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Datasheet for the decision of 21 October 2013

Case Number: T 1075/09 - 3.3.04

Application Number: 00927534.8

Publication Number: 1176976

IPC: A61K38/24, A61P15/08

Language of the proceedings: EN

Title of invention:
Use of LH administered in mid- or late-follicular phase for the treatment of anovulatory women

Patent Proprietor:
Laboratoires Serono SA

Opponent:
Ferring International Center S.A.

Headword:
Treatment of anovulatory women/LABORATOIRES SERONO SA

Relevant legal provisions:
EPC Art. 53(c), 56, 84, 123(2), 123(3)
RPBA Art. 13(1)

Keyword:
Main request, auxiliary requests 1 to 3: amendments - added matter (yes); exceptions to patentability - method for treatment by therapy (yes)
Auxiliary request 4: amendments - added matter (yes)
Auxiliary request 5: requirements of the EPC met (yes)

Decisions cited:
G 0002/08, T 1031/06, T 2017/07, T 0009/10

Catchword:
see points 30 to 34

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Case Number: T 1075/09 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 21 October 2013

Appellant: (Opponent)	Ferring International Center S.A. Chemin de la Vergognausaz 50 1162 Saint-Prex (CH)
Representative:	Polz, Leo HOFFMANN EITLE Patent- und Rechtsanwälte Arabellastrasse 4 81925 München (DE)
Respondent: (Patent Proprietor)	Laboratoires Serono SA Centre Industriel 1267 Coinsins, Vaud (CH)
Representative:	Lee, Nicholas John Kilburn & Strode LLP 20 Red Lion Street London WC1R 4PJ (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 24 March 2009 concerning maintenance of the European Patent No. 1176976 in amended form.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: R. Morawetz
B. Claes

Summary of Facts and Submissions

I. The appeal of the opponent (hereafter "appellant") lies against the decision of the opposition division posted on 24 March 2009, whereby European patent No. EP 1176976 was maintained in amended form on the basis of the main request filed during the oral proceedings before the opposition division on 20 January 2009.

II. The patent at issue has the title "Use of LH administered in mid- or late-follicular phase for the treatment of anovulatory women". It was granted on European application No. 00927534.8 which originated from international application PCT/GB2000/001745 published as WO 2000/067778 (hereinafter "application as filed").

Claims 1, 6, 7 and 8 as granted read as follows:

"1. The use of LH and/or a biologically-active analogue thereof in the production of a medicament for inducing paucifolliculogenesis or unifolliculogenesis in anovulatory women at a daily dose in the range of from 100 to 1500 IU, wherein the medicament is to be administered starting in the mid- to late-follicular phase.

6. The use as claimed in any preceding claim, wherein FSH and/or a biologically-active analogue thereof is used in the production of the medicament.

7. The use as claimed in claim 6, wherein the IU ratio of LH to FSH is in the range of from 1.5:1 to 20:1.

8. The use as claimed in claim 7, wherein the ratio is

in the range of from 1.5:1 to 10:1."

III. The patent was opposed under Article 100(a) EPC 1973 on the ground of lack of inventive step (Article 56 EPC 1973) and under Article 100(b) EPC 1973.

IV. The opposition division maintained the patent in amended form on the basis of the main request (which is identical to the present main request). Claim 1 of the main request read as follows (amendments compared to claim 1 as granted indicated by strikethrough or in bold by the board):

"1. The use of LH ~~and/or a biologically-active analogue thereof~~ in the production of a medicament for inducing paucifolliculogenesis or unifolliculogenesis in **WHO Group II** anovulatory women at a daily dose in the range of from 100 to 1500 IU, wherein the medicament is to be administered starting in the mid- to late-follicular phase, **and wherein folliculogenesis is induced by the administration of FSH**."

V. The opposition division decided that the claims of the main request found a basis in the application as filed and involved an inventive step.

VI. The appellant filed its statement of grounds of appeal on 3 August 2009 including substantial arguments why the main request contained subject-matter which extended beyond the content of the application as filed (Article 123(2) EPC) and lacked an inventive step (Article 56 EPC).

VII. In response the proprietor (hereafter "respondent") filed its submissions on 21 December 2009, maintaining the main request on file and filing three auxiliary

requests 1, 2 and 3.

Claim 1 of auxiliary request 1 read as follows (amendments compared to claim 1 as granted indicated by strikethrough or in bold by the board):

"1. The use of LH ~~and/or a biologically-active analogue thereof~~ in the production of a medicament for inducing paucifolliculogenesis or unifolliculogenesis in **WHO Group II** anovulatory women at a daily dose in the range of from 100 to 1500 IU, wherein the medicament is to be administered starting in the mid- to late-follicular phase, **when there are more than 3 follicles with a mean diameter in the range of from 8 to 13 mm and no larger follicles and wherein folliculogenesis is induced by the administration of FSH.**"

Claim 1 of auxiliary request 2 read as follows (amendments compared to claim 1 as granted indicated by strikethrough or in bold by the board):

"1. The use of LH ~~and/or a biologically-active analogue thereof~~ in the production of a medicament for inducing paucifolliculogenesis or unifolliculogenesis in **WHO Group II** anovulatory women at a daily dose in the range of from 100 to 1500 IU, wherein the medicament is to be administered starting in the mid- to late-follicular phase, **when there are more than 3 follicles with a mean diameter in the range of from 8 to 13 mm and no larger follicles, wherein folliculogenesis is induced by the administration of FSH and wherein the administration of FSH is discontinued when the medicament is administered.**"

Claim 1 of auxiliary request 3 read as follows (amendments compared to claim 1 as granted indicated by

strikethrough or in bold by the board):

"1. The use of LH ~~and/or a biologically-active analogue thereof~~ in the production of a medicament for inducing paucifolliculogenesis or unifolliculogenesis in **WHO Group II** anovulatory women at a daily dose in the range of from 100 to 1500 IU, wherein the medicament is to be administered starting in the mid- to late-follicular phase, **when there are more than 3 follicles with a mean diameter in the range of from 8 to 13 mm and no larger follicles and when the endometrium thickness is 8 mm or more, wherein folliculogenesis is induced by the administration of FSH and wherein the administration of FSH is discontinued when the medicament is administered.**"

VIII. By a communication of 16 January 2013 the parties were summoned to oral proceedings to be held on 26 September 2013.

IX. On 14 May 2013 the appellant filed a further written submission together with two additional documents. In this submission it made substantial observations on all the issues raised in the statement of grounds of appeal and raised new objections under Articles 53(c) and 123(3) EPC.

X. With its letter of 5 July 2013 the respondent filed a further written submission in which it made substantial observations on the issues raised by the appellant and requested that the new objection under Article 123(3) EPC be not admitted in the appeal proceedings.

XI. Oral proceedings before the board were held on 26 September 2013. When hearing the parties on

Article 123(2) EPC, the board raised the question whether the daily dose of LH recited in claim 1 of the main request found a basis in the application as filed. As part of its submissions under Article 56 EPC, the appellant stated that it relied only on document (D5) as closest prior art while document (D19) was no longer pursued as closest prior art. After the board announced its view on the main request and auxiliary requests 1 to 3, the respondent filed auxiliary requests 4 and 5.

Claims 1, 3 and 4 of auxiliary request 4 read as follows (amendments compared to claim 1 as granted indicated by strikethrough or in bold by the board):

"1. The use of **FSH and** LH ~~and/or a biologically-active analogue thereof~~ in the production of a medicament for inducing paucifolliculogenesis or unifolliculogenesis in **WHO Group II** anovulatory women **wherein the FSH is for inducing folliculogenesis and the LH is to be administered** at a daily dose of **225 IU or 450 IU** ~~in the range of from 100 to 1500 IU, wherein the medicament is to be administered~~ starting in the mid- to late-follicular phase **when there are more than 3 follicles with a mean diameter in the range of from 8 to 13 mm and no larger follicles and when the endometrium thickness is 8 mm or more, and wherein the administration of FSH is discontinued when the LH is administered.**

3. The use as claimed in any preceding claim, wherein the IU ratio of LH to FSH is in the range of from 1.5:1 to 20:1.

4. The use as claimed in claim 3, wherein the ratio is in the range of from 1.5:1 to 10:1."

Claims 1 and 2 of auxiliary request 5 read as follows (amendments of claim 1 compared to claim 1 as granted indicated by strikethrough or in bold by the board):

"1. The use of **FSH and** LH ~~and/or a biologically-active analogue thereof~~ in the production of a medicament for inducing paucifolliculogenesis or unifolliculogenesis in **WHO Group II** anovulatory women **wherein the FSH is for inducing folliculogenesis and the LH is to be administered subsequent to FSH** at a daily dose of **225 IU or 450 IU** ~~in the range of from 100 to 1500 IU, wherein the medicament is to be administered~~ starting in the mid- to late-follicular phase **when there are more than 3 follicles with a diameter in the range of from 8 to 13 mm and no larger follicles and when the endometrium thickness is 8 mm or more, and wherein the administration of FSH is discontinued when the LH is administered.**

2. The use as claimed in claim 1, wherein the LH is r-hLH."

XII. At the end of the oral proceedings the debate was closed. The parties were informed of the board's decision by a communication of 25 October 2013.

XIII. The following documents are referred to in this decision:

(D1) Sullivan M.W. et al., Journal of Clinical Endocrinology and Metabolism, vol. 84, pages 228-232 (January 1999)

(D2) The European recombinant human LH study group, Journal of Clinical Endocrinology and Metabolism, vol. 83, pages 1507-1514 (1998)

(D5) Hillier S.G., Human reproduction, vol. 9, pages

188-191 (1994)

(D8) WHO Geneva, WHO technical report series, No. 514, pages 5-30 (1973)

(D10) Hillier S.G., in The new frontier in ovulation induction, Jacobs H.S, editor, pages 39-47 (1993)

(D19) Lunenfeld B., Contracept. Fertil. Sex., vol. 21, pages 1-7 (1993)

XIV. The arguments of the appellant can be summarised as follows:

Main request
Amendments to claim 1 - Article 123(2) EPC

Claim 1 contained subject-matter which extended beyond the content of the application as filed. The feature "WHO II group" was isolated from an exemplified embodiment of the invention but the patient subgroup could not be isolated from the other features of example 1 because the absence of a functional or structural relationship among the features in example 1, in particular the patient subgroup, the stopping of the FHS treatment and the time point of the start of the LH treatment, was not clearly recognizable from the application as filed. On the contrary, these features were clearly related to each other by a functional relationship.

Page 6, lines 23 to 24 did not refer to the patient group and there was no positive teaching that it was not essential to stop FSH administration when commencing LH treatment in WHO Group II patients. The application considered discontinuation of the FSH treatment only once the required stage of follicular development had been reached.

The application disclosed clearly different points in time to administer LH (or to finish FSH administration), depending on the anovulatory patient subgroup to be treated. Therefore the skilled person would have had to assume that a distinct functional or structural relationship of the selected sub-group of patients with the other features of example 1 existed. The skilled person would have expected from his common general knowledge that the duration of FSH treatment during the follicular phase could have an influence on the number of maturing follicles in accordance with the patient type to be treated. The patient characteristics defined different points in time to commence LH treatment, which were different in WHO Group I and WHO Group II women.

That the daily dose of LH administered to the patients had an influence could also be seen from example 1. In fact it was shown in Table 2 that LH possibly had a negative effect in WHO Group II women already at low concentrations. The daily dose of LH could therefore not be chosen freely in the absence of any evidence that a daily dose of up to 1500 IU LH was not detrimental in WHO Group II anovulatory women. Accordingly, WHO Group II anovulatory women were also inextricably linked to the daily LH dose disclosed in example 1.

Page 1, lines 8 to 10 of the application as filed concerned the prior art treatment of anovulation. The skilled person would not have regarded the mentioning of WHO Group II as relevant at all for the invention because the passage did not mention the use of a specific LH treatment regime to promote uni- or paucifolliculogenesis.

Amendments to claim 1 - Article 123(3) EPC

The amendments introduced in claim 1 as granted resulted in an unallowable extension of the scope of protection. Deletion of the alternative "LH and/or a biologically-active analogue thereof" from claim 1 as granted confined the maximum daily dose of LH only to a "range of from 100 to 1.500 IU". Due to the term "comprising" in the claim, however, the presence of additional LH analogues was not excluded. This might - in addition to the LH anyhow present in the medicament - give rise to a combined LH activity of more than the originally granted upper limit of 1.500 IU (see decisions T 2017/07 and T 9/10).

Article 53(c) EPC - claim 1

Claim 1 was worded in such a way that it taught the direct administration of FSH to the patient for inducing folliculogenesis because the feature "*and wherein folliculogenesis is induced by the administration of FSH*" was not covered by the Swiss-type format. Therefore this feature constituted a therapeutical method of its own involving a direct physical intervention on the human body. Claim 1 of the main request and auxiliary requests 1 to 3 were unallowable pursuant to Article 53(c) EPC (see decision G 2/08, reasons, point 5.7).

Auxiliary requests 1, 2, and 3

Amendments (Articles 123(2) and (3) EPC) and Article 53(c) EPC

No further arguments were submitted for these requests.

Auxiliary request 4

Admissibility

Not only did this request not address all the objections raised so far, it also gave rise to new objections. Accordingly it should not be admitted into the proceedings.

Amendments (Article 123(2) EPC) - claims 1, 3, and 4

As a consequence of the amendment of independent claim 1 the combination of features covered by dependent claims 3 and 4 had no basis in the application as filed.

Auxiliary request 5

Admissibility

No objections were raised.

Amendments (Article 123(2) EPC)

According to example 1 the patients underwent routine ovulation induction with FSH whereas claim 1 did not specify that the ovulation induction was routine.

Article 84 EPC

Claim 1 was unclear because it referred to both "inducing folliculogenesis" and "inducing paucifolliculogenesis or unifolliculogenesis". These two terms were mutually exclusive.

Article 56 EPC

Document (D5) represented the closest prior art. Document (D19) was relied on as representing the common general knowledge but no longer as closest prior art. Document (D5) suggested that exogenous LH might be used as an adjuvant to therapy with exogenous FHS in clinical ovulation induction regimes where the aim was to induce monoovulation. Hence document (D5) addressed the same technical problem as the patent in suit.

The principles relied on in the patent, i.e. the FSH threshold hypothesis and the LH ceiling hypothesis were known in the art (see document (D5), Tables I and II). Document (D5) rendered the use of FSH to induce folliculogenesis, the stopping of the FSH administration and the use of LH to induce paucifolliculogenesis or unifolliculogenesis obvious to try (see page 191, left hand column last paragraph). The patent had put this principle into practice but provided no unexpected effects beyond confirming the LH ceiling hypothesis. It was routine to give FSH to trigger folliculogenesis. Document (D5) disclosed (see abstract) that due to increases in its responsiveness to FSH and LH, one of the follicles induced by FSH was selected to ovulate, while the remainder became atretic, i.e. disappeared. This was achieved at mid-follicular phase where the follicle reached a size of 10 or more mm. Considering the teaching of document (D5), the skilled person would have understood that document (D5) suggested on page 191, left hand column, last paragraph, a regime where follicular stimulation was started with FSH alone during the early follicular phase. It was clear from document (D5) that LH took effect only once the leading follicle had gained sufficient LH-responsiveness, i.e. in the mid-

follicular phase. It would not make sense to administer LH as an adjunct to FSH therapy to stimulate monoovulation at an earlier point in time. The feature "*maintaining tonic (subceiling) stimulation*" meant that the stimulation of the dominant follicle should be maintained. Document (D5) referred to document (D10), but the relevant sentence of document (D10), see page 44, last paragraph, was missing in document (D5). Document (D5) did disclose the principle of the claimed invention but not the amount of LH recited in the claim or the patient sub group or the exact time point for the administration of LH. The limitation to WHO Group II anovulatory women and the exact time point for the administration of LH were arbitrary and did not contribute to the technical effect.

The objective technical problem over document (D5) could be regarded as defining an appropriate LH dosage in a treatment protocol wherein "exogenous LH was used as an adjunct to therapy with exogenous FSH in clinical ovulation induction regimes where the aim was to induce monoovulation".

Document (D5) in combination with documents (D1), (D19) or (D2) rendered the claimed solution obvious.

Document (D19) disclosed that 1.2 % of all anovulatory women belonged to WHO Group I. Considering that WHO Group III patients were also very rare, the majority of all anovulatory women, at least over 95%, belonged to WHO Group II. Document (D5) did not specify the patient group but the authors of document (D5) as well as the skilled reader would have considered WHO group II patients as being included. The limitation to WHO Group II patients was anyway arbitrary as no improved technical effect that was linked to this particular

patient group had been disclosed. WHO Group I and Group II patients could be treated as equal, because their clinical condition, i.e. anovulation, was the same and the treatment was the same, i.e. the use of FSH to induce folliculogenesis.

Document (D1) explicitly contemplated the sequential use of FSH and LH in ovarian stimulation protocols (see page 232, left hand column, first paragraph). The skilled person would have been motivated to refer to document (D1) when wishing to implement a protocol to treat anovulatory women irrespective of their subgroup, wherein folliculogenesis was induced by FSH and subsequently LH was given to secure uni-or paucifolliculogenesis. Document (D19) equalled the patient group disclosed in document (D1) to those patients belonging to Group II (see page 3, right hand column, fourth paragraph). Document (D1) disclosed daily doses of 300 IU and 750 IU LH.

Document (D19) disclosed that pure FSH was enough to induce folliculogenesis in WHO Group II women and thus rendered the sole use of FSH to induce folliculogenesis obvious.

Document (D2) concerned the use of LH in the treatment of WHO group I anovulatory women and pointed out that LH at higher concentrations could be used to achieve folliculogenesis of fewer follicles (page 1512, left hand column, second full paragraph). Document (D2) disclosed daily doses of 150 IU and 450 IU LH.

XV. The arguments of the respondent can be summarised as follows:

Main request
Amendments to claim 1 - Article 123(2) EPC

Claim 1 did not contain added matter because the application provided a clear teaching that FSH treatment could be either discontinued or continued, once LH is administered (see page 6, lines 22 to 26). A person skilled in the art reading the application with a mind willing to understand would have considered that the teaching of page 6, lines 23 to 34 could be applied to example 1 and understood that it was not essential for the FSH treatment to be stopped before LH administration began. The application also taught that LH should be administered at an appropriate stage of follicular development and that this stage could be decided by the physician administering the medicament (see page 6, 2nd paragraph, lines 4 to 14). The application thus taught that the precise number and size of follicles at the start of the LH treatment was not essential to the invention. The application disclosed on page 5, line 8 to 12 that the inventors had found that that administration of LH at a dose of 100 to 1500 IU/day could promote paucifollicular development. This was a generic statement and in the absence of any functional relationship with the patient group it could be combined with the other features of claim 1.

Amendments to claim 1 - Article 123(3) EPC

The argument that the objection under Article 123(3) EPC was inadmissible because the objection amounted to a new ground for opposition which could not be introduced at the appeal stage unless the patentee approved (see decision G 9/91 and G 10/91, reasons, point 18) was not pursued during oral

proceedings. However, the objection under Article 123(3) EPC could and thus should have been raised earlier and was thus late. The objection should be dismissed because it was based on the notion that the wording "comprising" was present in claim 1, which it was not. The claim did not cover analogs. The case law referred to by the appellant did not support its case.

Article 53(c) EPC - claim 1

No objection to the admission of this objection was raised. The feature *"and wherein folliculogenesis is induced by the administration of FSH"* was part of the definition of the patient group to be treated by the medicament of claim 1 and could not be considered to be a claimed therapeutic method involving a direct physical intervention of the human body. It defined that the WHO Group II anovulatory women had FSH administered to stimulate folliculogenesis prior to any administration of LH to induce pauci-or unifolliculogenesis. The claim was formulated in the Swiss-type format, accordingly no objection under Article 53(c) EPC could possibly be raised.

Auxiliary requests 1, 2, and 3
Amendments (Articles 123(2) and (3) EPC) and Article 53(c) EPC

No further arguments were submitted for these requests.

Auxiliary request 4

Admissibility

The request should be admitted because it addressed the

objections raised against the higher ranking requests.

Amendments (Article 123(2) EPC) - claim 1, 3, and 4

Example 1 provided a basis for claim 1. Claims corresponding to claims 3 and 4 were present in the set of claims as granted. Accordingly, no objection could be raised under Article 123(2) EPC against claims 3 and 4.

Auxiliary request 5

Amendments (Article 123(2) EPC)

Example 1 provided a basis for claim 1. The skilled person knew what the routine treatment with FSH was, the claim related in effect to the routine treatment with FSH.

Article 84 EPC

Folliculogenesis had to be induced before paucifolliculogenesis or unifolliculogenesis could be induced.

Article 56 EPC

Document (D5) represented the closest prior art. Document (D5) did not disclose a switching of FSH to LH as suggested by the appellant. Document (D5) disclosed to maintain - not to start - tonic stimulation with exogenous LH (page 191, left hand column, last paragraph). The term "maintaining" in this section of document (D5) clearly implied that exogenous LH was already present before FSH was withdrawn. Further evidence for this interpretation could be found in

document (D10) to which document (D5) referred back at the end of the paragraph on page 191. Document (D10) (see page 44, lines 29 to 33, page 46, last paragraph, and Fig 1C), confirmed what was meant in document (D5), i.e. that LH should be administered throughout the treatment. Document (D5) did not disclose the administration of LH in the mid- to late-follicular phase. Both documents (D5) and (D10) disclosed LH administration throughout. Claim 1 differed from the disclosure of document (D5) in that i) it related to WHO Group II patients, (ii) in the dosage of LH and iii) the administration of LH starting in mid- to late-follicular phase. It was uncontested that document (D5) did not disclose features ii) and iii). WHO Group II women were a subgroup of the patient group of the prior art. Example 1 demonstrated that there was a functional relationship between the pharmacological effect and WHO Group II women.

The problem to be solved could be defined as providing a method for inducing paucifolliculogenesis or unifolliculogenesis in WHO Group II anovulatory women. The solution consisted in the provision of LH in mid- to late-follicular phase. That the problem was solved could be taken from Table 3 of the patent. Table 3 of the patent in suit showed that treatment with r-hLH resulted in less follicles with a diameter equal or larger than 14 mm.

The solution was not obvious from document (D5). This solution was also not obvious from document (D19) because this document merely taught that high levels of LH at the start of stimulation were undesirable but did not suggest that LH should administered starting in the mid- to late-follicular phase. It could be taken from the prior art that the treatment of WHO Group I and WHO

Group II patients was different, see document (D8), page 7 and document (D2), page 1507, right hand column, lines 12 to 16. Accordingly, it was inappropriate to contend that group I and II women were the same. Also document (D19) distinguished between WHO Group I and II patients (see page 3, right hand column, fourth paragraph). Accordingly WHO Group I and II patients were not the same for the purpose of treatment. Document (D5) did not mention WHO Group II patients at all. There was nothing in the prior art that suggested that LH should not be administered until the mid-to late-follicular phase was reached.

Document (D1) disclosed a sequential FSH and LH ovarian stimulation protocol (page 232, left hand column, first paragraph). But the skilled person faced with the technical problem would not consider document (D1). The patients of document (D1) did not belong to WHO Group II and could not be equated to WHO Group II anovulatory women either. These women had no ovarian dysfunction but were rendered artificially anovulatory by administration of leuprolide acetate to minimize endogenous gonadotropin secretion (page 229, left hand column, fourth paragraph). In contrast thereto WHO Group II anovulatory women had normal and fluctuating levels of serum FSH and LH. Although the LH levels were apparently the same in these two patient groups there was no evidence that any other levels were the same. Document (D1), page 232, paragraph 1 had to be read in the light of what went before. Document (D1) disclosed that FSH treatment was arbitrarily discontinued when one or more follicles reached a diameter of 14 mm and also that the exact size at which a follicle became LH responsive was not known (paragraph bridging pages 231 and 232). Nobody knew where the LH ceiling was - it was a hypothesis. The

patent provided the appropriate time point for the administration of LH.

The features that were missing in document (D5) were not disclosed in document (D19) either. Document (D2) related to WHO Group I anovulatory women. Furthermore, document (D2) disclosed administration of LH together with FSH from the beginning of the treatment.

XVI. The appellant requested that the decision under appeal be set aside and that the patent be revoked.
The respondent requested that the appeal be dismissed - in other words that the patent be maintained on the basis of its main request which was the main request upheld by the opposition division - or that the decision under appeal be set aside and the patent be maintained on the basis of one of its auxiliary requests 1, 2, 3, 4 or 5.

Reasons for the Decision

Main request

Amendments to claim 1 - Article 123(2) EPC

1. The claims as granted related to the treatment of anovulatory women in general. During the opposition proceedings the claims were restricted to the treatment of WHO Group II anovulatory women only. In the decision under appeal the opposition division has held that this amendment found a basis in the application as filed on page 1, lines 8 and 9 and in example 1.

2. Page 1, lines 8 to 9 form part of the introductory part of the description relating to the prior art treatment of women with WHO Group II and WHO Group I anovulation

using hMG (human menopausal gonadotrophin) or u-FSH (urinary human follicle stimulating hormone) for the induction of folliculogenesis and hCG (human chorionic gonadotrophin) for the induction of ovulation. This passage does not disclose the use of luteinising hormone (LH) for the induction of pauci- or unifolliculogenesis let alone the use of such a treatment in WHO Group II women. Accordingly, this passage cannot provide a basis for the amendment in claim 1.

3. The only other reference to WHO Group II anovulation in the application as filed is found in the context of example 1 in which the effect of LH, when administered after FSH stimulation, was assessed in WHO Group II anovulatory women. The patients underwent routine ovulation induction with FSH until there were 4 or more follicles in the range of from 8 to 13 mm in diameter, no larger follicles and an endometrium of 8 mm or more thickness. Then, FSH treatment was stopped and LH administration started with two different LH doses, 225 IU/day of r-hLH and 450 IU/day of r-hLH and a placebo as control (see page 10, line 18 to page 11, line 9 of the application as filed).

4. The subject-matter of present claim 1 differs from the disclosure in example 1 at least in that (i) it does not require that the FSH treatment be stopped when LH administration starts, (ii) the LH treatment starts in the mid- to late-follicular phase, and (iii) LH is used at a higher daily dose, namely in the range of from 100 to 1500 IU. The patient subgroup - WHO Group II anovulatory women - is therefore extracted from the specific combination of features disclosed in example 1.

5. According to established jurisprudence of the Boards of Appeal if a claim is restricted to a preferred embodiment it is normally not admissible under Article 123(2) EPC to extract isolated features from a set of features which have originally been disclosed in combination for that embodiment. An amendment of this nature is only justified in the absence of any clearly recognisable functional or structural relationship among said features (Case Law of the Boards of Appeal of the European Patent Office, 6th edition 2010, section III.A.2). The issue to be decided in the present case is thus whether or not there exists a functional or structural relationship between the patient sub-group, i.e. WHO Group II anovulatory women, and the other features disclosed in example 1, in particular the timing of the FSH and LH administration and the daily dose of LH used.

6. At the priority date of the application it belonged to the common general knowledge of the person skilled in the art that, based on their distinct clinical conditions, anovulatory women are classified into three groups termed WHO Group I to III anovulation (see document (D8), page 7 to 8). While WHO Group I anovulation is characterised by reduced hypothalamic or pituitary activity and resulting in abnormally low serum FSH and LH levels and negligible estrogen activity, WHO Group II anovulation is characterised by distinct estrogen activity and normal but fluctuating gonadotrophins. Finally, WHO Group III anovulation is characterised by low endogenous estrogen activity and pathologically elevated serum and urinary gonadotrophins. The women belonging to the different groups are thus characterised by different endogenous hormonal levels.

7. The application as filed discloses on page 6, lines 22 to 24 that "*LH can be administered only once the required stage of follicular development has been reached. In this case, the administration of FSH can be discontinued altogether or can be continued at the same dose as before, or at a lower or higher dose.*" This disclosure concerns recommendations for dosing and timing of the administration of the gonadotrophins, but there is no reference to any patient group, let alone the WHO Group II specifically. Hence this passage provides no information at all as to whether FSH treatment should be stopped or can be continued once a specific patient group is selected for treatment.

8. It would not escape the skilled person that the examples disclose different points in time to administer LH (or finish FSH administration), depending on the anovulatory patient subgroup to be treated. Thus, while in WHO Group II anovulatory women FSH treatment is stopped and LH administration started when there were 4 or more follicles in the range of from 8 to 13 mm in diameter, no larger follicles and an endometrium of 8 mm or more thickness (see example 1, page 11, lines 5 to 9 of the application as filed), in WHO Group I anovulatory women LH and FSH are administered in the late follicular phase which is defined to begin when at least one follicle with a mean diameter in the range of from 10 to 13 mm is present (see example 2, page 13, line 23 to page 15, line 11 of the application as filed). Bearing in mind that the application as filed (see page 6, lines 22 to 23) also emphasises that "*LH can be administered only when the required stage of follicular development has been reached*" the skilled person would, in the board's judgement, conclude that a distinct functional relationship exists between the subgroup of patients,

the administration of FSH and the point in time of LH administration, which point is defined in the examples on the basis of the number and size of follicles present.

9. The application as filed also discloses (see page 3, lines 14 to 23) that "*there is evidence that excessive exposure to LH will trigger follicular atresia and suppress granulosa proliferation. Developing follicles appear thus to have finite requirements for stimulation by LH, beyond which normal follicular development ceases. This is the "LH ceiling" concept.*" It would not escape the skilled person that in example 1 of the application as filed a LH dose of 450 IU/day results in all follicles becoming atretic in one out of eight patients (see Table 2). Therefore the skilled person would have also concluded that a distinct functional relationship existed between the subgroup of patients treated and the dose of LH administered.

10. The board concludes that the patient subgroup - WHO Group II anovulatory women - is inextricably linked to the other features disclosed in combination in example 1, in particular the stopping of the FHS treatment, the starting point of the LH treatment and the daily dose of LH administered. Accordingly, claim 1 presents the skilled person with technical information which is not directly and unambiguously disclosed in the application as filed.

11. The respondent submits that claim 1 does not contain added matter because the application teaches the absence of a functional and structural relationship between the patient sub-group and the remaining features of example 1. The respondent relies in particular on page 5, lines 8 to 12 and on page 6,

lines 9 to 14 and lines 22 to 26 of the application as filed.

12. The board notes that the passage on page 5, lines 8 to 12 discloses that a LH dose of 100 to 1500 IU/day has been found by the inventors to promote paucifollicular development in patients undergoing follicular induction. However, there is no reference to any particular patient subgroup. Hence this passage provides no information whether the daily dose of LH disclosed in example 1 for the treatment of WHO group II anovulatory women, i.e. 225 or 450 IU, can be altered and in particular exceeded threefold.

13. The passage on page 6, lines 9 to 14 merely indicates various points in time as reflected by the number of follicles having a certain size. These various definitions do not synonymously define the same time point. For example, the occurrence of a "single follicle having a mean diameter of 8 mm" necessarily takes place earlier in time than the occurrence of a follicle that has "a mean diameter in the range of 10 to 15 mm". Therefore this paragraph merely illustrates the actual bandwidth of the term mid- to late-follicular phase. It does not provide, however, any teaching that the beginning of LH administration is not inextricably linked with the patient group so that it could be singled out of the context of example 1.

14. The disclosure on page 6, lines 22 to 24 concerns recommendations for dosing and timing of administration of the gonadotrophins, but there is no reference to any patient subgroup. Hence this passage provides no information at all as to whether FSH treatment should be stopped or can be continued once a specific patient

group is selected for ovulation induction.

15. The board concludes from the above that the passages referred to by the respondent provide no basis in the application as filed for isolating the patient subgroup from the context in which it is disclosed in example 1 and then combining it with the remaining features defined in claim 1.

16. For these reasons, the subject-matter of claim 1 extends beyond the content of the application as filed and the main request is accordingly not allowable (Article 123(2) EPC).

Objection under Article 123(3) EPC - admissibility

17. In its letter of 14 May 2013 the appellant raised for the first time an objection under Article 123(3) EPC contending that deletion of the alternative "LH and/or a biologically-active analogue thereof" from claim 1 as granted extended the scope of protection. The respondent requested not to admit the objection in the appeal proceedings because it had been raised late.

18. The board notes that the objection under Article 123(3) EPC arises from an amendment made by the proprietor-respondent during the opposition proceedings before the department of first instance. Accordingly, any objection under Article 123(3) EPC could and thus should have been raised before the department of first instance. The objection has however been raised at a late stage in the appeal proceedings. Thus its admission in the appeal proceedings is at the discretion of the board (Article 13(1) RPBA). The appellant justified the lateness of the submission by arguing that the objection could not have been raised

earlier as it was based on recent case law (see decisions T 2017/07 of 26 November 2009 and decision T 9/10 of 16 November 2011).

19. The board notes that the decisions on which the appellant's argumentation under Article 123(3) EPC is based have issued after the time limit for filing the statement of grounds of appeal in the present case expired. Accordingly this case law was not available at the time of filing the statement of grounds of appeal and *a fortiori* not during the proceedings before the department of first instance. Thus, under the present circumstances, the board accepts that the objection, in this form, could not have been raised earlier. Being satisfied that the explanation provided by the appellant justifies the late raising of the objection under Article 123(3) EPC in the appeal proceedings the board decides in the exercise of its discretion to admit the objection in the appeal proceedings (Article 13(1) RPBA).

Amendments to claim 1 - Article 123(3) EPC

20. Pursuant to Article 123(3) EPC the European patent may not be amended in such a way as to extend the protection it confers. In order to decide whether or not an amendment of the granted patent satisfies that requirement, it is necessary to compare the protection conferred by the claims as granted with that of the claims as amended.

21. Claim 1 as granted concerned the use of LH and/or a biologically-active analogue thereof in the production of a medicament for inducing paucifolliculogenesis or unifolliculogenesis in anovulatory women at a daily dose in the range of from 100 to 1500 IU. This is

understood by the board to mean *inter alia* that the daily dose of LH - if used alone - must not exceed 100 to 1500 IU.

22. Claim 1 as amended is directed to the use of LH at a daily dose in the range of from 100 to 1500 IU and is thus limited to one of the three alternative embodiments of claim 1 as granted. The daily dose of LH used alone must not exceed 100 to 1500 IU which corresponds exactly to - and does not exceed - the daily dose of LH according to one of the embodiments of claim 1 as granted.

23. The appellant submitted that claim 1 as amended confined the maximum daily dose of LH to a range of from 100 to 1500 IU. Due to the term "comprising" in claim 1, however, the presence of additional LH analogues was not excluded. In analogy to the cases underlying decisions T 9/10, *supra*, and T 2017/07, *supra*, this might result in a combined LH activity of more than the originally granted upper limit of 1500 IU and thus in a broadening of scope.

24. The board does not consider this line of reasoning persuasive. The wording of claim 1 of the main request does in fact not contain the term "comprising" but relates to "the use of LH in the production of a medicament" (see section IV above, for the complete wording of the claim) and the argumentation of the appellant fails for this reason alone.

25. If, for the sake of argument only, the board were however to accept the interpretation advanced by the appellant, then that same interpretation would of course also have to apply to claim 1 as granted which encompassed as one of the three alternative embodiments

the use of LH (alone). In other words, the embodiment of claim 1 as granted directed to the use of LH would not have excluded the presence of any other compound - for example LH analogues - in any amount, also resulting in a combined LH activity of more than 1500 IU. The board would like to emphasise that the mere deletion of two alternative embodiments from claim 1 as granted cannot justify a different interpretation of the term "LH" in the context of claim 1 as granted vis-à-vis claim 1 as amended. In summary, the board is not persuaded that claim 1 as amended covers any use that was not covered by claim 1 as granted.

26. Finally, the board is not persuaded that the case law relied on by the appellant (decisions T 9/10 and T 2017/07, *supra*) is at all relevant to the present situation for the following reasons.

27. In the case underlying decision T 2017/07, *supra*, claim 1 as granted related to a composition openly defined as **comprising** *inter alia* a class of compounds (alkylene carbonate having 3 to 5 carbon atoms) in an amount which was defined by a numerical range and therefore excluded the presence of that component in an amount outside of that range. In claim 1 as amended the class of compounds had been restricted to a single species (propylene carbonate). The competent board decided that this amendment violated Article 123(3) EPC because other alkylene carbonates having 3 to 5 carbon atoms might be present in any amount due to the open language of the claim. Decision T 9/10, *supra*, dealt with an analogous situation and reached a similar conclusion.

28. The present situation is different from that decided in decision T 2017/07, *supra*, at least because in the

present case the claim as granted was not directed to a composition specified to comprise LH, i.e. openly defined, but was directed to the use of LH as one of three possible alternative embodiments. Nor has the claim been amended to restrict the breadth of the component from a generic class to a specific component within that class. Rather, in the present case, two out of three embodiments were deleted. For these reasons the findings of decision T 2017/07, *supra*, are not relevant to the present case. For the same reasons the findings of decision T 9/10, *supra*, are also irrelevant.

29. The board concludes that the scope of protection conferred by present claim 1 has not been extended vis-à-vis that of claim 1 as granted, such that the requirements of Article 123(3) EPC are satisfied.

Article 53(c) EPC - claim 1

30. Claim 1 as granted has been amended during the proceedings before the opposition division by including the feature relating to the administration of FSH. In its letter of 14 May 2013 the appellant raised for the first time an objection under Article 53(c) EPC against claim 1. The board notes that this objection also arises out of an amendment made by the respondent during the proceedings before the opposition division and has also been raised late in the appeal proceedings. The respondent did not object to the admission of this objection in the appeal proceedings. The board considers the objection *prima facie* of high relevance and therefore decides to admit it in the appeal proceedings in the exercise of its discretion under Article 13(1) RPBA.

31. Present claim 1 concerns two different therapeutic methods, namely (i) the administration of FSH for the induction of folliculogenesis and (ii) the administration of LH for inducing paucifolliculogenesis or unifolliculogenesis in WHO Group II anovulatory women (see section IV, above for the complete wording of the claim). The board notes that claim 1 is worded such that the purpose defined in the Swiss-type format is restricted to the administration of LH only while the administration of FSH is not covered by the Swiss-type format. Therefore claim 1 teaches the direct administration of FSH to the patient for inducing folliculogenesis which feature constitutes a method of treatment of the human body by therapy involving a direct physical intervention on the human body. The Enlarged Board has held in decision G 2/08 (see OJ EPO, 2010, page 456, reasons, point 5.6) that it is established case law "*(…) that any method claim containing even a single step pertaining by nature to a treatment by therapy is not allowable.*" The board concludes that claim 1 can be read as a sequence of two separate activities, the induction of folliculogenesis by the administration of FSH which is not drafted in Swiss-type format followed by the administration of LH drafted in the Swiss-type format and is therefore excluded from patentability pursuant to Article 53(c) EPC.

32. The respondent submitted that the feature "*and wherein folliculogenesis is induced by the administration of FSH*" was part of the definition of the patient group to be treated by the medicament of claim 1 and could not be considered to be a claimed therapeutic method involving a direct physical intervention on the human body.

33. The board does not consider this argument persuasive. The patient group is clearly indicated as being the WHO Group II anovulatory women and in the judgement of the board the wording of the feature "*and wherein folliculogenesis is induced by the administration of FSH*" leaves no doubt that the administration of FSH for the induction of folliculogenesis is carried out as an active step as part of the treatment of these WHO Group II anovulatory women.

34. For the above reasons the board decides that the main request is excluded from patentability pursuant to Article 53(c) EPC and hence unallowable.

Auxiliary requests 1, 2, and 3
Amendments (Article 123(2) EPC) and Article 53(c) EPC

35. The respondent submitted no further arguments for these requests and conceded that the objections that applied to the main request also applied to these requests.

36. The point in time for administration of LH and the daily dose of LH as defined in claim 1 of these requests do not correspond to the point in time and the daily dose disclosed in example 1. Accordingly, all these requests also fail the requirements of Article 123(2) EPC for the same reasons as set out above for the main request.

37. Moreover, claim 1 of all of these requests encompasses the step relating to the induction of folliculogenesis by the administration of FSH and therefore all requests are excluded from patentability pursuant to Article 53(c) EPC for the same reasons as set out above for the main request.

Auxiliary request 4
Admissibility

38. Auxiliary request 4 was filed during the oral proceedings before the board. The appellant submitted that this request not only failed to address all objections raised so far but also lead to new objections. Accordingly it requested that it should not be admitted in the proceedings.

39. The board considers that auxiliary request 4 constitutes a fair attempt to address the objections raised with regard to the higher ranking requests. The amendments made in this request are straightforward and do not lead to any surprising turn of events. Under these circumstances the board decides to admit this request into the proceedings in the exercise of its discretion under Article 13(1) RPBA.

Amendments (Article 123(2) EPC) - claims 1, 3, and 4

40. The respondent indicated example 1 as a basis for the amendments carried out in claim 1.

41. Pursuant to example 1, LH administration starts when there are 4 or more follicles in the range of from 8 to 13 mm in diameter, no larger follicles and an endometrium of 8 mm or more thickness while according to present claim 1, LH administration starts when there are more than 3 follicles with a mean diameter in the range of from 8 to 13 mm and no larger follicles and when the endometrium thickness is 8 mm or more. The diameter and the mean diameter are different parameters and the number and size of the follicles and hence the timepoints defined by the expressions used in example 1 and claim 1, respectively, are therefore different. The

timepoint defined in present claim 1 has therefore no basis in example 1 and extends beyond the content of the application as filed. This was not disputed by the respondent.

42. Claim 1 defines the daily dose of LH as 225 IU or 450 IU. Claims 3 and 4 depend on claim 1 and specify the IU ratio of LH to FSH as being in the range of from 1.5:1 to 20:1 and from 1.5:1 to 10:1, respectively, thus defining possible ranges of amounts for FSH (see section XI above for the complete wording of the claims). Example 1, which forms the basis of claim 1, does disclose the amount of LH used (225 IU/day or 450 IU/day) but does not disclose the amount of FSH being used. The combinations of features arising from the combination of present claim 1 and claims 3 or 4, in other words the specific ratios of LH to FSH, have not been disclosed in example 1 or anywhere else in the application as filed. Therefore, the subject-matter of claims 3 and 4 extends beyond the content of the application as filed.

43. The respondent submitted that claims corresponding to claims 3 and 4 were present in the set of claims as granted and accordingly no objection could be raised under Article 123(2) EPC. The board understand this argument as relying implicitly on the absence of any objection under Article 100(c) EPC against the claims as granted (see section III, above).

44. The board is not persuaded. It is correct that the wording of claims 7 and 8 as granted corresponds to the wording of present claims 3 and 4. In the set of claims as granted, claims 7 and 8 were dependent on claim 1 which related to a daily dose of LH in the range of from 100 to 1500 IU while present claim 1, on which

claims 3 and 4 depend, relates to a daily LH dose of 225 IU or 450 IU. Thus, although claims corresponding to present claims 3 and 4 were present in the set of claims as granted, the combination of features covered by present claims 3 and 4 was not. That no objection under Article 100(c) EPC has been raised against the claims as granted is therefore irrelevant.

45. For these reasons auxiliary request 4 is not allowable under Article 123(2) EPC.

Auxiliary request 5
Admissibility

46. The appellant has not contested the admissibility of this request and the board is satisfied that the amendments made in the request are straightforward and do not lead to any surprising turn of events. Under these circumstances the board decides to admit this request into the proceedings in the exercise of its discretion under Article 13(1) RPBA.

Amendments (Article 123(2) EPC)

47. The request consists of claims 1 and 2. The respondent indicated example 1 as a basis for the amendments carried out in claim 1 and submitted that claim 2 corresponded to claim 3 as granted.

48. The appellant observed that according to example 1 the patients underwent routine ovulation induction with FSH whereas claim 1 did not specify that the ovulation induction was routine. In its view therefore claim 1 violated Article 123(2) EPC.

49. According to established case law of the Boards of Appeal (Case Law of the Boards of Appeal of the European Patent Office, 6th edition 2010, section II.B. 5.3.3) terms used in patent documents should be given their normal meaning in the relevant art. In the board's judgement, in the absence of any information in the claim as regards the procedure to be followed when using FSH for inducing folliculogenesis, the skilled person giving the terms their normal meaning in the relevant art would understand that the protocol to be followed for the induction of folliculogenesis with FSH is the protocol normally, i.e. routinely, used. Therefore, in the board's judgement, the fact that the claim does not refer to "routine" in the context of induction of folliculogenesis does not result in the skilled person being presented with information which was not clearly and unambiguously set out in the application as filed.

50. For these reasons auxiliary request 5 complies with the requirements of Article 123(2) EPC.

Article 84 EPC

51. The appellant objected to claim 1 because it referred to both "inducing folliculogenesis" and "inducing paucifolliculogenesis or unifolliculogenesis". In its view these two terms were mutually exclusive and claim 1 was thus unclear.

52. Claim 1 relates to the treatment of anovulatory women. While in a first step of the treatment administration of FSH induces folliculogenesis, in a second step administration of LH reduces the number of preovulatory follicles per treatment cycle, i.e. promotes paucifolliculogenesis or even unifolliculogenesis. In

other words, the induction of folliculogenesis is a necessary prerequisite for the subsequent induction of of paucifolliculogenesis or unifolliculogenesis. In the board's judgement claim 1 is thus clear.

Amendments (Article 123(3) EPC)

53. The appellant has not raised any objections under Article 123(3) EPC. Since the board has no objections either, the amendments introduced in the claims are regarded as fulfilling the requirements of Article 123(3) EPC.

Article 53(c) EPC

54. The appellant has not raised any objections under Article 53(c) EPC and the board is satisfied that the requirements of Article 53(c) EPC are fulfilled.

Article 83 EPC

55. The appellant has not raised any objections under Article 83 EPC and the board is satisfied that the requirements of Article 83 EPC are fulfilled.

Article 56 EPC
Closest prior art

56. The patent in suit concerns the use of LH for promoting paucifollicular and unifollicular development, when inducing ovulation in anovulatory women. It is common ground between the parties that document (D5) represents the closest prior art. The board sees no reason to disagree.

56.1 Document (D5), a review article, summarises the relative contributions of FSH and LH to folliculogenesis in spontaneous menstrual cycles. According to the last sentence of the abstract the development-related response to LH shown by the pre-ovulatory follicle raises the possibility that exogenous LH might be used as an adjunct to therapy with exogenous FSH in clinical ovulation induction regimes where the aim is to induce monovulation.

56.2 In particular, document (D5) explains the FSH threshold hypothesis and the LH ceiling hypothesis (Figure 1, Table I, Table II). According to the FSH threshold hypothesis ovarian follicles have development-related requirements for stimulation by FSH. Beyond a certain "threshold" level, FSH stimulates granulosa proliferation and functional maturation (including expression of aromatase and the LH receptor). As follicles mature they become increasingly sensitive to FSH. According to this hypothesis, the FSH dose should exceed the threshold of the most mature follicle during ovulation induction.

56.3 By mid-follicular phase, the dominant follicle is recognizable as the largest healthy follicle in either ovary. Maintenance of its status as the dominant follicle becomes increasingly dependent on LH. According to the LH ceiling hypothesis ovarian follicles also have development-related requirements for stimulation by LH. Beyond a certain ceiling level, LH suppresses granulosa proliferation and initiates atresia. Mature follicles are more resistant to LH than immature follicles. According to this hypothesis, the LH dose should not exceed the ceiling of the most mature follicle during ovulation induction.

56.4 As regards the clinical implications of these hypotheses, document (D5) proposes that FSH and LH can be used to develop improved clinical strategies for stimulating ovarian function. According to document (D5) it is desirable to stimulate monovulation in women receiving treatment for ovulatory dysfunction and the challenge is to tailor therapy with FSH and LH, individually or combined, based on the principles put forward.

56.5 Finally, document (D5) proposes (page 191, left hand column, last paragraph) that "*Pure LH may be of particular use in treatment regimes that aim to achieve monovulation for conception in vivo. Once an appropriate (i.e. LH-responsive) stage of follicular development has been achieved in response to treatment with FSH, there are theoretical grounds for reducing or completely withdrawing FSH and* ***maintaining*** *tonic (subceiling) stimulation of the dominant follicle with exogenous LH. Such a low-dose LH "coast", for no more than 1 or 2 days, could have the dual advantage of promoting the terminal maturation of a single pre-ovulatory follicle and simultaneously arresting the development of multiple less mature follicles that would otherwise occur in response to treatment with FSH (Hillier 1993)*" (emphasis added). Document (D5) concludes with stating that "*Controlled clinical trials are required to evaluate these possibilities*".

56.6 The parties disagree on the interpretation of the feature "*withdrawing FSH and* ***maintaining*** *tonic (subceiling) stimulation of the dominant follicle with exogenous LH*", see sections XIV and XV above.

56.7 The board notes that document (D5) discloses to maintain - not to start - tonic stimulation with

exogenous LH. The term "maintaining" in this passage of document (D5) clearly implies that exogenous LH is already present before FSH is withdrawn. In the board's judgment, further evidence that this interpretation is correct can be found in document (D10) which is the document "*(Hillier 1993)*" to which document (D5) explicitly refers at the end of the passage under dispute. Accordingly, document (D10) can be consulted when assessing the teaching of document (D5). Document (D10) is by the same author as document (D5) and proposes that the availability of pure LH could be particularly beneficial to patients with forms of anovulation amenable to gonadotropin therapy in which the object is to stimulate the development of a single ovulatory follicle so that conception might occur *in vivo* (see page 44, last paragraph). According to the last sentence on page 44 of document (D10): "*The strategy involving pure LH would be that once a preovulatory follicle had begun to develop in response to a suprathreshold dose of FSH (given in combination with a tonic amount of LH), treatment with FSH could be gradually withdrawn while tonic stimulation with LH was maintained.*" This passage therefore explicitly teaches that LH is given at a tonic amount concurrently with FSH. Under the heading "conclusions", document (D10) discloses on page 46, last paragraph, that: "*Pure LH could be of particular use in stimulation regimens aiming to achieve mono-ovulation and for conception in vivo. Once the appropriate (i.e. LH-responsive) stage of preovulatory development has been achieved in response to treatment with FSH, it would seem rational to withdraw FSH and maintain tonic (subceiling) stimulation with LH.*" This passage corresponds almost *verbatim* to the passage in question of document (D5). In the light of the passages on pages 44 and 46 of document (D10) the board is satisfied that

"maintaining" tonic (subceiling) stimulation with LH means that exogenous LH is given concurrently with FSH and is continued after FSH is withdrawn.

56.8 In this regard, the board also notes that document (D5) discloses on page 190, left hand column, third paragraph that: "*LH receptors are constitutively present on thecal cells and appear on granulosa cells that have been adequately stimulated by FSH. Tonic exposure to LH facilitates the inductive function of FSH during follicular selection.*" Document (D5) thus discloses explicitly the simultaneous presence of LH and FSH and its advantages. Accordingly, the board is not persuaded by appellant's argument that the skilled person, when considering the whole content of document (D5), would have understood that document (D5) suggested a regime where follicular stimulation was started with FSH alone during the early follicular phase.

56.9 The board concludes that document (D5) proposes on page 191, left hand column, last paragraph, a treatment regimen that aims to achieve monovulation for conception *in vivo* which involves continuous stimulation with LH at a subceiling dose while FSH is withdrawn once an appropriate (i.e. LH-responsive) stage of follicular development has been achieved.

The technical problem to be solved

57. The board considers that the subject-matter of claim 1 differs from the teaching of document (D5) in i) that it relates to the treatment of WHO group II patients, (ii) the daily dose of LH administered and iii) the time point of the administration of LH. Table 3 of the patent in suit shows that this treatment results in

less follicles with a diameter equal or larger than 14 mm.

58. The problem to be solved is therefore defined as the induction of uni-or paucifolliculogenesis in WHO group II anovulatory women. The solution consists in the treatment according to claim 1.

59. The claim under consideration is drawn up in the Swiss-type format and the statement of purpose thus limits the claim such that the whole subject-matter is to be regarded as a solution to the problem (see e.g. decision T 1031/06 of 9 April 2009, reasons, point 23). The board is thus satisfied that the problem is plausibly solved by the subject-matter of claim 1.

60. The appellant submitted that document (D5) disclosed the principle of the claimed invention but not the amount of LH recited in the claim, the patient subgroup and the exact time point for the administration of LH. However, the limitation to WHO group II anovulatory women and the exact time point for the administration of LH were arbitrary and did not contribute to the technical effect. The objective technical problem over document (D5) was regarded as defining an appropriate LH dosage in a treatment protocol wherein "exogenous LH was used as an adjunct to therapy with exogenous FSH in clinical ovulation induction regimes where the aim was to induce monovulation".

61. In the board's judgement this argumentation fails because it has been established that i) document (D5) does not disclose the principle of the claimed invention (see points 56.1 to 56.9 above) and ii) that a distinct functional relationship exists between the sub-group of patients, the administration of FSH, the

time point of LH administration and the daily dose of LH administered (see points 1 to 16 above). These features are thus not arbitrarily chosen but contribute to the claimed technical effect.

Obviousness

62. It remains to be answered whether the skilled person, when faced with the technical problem defined in point 58 above, would have modified the teaching in the closest prior art document (D5) - possibly in the light of other teachings in the prior art - so as to arrive at the claimed invention in an obvious manner.

63. Document (D5) discloses LH administration throughout and does not disclose or suggest the administration of LH only at a later point during follicular development, in particular during the mid- to late-follicular phase. Moreover, document (D5) does not mention any suitable daily dose of LH. Accordingly, the claimed solution is not obvious from document (D5) alone.

64. Document (D1) studies the ovarian response to r-hFSH and r-hLH in women that have been rendered artificially anovulatory. Document (D1) discloses in the paragraph bridging pages 231 and 232 that: "*Defining a cut-off point below which LH or hCG will not maintain follicular growth could be helpful to control the number of preovulatory follicles in ovulation induction protocols.* ***Theoretically****, a sequential FSH and LH ovarian stimulation protocol could be used to limit follicular recruitment, thereby reducing the complications now associated with ovulation induction protocols.*" (emphasis added). Document (D1) thus proposes a protocol which involves sequential FSH and

LH ovarian stimulation to limit follicular recruitment.

65. The first question to be answered is whether the skilled person, when faced with the technical problem formulated above, would even consider document (D1). The women treated in this document have no ovarian dysfunction but are rendered artificially anovulatory by administration of leuprolide acetate to minimize endogenous gonadotropin secretion (see page 229, left hand column, fourth paragraph). In contrast thereto WHO Group II anovulatory women have normal and fluctuating levels of serum FSH and LH. In that regard, the board is not persuaded by appellant's argument that document (D19) equates the patient group disclosed in document (D1) to those patients belonging to WHO group II anovulatory women. Document (D19) merely discloses that in WHO group II anovulatory women or in women treated with analogues of gonadotrophin releasing hormone, pure FSH can stimulate the follicular development (see page 3, right hand column, fourth paragraph). Accordingly, the patients of document (D1) are not WHO group II anovulatory women and can not be equated to WHO group II anovulatory women either.

66. Assuming, for the sake of the argument, that the skilled person would consider document (D1), when faced with the technical problem formulated above, the board notes that document (D1) fails to disclose or suggest the point in time when FSH should be stopped and administration of LH started according to claim 1. Thus, document (D1) discloses in the right hand column of page 231, last paragraph, that: "*Although our data show that LH is capable of maintaining the maturation of follicles with diameters of 14 mm, the actual stage of follicular development when LH can sustain follicular development in the presence of declining*

serum FSH concentrations is not known." In the same paragraph, further down, document (D1) discloses that "*FSH treatment was arbitrarily discontinued when one or more follicles reached a diameter of 14 mm.*" Finally, in the paragraph bridging pages 231 and 232 document (D1) states that: "*Although studies in human have indicated that LH receptors are present on the granulosa cells by the midfollicular phase (day 7) and increased throughout the late follicular phase, the exact size at which a follicle becomes LH responsive is not known".* The board concludes from the above that, even if the skilled person could have considered the teaching of document (D1), it is not established that he would have arrived at the appropriate time point for the administration of LH in WHO group II anovulatory women with a reasonable expectation of success.

67. Document (D19) discloses that FSH can be used to stimulate folliculogenesis in WHO Group II patients (see page 3, right hand column, fourth paragraph). Document (D19) moreover teaches that high levels of LH at the start of stimulation are undesirable (see page 3, left hand column, first paragraph). Document (D19) does however not disclose or suggest that LH should be administered starting in the mid- to late-follicular phase in WHO group II anovulatory women. Accordingly, the skilled person would not have arrived at the claimed solution by combining the teaching of documents (D5) and (D19).

68. Document (D2) relates to a dose finding study on rLH to support rFSH induced follicular development in LH-FSH-deficient anovulatory women, i.e. in women belonging to WHO group I anovulatory women. Document (D2) discloses administration of LH together with FSH from the beginning of the treatment of WHO Group I anovulatory

women (see abstract). Therefore, the skilled person would not obtain any hint from document (D2) to start the administration of LH only in the mid- to late-follicular phase in WHO group II anovulatory women.

69. The appellant submitted that document (D2) also suggested that LH at higher concentrations could be used to achieve folliculogenesis of fewer follicles (page 1512, left hand column, second full paragraph). However the board notes that document (D2) also discloses that this is a hypothesis which requires further investigation (*ibid.*). Under these circumstances, even if it might have been obvious to try in the light of document (D2), to use LH to reduce the number of growing follicles - no case has been made out that the skilled person had also a reasonable expectation of success.

70. In summary, the board concludes that none of the documents relied on by the appellant suggests that LH should not be administered in WHO group II anovulatory women until the mid- to late-follicular phase was reached. Already for this reason alone, none of the documents provides any hint that would have motivated the skilled person to modify the teaching in the closest prior art document (D5) so as to arrive at the claimed invention in an obvious manner. The above considerations in respect of claim 1 apply also to the subject-mater of claim 2 which is dependent on claim 1. For these reasons auxiliary request 5 complies with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of auxiliary request 5 filed during oral proceedings on 26 September 2013 and a description and figures to be adapted thereto.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith

Decision electronically authenticated