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Datasheet for the decision of 30 June 2022

Case Number: T 1752/19 - 3.3.01

Application Number: 14191419.2

Publication Number: 2868323

IPC: A61K31/56, A61P5/46

Language of the proceedings: EN

Title of invention:
A pharmaceutical composition or group of compositions for inhibiting autocrine HCG production in adult human cells

Applicant:
Flamina Holding AG

Headword:
Carcinogenesis/FLAMINA

Relevant legal provisions:
EPC Art. 83

Keyword:
Sufficiency of disclosure - main (sole) request (no)

Decisions cited:
T 0609/02, T 1842/06, T 0895/13

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Case Number: T 1752/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 30 June 2022

Appellant: (Applicant)	Flamina Holding AG Industriestrasse 16 6304 Zug (CH)
Representative:	Rutz & Partner Alpenstrasse 14 Postfach 7627 6304 Zug (CH)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 14 January 2019 refusing European patent application No. 14191419.2 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	D. Luis Alves
	F. Bostedt

Summary of Facts and Submissions

I. The applicant (appellant) filed an appeal against the decision of the examining division refusing the European patent application No. 14 191 419.2, entitled "*A pharmaceutical composition or group of compositions for inhibiting autocrine HCG production in adult human cells*".

II. In the decision under appeal the examining division held that the application did not disclose the invention as defined in the claims according to the sole claim request on file in a manner sufficiently clear and complete for it to be carried out by a skilled person (Article 83 EPC).

III. The examining division essentially reasoned that the theoretical concept underlying the claimed therapeutical application, namely that abnormal hCG autocrine production was the cause of carcinogenesis, went against what was generally accepted in the technical field. Therefore, it was on the applicant to show that the prevention of oncogenesis was attained by the inhibitors defined in claim 1. The prevention of carcinogenesis before it starts, and the use of hCG inhibitors for any type of cancer, i.e. including cancers other than those related to hCG, lacked sufficient disclosure in the application in the form of either experimental results or an explanation. This lack of disclosure was not resolved by the prior art cited by the appellant.

IV. With the statement setting out the grounds of appeal the appellant filed documents D39 to D46 and maintained

the claims on the basis of which the decision under appeal was taken.

V. Independent claim 1 reads as follows:

"1. A pharmaceutical composition for use in a method of preventing carcinogenesis in adult human cells by inhibiting autocrine Human Chorionic Gonadotropin (HCG) production, the composition comprising at least one pharmaceutically acceptable carrier medium and an active agent that is a competitively binding progesterone antagonist binding to steroid receptors of human cells, wherein the composition is administered monthly, semi-annually or annually, whereby the annual dosage of the active agent is in the range between 0.1 mg to 10.0 mg per kg of person/body-weight."

VI. The board appointed oral proceedings and, in a communication pursuant to Article 15(1) RPBA 2020, set out its preliminary opinion on the appeal.

VII. In reply to the board's communication, the appellant filed documents D47 to D49 and with a further letter documents D50 and D51.

VIII. Oral proceedings were held as scheduled and at their end the Chair announced the board's decision.

IX. The following documents are relevant for this decision:

D5: Cole, L.A., Reproductive Biology and Endocrinology 10(24), 2012, pages 1-18

D7: "On the Origin of Malignant Neoplasia", pages 1-13, by the inventor, unpublished, submitted during examination proceedings

D19: Heidegger, H. and Jeschke, U., International Journal of Molecular Sciences 19, 1502, 2018, pages 1-3

D21: Ferretti, C. *et al.*, Human Reproduction Update 13(2), 2007, pages 121-141

D29: Zenzmaier, C. *et al.*, Reproductive Biology and Endocrinology 9(114), 2011, pages 1-10

D39: Pardee, A.B. and Li, C.J., Journal of Cellular Physiology 233, 2018, pages 8437-8440

D40: Campisi, J. *et al.*, Journal of Cellular Physiology 209, 2006, pages 587-588

D41: Stein, G.S. and Pardee, A.B., "Cell Cycle and Growth Control - Biomolecular Regulation and Cancer", 2nd edn, John Wiley & Sons, 2004, pages ix-xi, dedication and 1-3

D42: Email from Arthur B. Pardee to the inventor on 3 August 2017

D43: PubMed abstract of Esteve, J.L. *et al.*, European Journal of Contraception and Reproductive Health Care 12(2), 2007, pages 162-167

D44: PubMed abstract of Pei, K. *et al.*, Contraception 75(1), 2007, pages 40-44

D45: PubMed abstract of Grunberg, S.M. *et al.*, Cancer Investigation 24(8), 2006, pages 727-733

D46: Supplement Materials for Tomasetti, C. and Vogelstein, B., Science 347(78), 2015

D47: Abstract of Bischof, P. *et al.*, Human Reproduction 1(1), 1986, pages 3-6

D48: Abstract of Das, C. and Catt, K.J., The Lancet, 1987, pages 599-601

D49: Aronson, J.K., "Mifepristone" in Meyler's Side Effects of Drugs, 2016, first page

D50: (identical to D39) Pardee, A.B. and Li, C.J., Journal of Cell Physiology 233, 2018, pages 8437-8440

D51: Bibliographic data of document D41

D52: Tsampalas, M. *et al.*, Journal of Reproductive Immunology, 85, 2010, pages 93-98

Annex 2: pages 3/15-5/15 of the annex filed at oral proceedings before the examining division

X. The appellant's arguments relevant to this decision will be dealt with in the Reasons.

XI. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the set of claims considered by the examining division in the decision under appeal, i.e. the set of claims submitted with the letter dated 27 May 2016.

Reasons for the Decision

1. Claim 1 is drafted in the form of a purpose-limited product claim, pursuant to Article 54(5) EPC, a so-called second or further medical use. The claim is directed to a composition comprising progesterone antagonists binding to steroid receptors for use in the prevention of carcinogenesis in adult humans. The therapeutic application is further defined by the mechanism "by inhibiting autocrine Human Chorionic Gonadotropin", the dose and the frequency of administration.

2. In the case law of the boards of appeal, where a therapeutic application is claimed in the form according to Article 54(5) EPC, attaining the claimed therapeutic effect is a functional technical feature of the claim. As a consequence, in order to fulfil the requirements of Article 83 EPC, the suitability of the product for the claimed therapeutic application must be derivable from the application, unless this is already known to the skilled person at the priority date (see T 609/02, point 9 of the Reasons and T 895/13 of 21 May 2015, points 3 to 5 of the Reasons).

3. Thus, in the case in hand, the suitability of a progesterone inhibitor as defined in the claim for preventing cancer must be assessed.

4. The applicant argued, referring to decision T 1842/06, that the applicant bears the burden to show that the claimed invention is reproducible only in cases where the invention relates, for example, to a technical effect that is *a priori* contrary to the laws of physics.

5. The board is not convinced by this argument because, as stated in point 2., it is established case law that the suitability of the product for the claimed therapeutic application must be derivable from the application unless already known to the skilled person. The board notes that the decision referred to by the appellant does not deal with a claim for a medical use and its content is, therefore, not relevant for the case in hand.

Disclosure in the application

6. It is undisputed that the application does not include experimental results showing that a progesterone antagonist as defined in claim 1 was suitable for preventing cancer. Rather, to demonstrate the mechanism underlying the claimed therapeutic application, namely that abnormal autocrine hCG production causes carcinogenesis, the appellant relied on a theoretical explanation. The board concurs with the appellant that, in principle, the suitability of a composition for a claimed therapeutic application may be derivable from the application or common general knowledge even in the absence of experimental results.

Theoretical explanation in Annex 2 and document D7

7. According to the appellant, the suitability was demonstrated by a conclusive theoretical concept, explained in document D7 and in Annex 2.

8. From Annex 2 it can be seen that the theoretical concept involves five "cornerstones" A to E, as follows (see Annex 2, page 3/15):

A) The processes of embryogenesis and carcinogenesis are practically identical.

B) The starting points of embryogenesis and carcinogenesis are similar.

Proof of A) and B) leads to conclusion C):

C) The primary agonist of embryogenesis and carcinogenesis is the same.

D) Analysis of embryogenesis leads to the conclusion that hCG is the primary agent of the related processes. Consequently hCG is also the driver of carcinogenesis.

Proof of A), B), C) and D) leads to conclusion E):

E) Suppressing hCG by a competitively binding progesterone antagonist inhibits not only processes of embryogenesis, but also processes of carcinogenesis.

9. In support of steps A to E, Annex 2 refers to document D21 to show the parallelisms between embryogenesis and carcinogenesis (step A). In relation to step D, Annex 2 refers to documents D52 and D29 to show that hCG is the primary agonist of embryogenesis, and to documents D5 and D19 for disclosing the functions of hCG.

10. In the board's view, steps B to E are not supported by the documents cited in this context by the appellant. None of the cited documents discloses that hCG "is the starting point of carcinogenesis", corresponding to step B in the appellant's theoretical concept. No document has been cited demonstrating this step. The only information found in Annex 2 in this respect is

"*[a]nalysis of various cell types of different malignant neoplasias (MN) reveal [sic] essential common characteristics: anti-apoptosis, pluripotency, particular growth potential, and anti-senescence. These characteristics essentially match those of stem cells*" (see page 4/15, last paragraph). This list of characteristics in essence supplements the similarities between embryogenesis and carcinogenesis already addressed by step A. It does not lead to the conclusion that "*C) the primary agonist of embryogenesis and carcinogenesis is the same*". Annex 2 makes no reference to any document in respect of step C either.

11. The board notes that despite the parallelisms between the processes of embryogenesis and carcinogenesis highlighted by the appellant, the two processes lead to quite different cell structures: from the first result ordered structures of differentiated cells organised in tissues and organs, while from the second result cells with uncontrolled growth and the potential to invade other tissues. Hence, the board does not agree with the appellant's argument that parallelisms between embryogenesis and carcinogenesis on their own lead to the conclusion that both processes have the same cause or agonist.

12. As set out above, document D21 was cited in relation to step A, and documents D52 and D29 were cited to show the role of hCG in embryogenesis. Therefore, they cannot support step C of the theoretical concept. Documents D5 and D19 are cited for disclosing the functions of hCG. Document D19 was published after the date of filing of the current patent application, and therefore in principle cannot be used to establish what belonged to the common general knowledge at the relevant date. Document D5 is addressed below.

13. Document D7 was also cited for disclosing the theoretical concept. However, no specific passages or arguments were pointed out in relation to this document, so what has been set out above in respect of Annex 2 applies equally here.

Document D5

14. Document D5 addresses the functions of hCG. Five different forms and subunits of the molecule are considered. A first part of the document is dedicated to the role of hCG in both the implantation of the trophoblast in the uterus and uterine angiogenesis. In a second part, the document discloses that hCG is a marker for a number of specific cancers and that hCG free β-subunit secreted by cancer cells directly stimulated cancer cell growth and blocked apoptosis. It refers to two types of cancer: in type 1, hyperglycosylated hCG is produced from the start – this type includes choriocarcinoma, gestational trophoblastic neoplasm and ovarian and testicular germ cell cancer; in type 2, which includes all other cancers, the start of cancer is hCG-independent (see page 14, left-hand column, second paragraph to right-hand column, last paragraph). For all cancers of type 2, hCG free β-subunit is not produced until the cancer progresses and becomes established (see paragraph bridging pages 14 and 15).

15. Thus, although document D5 addresses both embryogenesis and carcinogenesis side by side, it does not draw the conclusion that cancer is caused by hCG. On the contrary, it states that the start of cancer is hCG-independent, with the exception of four specific cancers. However, these four exceptions share the

characteristic that they are tumours of germ cells or cells of the early embryonic stage which will develop to form the placenta.

16. Thus, the board considers that the disclosure in document D5 does not support the applicant's case; on the contrary, for almost every cancer it calls into question whether the inhibition of hCG production is suitable for preventing carcinogenesis.

Document D39

17. Together with the statement of grounds of appeal, the appellant submitted documents D39 to D42 to show that the theoretical concept had acceptance in the scientific community. Documents D40 to D42 were filed merely to show that the authors of document D39 were well recognised (see also D50 and D51) and hence these documents do not need to be considered further.

18. Document D39 discloses experiments designed to show the role of hCG in cancer cell proliferation *in vitro*. It reports that no effect was observed when the expression of hCG was inhibited in Hela (human cervical cancer), U2OS (human osteosarcoma) and RKO (human colon cancer) cell lines. The authors concluded that the proliferation of cancer cells is hCG-independent (see page 8439, left-hand column, second paragraph to right-hand column, first paragraph). They propose instead that hCG only has a role at the level of the "*primitive cell cycle regulation*" of cancer stem cells (see page 8439, right-hand column, second paragraph, and page 8440, last paragraph). The board notes, however, that this document does not contain any disclosure that if hCG did have a role in cancer stem cell regulation,

there would be any effect in terms of cancer prevention.

19. In conclusion, the application presents a theory which has not been validated by any experimental evidence. The appellant refers to prior art documents and to a theoretical concept consisting of steps A to E to show that the only logical conclusion is that hCG production is the cause of cancer. However, in the board's view document D5 shows that alternative theoretical conclusions are possible. In fact, the application acknowledges that the author of document D5 came to a different conclusion despite having investigated the functions of hCG in cancer and embryogenesis (see application, page 7, third paragraph). Document D39 does not support the idea that cell proliferation can be inhibited in all cancers by antagonising hCG, as claimed. In light of the above, the board concludes that prevention of carcinogenesis by inhibiting hCG production is not disclosed in a manner sufficiently clear and complete (Article 83 EPC).

Further arguments made by the appellant

20. The appellant filed documents D43 to D46 to address sufficiency of disclosure in relation to embodiments involving the lowest and highest antagonist dosages defined in claim 1.

21. The board did not consider the dosages defined in claim 1 in reaching its conclusion in point 19. above. For this reason, the arguments based on documents D43 to D46 need not be considered further.

22. The appellant filed documents D47 to D49 to show a link between the active agent in claim 1 and the inhibition

of hCG production. However, the board reached the conclusion in point 19. above without questioning this link. Therefore, further consideration of these documents is not relevant to the decision.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

M. Schalow T. Sommerfeld

Decision electronically authenticated