Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 18 May 2020

Case Number: T 1971/17 - 3.3.02

Application Number: 10720343.2

Publication Number: 2421887

IPC: C07K7/23

Language of the proceedings: EN

Title of invention:
METHOD FOR THE MANUFACTURE OF DEGARELIX

Patent Proprietor:
Polypeptide Laboratories A/S

Opponent:
Fresenius Kabi Deutschland GmbH

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1971/17 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 18 May 2020

Appellant: (Opponent)	Fresenius Kabi Deutschland GmbH Else-Krömer-Strasse 1 61352 Bad Homburg (DE)
Representative:	Fresenius Kabi Deutschland GmbH Patent Department Borkenberg 14 61440 Oberursel (DE)
Respondent: (Patent Proprietor)	Polypeptide Laboratories A/S Herredsvejen 2 3400 Hilleröd (DK)
Representative:	Schöneborn, Holger Schneiders & Behrendt PartmbB Rechts- und Patentanwälte Huestraße 23 (Kortumkarree) 44787 Bochum (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 30 June 2017 rejecting the opposition filed against European patent No. 2421887 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	A. Lenzen
	R. Romandini

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the opponent (appellant) against the decision of the opposition division (decision under appeal) to reject its opposition to European patent No. 2 421 887 (patent in suit).

II. In its notice of opposition, the appellant requested revocation of the patent in suit in its entirety based on the grounds for opposition pursuant to Article 100(a) (lack of an inventive step), Article 100(b) and Article 100(c) EPC.

III. The following documents that were cited during the opposition proceedings are relevant to this decision:

D1 WO 98/46634 A1

D2 Methods and Protocols of Modern Solid Phase Peptide Synthesis, M. Amblard et al., Molecular Biotechnology, vol. 33, 2006, pages 239 to 254

D3 G. B. Fields et al. in Synthetic Peptides - A User's Guide (ed.: G. A. Grant), Oxford University Press, 2nd edition, 2002, pages 93 to 173

D4 J. Jones, Amino Acid and Peptide Synthesis, Oxford University Press, 2nd edition, 2002, pages 67 to 80

D5 G. B. Fields in Methods in Molecular Biology, vol. 35 (eds.: M. W. Pennington, B. M. Dunn),

Humana Press Inc., 1994, pages 17 to 27

D9 J. Kaneti et al., Org. Biomol. Chem. 2004, 2, pages 1098 to 1103

D11 M. P. Samant et al., J. Med. Chem. 2005, 48, pages 4851 to 4860

IV. With its statement of grounds of appeal, the appellant filed:

D12 M. Bodanszky, Peptide Chemistry - A Practical Textbook, Springer-Verlag, 1988, pages 156 to 159

D13 N. Sewald et al., Peptides: Chemistry and Biology, Wiley-VCH, 2003, pages 224 to 228 and 237

D14 WO 2011/066386 A1

V. On 10 January 2020, the board issued a communication pursuant to Article 15(1) RPBA 2020.

VI. With its letter dated 10 February 2020, the respondent filed:

D15 US patent application No. 61/407,175

VII. By letter dated 7 May 2020, the appellant confirmed that it would be attending the oral proceedings.

VIII. By letter dated 7 May 2020, the respondent requested that the oral proceedings be postponed. This request was rejected by the board in its communication dated 15 May 2020, sent to both parties by fax on that date.

IX. The **appellant** requested

- that the decision under appeal be set aside and that the patent in suit be revoked in its entirety,
- that the following not be admitted into the proceedings:
  - the respondent's submission regarding the complexity of replacing Fmoc side chain protecting groups,
  - the respondent's submission that D16 confirmed the existence of a prejudice, and
  - auxiliary requests 3 and 4.

X. The **respondent** requested

- that the appeal be dismissed (main request), and hence that the patent in suit be maintained as granted, or in the alternative
- that the patent in suit be maintained in amended form based on the sets of claims
  - of auxiliary requests 1 or 2, filed with its reply to the statement of grounds of appeal, or
  - of auxiliary requests 3 or 4, filed with its letter dated 3 April 2020.

XI. The appellant's arguments, where relevant to the present decision, can be summarised as follows.

D1, example 1, was the closest prior art. The respondent had not compared degarelix obtained according to claim 1 with that of D1 in respect of the purity requirement of claim 1. Thus, the subject-matter of claim 1 of the main request differed from D1 only in that Fmoc was used as the protecting group for the α-NH_2 groups. The technical effect was that the synthesis according to claim 1 was less hazardous for humans and

the environment. The objective technical problem had to be seen as the provision of a synthesis of degarelix that was less hazardous for humans and the environment. Both Boc and Fmoc were commonly used as a protecting group for the α-NH_2 group of amino acids in SPPS. On this basis, it was obvious to the skilled person that the objective technical problem would have been solved simply by replacing all the Fmoc protecting groups by Boc groups and *vice versa*. In doing so, the skilled person would not have changed the conditions used in D1 for removing these two protecting groups, as both had to be independently removable. No further modifications to the synthesis of D1 would have been necessary. D9, D11, the scientific paper referred to therein and D1 could not serve as evidence of a prejudice that Fmoc protecting groups should be avoided in molecules also containing a Hor group. There were non-technical reasons why, over a long period, degarelix was only synthesised using a Boc protecting group strategy. In addition, the skilled person would have considered the observations described in D9 irrelevant in the context of a SPPS of degarelix, since the alkaline conditions to be used in the course of Fmoc deprotection were not comparable to those used in D9. The respondent's submission based on D16 that this document could prove this prejudice was not to be admitted. It could and should have been submitted much earlier. The conditions under which a peptide could be cleaved from a solid phase depended on the actual resin used; however, the resin was not structurally defined in claim 1. The passage in D1 on page 10, line 29 to page 11, line 5 had to be interpreted in the overall context of D1. It was fully in line with D1, example 1, and could not be interpreted as indicating that a replacement of protecting groups was not obvious. The main request was therefore not allowable. The amendments to claim 1 of

auxiliary requests 1 to 4 did not add any further distinguishing feature to claim 1 of the main request. Therefore, they were not allowable either.

XII. The respondent's arguments, where relevant to the present decision, can be summarised as follows.

D1, example 1, was the closest prior art. Vis-à-vis D1, the objective technical problem of claim 1 of the main request was the provision of degarelix by a method that maintained the purity of degarelix with regard to the rearrangement product referred to in claim 1 and that was less hazardous for humans and the environment. As was evident from D9, there was a prejudice in the art against the use of Fmoc groups in molecules also containing a Hor group. That prejudice could also be seen in the fact that (i) the prior art, dealing with the SPPS of degarelix, only ever used Boc protecting groups for the α-NH_2 groups, and (ii) the Fmoc protecting group had been known long before the priority date of D1 and yet was not used therein as a protecting group for the α-NH_2 groups. D16 disclosed that Fmoc protecting groups were to be avoided when synthesising peptides containing base-sensitive moieties such as a Hor group. This was a confirmation of the above prejudice. The submission based on D16 was to be admitted, as it reflected the common general knowledge of the skilled person. The method of claim 1 allowed the peptide strand to be cleaved from the resin using less hazardous reagents, namely TFA (patent in suit) instead of HF (D1). A rearrangement of the Hor group was observed both with DBU and DCHA but not with piperidine. Similarly to the patent in suit, D14 and D15 disclosed a synthesis of degarelix based on an Fmoc strategy. These documents were not prior art, but the authors of D14 and D15 considered the use of an Fmoc

strategy for preparing degarelix to be an invention worth filing a patent application. The solution to the objective technical problem suggested by the appellant, namely the replacement of all the Boc by Fmoc groups and *vice versa*, could not be reconciled with the teaching of D1. Therefore, the method of claim 1 of the main request was not obvious. In relation to claim 1 of auxiliary requests 1 and 2, the submissions made with regard to claim 1 of the main request applied. Claim 1 of auxiliary requests 3 and 4 excluded the sequential approach taken in D1, namely the attachment of the Hor group only after the amino acid 4Aph had been attached to the peptide strand. For that reason, the skilled person would not have arrived at their subject-matter in an obvious manner from D1.

Reasons for the Decision

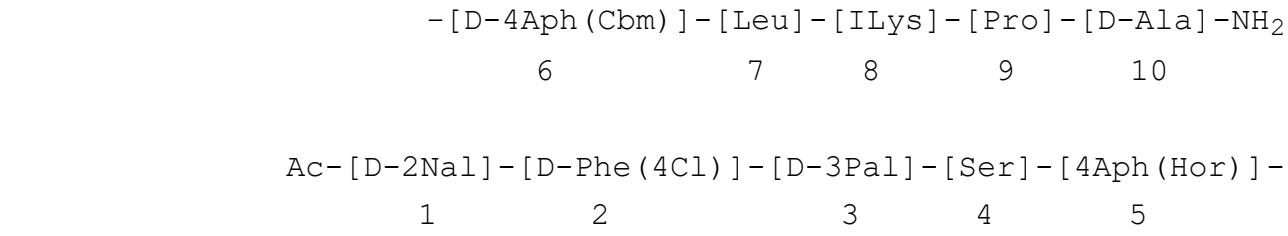
Main request (patent as granted) - Inventive step

1. Claim 1 of the main request reads as follows:

"*A method of manufacture of degarelix, Ac-D-2Nal-D-Phe(4Cl)-D-3Pal-Ser-4Aph(Hor)-D-4Aph(Cbm)-Leu-ILys-Pro-D-Ala-NH_2, wherein degarelix comprises 0.3 % by weight or less, in particular 0.1 % by weight or less, most particularly 0.01 % by weight or less, of Ac-D-2Nal-D-Phe(4Cl)-D-3Pal-Ser-X-D-4Aph(Cbm)-Leu-ILys-Pro-D-Ala-NH2, wherein X is 4-([2-(5-hydantoyl)]acetylamino)-phenylalanine, the method comprising step-wise synthesis on a solid support comprising an amino group linked to the support, wherein the steps comprise providing a solution of an amino acid or peptide of which the α-amino group is protected by Fmoc; contacting the support with the solution in the presence of reagent for forming a peptide bond between*

a carboxyl group of the dissolved amino acid or peptide and the amino group linked to the support for a time sufficient to form said peptide bond; removing Fmoc by contacting the support with an organic base selected from piperidine and C-alkyl substituted piperidine, in particular 2-alkylpiperidine, 3-alkylpiperidine, 2,4-dialkylpiperidine, 2,5-dialkyl-piperidine, 2,6-dialkylpiperidine, wherein alkyl is branched or straight chain from 1 to 6 carbon, in particular methyl or ethyl, most particularly methyl, in an organic solvent."

Thus, it relates to a synthesis of the decapeptide degarelix. According to claim 1, it has the following structure:



Here and in the following, for the sake of clarity, the amino acids are given in squared brackets when written as part of a peptide strand. The numbering above indicates their position in the peptide strand starting at the (acylated) N-terminus and ending at the (amidated) C-terminus. Of particular importance for the present decision are the amino acids at positions 5 and 6. Those are based on 4-aminophenylalanine (4Aph) and D-4-aminophenylalanine (D-4Aph) respectively. They further contain a hydroorotyl group (Hor) and a carbamoyl group (Cbm) bound to the aromatic NH_2 group of 4Aph and D-4Aph respectively.

Claim 1 further requires that "*degarelix comprises 0.3 % by weight or less [...] of Ac-D-2Nal-D-Phe(4Cl)-D-3Pal-Ser-X-D-4Aph(Cbm)-Leu-ILys-Pro-D-Ala-NH2, wherein X is 4-([2-(5-hydantoyl)]acetylamino)-phenylalanine*". This decapeptide is an impurity of degarelix which is formed by rearrangement of the Hor group under certain alkaline conditions.

2. D1 (example 1) discloses a synthesis of degarelix. It was common ground between the parties, and the board has no reason to doubt, that this synthesis is the prior art closest to the subject-matter of claim 1.

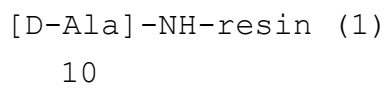
In example 1, D1 uses a different terminology for the amino acids at positions 2 (in D1: D-4Cpa) and 8 (in D1: Lys(isopropyl)) of degarelix. In the following, the terminology used in the patent in suit for the amino acids at these positions will be adopted (position 2: D-Phe(4Cl) and position 8: ILys).

3. The synthesis of D1 is a solid-phase peptide synthesis (SPPS) in which the α-NH_2 groups of the incoming amino acids are Boc-protected. More specifically, two different synthesis strategies are disclosed in D1, summarised in the following.

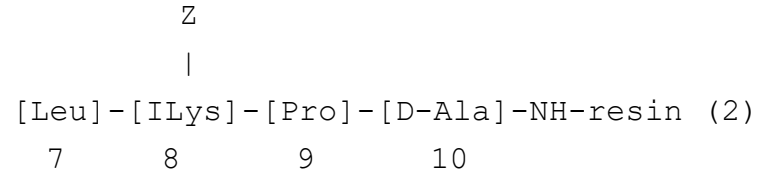
3.1 The first synthesis strategy

The synthesis starts at the C-terminus (position 10). Boc-protected D-Ala is coupled to the amino group of the solid support by an amide bond (D1: page 16, line 30 f). This amide bond formation and the subsequent ones along the peptide strand are performed in an organic solvent (dichloromethane (DCM) together with either dimethylformamide (DMF) or N-methylpyrrolidone (NMP)) in the presence of hydroxybenzotriazole (HOBt)

and a carbodiimide (either diisopropyl carbodiimide (DIC) or dicyclohexyl carbodiimide (DCC)). The Boc protecting group on D-Ala and the Boc protecting groups introduced into the peptide strand in the subsequent steps are removed under acidic conditions with trifluoroacetic acid (TFA) in DCM. This gives intermediate 1:

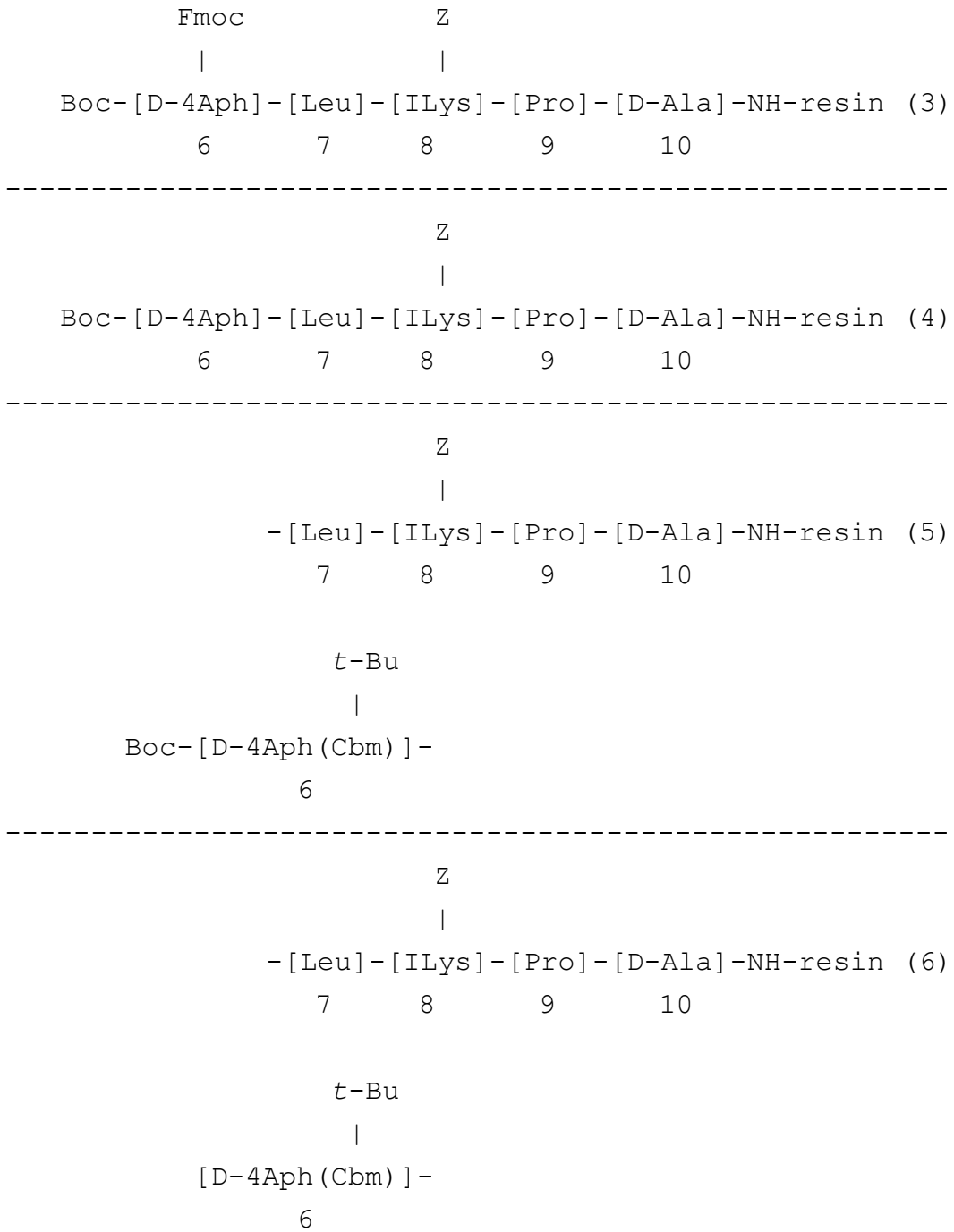


Using Boc-Pro, Boc-ILys(Z) and Boc-Leu in this order, the same sequence of amino acid coupling and Boc deprotection for each of these amino acids gives intermediate 2 (Z stands for benzyloxycarbonyl and serves as a protecting group for the secondary amino group in the side chain of ILys; here and in the following, the side chain protecting groups are shown above the peptide strand):

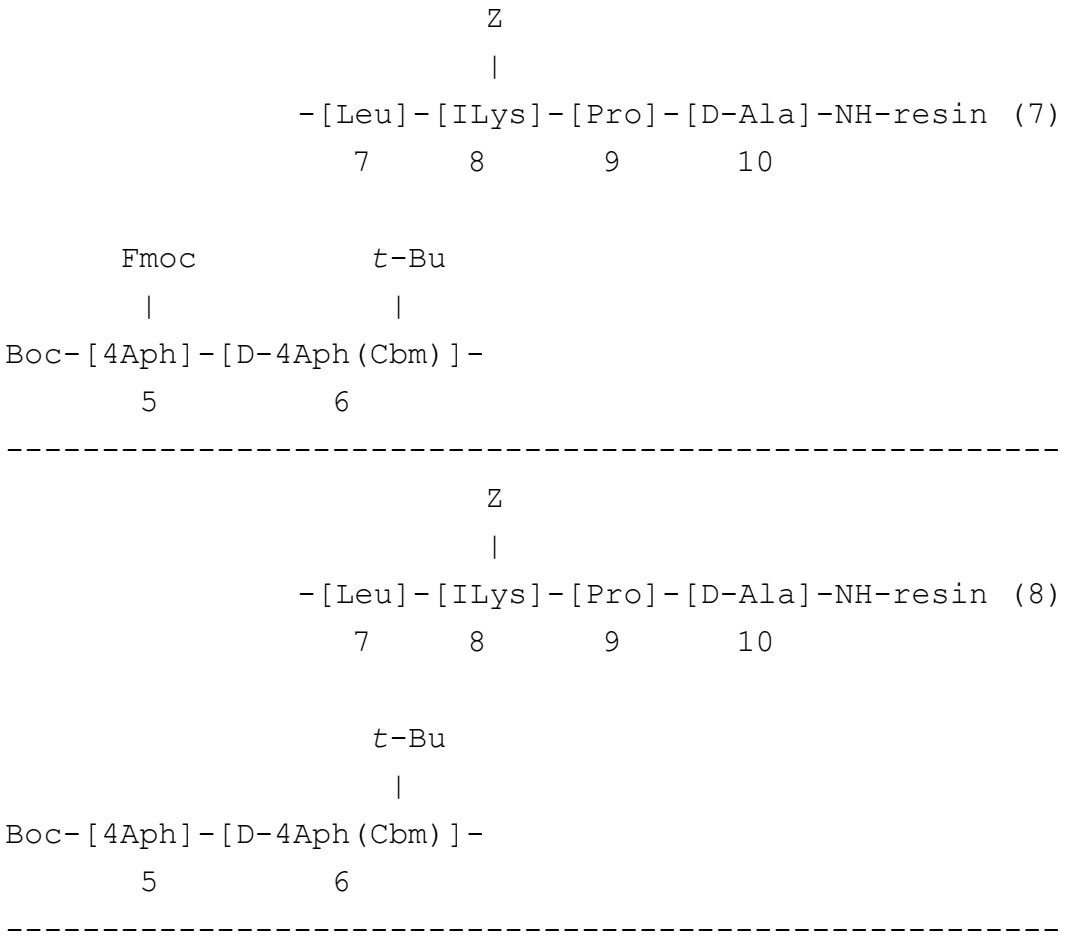


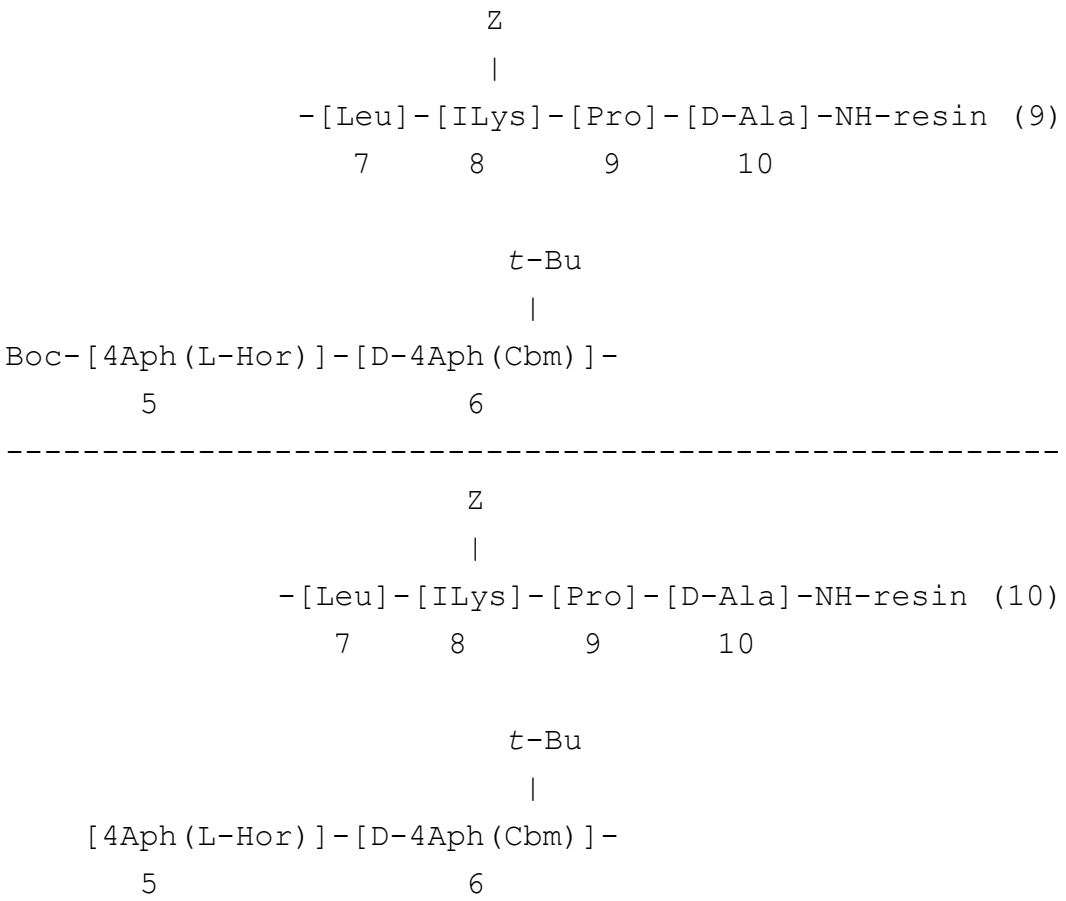
The amino acid at position 6 is not coupled as such, but assembled sequentially on the peptide strand. To this end, double-protected D-4Aph is used, bearing a Boc and an Fmoc protecting group on the α-NH_2 and the aromatic NH_2 group respectively. This building block is coupled to the peptide strand (intermediates 2→3). The Fmoc protecting group on the aromatic NH_2 group is selectively removed under basic conditions using 25% piperidine in DMF while leaving the Boc group unaffected (intermediates 3→4). The Cbm group is attached to the aromatic NH_2 group (intermediates 4→5)

by reacting intermediate 4 with *t*-butyl isocyanate. This results in a Cbm group bearing an intermediate *t*-Bu protecting group (intermediate 5). Boc removal is performed with TFA (intermediates 5→6).

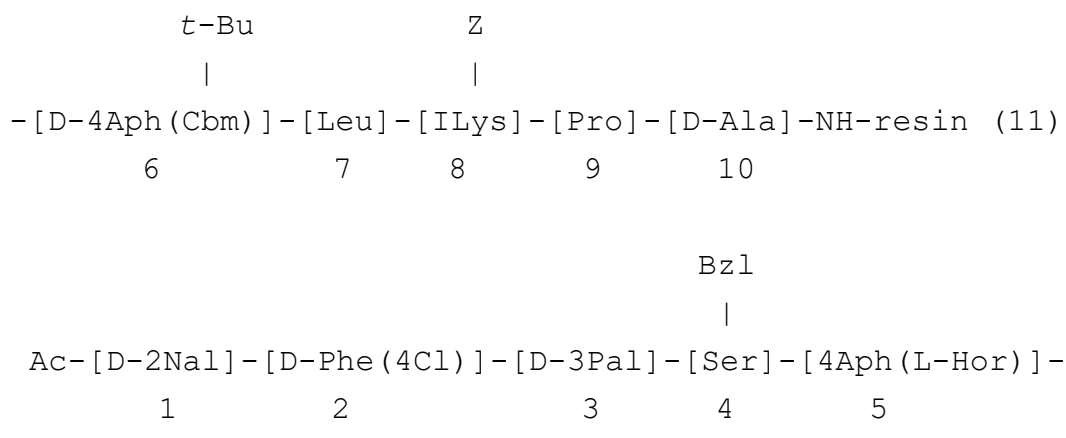


In the succeeding steps, the amino acid at position 5, 4Aph(L-Hor), is assembled sequentially on the peptide strand. This is done in a manner similar to that described above for the amino acid at position 6, by the following steps: coupling of Boc-4Aph(Fmoc) to the peptide strand (intermediates 6→7), selective removal of Fmoc (intermediates 7→8), attachment of the L-Hor group to the aromatic NH_2 group (intermediates 8→9) and removal of the Boc protecting group on the α-NH_2 group (intermediates 9→10).





The synthesis continues by coupling Boc-Ser(Bzl), Boc-D-3Pal, Boc-D-Phe(4Cl) and Boc-D-2Nal in this order and under the conditions described above (Bzl stands for benzyl, the protecting group for the hydroxy group in serine). Boc removal and acylation at the N-terminus yields the following intermediate 11:



Treating intermediate 11 with HF cleaves the peptide strand from the resin and removes the three side chain protecting groups Bzl, *t*-Bu and Z (D1: page 18, lines 27 to 32 and page 13, lines 27 to 34). This yields the end product 12, i.e. degarelix:

-[D-4Aph(Cbm)]-[Leu]-[ILys]-[Pro]-[D-Ala]-NH_2 (12)
6 7 8 9 10

Ac-[D-2Nal]-[D-Phe(4Cl)]-[D-3Pal]-[Ser]-[4Aph(L-Hor)]-
1 2 3 4 5

3.2 The second synthesis strategy

In the first synthesis strategy outlined above, the L-Hor group is attached to the peptide strand before the amino acids at positions 4 to 1. As a side note, D1 (page 18, lines 23 to 26) also discloses a second synthesis strategy wherein the attachment of the L-Hor group is delayed until after the acylation of the N-terminus, and thus after the amino acids at positions 4 to 1 have been attached to the peptide strand.

4. During the oral proceedings, the board stated that the first and the second synthesis strategy were both equally suitable embodiments of D1 and that the subject-matter of claim 1 had to be inventive over both for an inventive step to be acknowledged.

5. Distinguishing features (first synthesis strategy)

5.1 It follows from the preceding point that the first synthesis strategy of D1 discloses the following features of claim 1:

5.1.1 "*[a] method of manufacture of degarelix, Ac-D-2Nal-D-Phe(4Cl)-D-3Pal-Ser-4Aph(Hor)-D-4Aph(Cbm)-Leu-ILys-Pro-D-Ala-NH_2*"

The absolute configuration of the Hor group is not specified in claim 1. Thus, a decapeptide with either an L-Hor or a D-Hor group falls within the structural definition for degarelix in claim 1. This was also explained by the board in its communication pursuant to Article 15(1) RPBA 2020 (point 3.3.1), and was not contested by either party. The degarelix disclosed in D1 contains an L-Hor group (see end product 12 above) and is therefore a degarelix according to claim 1.

5.1.2 "*the method comprising step-wise synthesis on a solid support comprising an amino group linked to the support*"

The fact that the support comprises an amino group linked to it can be inferred from the fact that the carboxylic acid group of D-Ala is attached to the resin by an amide bond (D1: page 16, line 30 f).

5.1.3 "*wherein the steps comprise providing a solution of an amino acid or peptide of which the α-amino group is protected*"

In D1, the reactions are performed in organic solvents. The α-NH_2 group of each incoming amino acid is Boc-protected.

5.1.4 "*contacting the support with the solution in the presence of reagent for forming a peptide bond between a carboxyl group of the dissolved amino acid or peptide and the amino group linked to the support for a time sufficient to form said peptide bond*"

HOBt and a carbodiimide are used in D1 to activate the Boc-protected amino acids and thus to bind them to the α-NH_2 group of the peptide strand or the NH_2 group of the resin.

5.2 Claim 1 further requires that the amount of by-product in the claimed degarelix is below a certain limit, more specifically that "*degarelix comprises 0.3 % by weight or less [...] of Ac-D-2Nal-D-Phe(4Cl)-D-3Pal-Ser-X-D-4Aph(Cbm)-Leu-ILys-Pro-D-Ala-NH2, wherein X is 4-([2-(5-hydantoyl)]acetylamino)-phenylalanine*"; see point 1 above.

In examples 1 and 2, the patent in suit states that the by-product referred to in claim 1 is the result of a rearrangement of the Hor group under certain alkaline conditions. The synthesis of D1 does not use such alkaline conditions, however. It must therefore be concluded that degarelix prepared according to D1 is of a purity as required by claim 1. In fact, the respondent acknowledged this when formulating the objective technical problem in relation to D1 ("by a method that **maintains the purity** of degarelix with regard to the rearrangement product referred to in claim 1"; see below).

5.3 In the first synthesis strategy disclosed in D1, the amino acids at positions 6 and 5 are not incorporated as such but are built up on the peptide strand sequentially, as outlined above. However, such a strategy is not excluded by the wording of claim 1. This is because claim 1 does not in any way define the amino acid to be used, for example in structural terms ("*wherein the steps comprise providing a solution of **an** amino acid or peptide*"), and because it also allows

further steps to be carried out, i.e. those steps which go beyond simply attaching an amino acid to the resin or the peptide strand ("*A method of manufacture of degarelix, [...],* ***the method comprising*** *[...].*"). This was also explained in the board's communication pursuant to Article 15(1) RPBA 2020 (point 3.3.2, last paragraph), and was not contested by either party.

It follows that the method of claim 1 differs from the first synthesis strategy of D1 only in that a different protecting group is used for the α-NH_2 group of the incoming amino acids, namely Fmoc instead of Boc, and that the Fmoc protecting group is removed with an organic base selected from piperidine and a C-alkyl substituted piperidine.

6. Technical effect (first synthesis strategy)

The Boc protecting groups in D1 are removed with TFA. In the method of claim 1, the Fmoc protecting groups are removed with piperidine or a C-alkyl substituted piperidine.

It was common ground between the parties that the use of piperidine or a C-alkyl substituted piperidine is generally less hazardous for humans and the environment than the use of TFA. Thus, the technical effect is that the method of claim 1 is less hazardous for humans and the environment because TFA is replaced by piperidine or a C-alkyl substituted piperidine for the removal of the α-NH_2 protecting groups.

7. Objective technical problem (first synthesis strategy)

Based on the above, the respondent formulated the objective technical problem vis-à-vis D1 as the

provision of degarelix by a method that maintains the purity of degarelix with regard to the rearrangement product referred to in claim 1 and that is less hazardous for humans and the environment. In the respondent's favour, this objective technical problem is adopted in the following.

8. Obviousness (first synthesis strategy)

8.1 The skilled person confronted with this problem would have replaced all the Boc protecting groups on the α-NH_2 groups of each of the incoming amino acids by Fmoc groups.

This is for the following reasons.

Given the objective technical problem above together with the well-known hazardous properties of TFA, the skilled person would have tried to reduce the total amount of TFA needed for the synthesis of degarelix. Since TFA is used in D1 to remove Boc protecting groups, the skilled person would have reduced the overall number of Boc protecting groups necessary for the synthesis of degarelix. Furthermore, as explained by the board in its communication pursuant to Article 15(1) RPBA 2020 (point 3.5.1) and not contested by the respondent, the use of Fmoc groups is commonly known as an alternative to the use of Boc groups for protecting the α-NH_2 group of amino acids in SPPS. On this basis, the skilled person trying to reduce the overall number of Boc protecting groups would have replaced all the α-NH_2 Boc protecting groups on the incoming amino acids by Fmoc groups.

8.2 The above reasoning was discussed during the oral proceedings before the board. In order to rebut it, the respondent put forward the following counter-arguments.

8.2.1 The respondent pointed to the following passage in D1 (page 10, line 29 to page 11, line 5; emphases added):

> "*One example of a chemical intermediate, which might be used to synthesize a GnRH antagonist having a desired residue in the 5- and 6-positions containing hydroorotyl or the like is represented by the formula:* X^1*-D-Nal-D-4Cpa-D-Pal-Ser(*X^2*)-Aph(***X^3***)-D-Aph(***X^3***)-Leu-ILys(*X^4*)-Pro-*X^5*. In synthesizing peptide intermediates having this formula and other analogs, groups* X^1 *to* X^5 *as set forth hereinafter may be employed.*"

It argued that, for a Boc SPPS strategy, Fmoc was preferred as X^3, i.e. the protecting group of the two aromatic NH_2 groups (D1: page 12, line 13). Now, if the skilled person was considering replacing all the α-NH_2 Boc protecting groups by Fmoc groups in the first synthesis strategy of D1 (point 8.1 above), Fmoc groups would be used to protect both the α-NH_2 and the aromatic NH_2 groups. In such a scenario, the same protecting group would be used for both types of amino group, and it would not then be possible to deprotect them independently of each other, which would be problematic in the further course of the synthesis.

This argument fails to convince. It is of paramount importance for the first synthesis strategy of D1 that the α-NH_2 protecting groups can be removed independently of the aromatic NH_2 protecting groups (in other words: that they are orthogonal to each other). The fact that the same protecting groups are removed

simultaneously while different protecting groups can be removed independently of each other is a trivial matter. The skilled person would thus have known that simultaneous deprotection can be avoided by using different protecting groups. To ensure that the α-NH_2 and aromatic NH_2 groups are protected by different protecting groups, the skilled person would therefore not only have replaced all the Boc protecting groups at the ten α-NH_2 groups by Fmoc groups, but would also have replaced all the Fmoc protecting groups by Boc groups on the two aromatic NH_2 groups in the incoming amino acids. Proceeding in this way, the skilled person would have arrived at ten Fmoc and two Boc protecting groups, instead of the ten Boc and two Fmoc protecting groups in the first synthesis strategy of D1. Therefore, such an exchange of protecting groups would have required the use of much less TFA. By keeping to the conditions already taught in D1 for their removal (i.e. TFA for Boc and 25% piperidine in DMF for Fmoc), both types of amino protecting groups would have remained independently removable.

Further, there would have been no evident reason for the skilled person to assume, as the respondent did, that the purity of degarelix could deteriorate, given that the adapted synthesis would have made use of the same protecting groups and conditions for their removal as the first synthesis strategy of D1.

It goes without saying that, apart from the exchange of protecting groups as described above, further adjustments to the first synthesis strategy of D1 would not have been necessary, because all three side chain protecting groups (Bzl, *t*-Bu and Z) are only removed at the very end of the synthesis, when degarelix is cleaved from the resin with HF.

When taken in isolation from the rest of the disclosure of D1, the passage from D1 quoted above could also be understood to mean that both aromatic NH_2 protecting groups X^3 had necessarily to be present in the intermediate at the same time. Upon deprotection, both groups X^3 would then be removed from the molecule simultaneously. The consequence thereof would be that the groups attached to the aromatic NH_2 groups after removal of X^3 would have to be identical, since there will not be any or only a very low degree of selectivity between the two different deprotected aromatic NH_2 groups. Such an understanding, however, would disregard completely what the skilled person would have understood when taking the entire document into account. D1 essentially aims to provide GnRH antagonists with modifications to the 5- and 6-position residues (D1: page 2, lines 35 ff). Therefore, it cannot be the intention of D1 to limit itself to structures with identical residues at these positions. Rather, this passage of D1 is to be interpreted such that it also encompasses the sequential attachment as explained above in relation to D1, example 1. In fact, and in addition to the above, the approach taken in example 1 is actually specifically addressed later in D1 (page 15, lines 27 ff.).

8.2.2 The respondent submitted that replacing the Fmoc protecting groups used in the first synthesis strategy of D1 for the two aromatic NH_2 groups by other protecting groups was not in fact simple but highly complex. If Fmoc was replaced by other protecting groups, side reactions could not be ruled out. This was important because such side reactions resulted in a less pure product and because the end product of the synthesis was a pharmaceutical, i.e. a compound for

which a high degree of purity was required. The appellant requested that this submission not be admitted into the proceedings. The board decided to admit it.

As already explained above, an obvious solution of the objective technical problem would have been to replace all the Boc protecting groups on the incoming amino acids by Fmoc groups and *vice versa*, and to continue to use the same conditions for their deprotection. Such an approach would have made use only of protecting groups and reaction conditions which are already disclosed in D1. It cannot therefore be seen why such an approach should have led to side reactions. Thus, the respondent's submission is not convincing and its admittance does not support its argumentation. Therefore, no reasons need to be given for its admittance.

8.2.3 The respondent argued that there was a prejudice in the art against the use of Fmoc protecting groups in molecules that also contained a Hor group. As was evident from D9, hydroorotic acid underwent a rearrangement to hydantoinacetic acid under alkaline conditions. Consequently, the skilled person would not have modified the synthesis of D1, as suggested by the appellant. More specifically, by using 25% piperidine in DMF, i.e. a base, he or she would have expected the purity of degarelix to be reduced. The respondent also pointed out that the prior art relating to the SPPS of degarelix only ever used Boc protecting groups for the α-NH_2 groups. D1 and D11 were such prior art documents. D11 referred to a paper by Theobald et al. Both used the same Boc protecting group strategy; however, D11 had been published 14 years later than the paper by Theobald et al. This showed the reluctance to use Fmoc

protecting groups in the SPPS of degarelix. Further, the Fmoc protecting group had been known long before the priority date of D1 and yet was not used therein as a protecting group for the α-NH_2 groups. This also showed that there must have been such a prejudice in the art.

This is not convincing. As set out above, in arguing that a prejudice existed, the respondent relied on D9, D11, the paper by Theobald et al., referred to in D11, and D1. D9 is a research paper which investigates the influence of the Thorpe-Ingold effect on the formation of five-membered rings from the rearrangement of hydroorotic to hydantoinacetic acids in aqueous solutions of KOH (D9: scheme 3). D11 was published in 2005 and is another research paper. It reports on the discovery of novel degarelix analogues (D11: abstract). To this end, it uses the same protecting group strategy as D1 (Boc-protected α-NH_2 groups). The paper by Theobald et al., referred to in D11 (page 3, paragraph 2), is another scientific paper, published in 1991. D1 is a patent document which describes the synthesis of degarelix as outlined above. Now, a prejudice in any particular field relates to an opinion or preconceived idea **widely or universally held by experts in that field** (Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, I.D.10.2). None of these documents - D9, D11, the paper by Theobald et al. or D1 - teaches explicitly against using Fmoc in molecules which also contain a Hor group. For that reason alone, these documents cannot confirm the prejudice alleged by the respondent. Moreover, even if it had indeed been the case, it might still not necessarily have served as evidence of an opinion or preconceived idea widely or universally held by experts in the field of SPPS, because such a statement in a

research paper (D9/D11/Theobald et al.) or patent document (D1) might merely have reflected the personal opinion of the authors or inventors. Nor can the fact that degarelix had been prepared using only the Boc protecting group strategy for quite some time before the priority date of the patent in suit serve as an indication, let alone as proof, of the existence of a prejudice. As put forward by the appellant in its statement of grounds of appeal (page 20, paragraphs 1 and 2), non-technical reasons could very well have been responsible for the fact that the Boc strategy was adhered to for a certain period of time. For example, filing of the patent application D1 and the patent granted therefrom might have deterred competitors from devising alternative syntheses for degarelix. Likewise, alternative syntheses for degarelix might have become commercially valuable only after it had received regulatory approval as a drug. Thus, in the present case, none of the documents relied upon by the respondent is suitable evidence for the alleged prejudice.

In addition, the following is noted with regard to D9. This document is not related in any way to the field of peptide synthesis, let alone SPPS. Therefore, it is highly questionable whether the skilled person would have taken it into account at all. Yet even if, for the sake of argument, the skilled person had considered it, this would not have prevented him or her from modifying the synthesis of D1 as outlined above. The reason for this is that, first, the rearrangement reactions in D9 are carried out in aqueous KOH, i.e. under very strong alkaline conditions that should generally be avoided in peptide synthesis, and, secondly, these conditions are by no means comparable to the very mild alkaline conditions used in D1 for Fmoc removal.

8.2.4 During the oral proceedings before the board, the respondent also referred to D16, page 5, paragraph 2 for the first time. This document disclosed that Fmoc protecting groups were to be avoided when synthesising peptides containing base-sensitive moieties. The respondent saw this as a confirmation of the above-mentioned prejudice. The appellant requested that this submission not be admitted.

As is clear from the respondent's reply to the notice of opposition (page 12, paragraphs 3 ff.), the question of whether there was a prejudice in the art against the use of Fmoc protecting groups was already discussed at the beginning of the opposition proceedings. In fact, the opposition division pointed out that this issue had to be given particular consideration during the oral proceedings (annex to the summons to oral proceedings, point 17). Consequently, this point is discussed extensively in the decision under appeal (points 31 to 33). It follows that the above submission based on D16 could and in fact should already have been filed during the proceedings at first instance. Therefore, the board decided not to admit the respondent's submission in relation to D16 into the proceedings, pursuant to Article 12(4) RPBA 2007 in conjunction with Article 25(2) RPBA 2020.

8.2.5 The respondent held that the use of Fmoc as protecting group for the α-NH_2 group of amino acids made it possible to cleave the peptide strand from the resin using less hazardous reagents. While D1 had to use HF for this purpose, examples 3 and 4 of the patent in suit showed that the less hazardous TFA could be used.

This argument is not convincing, if only because degarelix no longer bears any α-NH_2 protecting groups at all when it is cleaved from the resin. On the contrary, the fact that, in D1 and the patent in suit, different agents for cleaving degarelix from the resin can be used and in fact are used is a consequence of using different resins, more specifically different anchor groups, by which degarelix is bound to the actual solid support. However, claim 1 is not restricted in that respect, and allows the same resin to be used as in D1.

8.2.6 The respondent also referred to examples 1 and 2 in the patent in suit and submitted that a rearrangement of the Hor group was observed with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) and dicyclohexyl amine (DCHA) but not with piperidine. Since DBU at least was also commonly used for removing Fmoc protecting groups, the use of piperidine in the method of claim 1 was not obvious.

As explained above, when modifying the synthesis of D1 by replacing all the Boc by Fmoc groups and *vice versa* the skilled person would have kept to the removal conditions applied in D1, i.e. 25% piperidine in DMF for Fmoc. Moreover, even without any guidance from D1, the use of piperidine in DMF would first have been tested by the skilled person for the removal of Fmoc groups on the basis of the evidence available in the present case (e.g. D2: page 249, left column, last paragraph; D3: page 100, lines 4 to 6; D4: page 76, scheme 9.8; D5: page 17, lines 2 to 6 from the bottom). Against this background, the fact that less commonly used reagents for removing Fmoc protecting groups (DBU and possibly DCHA) yield degarelix with a lower degree

of purity cannot argue in favour of an inventive step for a much more commonly used reagent (piperidine).

8.2.7 The respondent pointed to D14 (claim 8) and one of its priority applications, D15 (page 9, line 23 f). These documents did not constitute prior art, because their effective dates were later than that of the patent in suit. Nevertheless, they also disclosed the synthesis of degarelix comprising step-wise synthesis on a solid-phase using amino acids with an Fmoc protecting group on the α-NH_2 groups. Clearly, the authors of D14 and D15 considered the use of an Fmoc strategy for preparing degarelix to be an invention worth filing a patent application. This was a strong indication that it was not obvious to those skilled in the art to switch from Boc to Fmoc when synthesising degarelix.

The board does not agree. There might be numerous reasons for filing patent applications, and to point to the existence of a later-filed patent application to support an inventive step of a patent application filed earlier is, in the board's judgement, not a sensible approach. In fact - without intending to imply that this is so in the present case - if such an argument were accepted, an applicant for a patent application A would only need to file (or ask someone to file) a series of further patent applications relating to the same subject-matter shortly after the filing of A, in order for its inventive step argument in relation to A to be supported.

8.3 Consequently, starting from D1 as closest prior art and after making an obvious modification to the first synthesis strategy, the skilled person would have arrived at the subject-matter of claim 1 without the need for inventive skills. The subject-matter of claim

1 does not therefore involve an inventive step, and the main request is not allowable.

9. As is clear from the assessment above, claim 1 is not inventive over the first synthesis strategy of D1. Therefore, the presence or absence of an inventive step over the second synthesis strategy does not have to be assessed.

Auxiliary requests 1 and 2 - Inventive step

Claim 1 of auxiliary requests 1 and 2 differs from claim 1 of the main request only

- in that the Hor group of degarelix has been defined as having the L-configuration (both requests) and
- in that the method is now based on the use of amino acids only and no longer allows peptides (i.e. fragments of degarelix comprising more than one amino acid) to be used in the synthesis (auxiliary request 2).

As explained above, the first synthesis strategy of D1 attaches L-hydroorotic acid to the peptide strand, and also uses only simple amino acids. Consequently, the amendments above do not introduce additional distinguishing features vis-à-vis the first synthesis strategy of D1.

Therefore, the reasoning above in relation to claim 1 of the main request applies *mutatis mutandis*. As a consequence, auxiliary requests 1 and 2 are not allowable.

Auxiliary requests 3 and 4 - Admittance

The respondent filed the sets of claims of auxiliary requests 3 and 4 with its letter dated 3 April 2020. The appellant requested that they not be admitted into the proceedings. During the oral proceedings the board decided to admit them. In view of the fact that neither of them is allowable (see below), there is no need to give reasons for their admittance.

Auxiliary request 3 - Inventive step

10. Compared to claim 1 of auxiliary request 2, claim 1 of auxiliary request 3 contains the following additional feature:

> "*wherein the 4Aph(L-Hor) moiety does not undergo rearrangement during the solid-phase synthesis of degarelix in spite of being subjected to several cycles of Fmoc protection and deprotection under basic conditions*".

10.1 In this context, in its letter dated 3 April 2020 (pages 4 ff) the respondent argued that the wording of claim 1 implied the use of Fmoc-4Aph(L-Hor)-OH as a reagent. This ruled out the sequential approach of D1, in which the L-Hor group was attached to the amino acid 4Aph already bound to the peptide strand. This had a number of advantages. For example, the overall yield of degarelix was increased, and racemisation of the L-Hor group was avoided, as it did not have to be attached separately to the peptide strand.

However, this argument was not relied upon during the oral proceedings. In any case, it is not convincing. Similarly to claim 1 of auxiliary request 2, the

wording of claim 1 of auxiliary request 3 is still such that it does not rule out the sequential approach of D1. Although claim 1 refers to the "*4Aph(L-Hor) moiety*" it does not in any way specify how this moiety is to be incorporated into the peptide strand.

10.2 The additional feature above states "*does not undergo rearrangement during the solid-phase synthesis of degarelix*". This is not a step of the synthesis but merely reflects an observation by the inventors when carrying out the method of claim 1. The feature also states "*in spite of being subjected to several cycles of Fmoc protection and deprotection under basic conditions*". However, in the first synthesis strategy of D1 the L-Hor group is attached to the peptide strand before amino acids 4 to 1. This implies that the L-Hor group is subjected to several deprotection reactions in the further course of this synthesis. Further, the fact that Fmoc is used as α-NH_2 protecting group and that basic conditions are used for its removal, namely piperidine or a C-alkyl substituted piperidine, is already indicated in the part of claim 1 which precedes the above feature.

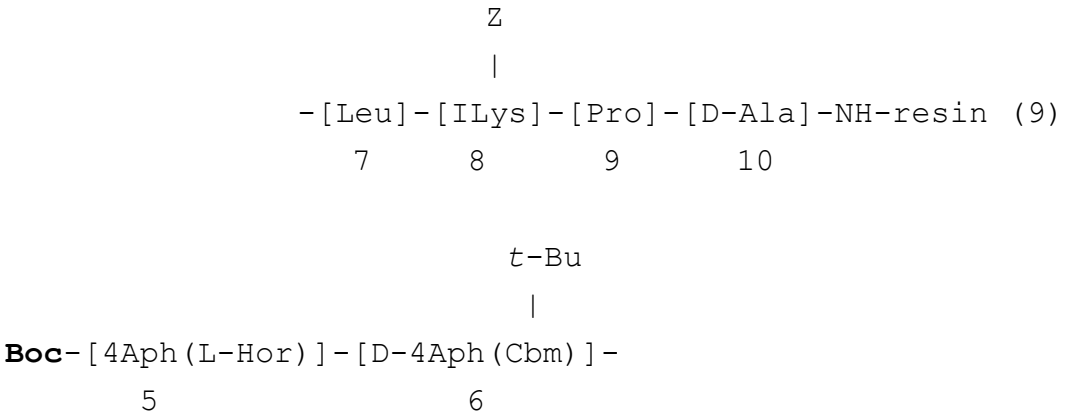
Consequently, the additional feature does not introduce a further distinguishing feature vis-à-vis the first synthesis strategy of D1. The reasoning above in relation to claim 1 of the higher-ranking requests applies *mutatis mutandis*, and auxiliary request 3 is not allowable.

Auxiliary request 4 - Inventive step

11. Compared to claim 1 of auxiliary request 3, claim 1 of auxiliary request 4 contains the following additional feature:

"*wherein in the course of the method **Fmoc**-4Aph(L-Hor)-D-4Aph(Cbm)-Leu-ILys-Pro-D-Ala-NH-Resin is an intermediate and the intermediate comprises side chain protection groups to protect side chains of amino acids particularly reactive or labile, wherein the side chain protection groups are removed once the full length of the growing peptide has been achieved*" (emphasis added).

As shown above, the first synthesis strategy of D1 proceeds via the following intermediate 9 (emphasis added):



This intermediate further comprises side chain protecting groups (*t*-Bu on D-4Aph(Cbm) and Z on ILys) to protect the side chains of the amino acids in positions 6 and 8. These side chain protecting groups are removed upon cleavage of degarelix from the resin, i.e. only once the full length of the growing peptide has been achieved.

Thus, the intermediate referred to in claim 1 differs from intermediate 9 of D1 only with regard to the α-NH_2 protecting group. However, the use of Fmoc as α-NH_2

protecting group is already indicated in the part of claim 1 which precedes the above feature.

Consequently, the above feature does not introduce a further distinguishing feature vis-à-vis the first synthesis strategy of D1. The reasoning above in relation to claim 1 of the higher-ranking requests applies *mutatis mutandis*, and auxiliary request 4 is not allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent in suit is revoked.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated