameters of all study participants. **The alleged public prior use, therefore, cannot have occurred across the entire group of enrolled participants, since the collective data were not part of the public domain**. If at all it could have taken place in individual patients, insofar as those were allowed to lay open information about their clinical progress.

Cabazitaxel (Jevtana®, Sanofi)

EPO (Opposition division) – Expectation of success – CPA: TROPIC Phase III Trial

7.16 For the present case this analysis requires the consideration of all the circumstances leading to and accompanying the initiation of the phase 3 TROPIC trial as disclosed in D1 or D2. It is evident that for an evaluation of expectation of success only evidence that was available to the skilled person before the effective date of the patent can be taken into consideration.

7.17 The TROPIC trial **did not follow the usual clinical upscaling**, since it was not preceded by a phase 2 clinical study for the same therapeutic indication, i.e. mCRPC.

7.22 Also regarded as **a positive pointer** was the fact that at the effective date of the patent the TROPIC trial with an expected reporting date of May 2010 (D2: page 3, table under "Efficacy and Safety") **was already nearing completion and had not been cancelled** despite a futility analysis that had been performed after 225 patients had a progression event (D15: page 1151, left hand column, 2nd full paragraph). The above observations show no more than the absence of major incidents that could have provoked a preterm discontinuation of the trial. Such incidents are not limited to negative events including unforeseen toxicities or complete absence of therapeutic effect, but can also reside in the occurrence of an unexpected positive treatment response that in case of a continuation would disadvantage the comparison group. **Thus, the fact that the trial was not discontinued cannot be rated as a pointer towards a successful outcome thereof.**

Cabazitaxel (Jevtana®, Sanofi)

7.24 The above allegedly **positive pointers** towards a successful treatment of the claimed HRPC patients progressing after DTX therapy are to be **balanced against the therapeutic options available** for this patient group at the effective date of the patent.

7.31 The paucity of available treatment options and the clinical failure of various drug candidates with comparable positive preclinical and early clinical results clearly demonstrates that **the claimed group of patients is particularly difficult to treat**. Despite this dissuasion and as shown with the data disclosed in the patent the claimed treatment with CTX provided a therapeutic effect that is superior to the established standard therapy with MXT. **This positive outcome of the phase 3 TROPIC trial, therefore, could not be forecast with sufficient expectation of success on the basis of the mere protocol disclosed in D1 or D2**. It follows that the follow-on CTX therapy as claimed is not rendered obvious, when departing from D1 or D2 as closest prior art.

Cabazitaxel (Jevtana®, Sanofi)

Tribunal Judiciare de Paris RG No. 21/06416. 6/09/2024

64. Il en résulte que la question de la nouveauté de la revendication 1 dépend ici de celle du caractère crédible de l'effet thérapeutique revendiqué tel qu'il est décrit dans chaque document invoqué contre sa nouveauté, à sa date respective (ou, autrement dit, si chaque document reflète cet effet pour la personne du métier).

65. À cet égard, les **documents cités ne font que décrire l'essai Tropic, de phase III**, en ce qu'il compare l'effet du cabazitaxel (avec prednisone) à celui de la mitoxantrone (avec prednisone) dans l'application thérapeutique revendiquée, **mais sans révéler aucune donnée clinique ou théorique sur les chances de succès de ce traitement**. Le fait qu'une application fasse l'objet d'un essai de phase III est certes un indice très important mais il ne s'agit en définitive que d'une information administrative et non d'une donnée technique en soi, qui ne peut donc pas suffire à prouver la crédibilité de l'effet thérapeutique, sauf à déléguer le contrôle de la validité des brevets aux organisateurs d'essais cliniques. Il ne permet donc pas de conclure, au stade de la nouveauté (qui interdit de prendre en compte d'autres éléments de l'art antérieur), à la divulgation de l'invention dans tous ses éléments.

https://www.courdecassation.fr/decision/66db4812f06e1567cdda7152?search_api_fulltext=jevtana&op=Rechercher&date_du=&date_au=&judilibre_juridiction=all&previousdecisionpage=&previousdecisionindex=&nextdecisionpage=&nextdecisionindex=

Cabazitaxel (Jevtana®, Sanofi)

Tribunal Judiciare de Paris RG No. 21/06416. 6/09/2024

114. Enfin, **l'essai Tropic était en cours depuis 3 ans à la date de priorité sans avoir été arrêté, ce qui indiquait à tout le moins que le promoteur de cet essai ne l'avait pas encore jugé décevant**. Le fait que d'autres essais de phase III sur des taxanes et notamment celui sur le cabazitxel dans le cancer du sein avaient été abandonnés (document Sanofi 2008) ne saurait remettre en cause de manière générale les éléments prometteurs décrits ci-dessus. Ces abandons pouvaient être diversement interprétés [...], sans conduire la personne du métier à modifier défavorablement l'enseignement des données antérieures corroborées par le lancement puis le maintien de l'essai Tropic.

115. À cet égard, les données statistiques invoquées par les sociétés Sanofi et disponibles à la date de priorité (document [E]), selon lesquelles les essais de phase III réussissent dans 41% des cas en oncologie, ne font que confirmer le fait que tout essai est incertain tout en indiquant qu'à ce state avancé du développement les chances de succès moyennes approchent de la moitié. En réalité, le même document précise que les chances de succès varient beaucoup selon les cas et il enseigne en particulier que le succès est plus probable pour les composés dont le mécanisme d'action est déjà mis en oeuvre par un autre composé (document [E], p. 713, 2e colonne, l. 4-11), ce qui est le cas du cabazitaxel sélectionné en raison de son appartenance à la même classe des taxanes que le docétaxel, à l'effet connu, tout en présentant des caractéristiques prometteuses face à la résistance rencontrée par les taxanes.

116. **Ainsi, au regard de ces données de l'art antérieur, la personne du métier aurait estimé que**, [...], l'expérimentation du cabazitaxel en deuxième ligne en cours dans **un essai de phase III depuis plus de trois ans, avait des chances raisonnables de montrer un effet favorable** incluant l'augmentation (modérée) de la survie.

117. **Par conséquent, la revendication 1 n'implique pas d'activité inventive.**

Cabazitaxel (Jevtana®, Sanofi)

Tribunal Judiciare de Paris RG No. 21/06416. 6/09/2024

102. Cette dernière approche, selon laquelle un essai clinique ne détruit pas en soi l'activité inventive mais est de nature à influencer et renforcer l'enseignement tiré du reste de l'art antérieur, est à privilégier, car elle permet la prise en compte des particularités de chaque cas d'espèce en évitant un critère trop catégorique et sans s'appuyer exclusivement sur des considérations abstraites relatives aux conditions supposées de l'autorisation des essais cliniques. Par ailleurs, dès lors qu'elle tient compte de l'ensemble des faits de l'espèce, une telle prise en compte des essais cliniques ne porte pas atteinte à la sécurité juridique des déposants de brevet. **En effet, si ceux-ci sont, comme le soulignent les sociétés Sanofi, soumis d'un côté à la nécessité de disposer de données rendant crédible l'effet technique, de l'autre à l'impossibilité de breveter une invention que les données disponibles ont rendu évidente, la jurisprudence assure déjà une marge assez étendue aux déposants en admettant, et ce depuis au moins l'époque du dépôt du brevet litigieux, de fonder la crédibilité de l'effet technique sur des données précliniques** (voir, par exemple, T 609/02, point 9, ainsi que la synthèse à ce sujet dans la décision G 2/21, points 73 et suivants**). En outre, l'objet du droit des brevets est d'inciter les inventeurs à divulguer leur contribution au progrès technique et non à protéger une contribution déjà rendue publique par ailleurs** (par exemple par un essai clinique décrit dans un document accessible) ; au demeurant, le cout engagé pour des essais cliniques, dans la mesure où ils sont spécialement nécessaires à une autorisation de mise sur le marché d'un médicament, est également pris en compte par l'exclusivité commerciale (protection de la mise sur le marché) d'une durée de 10 ans prévue par l'article 14, paragraphe 11, du règlement 726/2004 et l'article 10 de la directive 2004/24, relatifs aux médicaments, tandis que le délai supplémentaire qu'ils impliquent après le dépôt du brevet est pris en compte par le régime des certificats complémentaires de protection.

https://www.courdecassation.fr/decision/66db4812f06e1567cdda7152?search_api_fulltext=jevtana&op=Rechercher&date_du=&date_au=&judilibre_juridiction=all&previousdecisionpage=&previousdecisionindex=&nextdecisionpage=&nextdecisionindex=

Cabazitaxel (Jevtana®, Sanofi)

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Este último enfoque, según el cual un ensayo clínico no destruye por sí solo la actividad inventiva pero puede influir y reforzar las enseñanzas extraídas del resto del estado de la técnica, es preferible porque permite tener en cuenta las particularidades de cada caso concreto evitando un criterio demasiado categórico y sin basarse exclusivamente en consideraciones abstractas relativas a las supuestas condiciones de autorización de los ensayos clínicos. Además, dado que tiene en cuenta todos los hechos del caso, dicha consideración de los ensayos clínicos no socava la seguridad jurídica de los solicitantes de patentes. **En efecto, si, como señalan las empresas Sanofi, están supeditadas, por un lado, a la necesidad de disponer de datos que hagan creíble el efecto técnico, y, por otro, a la imposibilidad de patentar una invención que los datos disponibles lo han hecho evidente, La jurisprudencia ya garantiza un margen bastante amplio a los solicitantes al admitir, y esto al menos desde el momento de la presentación de la patente en litigio, basar la credibilidad del efecto técnico en datos preclínico** (véase, por ejemplo, T 609/02, punto 9, así como el resumen sobre este tema en la decisión G 2/21, puntos 73 y siguientes). **Además, el propósito de la ley de patentes es alentar a los inventores a divulgar su contribución al progreso técnico y no proteger una contribución ya hecha pública en otro lugar** (por ejemplo, mediante un ensayo clínico descrito en un documento accesible); además, los costes derivados de los ensayos clínicos, en la medida en que sean especialmente necesarios para la autorización de comercialización de un medicamento, también se tienen en cuenta en la exclusividad comercial (protección de la comercialización) durante un período de diez años previsto en el artículo 14.11 del Reglamento 726/2004 y el artículo 10 de la Directiva 2004/24, relativos a los medicamentos, mientras que el plazo adicional que suponen tras la presentación de la patente se tiene en cuenta por el régimen de certificados complementarios de protección.

Traducción automática – Google translate

Cabazitaxel .... Next level.... UPC?

EPO and UPC still to come

There is more to come, however, as in April 2025 the EPO Technical Boards of Appeal will hear the appeal against the granting of the patent.

In addition, an infringement action (case ID: ACT_16112/2024) and a counterclaim for revocation (case ID: ACT_44999/2024) are also pending at the UPC's Munich local division. Sanofi filed a lawsuit against the generics companies Accord, Zentiva, Dr Reddy's and Stada in May 2024. Accord filed its counterclaim for revocation this summer. The court has not yet handed down any rulings.

https://www.juve-patent.com/cases/paris-court-revokes-sanofi-cabazitaxel-patent-accord/?etcc_cmp=Paris%20court%20revokes%20Sanofi%20cabazitaxel%20patent&etcc_med=Social%20Media

Summary

- No general rule. Case – by – case
- Adherence to Good clinical practices:
  - Confidentiality – members of the public
  - Control of medicines
- Stage of development
  - New formulation or new use of know drug
  - First medical use
- Stage of the trials – Different data obtained Phase I, II , III
- Closest Prior art: Clinical trials vs actual therapies
- Obviousness – Expectation of success
  - Routine tests
  - Teaching away
  - Clinical trials (even approved by ethical committees) are not warrantee of success
  - Secondary pointers
- Novelty
  - Prior art must disclose therapeutic effect. Simple announcement of trials is not sufficient
- Sufficiency of disclosure
  - Therapeutic effect has to be made plausible at filing

3.10 [...] In this context it is pointed out that **drug compounds to be used in a clinical trial with human subjects are not selected based on a general "try-and-see" attitude, but based on existing favourable scientific data, for both ethical and economical reasons. Thus a clinical trial is not a mere screening exercise**.

3.12.2 [...] In any case, the patent proprietors' argument cannot succeed, since the general consideration that any clinical trial might fail does not throw additional doubt on the particular combination treatment envisaged and is therefore not sufficient to establish an inventive step**. The reason why clinical studies are carried out at all is that they have uncertain outcomes. But they are routine tests and the fact that their outcome is uncertain does not in itself turn their results into an invention.**

T2506/12- (PEGYLATED LIPOSOMAL DOXORUBICIN/Pharmamar) 04/10/2016

Thank you

EPO Decisions

case	title	Date	objection	point
T-2506/12	PEGYLATED LIPOSOMAL DOXORUBICIN/Pharmamar	04/10/2016	CPA	3.2
T-2154/14	Daptomycin II/CUBIST PHARMACEUTICALS	29/03/2017	CPA	38, 39
T-239/16	Zoledronic acid/NOVARTIS	13/09/2017	CPA	6.2
T-1123/16	Eosinophilic bronchitis/GLAXO	13/04/2021	CPA	5
T-96/20	Treatment of myasthenia gravis/ALEXION	22/04/2021	CPA	4
T-2963/19	Liposomal irinotecan/IPSEN	18/03/2022	CPA	4.1.2
T-2506/12	PEGYLATED LIPOSOMAL DOXORUBICIN/Pharmamar	04/10/2016	expectation of success	3.12.2
T-239/16	Zoledronic acid/NOVARTIS	13/09/2017	expectation of success	6.5
T-96/20	Treatment of myasthenia gravis/ALEXION	22/04/2021	expectation of success	7-11
T-1732/18	TREATMENT OF THROMBOEMBOLIC DISORDERS WITH RIVAROXABAN/Bayer	27/10/2021	expectation of success	9.22.4
T-1437/21	Empagliflozin/BOEHRINGER INGELHEIM	09/02/2024	expectation of success	4.3.1
T-158/96	Obsessive-compulsive-disorder/PFIZER	28/10/1998	novelty	3.4; 3.5
T-715/30	Use of ziprasidone for treating Tourette's syndrome/PFIZER)	16/01/2006	novelty	2.2
T-7/07	Ethinylestradiol and drospirenone for use as a contraceptive/BAYER PHARMA AG	07/07/2011	novelty	3.3
T-1859/08	Anti-ErbB2 antibodies/GENENTECH, INC.) 05-06-2012	05/06/2012	novelty	13
T-1457/09	CTL epitopes of WT-1/GANYMED PHARMACEUTICALS)	17/01/2014	novelty	36
T-239/16	Zoledronic acid/NOVARTIS	13/09/2017	novelty	4
T-670/20	Pharmaceutical composition/SANKYO	02/12/2022	novelty	4.3-4.5
T-1437/21	Empagliflozin/BOEHRINGER INGELHEIM	09/02/2024	novelty	3.2
T-1941/21	TAUROURSODEOXYCHOLIC ACID (TUDCA) FOR USE IN THE TREATMENT OF NEURODEGENERATIVE DISORDERS/Bruschettini S.r.l.)	05/06/2024	novelty	
T-1123/16	Eosinophilic bronchitis/GLAXO	13/04/2021	obviouness	11
T-1806/18	Nilotinib for treating chronic myeloid leukemia / NOVARTIS	21/10/2021	obviouness	7.2, 7.52
T-2963/19	Liposomal irinotecan/IPSEN	18/03/2022	obviouness	4.3.1
T-209/22	Umeclidinium, Vilanterol	21/03/2024	obviouness	6.2
T-1941/21	TAUROURSODEOXYCHOLIC ACID (TUDCA) FOR USE IN THE TREATMENT OF NEURODEGENERATIVE DISORDERS/Bruschettini S.r.l.)	05/06/2024	obviouness	1.5
T-799/16	Methods of Using Sustained Release Aminopyridine Compositions /Acorda	04/09/2019	routine testing	6.7-6.8.6
T-237/15	Saha /sloan	28/01/2019	routine testing	4.6.1
T-609/02	AP-1 complex/SALK INSTITUTE	27/10/2004	sufficiency	
T-1437/07	Botulinum toxin for treating smooth muscle spasm/ALLERGAN	26/10/2009	sufficiency	26
T-966/18	Synucleinopathic disease/PROTHENA BIOSCIENCES	10/11/2020	sufficiency	10