PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COPA Copenhagen Patents
Rosenvængets Allé 25
2100 Copenhagen Ø
DANEMARK

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18.07.2025

Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
P2123PC00	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2024/082514	15.11.2024	17.11.2023

Applicant
Gubra A/S

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
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Authorized Officer

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P2123PC00	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2024/082514	International filing date *(day/month/year)* 15.11.2024	Priority date *(day/month/year)* 17.11.2023
International Patent Classification (IPC) or national classification and IPC INV. C07K14/72		
Applicant Gubra A/S		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ a total of 8 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions).
      ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2).
      ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)).
   b. ☐ a separate electronic file containing a sequence listing *(sent to the International Bureau only)*

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.06.2025	18.07.2025

Name and mailing address of the international preliminary examining authority:

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2024/082514

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-62 as originally filed

Sequence listings, SEQ ID NO

1-262 as originally filed

Claims, Numbers

1-16 filed with the letter of 27-06-2025

Drawings, Sheets

1/8-8/8 as originally filed

☒ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-*bis*)):
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:

5. ☐ This report has been established:
   - ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-*bis*) and 70.2(e)).
   - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4*bis* and 70.2(e)).

6. ☒ With regard to top-up searches (Rules 66.1*ter* and 70.2(f)):
   - ☒ A top-up search was carried out by this Authority on 03.07.2025 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
     - ☐ Additional relevant documents have been discovered during the top-up search.
   - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.

7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* *If item 4 applies, some or all of those sheets may be marked "superseded".*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed.

   b. ☐ furnished subsequent to the international filing date for the purposes of international search and/or examination,

      ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

   c. ☐ furnished to this Authority as an amendment* under PCT Article 34 on .

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established to the extent that a meaningful opinion referred to in Article 33(1) could be formed without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

* *If item 4 in Box No. I applies, the sequence listing, which forms part of the basis of the report, may be marked "superseded."*

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1 WO 2022/038179 A1 (SANOFI SA [FR]) 24 February 2022 (2022-02-24)cited in the application

1 Claim 1 on file relates to analogues of UCN-2, wherein X^{36} and X^{40} have been selected to improve the solubility with glutamate residues and the lipidation has been limited to positions X^{32} or X^{33} being K. At the same time, claim 1 defines many positions with degenerations, but contains a functional limitation.

2 The subject-matter of claims 1-16 appears to be novel, because the prior art does not disclose analogues of UCN-2 as defined in claim 1.

3 The subject-matter of claims 1-16 appears to involve an inventive step in the sense of Article 33(3) PCT.

3.1 D1 is considered to be the closest prior art and discloses analogues of UCN-2 and their effects on systolic blood pressure, body mass and body fat content (see claims and examples therein).

3.2 The subject-matter of claims 1-16 relate to analogues of UCN-2 with glutamate residues in positions X36 and X40 together with the lipidated lysine residue in position X32 or X33.

3.3 Table 1 of the applications shows that SEQ ID NOs:5-7 with these differences resulted in good solubility without adversely affecting CRHR2 potency and increase CRHR2 selectivity (hCRHR1-EC_{50}/hCRHR2-EC_{50} of 4167, 1852, 2000 respectively as compared to 917 of control). Polypeptides according to SEQ ID NOs: 215, 238, 6 and 16 are shown to result in a dose-dependent reduction in body weight and fat tissue mass while lean tissue mass was maintained (see example 10 and fig. 5) and they are also shown to have desired properties (see example 6-9 and tables 6-14) and for example hCRHR1-EC_{50}/hCRHR2-EC_{50} of 5747 and 6329 for SEQ ID NOs:215 and 238, respectively (see table 5 and more values in table 10, also for SEQ ID NOs:6 and 16).

3.4 The technical problem may be regarded as the provision of analogues of UCN-2 with improved properties.

3.5 Since the prior art does not give any pointer to the claimed polypeptides and claim 1 contains a functional limitation that the hCRHR1-EC_{50}/hCRHR2-EC_{50} ratio is at least 1000, the technical problem is considered to have been solved over its entire breadth in a non-obvious manner.

Re Item VIII

Certain observations on the international application

1 In claim 12, the text refers to "Formula (I)", while the formula is labelled as "Ia".

2 The description contains many Formulas (I), but they are not identical to each other.

The European Patent Office
80469 Munich
Germany

COPA
copenhagen patents

Our ref.: P2123PC00 Date: 27 June 2025

DEMAND – PCT CHAPTER 2
International patent application no. PCT/EP2024/082514

The European Patent Office is hereby requested to carry out preliminary examination according to the enclosed DEMAND.

The official fees for examination are to be deducted from our EPO deposit account no. 28030266.

1. Amendments

Amended claim 1 reads as follows:

"A polypeptide or a pharmaceutically acceptable salt thereof comprising the structure of Formula (I)

X^4-V-L-S-L-D-V-P-I-G-L-L-Q-I-L-L-X^{20}-X^{21}-A-R-A-R-A-A-R-E-Q-A-X^{32}-X^{33}-N-X^{35}-E-I-X^{38}-A-E-X^{41}-NH_2

(I)

wherein
X^4 is selected as I, MeI or P;
X^{20} is selected as E, A, F, G, H, I, K, L, N, Q, R, S, T, or V;
X^{21} is selected as Q or L;
X^{32} is selected as T or K;
X^{33} is selected as T, E, K, V, Y, W, S, P, F, L, I, H, G, Q, A or Aib;
X^{35} is selected as A, E, W, T, S, F, K, L, H, G, Q, D, N, R, Aib, L, I, or V;
X^{38} is selected as L or Nle;
X^{41} is V, or I;
and wherein only one of X^{32} or X^{33}, is selected as K, and wherein the K is lipidated optionally through a linker/spacer and further wherein the hCRHR1-EC_{50}/hCRHR2-EC_{50} ratio is at least 1000."

Basis for said amendment can be found in claim 1 as filed in conjunction with page 6, lines 3-4 stating " *Preferably, the selectivity ratio is higher than native UCN2 (selectivity ratio of 917, see Table 2). Thus, preferably, the hCRHR1-EC50/hCRHR2-EC50 ratio is at least 1000,"*

The dependency of claim 7 has been amended to specify "*according to any one of claims 1-3*" instead of "*according to any one of the preceding claims*".

Formula (I) in claim 12 has been amended to Formula (Ia).

We submit that the amendments do not introduce any new subject-matter and hence do not contravene Art. 34(2)(b) PCT.

The general inventive concept of claim 1 resides in the finding that glutamate residues in the positions X^{36} and X^{40}, together with a lipidated lysine residue in position X^{32} or X^{33}, provides potent and selective hCRHR2 agonists. This is the common technical effect that is shared by the polypeptides of claim 1.

2. Comments on the ISR/WO

The Examiner is of the opinion that the subject-matter of previous claims 1-12 and 15-16 do not involve an inventive because claim 1 relates to a large number of analogues of UCN2, without a demonstrated effect for each of them, whereby the technical problem is not considered solved over the entire scope (see the ISR/WO - points 3.5 and 3.6). However, the Examiner acknowledges an inventive step for the functional limitation present in claim 14 (see the ISR/WO - point 3.8).

Albeit a functional limitation has been introduced, we respectfully disagree with the Examiner in the assessment that claim 1 as filed does not solve a technical problem over the entire scope. Hence, we kindly request the Examiner to reconsider whether a functional limitation is in fact appropriate in view of the data in the application and the reasoning set forth below.

a. Technical effect over the entire scope

Neither the PCT, nor the EPC, requires that a demonstrated technical effect is shown for each and every polypeptide falling within the ambit of the claim scope. If an effect was in fact required to be demonstrated for each peptide falling within claim 1, an invention could not be generalized to any extent, contrary to established patent law:

> *"Most claims are generalisations from one or more particular examples. The extent of generalisation permissible is a matter which the division must judge in each particular case in the light of the relevant prior art. Thus an invention which opens up a whole new field is entitled to more generality in the claims than one which is concerned with advances in a known technology. A fair statement of claim is one which is not so broad that it goes beyond the invention nor yet so narrow as to deprive the applicant of a just reward for the disclosure of his invention. The applicants are allowed to cover all obvious modifications of, equivalents to and uses of that which they have described. In particular, if it is reasonable to predict that all the variants covered by the claims have the properties or uses the applicants ascribe to them in the description, they are allowed to draw the claims accordingly. After the date of filing, however, the applicants are allowed to do so only if this does not contravene Art. 123(2)."* [EPO guidelines F-IV 6.2] [Our emphasis].

Thus, we respectfully submit that this is an erroneous requirement that cannot lead to an objection for lack of an inventive step. Rather, what is decisive is whether a technical effect is credibly achieved over the whole claim scope based on the data in the application as filed:

> *"The expression "technical problem" is interpreted broadly; it does not necessarily imply that the technical solution is an improvement to the prior art. Thus the problem could be simply to seek an*

alternative to a known device or process which provides the same or similar effects or is more cost-effective. A technical problem may be regarded as being solved only if it is credible that substantially all claimed embodiments exhibit the technical effects upon which the invention is based. Criteria for deciding whether lack of reproducibility of the claimed invention is to be treated under Art. 56 or 83 are explained in F-III, 12." [EPO guidelines F-IV 6.2] [Our emphasis].

We note that the Examiner only refers to the solubility of SEQ ID NOs: 5-7 in Table 1 as part of the technical effect in support of claim 1 (see point 3.3 of the ISR/WO):

"*Table 1 of the applications shows that SEQ ID Nos: 5-7 with these differences resulted in good solubility without adversely affecting CRHR potency and increase CRHR2 selectivity*" [point 3.3 of the ISR/WO].

Therefore, it appears that the Examiner has only taken a few sequences into account for which solubility data was presented. If so, we submit that this is a misunderstanding. It is well-known in the peptide field that charged amino acid residues, like glutamate, can be used to alter solubility because of its hydrophilic nature. Thus, the solubility improvement, as such, is not the surprising finding, but rather an expected effect of lowering the pI, and therefore applicable to all the claimed polypeptides. The surprising finding resides in the fact that glutamates can be introduced in X^{36} and X^{40}, without adversely affecting CRHR2 potency/selectivity (see matched molecular pairs SEQ ID NO: 3 and 4 versus SEQ ID NO: 2 in Table 1 and random forest model in Fig. 1). Likewise, the half-life extension obtained by introducing a lipidated lysine residue is also not a surprising finding, as such, as this is also a well-known effect of lipidation. The surprising finding resides in that a lipidated lysine residue in position X^{32} or X^{33} provides high CRHR2 potency/selectivity compared to the lipidation position used in the closest prior art D1 (see matched molecular pairs SEQ ID NO: 3 and 4 versus 261 in Table 1 and the complete lipidation scan shown in Fig. 2B).

3	X^{32}=K(lip); X^{36}=E; X^{40}=E	1.1	>5000	>4546	-6.1 / -15	No	4.5	10
4	X^{33}=K(lip); X^{36}=E; X^{40}=E	1.3	>5000	>3846	-1.3 / -3.9	No	ND	9.1
261	X^{15}=K(lip); X^{36}=E; X^{40}=E	24	>5000	>208	ND	ND	ND	ND

As can been seen from these matched molecular pairs, lipidation in position X^{15} was associated with a pronounced loss in hCRHR2 potency, and hence also a loss in selectivity, compared to lipidation in position X^{32} or X^{33}. This effect is further supported by roughly 200 additional polypeptides in Table 3 of the application as filed (see pEC_{50} values on hCRHR2 versus hCRHR1), wherein lipidation in X^{32} provides potent hCRHR2 agonists with high selectivity over hCRHR1.

Thus, we respectfully submit that the effect is supported over the whole claim scope and that the inventive step objection is not justified. We therefore submit that a functional feature should not be required for the acceptance of an inventive step.

We further note that the Examiner stated that "*At the same time, claim 1 defines many positions with degenerations*". For the sake of clarity, we would like to highlight that with respect to the three amino acid positions (i.e. X^{20}, X^{33} and X^{35}) in claim 1 that allow for a substantial number of different amino acid residues,

each of these amino acid residues have been exemplified in the claimed polypeptides (see Table 3 bottom and Table 4). For this reason, we submit that high CRHR2 potency/selectivity is also obtained when these amino acid residues are present in position X^{20}, X^{33} and/or X^{35}. Insofar a specific combination has not been made, it at least renders such a combination credible without any evidence to the contrary.

In summary, we submit that the large number of peptides exemplified (see Tables 3 and 4) in conjunction with the findings from the large peptide libraries (see e.g. Example 4 with a library of 1140 peptides, , render it credible that the technical effect of high of CRHR2 potency/selectivity is achieved over the entire scope of claim 1.

Hence, we kindly request the Examiner to reconsider whether a functional limitation is required in view of the extensive data provided in the application as filed and the explanation above.

b. Inventive step - Problem & solution approach

Closest prior art:
D1 may be considered the closest prior art to the present invention as it is directed to the same purpose or effect, of providing hCRHR2 agonists. D1 discloses analogues of UCN2, wherein the polypeptides are lipidated at a lysine residue in position X^{12} (corresponding to X^{15} using the numbering in the present application) (see claim 1, aspect 1 and Table 2 in D1).

The differentiating feature:
At least one differentiating feature is that the present polypeptides are lipidated in position X^{32} or X^{33}.

The technical effect:
The technical effect of the differentiating feature is that lipidation in position X^{32} or X^{33} provides higher hCRHR2 potency and higher selectivity compared to lipidation in position X^{15} (see SEQ ID NO: 3 and 4 versus SEQ ID NO: 261 in Table 1. The high potency and selectivity are further supported by the examples in Table 3 and 4.

The objective technical problem:
The objective technical problem may be worded as how to provide analogues of UCN2 with improved hCRHR2 potency and selectivity.

The solution is non-obvious:
What remains to be analysed is whether the skilled person, posed with the objective technical problem, and starting from D1 alone, or in view of any of D2-D5, would arrive at the claimed solution. As neither D1, nor any of D2-D5, teach or even suggest that improved potency and selectivity may be obtained by lipidation in X^{32} or X^{33}, we respectfully submit that claim 1 possesses an inventive step.

Final Remarks

In view of the above, we respectfully request positive reconsideration of the present application.

Best regards
COPA Copenhagen Patents

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CLAIMS

1. A polypeptide or a pharmaceutically acceptable salt thereof comprising the structure of Formula (I)

X^4-V-L-S-L-D-V-P-I-G-L-L-Q-I-L-L-X^{20}-X^{21}-A-R-A-R-A-A-R-E-Q-A-X^{32}-X^{33}-N-X^{35}-E-I-X^{38}-A-E-X^{41}-NH_2 (I)

wherein

X^4 is selected as I, MeI or P;

X^{20} is selected as E, A, F, G, H, I, K, L, N, Q, R, S, T, or V;

X^{21} is selected as Q or L;

X^{32} is selected as T or K;

X^{33} is selected as T, E, K, V, Y, W, S, P, F, L, I, H, G, Q, A or Aib;

X^{35} is selected as A, E, W, T, S, F, K, L, H, G, Q, D, N, R, Aib, L, I, or V;

X^{38} is selected as L or Nle;

X^{41} is V or I;

and wherein only one of X^{32} or X^{33} is selected as K, and wherein the K is lipidated, optionally through a linker/spacer and further wherein the hCRHR1-EC_{50}/hCRHR2-EC_{50} ratio is at least 1000.

2. The polypeptide or a pharmaceutically acceptable salt thereof according to claim 1, wherein X^{33} is selected as T, E, K, or Aib; X^{35} is selected as A, Aib, L, I, or V, and wherein X^{35} is selected as Aib, L, I, or V if X^{33} is T, or wherein X^{33} is selected as E, K, or Aib, wherein the K is lipidated, optionally through a linker/spacer if X^{35} is A.

3. The polypeptide or a pharmaceutically acceptable salt thereof according to any one of the preceding claims, wherein X^{38} is selected as Nle.

4. The polypeptide or a pharmaceutically acceptable salt thereof according to claim 3, wherein X^{20} is selected as A, F, G, H, I, K, L, N, Q, R, S, T, or V.

5. The polypeptide or a pharmaceutically acceptable salt thereof according to claim 3, wherein X^{20} is selected as N, F, G, K, Q, S, or T.

6. The polypeptide or a pharmaceutically acceptable salt thereof according to claim 3, wherein X^{20} is selected as S.

7. The polypeptide or a pharmaceutically acceptable salt thereof according to any one of the claims 1-3, wherein X^{20} is selected as S or E.

8. The polypeptide or a pharmaceutically acceptable salt thereof according to any one of the preceding claims, wherein X^{21} is selected as Q.

9. The polypeptide or a pharmaceutically acceptable salt thereof according to any one of the preceding claims, wherein X^{33} is selected T.

10. The polypeptide or a pharmaceutically acceptable salt thereof according to according to any one of the preceding claims, wherein X^{41} is selected as V.

11. The polypeptide or a pharmaceutically acceptable salt thereof according to any one of the preceding claims, wherein X^{4} is selected as MeI or P.

12. The polypeptide or a pharmaceutically acceptable salt thereof according to claim 1, comprising the structure of Formula (I)

X^4-V-L-S-L-D-V-P-I-G-L-L-Q-I-L-L-X^{20}-Q-A-R-A-R-A-A-R-E-Q-A-[K*]-X^{33}-N-X^{35}-E-I-[Nle]-A-E-V-NH_2

(Ia)

wherein X^4 is selected as MeI or P; X^{20} is selected as N, F, G, K, Q, S, or T, most preferably X^{20} is selected as S; X^{33} is selected as T, or Aib; X^{35} is selected as A or Aib; and further wherein X^{35} is selected as Aib if X^{33} is T, or wherein X^{33} is selected as Aib if X^{35} is A; * denotes a covalent attachment of a lipid, optionally through a linker/spacer, to the ε-amino group of the lysine side-chain.

13. The polypeptide or a pharmaceutically acceptable salt thereof according to claim 1, wherein the polypeptide comprises the sequence selected from the list consisting of [MeI]VLSLDVPIGLLQILLSQARARAAREQA[K*]TN[Aib]EI[Nle]AEV(NH_2) (SEQ ID NO: 215), PVLSLDVPIGLLQILLSQARARAAREQA[K*][Aib]NAEI[Nle]AEV(NH_2) (SEQ ID NO: 238), [MeI]VLSLDVPIGLLQILLEQARARAAREQAT[K*]NAEILAEV(NH_2) (SEQ ID NO: 6), or [MeI]VLSLDVPIGLLQILLEQARARAAREQA[K*]TN[Aib]EILAEV(NH_2) (SEQ ID NO: 16), wherein

the * denotes a covalent attachment of a lipid, optionally through a linker/spacer, to the ε-amino group of the lysine side-chain.

14. The polypeptide or a pharmaceutically acceptable salt thereof according to any one of the preceding claims, wherein the hCRHR1-EC_{50}/hCRHR2-EC_{50} ratio is at least 2000.

15. The polypeptide or a pharmaceutically acceptable salt thereof according to any one of the preceding claims, for use as a medicament in the treatment of a metabolic disorder, preferably obesity.

16. A pharmaceutical composition comprising a polypeptide or a pharmaceutically acceptable salt thereof according to any one of the claims 1-14.