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European biotech patent case law

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Speakers

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Summary

- T1437/21: novelty and inventive step of treating a patient subpopulation in view of prior art of a phase 3 clinical trial
- T1941/21: inventive step over clinical trial protocol & novelty over combination therapy
- T0197/22: insufficiency of a first medical use claim

A link to download these slides and a recording of this webinar will be emailed to you later this week.

Background: clinical trial information

- **Clinical trials** are publically conducted to assess the efficacy and risks of drugs. Information about clinical trails and their subsequent results are often publically available, creating problems for patent filings.
- Clinical trials information is potentially novelty destroying, but more often prejudices the inventive step of a case, as the skilled person understands that a **if a drug candidate is taken to clinical trial there is potentially an expectation of success**.

T 1437/21
(Empagliflozin/BOERINGER INGELHEIM)
Novelty and inventive step of treating a subpopulation of patients

T 1437/21: background

- Empagliflozin (Jardiance®) is an SGLT-2 inhibitor, for the treatment of type II diabetes.
- Empagliflozin's therapeutic efficacy is affected by impaired kidney function.
- The independent claim 1 of the patent (EP 2981271) as granted defined:

> *"Empagliflozin for use in a method for treating prediabetes, type 1 or type 2 diabetes mellitus in a patient or for improving glycemic control in a patient with prediabetes, type 1 or type 2 diabetes mellitus comprising administering empagliflozin to the patient,* ***wherein the patient has moderate renal impairment or stage 3 chronic kidney disease (CKD) or wherein the patient's estimated glomerular filtration rate (eGFR) is >=30 ml/min/1.73 m2 and <60 ml/min/1.73 m2."***

T 1437/21: background continued

- Eight oppositions were filed against the patent.
- The opposition division (OD) revoked the patent for lack of novelty in view of a press release by the patentee reporting the success of the phase three clinical trial of empagliflozin in type 2 diabetes with "mild, moderate and severe renal impairment" (D22/D29).
- The patentee appealed.

T 1437/21: novelty – cited prior art

- The cited prior art (D22/D29) were two clinical trial press releases reporting essentially the same thing - the success of phase three clinical trials:

  "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.

  *Study 1245.36 (n=741) evaluated 25 mg dose of empagliflozin in Type 2 Diabetes patients with mild, moderate or severe renal impairment, and 10 mg dose in those with mild renal impairment versus placebo for 52 weeks.**(1)"*

T 1437/21: novelty – patentee & respondent's arguments

- The patentee argued that the disclosure of 25 mg (once per day) only concerned the population as a whole. Further, D22/D29 did not disclose effective treatment of each subgroup of patents – in particular because there would be an expected lack of efficacy in patients with severe renal impartment (as reported in post-published document D53).
- The opponents argued that the skilled person would concluded that within each subgroup of patients, the primary efficacy end point compared to the placebo was reached.
  - Furthermore, the opponents argued that the efficacy of 10 mg in patients with mild renal impairment would suggest efficacy of 25 mg in patients with moderate renal impairment.
  - The opponents also cited D61, D62, D63, and D8 in support of their inventive step arguments which discussed the effect of other SGLT-2 inhibitors in patients with renal impairment to support their arguments that the skilled person would expect a clinical trial of Empagliflozin to be successful.

T 1437/21: novelty – board's opinion

- The Board of Appeal overturned the decision of the OD, and found the claims as granted to be novel.
- The board considered that D22/D29 announced efficacy of treatment with 25 mg empagliflozin was to be understood as relating to the patient population having mild, moderate, or severe renal impairment as a whole.
- The board considered that the skilled person cannot directly and unambiguously derive that the treatment is effective in each of the subgroups of patients – as the data on file only disclosed the total number of participants.
- Additionally, the reported efficacy of 10 mg in patients with mild renal impairment does not provide any basis to conclude that a dose of 25 mg would be efficacious in patients with moderate renal impairment as a matter of fact.

T 1437/21: novelty – board's opinion

- The board stated:

  "… the positive comments on the results from the trial expressed in the press releases [...] ('encouraged by the efficacy and safety results', 'pleased with these results for these Phase III clinical trials for empagliflozin') [...] do not provide any basis for the skilled reader to conclude that as a matter of fact the 25 mg dose must also have been effective in the patients with moderate renal impairment." (Reasons. 3.3).

T 1437/21: inventive step – board's opinion

- The board applying the problem/solution approach considered:

  A) That D22/D29 were not disputed as the closest prior art.

  B) Figure 2 of the patent demonstrated that treatment with empagliflozin in patients with moderate renal impairment led to increased urinary glucose excretion (UGE) and lowered HbA1c. However, Figure 2 also showed that treatment with empaglifozin in patients with severe renal impairment did not increase UGE or lower HbA1c. Thus the board considered that patients with moderate renal impartment were a distinct treatment group.

- The objective technical problem was thus formulated as:

  "the provision of effective treatment for diabetic patients with moderate renal impairment."

T 1437/21: inventive step – board's opinion

- Citing T 2506/12, T 239/16, T 1123/16 and T 2963/19 the board considered that:

  "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."

T 1437/21: inventive step – board's opinion

- However, the board further noted that:

  "… 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 [...] the authorisation of a clinical trial does not represent a scientific advice on the development programme of the investigational product tested."*

- The board noted that in T 2506/12, T 239/16, and T 1123/16, there was an expectation of success in view of the disclosure of clinical trials in particular the nature of the investigational product and of the condition to be treated and that furthermore there was an absence of information suggestive of failure of the trial.

T 1437/21: inventive step – T 2506/12

- In T 2506/12 - a combination therapy of ET-743 and PLD for the treatment of cancer.
- The cited prior art in T 2506/12 disclosing that the same drug combination was being tested in a clinical phase I study for the treatment of cancer, more specifically ovarian cancer.
- It was argued that since both ET-743 and PLD had efficacy for the relevant therapeutic application alone, it was therefore directly and unequivocally implicit that the combination treatment would also have the desired efficacy.
- The board further held however that a phase I study of a combination treatment did not guarantee the safety of that combination treatment – a treatment which caused unacceptable harm to patients would not be considered an effective treatment within the usual meaning of the term – claim was novel.

T 1437/21: inventive step – T 2506/12

- Regarding inventive step however, the board found that the invention was obvious.
- The board concluded the skilled person would consider both drugs individually to be efficacious alone and this would give rise to an expectation of efficacy of the combination of treatment of both drugs.
- The proprietor cited prior art showing that ET-743 had a known risk of increased myelosupression.
- The board held that there was no evidence put forward that the combination therapy with PLD would potentiate this risk.
- The skilled person is aware that it is typical for combination treatments may give rise to increased toxicities, and such a fact would not preclude the skilled person from having a reasonable expectation of success.
- A clinical trial suggests to the skilled person an expectation of success, because such trials are not based on a “try-and-see” approach”.

T 1437/21: inventive Step – board's opinion

- It was thus critical in this case for the board to judge if in view of the prior art whether the skilled person would have a reasonable expectation of success of empagliflozin in the treatment of patients having moderate renal impairment.
- D8 disclosed SGLT-2 inhibition depends on the GFR of the kidneys, which would be reduced in patients with renal impairment.
- As argued by the patient proprietor and disclosed in post-published data (D53), efficacy of treatment was as a matter of fact not expected in patients with severe renal impairment.
- The board therefore considered that the mere inclusion of patients with renal impairment in the Phase III clinical trial described in documents D22/D29 could not by itself have provided the skilled person with a reasonable expectation of success of the treatment in patients with moderate or severe renal impairment.

T 1437/21: inventive step – board's opinion

- The board then further considered the opponents' arguments regarding the effects of other SGLT-2 inhibitors in diabetic patients:
  - D61/62 disclosed that ipragliflozin increased UGE in diabetic patients with moderate renal impairment. However, they do not demonstrated that ipragliflozin lowers glucose/HbA1c, which ultimately determinis clinical utility.
  - D63 disclosed the effects luseogliflozin in diabetic patients with moderate renal impairment. While D63 disclosed an increase in UGE and a decrease in PPG and FPG, it does not disclose significant clinical efficacy. D63 disclosed that a long term trial of diabetic patients with moderate renal impairment to assess the efficacy of luseofliglozin was still ongoing.
  - D8 disclosed that dapagliflozin had failed to decrease FPG and HbA1c in patients with moderate renal impairment.
  - D32 did disclose the canagliflozin had efficacy in diabetic patients with moderate renal impairment. However canagliflozin was known as an SGLT-2 inhibitor with only moderately selective for SGLT-2 with respect to SGLT-1, whereas empagliflozin was known to be highly selective for SGLT-2. The board held that the skilled person would expect this difference in SGLT selectivity to play a role in the efficacy of the inhibitors.
- The board concluded that the skilled person would from the known effects of other SGLT-2 inhibitors in patients with moderate renal impairment not have derived a reasonable expectation of efficacy of empagliflozin in the treatment of diabetes this group of patients

T 1437/21: inventive step – board's opinion

- Additionally, the board considered:

  "The skilled person would furthermore not have expected the efficacy of the 25 mg dose of empagliflozin in patients with moderate renal impairment on the basis of the efficacy of the 10 mg dose in patients with mild renal impairment reported in documents D22/D29 due to the distinctive status of patients with moderate renal impairment which directly affects the mechanism of action of empaglifolozin"

T 1437/21: conclusion

Novelty can be achieved for patient subgroups if prior art clinical trial data does not individualise such groups but merely report on whole patient population.

Arguing that prior art indicates an expectation of failure can help to establish inventive step over e.g., clinical trial prior protocols.

T 1941/21
(TUDCA for use in treating ALS/Bruschettini s.r.l.)
Inventive step over clinical trial protocol & novelty over combination therapy

T 1941/21: background

- “1. Tauroursodeoxycholic acid (TUDCA) or a pharmaceutically acceptable salt thereof for use in the treatment of a neurodegenerative disorder in a mammal, characterized in that said neurodegenerative disorder is **amyotrophic lateral sclerosis**.”
- Claim 1 therefore encompasses a **monotherapy**.
- However, the data in the patent only showed that ALS patients treated with **combination therapy** of TUDCA + riluzole + vitamin E had significantly higher ALSFRS-R score and lower mortality than those treated with riluzole + vitamin E alone.

T 1941/21: inventive step from D4

- An inventive step objection was raised starting from D4.
- D4 was a clinical trial protocol relating to “Efficacy and Tolerability of TUDCA in Amyotrophic Lateral Sclerosis”. **The results of the trial have <u>not</u> been made available to the public.**
- The problem was defined by the OD as the **provision of an effective treatment for ALS**.
- The OD had held that, whilst D4 fails to provide experimental data confirming a successful treatment, the mere absence of such information would **not** lead the skilled person **to expect the treatment to fail**.

T 1941/21: inventive step from D4

- 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.
- 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.

T 1941/21: inventive step from D4

- The board found that the state of the art suggested to the skilled person **a clear expectation of failure** in view of common general knowledge:
  - D9 was **general review** of the treatment of ALS and mentioned 89 different drugs which had been used in clinical trials for ALS based on allegedly promising preclinical data.
  - Disclosed that for all the drugs listed, promising preclinical data have been provided, but nevertheless **the majority of the clinical trials failed**.
  - Mentions the trials of many drugs having the same pharmacological properties as TUDCA, i.e. anti-oxidant, neuroprotectant and/or anti-apoptotic properties, **all of which having been found to be ineffective**.

T 1941/21: inventive step from D4

- A reasonable expectation of success was also not supported by the treatment of ALS by UDCA, an *in vivo* precursor of TUDCA:
  - Only **preclinical** experimental results for UDCA were provided.
  - It was not made credible that, if UDCA might be useful in the treatment of ALS, this would also apply to TUDCA or any other metabolite or analogue or that the effect relies on one of the metabolites.
  - UDCA and TUDCA are different from both a **chemical** and **physical** point of view.

T 1941/21: inventive step summary

- The board agreed with the appellant that the claims did have an inventive step.
- Obviousness in view of clinical trial protocols must be assessed on a **case by case basis**.
- The crux of the inventiveness rested on the prior art documents showing a **clear expectation of failure**.

T 1941/21: novelty over D8

- D8 was a patent application relating to compositions comprising low doses of **diazoxide** for use in the treatment of a mammal afflicted with ALS, in particular a human.

  > "1. **Diazoxide** or a pharmaceutically acceptable salt thereof for use as a medicament at a daily dose of from 0.15 mg/m^2/day to 13.00 mg/m^2/day expressed as mg/m^2/day of diazoxide free base **in the treatment of a mammal afflicted with amyotrophic lateral sclerosis (ALS)**."

- Example showing that low doses of diazoxide improve survival in a mouse model for ALS. The utility of diazoxide in treatment of ALS described in D8 had not been disproved.

T 1941/21: novelty over D8

“8. Diazoxide or a pharmaceutically acceptable salt thereof for use according to claims 1 to 6, wherein the medicament is prepared for the **combined administration of diazoxide and one or more therapeutic agents** useful in the treatment of amyotrophic lateral sclerosis.

9. Diazoxide or a pharmaceutically acceptable salt thereof for use according to claim 8, wherein the medicament comprises diazoxide and one or more additional therapeutic agents useful in the treatment of amyotrophic lateral sclerosis selected from CK-2017357, olesoxime (TRO19622), arimoclomol, riluzole, tretionin and pioglitazone HC1, AVP-923, memantine, talampanel, **tauroursodeoxycholic acid (TUDCA)**, thalidomide, olanzapine, KNS-760704, lithium carbonate, NP001, ONO-2506PO, tamoxifen, creatine monohydrate, coenzyme Q10, YAM80, sodium phenylbutyrate, pyrimethamine, R(+)pramipexole dihydrochloride monohydrate, vitamin E, minocycline, topiramate, gabapentin, AEOL-10150, stem cell injections, SB-509, autologous bone marrow-derived stem cells, ceftriaxone, E0302 (mecobalamin), MCI-186, glatiramer acetate, insulin-like growth factor-1 (IGF-I), ISIS 333611, sNN0029, GSK1223249, brain-derived neurotrophic factor (BDNF) and anti-CD40L antibody.”

T 1941/21: novelty over D8

- "A **composition** comprising diazoxide and TUDCA for use in the treatment of a mammal afflicted with ALS is **derivable directly and unambiguously** from D8."
- "…even if D8 does not provide any *in vitro* or *in vivo* experiments with regard to the efficacy of TUDCA in the treatment of ALS, D8 provides **an enabling disclosure** for a combination treatment based on diazoxide and TUDCA, in view of the explicit disclosure in D8 of the efficacy of diazoxide."

T 1941/21: novelty over D8

- “In the Board's view, the discovery of **a new property** of a particular ingredient of a known composition, i.e. here TUDCA in the composition comprising diazoxide and TUDCA, used for a known and identical general purpose, i.e. here the treatment of a mammal afflicted with ALS, can indeed **not confer novelty** to the particular ingredient used for the same general purpose, namely TUDCA for the treatment of ALS. Novelty can only be recognized if this new property is applied **in a new use**.”
- Consequently, the disclosure in D8, wherein the efficacy of diazoxide is supported by experimental data and **has not been disproven**, anticipates the claimed subject-matter.

T 1941/21: novelty over D8

- **AR1 -** the treatment is "in an human"
- Also lacks novelty, since D8 is directed to the treatment of a mammal afflicted with ALS, **in particular a human** (although no data in humans in D8)
- **AR2 -** "characterized in that it is administered for at least 30 weeks"
- Novel over D8 and inventive for same reasons as main request
- **No consideration of inventive step over D8**

T 1941/21: novelty summary

- The board appears to have taken a strict approach to novelty:
  - TUDCA was **arbitrary selection** from a very long list.
  - Has a **new clinical situation** arisen? Claim at issue referred to "**substance**" for use (i.e. TUDCA or a pharmaceutically acceptable salt thereof) not a "**composition**" for use.
  - Does D8 provide an **enabling disclosure** for each combination?
  - Does D8 provide an **enabling disclosure** for use in humans?
  - Are **multiple selections** required: (i) TUDCA is combination agent; (ii) mammal is human?
- How would the board have dealt with inventive step from D8?

T 1941/21: takeaways

- Medical use claims are usually **novel over clinical trial protocol** (provided no results are disclosed).
- Assessment of inventive step over clinical trial protocol is assessed on a **case-by-case basis**. A claim will likely be inventive if there is a **clear expectation of failure** in the art (e.g. CGK).
- Disclosure of “A+B for use in treating disease X” may be **novelty-destroying** for “B for use in treating disease X”, even if there is **no data for A+B** and the **selection of B is arbitrary**.

T 0197/22
(Delivery of mRNA/Translate Bio)
Insufficiency of a first medical use claim

First medical use claims: background

- Where a substance or composition is already known, it may still be patentable under Art. 54(4) EPC if the known substance or composition was not previously disclosed for use in a method referred to in Art. 53(c) EPC (e.g. methods for treatment of the human or animal body by surgery or therapy, in vivo diagnostics).
- A claim in the form "Substance X for use as a medicament" is acceptable, even if X is a known substance, provided its use in medicine is not known.

First medical use claims: scope

- Possible claim formats:

  Substance or composition X for use as a medicament

  Substance or composition X for use in medicine

  Substance or composition X for use in therapy

  Substance or composition X for use in surgery

  Substance or composition X for use in *in vivo* diagnostics

- A first medical use claim protects that substance or composition for use in treatment or diagnosis in medicine **generally**.

First medical use claims: basis

- **T 0419/16** – the disclosure in an application of a substance or composition for a specific medical use is a basis for a claim directed to a first medical use.
- A logical consequence of the availability of purpose-limited substance protection for a first medical use is that **the disclosure of a single therapeutic use of a compound** is both sufficient to meet the requirements of Article 83 EPC and to serve as a basis for such a claim in the sense of Articles 87(1) EPC and Article 123(2) EPC, respectively.

First medical use claims: sufficiency

- **T 128/82 -** where a known compound was for the first time proposed and claimed for use in therapy, **the fact that a specific use was disclosed in the specification does not in itself call for a restriction of the purpose-limited product claim to that use**.
- **T 0424/21 -** For a first medical use of a substance or composition according to Article 54(4) EPC to be sufficiently disclosed **it is not required to show the suitability for each and every disease**, but it usually suffices to show that at least one medical use is credibly achieved.

T 0197/22: background

- "A pharmaceutical composition comprising a pharmaceutically acceptable excipient and at least one mRNA molecule encoding a peptide or polypeptide **for use in therapy**, wherein the at least one mRNA molecule is encapsulated in a liposome having a size of less than 100 nm, wherein said liposome comprises one or more cationic lipid(s), one or more non-cationic lipid(s), and one or more PEG-modified lipid(s), and wherein said at least one mRNA encodes a functional protein or enzyme."

T 0197/22: first instance decision

- **Serious doubts** that the claimed invention could be practiced over the **whole claimed** scope for any therapy and any disease.
- Since a therapeutic effect was not credibly achievable for **all diseases** resulting from a protein deficiency, showing at least one way of carrying out the invention in the patent was not sufficient to enable the invention as claimed.

T 0197/22: appeal decision

- It is not generally required for compliance with Article 83 EPC that a patent discloses the therapeutic suitability of the defined compositions in treatment of **a plurality of disease**.
- However, the patent must provide the skilled person with sufficient instructions for applying the compositions within the scope of the claim **in some form of therapy** without undue burden.

T 0197/22: appeal decision

- The patent demonstrates with *in vivo* experiments in mice that mRNA encoding **a reporter gene** may be effectively transfected and expressed using a liposomal transfer vehicle as defined in claim 1.
- However, the expression of a reporter gene serves **no purpose in any therapy**.

T 0197/22: appeal decision

- The results reported in the patent **do not quantify the actual expression** of the transferred mRNA.
- However, common general knowledge that formulations for gene transfer which allowed for the generation of a detectable level of expression of a particular gene **still failed to achieve** the quantitatively adequate levels of expression required for effective gene therapy.
- Therefore, there are **serious doubts** that the patent provides the skilled person with a sufficient disclosure to generally achieve effective therapy using a formulation within the definition of claim 1.

T 0197/22: appeal decision

- Without substantiation of the suitability of a formulation for therapy to start with, suggestions for optimization and dosing remain **proposals for a research project** which do not overcome the doubts regarding the suitability of the claimed formulations for use in therapy.
- A lack of sufficiency of disclosure **cannot be remedied by post-published evidence**.
- Board held that claim 1 did **not** meet requirements of Article 83 EPC.

T 0197/22: takeaways

- It is **not** required to show the suitability for each and every disease, **but <u>at least one medical use</u> must be credibly achieved**.
- Data with only a **reporter construct may not be sufficient** to substantiate use in therapy where there are **serious doubts** in the technical field.
- A lack of sufficiency of disclosure **cannot be remedied by post-published evidence**.

Webinar invitation

UPC case law, observations and analysis

1pm, 13 November 2024

An analysis of the Unified Patent Court's decisions, with D Young & Co's observations and analysis.

Registration and further information:
dycip.com/webinar-upc-nov2024

Questions?

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