

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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RECEIVED

13 JUN 2017

MEWBURN ELLIS LLP

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing
(day/month/year)

09.06.2017

Applicant's or agent's file reference
GRF/FP7180169

IMPORTANT NOTIFICATION

International application No
PCT/EP2016/055793

International filing date (day/month/year)
17.03.2016

Priority date (day/month/year)
18.03.2015

Applicant
ZEALAND PHARMA 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



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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 GRF/FP7180169	FOR FURTHER ACTION		See Form PCT/PEA416
International application No PCT/EP2016/055793	International filing date (day/month/year) 17.03.2016	Priority date (day/month/year) 18.03.2015	
International Patent Classification (IPC) or national classification and IPC INV. C07K14/575			
Applicant ZEALAND PHARMA 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 <u>9</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>26</u> 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. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 31er of Annex C of the Administrative Instructions).			
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 21.09.2016		Date of completion of this report 09.06.2017	
Name and mailing address of the international preliminary examining authority  European Patent Office D-80298 Munich Tel +49 89 2399 - 0 Fax +49 89 2399 - 4465		Authorized officer Ury, Alain Telephone No +49 89 2399-8411	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2016/055793

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

1-75 as originally filed

Claims, Numbers

1-47 filed with the letter of

14-02-2017

- ☒ 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 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2016/055793

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 01.03.2017 (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	<u>1-47</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-47</u>
Industrial applicability (IA)	Yes: Claims	<u>1-47</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

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:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☒ furnished subsequent to the international filing date for the purposes of international search and/or examination:
 - ☒ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
 - d. ☐ furnished to this Authority as an amendment* under PCT Article 34 on :
 - ☐ in the form of an Annex C/ST.25 text file, and preferably identified as "Amended" at the first line of text.
 - ☐ on paper or in the form of an image file.
2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

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."*

Reference is made to the following documents:

- D1 WO 93/10146 A1 (AMYLIN PHARMACEUTICALS INC [US]) 27 May 1993 (1993-05-27)cited in the application
- D2 WO 2013/156594 A1 (NOVO NORDISK AS [DK]) 24 October 2013 (2013-10-24)cited in the application
- D3 WO 2012/168432 A1 (NOVO NORDISK AS [DK]; SCHAEFFER LAUGE [DK]; KRUSE THOMAS [DK]; THOEGER) 13 December 2012 (2012-12-13)cited in the application
- D4 TSAI HUI-HSU GAVIN ET AL: "Energy landscape of amyloidogenic peptide oligomerization by parallel-tempering molecular dynamics simulation: Significant role of Asn ladder", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 102, no. 23, June 2005 (2005-06), pages 8174-8179, ISSN: 0027-8424
- D5 MORIARTY D F ET AL: "Effects of sequential proline substitutions on amyloid formation by human amylin₂₀₋₂₉", BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 38, no. 6, 9 February 1999 (1999-02-09), pages 1811-1818, XP002249402, ISSN: 0006-2960, DOI: 10.1021/BI981658G
- D6 TENIDIS K ET AL: "Identification of a penta- and hexapeptide of islet amyloid polypeptide (IAPP) with amyloidogenic and cytotoxic properties", JOURNAL OF MOLECULAR BIOLOGY, ACADEMIC PRESS, UNITED KINGDOM, vol. 295, no. 4, 28 January 2000 (2000-01-28), pages 1055-1071, XP004465889, ISSN: 0022-2836, DOI: 10.1006/JMBI.1999.3422

- D7 LI LING-BO ET AL: "Suppression of polyglutamine toxicity by the yeast sup35 prion domain in Drosophila",
JOURNAL OF BIOLOGICAL CHEMISTRY,
vol. 282, no. 52, December 2007 (2007-12), pages 37694-37701,
ISSN: 0021-9258
- D8 KAJAVA ANDREY V ET AL: "A model for Ure2p prion filaments and other amyloids: The parallel superpleated beta-structure",
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA,
vol. 101, no. 21, 25 May 2004 (2004-05-25), pages 7885-7890,
ISSN: 0027-8424

Re Item V

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

- 1 The present application meets the criteria of Article 33(2) PCT, because the subject-matter of present claims is new.
- 1.1 Most of the claims are limited to amylin analogues wherein the 2 Asn at positions 21 and 22 are absent. Such analogues are not disclosed in the available prior art and are therefore novel under Article 33.2 PCT.
- 1.2 The few amylin analogues wherein the 2 Asn at positions 21 and 22 are present (see for instance claims 19 and 27) recite very specific amino acid sequences comprising Gly(Me), Ile(Me) and Apr. Such analogues are also not disclosed in the art, in particular in D1-D3.
- 2 The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of claims 1-47 does not involve an inventive step.

- 2.1 Many documents of the prior art can be regarded as being the prior art closest to the subject-matter of present claims. For instance:

WO 93/10146 (D1) discloses *inter alia* amylin analogues known as pramlintide and having the sequence Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr, which also possesses a disulphide bridge between the Cys residues at positions 2 and 7.

Further analogues of amylin or pramlintide are described in W02013/156594 (D2) and W02012/168432 (D3).

The subject-matter of present claims essentially differs from said documents in that the amylin analogues have the 2 Asn at positions 21 and 22 deleted.

The technical effect linked to this difference is allegedly an enhanced chemical stability, especially at neutral and/or alkaline pH and an increased agonist activity at some receptors (see page 4 and 75 of the application). In addition, said analogues allegedly show a reduced tendency for fibrillation at or around pH 7 (see page 2, line 15 and Table 1).

The problem to be solved by the present invention may therefore be regarded as being the provision of further amylin analogues showing a reduced tendency for fibrillation and/or higher chemical stability at or around pH 7 (see page 2 of application).

The solution proposed in present claim cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

D4 reveals the significant role played by Asn-Asn stacking in the fibril and amyloid formation by amylin (see the whole document).

More generally, D7 and D8 disclose the importance of the Asn-rich domains in the formation of amyloid fibrils by amyloidogenic proteins (see the abstracts).

Although D4, D7 and D8 relate to entirely different peptides their teaching is the significant role of the Asn residue in amyloid formation. This is independent from the other amino acids which may or may not have the same effect.

D5 and D6 teach the key role of residue Asn 22 in formation of amyloid fibrils by amylin, i.e. the same peptide as in the present application (see D5, abstract and page 1816, col.2, second full paragraph and D6, page 1066, first paragraph).

Although other factors such as local concentration, conditions in which amylin is secreted, synthesized and stored play a part in amyloid formation (see D5, page 1816, col.2, second full paragraph), D5 confirms the significant role of the Asn residue in amyloid formation. The same applies to D6.

Other prior art documents such as Westermarck et al. (1990), PNAS, Vol.87 pp.5036-40 may point to the importance of other amino acids in the formation of amyloid fibrils. However, this does not contradict the fact that the Asn residues are also essential in amyloid formation.

All these data relating to the importance of Asn for fibrillation (amyloid formation) are not highly equivocal but give the skilled person a reasonable expectation that replacement or deletion of the Asn residues 21 and/or 22 will reduce the tendency for fibrillation.

Thus, in order to solve the underlying technical problem, i.e. provide amylin analogues showing a reduced tendency for fibrillation, the skilled person would have tried with reasonable expectation of success to delete the Asn in positions 21 and/or 22. With trial and error experimentation he would have found the deletions that provide the desired effect.

Even if the technical problem was seen as the provision of further amylin analogues showing a reduced tendency for fibrillation, increased solubility, or increased chemical stability at or around pH 7 while retaining amylin agonist activity inventive step would be denied. Indeed, there was no reason to believe that the deletion of the Asn in positions 21 and/or 22 would suppress the agonist activity. It is furthermore noted that according to the claims, the remaining agonist activity of the analogues is not quantified and may be strongly reduced while still present.

Dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

Thus, present claims lack an inventive step under Article 33.3 PCT.

- 2.2 In addition, the technical effect(s) have only been shown for a limited number of the claimed analogues, and even a limited number of the tested analogues (see Tables 1, 4-6) falling within the scope of the claims. Therefore, another fundamental aspect of the present lack of inventive step objection is that the claims have no relevant functional limitation(s) which would limit their scope to the analogues actually solving the technical problem. A problem should be solved over the whole breadth of the claims in order for the claim to be inventive. This is obviously not the case in the present claims. For this reason also inventive step is denied.
- 2.3 The functional limitation "wherein said amylin analogue has agonist activity at one or more of hAMYR1, hAMYR2 and hAMYR3" does not limit the scope of the claims to analogues having properties going beyond those of the wild type amylin. As mentioned above, the remaining agonist activity of the analogues is not quantified in the claim and may be strongly reduced while still present. Analogues having such functions merely represent arbitrary analogues which do not solve the above mentioned problem of having reduced tendency for fibrillation and/or higher chemical stability at or around pH 7.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/ year)	Filing date (day/month/ year)	Priority date (valid claim) (day/month/year)
WO2015/040182	26.03.15	19.09.14	19.09.13

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21 September 2016

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Dear Sirs

International Application No. PCT/EP2016/055793
Applicant: ZEALAND PHARMA A/S et al.
Our Ref: GRF/FP7180169

This letter accompanies a Demand for International Preliminary Examination of this application.

The fee is being paid alongside this letter.

An amended set of claims is enclosed. Comments on the objections raised in the Written Opinion of the International Searching Authority are provided below.

Amendments

Claim 1 has been amended to recite that the amylin analogue "*has agonist activity at one or more of hAMYR1, hAMYR2 and hAMYR3*", i.e. at one or more of the human amylin receptors. Basis is found at page 39 line 21 to page 40 line 7.

Three compounds which fall within the scope of claim 19 (rather than claim 1) have been deleted from claim 26 and made the subject of new claim 27. Subsequent claims have been renumbered accordingly.

Novelty

The Examiner has objected that claims 19 and 26 are not novel because they "*comprise amylin analogues wherein the 2 Asn at positions 21 and 22 are present*".

It is true that some of the claimed compounds do possess Asn at positions 21 and 22. However, these claims recite very specific amino acid sequences, and we have been unable to identify any of those specific sequences in D1 to D3. We therefore respectfully request the Examiner to indicate exactly where the relevant sequences are found in D1 to D3 or withdraw the objection.

Inventive Step

We agree with the Examiner that any of D1 to D3 could be taken as the closest prior art. However, we strongly disagree that any of the other documents cited would render it obvious to delete the residues at positions 21 and 22.

D4 describes results obtained with a 5-mer peptide derived from calcitonin and having the sequence DFNKF. This sequence does not appear in amylin, and so it is not possible to extrapolate the results to amylin analogues as claimed. D7 and D8 also relate to entirely different proteins and so are not relevant to inventive step of claims directed to analogues of amylin.

Only D5 and D6 attempt to investigate the physical properties of amylin. However, they do not analyse the whole molecule, but only short peptides derived from the amylin sequence. The significance of this is explained below.

D5 uses synthetic 10-mer peptides to investigate the effect on amyloid formation of introducing proline residues into the "central region" (residues 20 to 29) of the amylin sequence. However, D5 itself (page 1816, col. 2) notes three serious limitations of the methodology used:

- (i) *"Although the primary sequence of the 20-29 region of amylin is clearly a very important determinate of amyloid formation, it is important to realize that it cannot be the sole determinate. For example, previous work has demonstrated that in vitro amyloid formation by full-length amylin is pH-dependent and that the rate is faster at pH values above the pK_a of histidine 18 (12). Our model peptides lack this residue and thus should not be expected to reproduce the pH-dependent behavior observed for the full-length peptide."*
- (ii) *"It is also worth noting that synthetic peptides corresponding to the primary sequence of residues 20-29 of the rabbit and the European hare are amyloidogenic in vitro even though islet amyloid is apparently not observed in these species."*
- (iii) *"In addition, the sequences of canine (42) and feline (43) amylin are identical from residue 20 to 29; however, cats form islet amyloid, while dogs do not."*

It is therefore very questionable whether the results described in this paper actually reflect the properties of the full-length molecule. Certainly extreme care is required when interpreting them.

D6 notes that while *"the sequence of IAPP is strongly conserved over a number of animal species, IAPP-derived amyloid is only formed by humans, cats, and some non-human primates"*. Furthermore, *"Rodents do not form pancreatic amyloid, although there are only six amino acid residues by which the rat sequence (rIAPP) differs from its human (hIAPP) analog"* (Page 1056, col. 2).

The skilled person would therefore regard the positions at which the human and rat sequences differ as the best candidates to focus on when attempting to modulate the physical properties of amylin. Notably, though, the Asn-Asn doublet at positions 21 and 22 is identical in rat and human amylin, as shown in Scheme 1 on page 1056 of D6.

Indeed, the alignment in Fig. 2 of D1 (reproduced below) shows that the Asn-Asn doublet is extensively conserved in mammalian amylin, appearing in human, cat, dog, rat, mouse and hamster sequences, most of which do not form amyloid according to D6:

Human:	KCNTATCATQRLANFLVHSSNNFGAILSSINVGSNTY
Cat:	-----IR-----P-----
Dog:	-----RT-----P-----
Rat:	-----R-----L-PV-PP-----
Mouse:	-----R-----L-PV-PP-----
Hamster:	-----N-----L-PV--P-----
Guinea pig:	-----T-----R--H-L--A-LP-D-----

Overall, then, the teaching provided by D4, D5 and D6 about the significance of Asn21 and Asn22 for amyloid formation is (at best) highly equivocal. The skilled person cannot confidently draw any conclusions about the effect which modifying these residues would have on the physical stability of amylin.

Furthermore, D5 and D6 both focus exclusively on substitutions. Neither makes any suggestion to delete residues from amylin.

Amylin is a relatively short molecule, having the same length of 37 amino acids in all of the mammalian species shown in the alignment above. This alone suggests that deletion of any residue might be expected to have a significant effect on activity.

Indeed, it has been known for many years that the disulphide bond between residues 2 and 7, and the C-terminal amide, are both required for activity. (See Roberts et al., 1989, enclosed.) This implies that both of these elements are involved in receptor binding. Thus, the spacing between these elements and their relative orientation can also be expected to be important for activity, both of which could be affected by deletion of intervening residues. Thus the skilled person would be strongly dissuaded from deleting any residue within the sequence of amylin, still less two consecutive residues which are extensively conserved in mammalian amylin.

This view is supported by the fact that none of D1 to D3 (all which are concerned with generation of amylin analogues) suggests deletion of any internal residues between the disulphide bridge and the C-terminal amide. Both D1 (e.g. page 11 lines 2-4 and Example 4) and D3 (e.g. Formula I in claim 6) suggest that the residue at position 1 may be deleted, but neither document indicates any other specific residue which can be deleted.

Thus, when starting from any of D1 to D3, the skilled person could have no incentive to delete Asn21 and Asn22, and no expectation that functional analogues would still be obtained.

The claims now specifically require that the analogues have agonist activity at at least one of the human amylin receptors. Table 1 shows data for 96 compounds, all of which have considerably potency at amylin receptors *in vitro* and many of which also have extremely favourable chemical stability and fibrillation properties.

We therefore believe that the subject matter of the claims is inventive.

We look forward to receiving a positive International Preliminary Report on Patentability in due course. If the Examiner believes that any objections remain outstanding, a further written communication is requested.

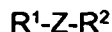
Yours faithfully

/ GRAHAM FORREST /

Graham Forrest
Appointed Agent
for MEWBURN ELLIS LLP
graham.forrest@mewburn.com

CLAIMS

1. An amylin analogue which is a compound having the formula:



wherein

5 R^1 is hydrogen, C_{1-4} acyl, benzoyl or C_{1-4} alkyl, or a half-life extending moiety M, wherein M is optionally linked to Z via a linker moiety L;

R^2 is OH or NHR^3 , wherein R^3 is hydrogen or C_{1-3} -alkyl; and

Z is an amino acid sequence of formula I:

Arg-Cys-X3-Thr-Ala-Thr-Cys-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-
10 Phe-Gly(Me)-Ala-Ile(Me)-Leu-Ser-Ser-Thr-X31-Val-Gly-Ser-X35-Thr-X37 (I);

wherein

X3 is selected from the group consisting of Asn, Gly, Pro and Gln;

X10 is selected from the group consisting of Gln, Asp and Glu;

X14 is selected from the group consisting of Asp, His, Asn and Aad;

15 X17 is selected from the group consisting of His, Asn, Gln, Glu, Thr, Val, Lys and Aad;

X19-X20 is selected from the group consisting of Ser-Ser, Val-Val, Ser-Val and Val-Ser, or is absent;

X31 is selected from the group consisting of Asp, Glu and Asn;

X35 is selected from the group consisting of Asp, Glu, Asn, Ser, Phe, Orn, Aad, Gly and
20 Thr; and

X37 is selected from the group consisting of Pro, Apr and Hyp;

and wherein the compound has at least one residue selected from:

X3 is Gln;

X14 is His, Asn or Aad;

25 X17 is Asn, Gln, Glu, Thr or Aad;

X19-X20 is Val-Ser or Ser-Val; and

X35 is Ser, Phe, Orn, Aad, Gly or Thr;

or a pharmaceutically acceptable salt or solvate thereof; wherein said amylin analogue has agonist activity at one or more of hAMYR1, hAMYR2 and hAMYR3.

5

2. An amylin analogue according to claim 1 wherein X31 is Glu

3. An amylin analogue according to claim 1 or claim 2 wherein X19-X20 is Ser-Ser or is absent.

10

4. An amylin analogue according to any one of claims 1 to 3 wherein X37 is Hyp or Pro.

15

5. An amylin analogue according to claim 1 wherein Z is an amino acid sequence of formula II:

Arg-Cys-X3-Thr-Ala-Thr-Cys-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-Phe-Gly(Me)-Ala-Ile(Me)-Leu-Ser-Ser-Thr-Glu-Val-Gly-Ser-X35-Thr-X37 (II);

wherein

X3 is selected from the group consisting of Asn, Gly and Gln;

20 X10 is selected from the group consisting of Gln, Asp and Glu;

X14 is selected from the group consisting of Asp, His and Aad;

X17 is selected from the group consisting of His, Asn, Gln, Glu, Lys and Aad;

X19-X20 is Ser-Ser or is absent;

25

X35 is selected from the group consisting of Asp, Glu, Asn, Ser, Orn, Aad, Gly and Thr; and

X37 is selected from the group consisting of Pro and Hyp;

and wherein the compound has at least one residue selected from:

X3 is Gln;

X14 is His or Aad;

X17 is Asn, Gln, Glu or Aad; and

5 X35 is Ser, Phe, Orn, Aad, Gly or Thr.

6. An amylin analogue according to any one of the preceding claims wherein X17 is selected from His and Gln.

10 7. An amylin analogue according to claim 1 wherein Z is an amino acid sequence of formula III:

Arg-Cys-X3-Thr-Ala-Thr-Cys-Ala-Thr-X10-Arg-Leu-Ala-X14-Phe-Leu-X17-Arg-X19-X20-Phe-Gly(Me)-Ala-Ile(Me)-Leu-Ser-Ser-Thr-Glu-Val-Gly-Ser-X35-Thr-X37 (III);

wherein

15 X3 is selected from the group consisting of Asn, Gly and Gln;

X10 is selected from the group consisting of Gln, Asp and Glu;

X14 is selected from the group consisting of Asp, His and Aad;

X17 is selected from the group consisting of His and Gln;

X19-X20 is Ser-Ser or is absent;

20 X35 is selected from the group consisting of Asp, Glu, Asn, Aad and Gly; and

X37 is selected from the group consisting of Pro and Hyp;

and wherein the compound has at least one residue selected from:

X3 is Gln;

X14 is His or Aad;

X17 is Gln; and

X35 is Aad.

8. An amylin analogue according to any one of the preceding claims wherein:

5 X10 is selected from Gln and Glu;

and/or

X35 is selected from Asp, Glu, Asn and Aad.

9. An amylin analogue according to any one of the preceding claims wherein

10 X3 is selected from Asn and Gly, and/or X17 is Gln.

10. An amylin analogue according to any one of the preceding claims wherein X35 is Asn and/or X37 is Hyp.

15 11. An amylin analogue according to any one of claims 1 to 7 wherein:

X3 is Gln;

X10 is selected from Glu and Asp;

X14 is selected from His and Aad;

X35 is selected from Gly and Asn; and

20 X37 is selected from Pro and Hyp.

12. An amylin analogue according to any one of the preceding claims comprising the residues:

X3 is Gly;

X10 is selected from Glu and Asp;

X14 is selected from His and Aad;

X35 is selected from Gly and Asn; and

X37 is selected from Pro and Hyp.

5

13. An amylin analogue according to any one of the preceding claims comprising the residues:

Gly3 + Glu10;

Asn3 + Glu10;

10 Gln3 + Glu10;

Asn3 + Gln10; or

Gln3 + Asp10.

14. An amylin analogue according to any one of the preceding claims wherein X14 is
15 selected from His and Aad, and/or X17 is Gln.

15. An amylin analogue according to any one of the preceding claims comprising the residues:

Gln17 + Glu31 + Hyp37

20 Gly3 + Glu10 + His14

Asn3 + Glu10+ His14;

Gln3 + Glu10+ His14;

Gly3 + Glu10 + Aad14;

Gly3 + Glu10 + Asp14;

25 Asp10 + Aad14;

His14 + Glu31 + Pro37

His14 + Glu31 + Hyp37

Aad14 + Glu31 + Pro37;

Aad14 + Glu31 + Hyp37;

Gly3 + Glu31; or

Gly3 + Glu10 + Glu31 + Asn35 + Hyp37.

- 5 16. An amylin analogue according to any one of the preceding claims wherein X19-X20 is Ser-Ser.

17. An amylin analogue according to claim 16 comprising the residues:

Gly3 + Ser19 + Ser20 + Glu31 or

- 10 Gly3 + Glu10 + Ser19 + Ser20 + Glu31 + Asn35 + Hyp37.

18. An amylin analogue according to any one of the preceding claims wherein Z is:

RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

RCNTATCATQRLANFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

- 15 RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSN-T-Hyp

RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSN-T-Hyp

RCGTATCATERLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSN-T-Hyp

RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-T-Hyp

RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGST-T-Hyp

- 20 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVG-S-Orn-T-Hyp

RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVG-S-Aad-T-Hyp

RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSG-T-Hyp

RCNTATCATQRLAHFLHRF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP

- 25 RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP

RCGTATCATERLANFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSN-T-Hyp

RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSN-T-Hyp

RCGTATCATERLAHFLKRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSN-T-Hyp

RCNTATCATQRLAHFLHRSVF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

- 30 RCNTATCATQRLAHFLHRVSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP

- RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP
 RCPTATCATDRLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSDTP
 RCNTATCATQRLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP
 RCPTATCATDRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSNTP
 5 RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP
 RCPTATCATDRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSDTP
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 10 RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFT-Hyp
 RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFT-Hyp
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP
 RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP
 15 RCGTATCATERLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP
 RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP
 RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP
 RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFTP
 RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFTP
 20 RCGTATCATERLADFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 RCGTATCATERLADFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFT-Hyp
 RCGTATCATERLA-Aad-FLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp
 RCGTATCATERLA-Aad-FLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-T-Hyp
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Apr
 25 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-TP
 RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp
 RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp
 RCNTATCATQRLAHFL-Aad-RSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp

- RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGS-Orn-T-Hyp
RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGS-Aad-T-Hyp
RCGTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGSNT-Hyp
5 RCGTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGSNT-Hyp
RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGSNT-Hyp
RCQTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGSNT-Hyp
RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGSNT-Hyp
RCPTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSNT-Hyp
10 RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSDT-Hyp
RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGSNT-Hyp
RCPTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGSNT-Hyp
15 RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
RCNTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
RCPTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
RCNTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGSNT-Hyp
RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp
20 RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp
RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp
RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp
25 RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGS-Aad-T-Hyp
RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGGS-Aad-T-Hyp
RCGTATCATERLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGGSNT-Hyp
RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
RCNTATCATQRLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp

- RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGTP
 RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
 RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTTP
 RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp
 5 RCNTATCATQRLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP
 RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP
 RCNTATCATQRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH-Hyp
 RCNTATCATQRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSH-Hyp
 RCNTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH-Hyp
 10 RCNTATCATDRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH-Hyp
 RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
 RCNTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp
 RCNTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
 RCNTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP
 15 RCNTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGTP
 RCNTATCATDRLA-Aad-FLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNH-Hyp or
 RCNTATCATERLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP

19: An amylin analogue which is a compound having the formula:

20 R^1-Z-R^2

wherein

R^1 is hydrogen, C_{1-4} acyl, benzoyl or C_{1-4} alkyl, or a half-life extending moiety M, wherein M is optionally linked to Z via a linker moiety L;

R^2 is OH or NHR^3 , wherein R^3 is hydrogen or C_{1-3} -alkyl; and

25 Z is an amino acid sequence selected from the group consisting of:

RCNTATCATQRLADFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP;

RCNTATCATQRLADFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr; and

RCNTATCATQRLAHFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr;
or a pharmaceutically acceptable salt or solvate thereof.

20. An amylin analogue according to any one of the preceding claims wherein R¹ is M-
5 or M-L-.

21. An amylin analogue according to claim 20, wherein M is an alkanoyl group.

22. An amylin analogue according to claim 21, wherein M is selected from 15-carboxy-
10 pentadecanoyl, 17-carboxy-heptadecanoyl and 19-carboxy-nonadecanoyl.

23. An amylin analogue according to any one of the preceding claims wherein R¹ is M-
L- and L is a residue of an amino acid selected from the group consisting of Gly, Pro, Ala,
Val, Leu, Ile, Met, Cys, Phe, Tyr, Trp, His, Lys, Arg, Gln, Asn, α -Glu, γ -Glu, ϵ -Lys, Asp, β -
15 Asp, Ser, Thr, Gaba, Aib, β -Ala, 4-aminobutanoyl, 5-aminopentanoyl, 6-aminohexanoyl, 7-
aminoheptanoyl, 8-aminooctanoyl, 9- aminononanoyl, 10-aminodecanoyl and 8Ado.

24. An amylin analogue according to claim 23 wherein L is a γ -Glu residue.

20 25. An amylin analogue according to any one of the preceding claims wherein R² is
NH₂.

26. An amylin analogue according to claim 1 which is selected from the group consisting
of:

25 [19CD]-isoGlu-RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂

[19CD]-isoGlu-RCNTATCATQRLANFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGsNT-Hyp-
NH₂

30 [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGsNT-Hyp-
NH₂

[19CD]-isoGlu-RCGTATCATERLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGsNT-Hyp-
NH₂

- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGST-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSO-T-Hyp-NH₂
- 5 [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSA-T-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- 10 [19CD]-isoGlu-RCNTATCATQRLAHFLHRF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCGTATCATERLANFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- 15 [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLKRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLHRVSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- 20 [19CD]-isoGlu-RCNTATCATQRLAHFLHRVSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCPTATCATDRLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSDTP-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCPTATCATDRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSNTP-NH₂
- 25 [19CD]-isoGlu-RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂
- [19CD]-isoGlu-RCPTATCATDRLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSDTP-NH₂

- [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂
- 5 [19CD]-isoGlu-RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂
- 10 [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFT-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFT-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP-NH₂
- 15 [19CD]-isoGlu-RCGTATCATERLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLVRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFTP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLNRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFTP-NH₂
- 20 [19CD]-isoGlu-RCGTATCATERLADFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLADFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSFT-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLA-Aad-FLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂
- 25 [19CD]-isoGlu-RCGTATCATERLA-Aad-FLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-T-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Apr-NH₂

- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSSTP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-TP-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLTRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp-NH₂
- 5 [19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFL-Aad-RSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Orn-T-Hyp-NH₂
- 10 [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSS-Aad-T-Hyp-NH₂
- 15 [19CD]-isoGlu-RCGTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp-NH₂
- 20 [19CD]-isoGlu-RCQTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSNT-Hyp-NH₂
- 25 [19CD]-isoGlu-RCPTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTDVGSNT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSDT-Hyp-NH₂

- [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCNTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- 5 [19CD]-isoGlu-RCPTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCNTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- [19CD]-isoGlu-RCPTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂
- 10 [19CD]-isoGlu-RCNTATCATERLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂
- [19CD]-isoGlu-RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSST-Hyp-NH₂
- 15 [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- [19CD]-isoGlu-RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp-NH₂
- [19CD]-isoGlu-RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSAad-T-Hyp-NH₂
- 25 [19CD]-isoGlu-RCPTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSAad-T-Hyp-NH₂

- [19CD]-isoGlu-RCGTATCATERLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- [19CD]-isoGlu-RCGTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGTP-Hyp-NH₂
- 5 [19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTTP-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLADFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTT-Hyp-NH₂
- 10 [19CD]-isoGlu-RCNTATCATQRLAHFLERSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTTP-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSTTP-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- [19CD]-isoGlu-RCNTATCATQRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP-Hyp-NH₂
- 15 [19CD]-isoGlu-RCNTATCATQRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSSTP-Hyp-NH₂
- [19CD]-isoGlu-RCQTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- [19CD]-isoGlu-RCQTATCATDRLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- 20 [19CD]-isoGlu-RCQTATCATERLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- [19CD]-isoGlu-RCQTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGT-Hyp-NH₂
- [19CD]-isoGlu-RCQTATCATDRLAHFLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂
- 25 [19CD]-isoGlu-RCQTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂

[19CD]-isoGlu-RCQTATCATERLA-Aad-FLQRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSGTP-NH₂

[19CD]-isoGlu-RCQTATCATDRLA-Aad-FLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-Hyp-NH₂

5 [19CD]-isoGlu-RCQTATCATERLAHFLQRF-Gly(Me)-A-Ile(Me)-LSSTEVGSNTP-NH₂

wherein [19CD] represents [19-carboxynonadecanoyl];

and pharmaceutically acceptable salts and solvates thereof.

27. An amylin analogue according to claim 19 which is selected from the group consisting of:

[19CD]-isoGlu-RCNTATCATQRLADFLHRSSF-Gly(Me)-A-Ile(Me)-LSSTEVGSETP-NH₂;

[19CD]-isoGlu-RCNTATCATQRLADFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr-NH₂; and

15 [19CD]-isoGlu-RCNTATCATQRLAHFLHRSSNNF-Gly(Me)-A-Ile(Me)-LSSTNVGSNT-Apr-NH₂.

28. An amylin analogue according to any one of the preceding claims, comprising an intramolecular disulphide bridge formed between the cysteine residues present at positions 2 and 7 of the amino acid sequence.

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29. A pharmaceutical composition comprising an amylin analogue according to any one of the preceding claims, in combination with a pharmaceutically acceptable carrier, excipient or vehicle.

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30. A device comprising an amylin analogue according to any one of claims 1 to 28, for delivery of the amylin analogue to a subject.

31. A kit comprising an amylin analogue according to any one of claims 1 to 28, and optionally further comprising packaging and instructions for use.

32. A device according to claim 30 or a kit according to claim 31 further comprising an anti-diabetic agent, an anti-obesity agent, an agent for treatment of metabolic syndrome, an anti-dyslipidemia agent, an anti-hypertensive agent, a proton pump inhibitor, or an anti-inflammatory agent.
- 5
33. A method for the synthesis of an amylin analogue according to any one of claims 1 to 28.
34. A method according to claim 33 comprising synthesizing the amylin analogue by solid-phase or liquid-phase methodology, optionally isolating and purifying the final product, and further optionally comprising the step of forming a disulfide bond between the thiol groups of the cysteine side chains at positions 2 and 7.
- 10
35. An amylin analogue according to any one of claims 1 to 28 for use in a method of medical treatment.
- 15
36. An amylin analogue according to any one of claims 1 to 28 for use in a method of treating, inhibiting or reducing weight gain, promoting weight loss, reducing food intake, and/or reducing excess body weight.
- 20
37. An amylin analogue according to any one of claims 1 to 28 for use in a method of treating obesity, morbid obesity, obesity prior to surgery, obesity-linked inflammation, obesity-linked gallbladder disease, obesity-induced sleep apnea and respiratory problems, degeneration of cartilage, osteoarthritis, or reproductive health complications of obesity or overweight such as infertility.
- 25
38. An amylin analogue for use according to claim 37 wherein said obesity is accompanied by at least one weight-related co-morbid condition, such as diabetes (e.g. type 2 diabetes), hypertension, dyslipidemia, sleep apnea and cardiovascular disease.
- 30

39. An amylin analogue according to any one of claims 1 to 28 for use in a method of prevention or treatment of Alzheimer's disease, diabetes, type 1 diabetes, type 2 diabetes, pre-diabetes, insulin resistance syndrome, impaired glucose tolerance (IGT), disease states associated with elevated blood glucose levels, metabolic disease including metabolic syndrome, hyperglycemia, hypertension, atherogenic dyslipidemia, hepatic steatosis ("fatty liver"), kidney failure, arteriosclerosis (e.g. atherosclerosis), macrovascular disease, microvascular disease, diabetic heart (including diabetic cardiomyopathy and heart failure as a diabetic complication) coronary heart disease, peripheral artery disease or stroke, and combinations thereof.
40. An amylin analogue according to any one of claims 1 to 28 for use in a method of lowering circulating LDL levels and/or increasing HDL/LDL ratio.
41. An amylin analogue for use according to any one of claims 35 to 40 wherein said amylin analogue is administered in conjunction with an anti-diabetic agent, an anti-obesity agent, an agent for treatment of metabolic syndrome, an anti-dyslipidemia agent, an anti-hypertensive agent, a proton pump inhibitor, or an anti-inflammatory agent.
42. An amylin analogue for use according to claim 41 wherein said anti-diabetic agent is metformin, a sulfonylurea, a glinide, a DPP-IV inhibitor, a glitazone, a GLP-1 receptor agonist, an SGLT2 inhibitor, a GPR40 agonist, an insulin, or an insulin analogue.
43. An amylin analogue for use according to claim 41 wherein said anti-obesity agent is peptide YY or an analogue thereof, neuropeptide Y (NPY) or an analogue thereof, a cannabinoid receptor 1 antagonist, a lipase inhibitor, Human proislet Peptide (HIP), a melanocortin receptor 4 agonist, a GLP-1 receptor agonist, Orlistat™, Sibutramine™, phentermine, a melanin concentrating hormone receptor 1 antagonist, CCK, amylin, pramlintide or leptin.

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44. An amylin analogue for use according to claim 41 wherein said anti-hypertension agent is an angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocker, a diuretic, a beta-blocker or a calcium channel blocker.
- 5 45. An amylin analogue for use according to claim 41 wherein said anti-dyslipidemia agent is a statin, a fibrate, a niacin, a PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitor or a cholesterol absorption inhibitor.
- 10 46. An amylin analogue for use according to claim 41 wherein said proton pump inhibitor is an agent of the benzimidazole derivative type or of the imidazopyridine derivative type.
- 15 47. An amylin analogue for use according to claim 41 wherein said anti-inflammatory agent is a steroid or corticosteroid, non-steroidal anti-inflammatory agent (NSAID), a COX II inhibitor, 5-aminosalicylic acid or metformin.

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12 May 2017

ELECTRONICALLY FILED

Dear Sirs

International Application No. PCT/EP2016/055793
Applicant: ZEALAND PHARMA A/S et al.
Our Ref: GRF/FP7180169

We write in response to the communication dated 14 March 2017.

We appreciate the Examiner's acknowledgement that the claims are novel. However, we respectfully disagree with the Examiner's conclusions regarding inventive step. In particular, we believe that the Examiner's approach disregards certain differences between the claimed subject matter and the prior art, mis-characterises the technical problem, and impermissibly applies hindsight knowledge of the present invention. These points are explained in detail below.

Difference from the prior art

The Examiner suggests that any of D1, D2 or D3 can be regarded as the closest prior art, and that "[t]he subject-matter of present claims essentially differs from said documents in that the amylin analogues have the 2 Asn at positions 21 and 22 deleted".

However, it is important to note that the analogues of the present invention are all required to have N-methylated residues at positions 24 (Gly(Me)) and 26 (Ile(Me)), a feature believed to reduce fibrillation See page 4 lines 10-21, as well as page 2 lines 1-3 discussing the prior art analogue IAPP-GI.

The effect of deleting Asn21 and Asn22 appears to be different in molecules containing N-methylated and unmethylated residues at these positions. This is illustrated in Table 6 on page 75 of the present application. Table 6 compares various pairs of molecules which differ only by the presence of residues Asn21-Asn22 or the claimed deletion. In backbones with N-methylated residues at positions 24 and 26, the deletion of Asn21-Asn22 increases activity (i.e. lowers EC50) at the hCTR2 and hAMYR3 receptors. (Compounds 55, 57 and 89 have lower EC50 values than comparison compounds 98, 99 and 100). However, in the backbone with unmethylated residues, the deletion has little or no effect on activity. (NN96 and compound 97 have similar EC50 values.)

None of D1, D2 or D3 suggest incorporation of N-methylated residues. Thus, even if deletion of residues 21 and 22 were rendered obvious by documents D4-D8 (which we deny), the skilled person still could not arrive at the claimed molecules by introducing such deletions into the analogues of D1 to D3.

Formulation of the technical problem

The Examiner suggests that the technical problem is "*the provision of further amylin analogues showing a reduced tendency for fibrillation and/or higher chemical stability at or around pH 7 (see page 2 of application)*".

We note that the application also describes increased solubility and increased activity as effects associated with the claimed compounds, as well as reduced fibrillation and increased chemical stability.

More importantly, though, the Examiner has disregarded the requirement that the analogues have amylin agonist activity. This is now specifically recited in the claims. We therefore believe that the technical problem should more properly be seen as the provision of amylin analogues which have reduced tendency for fibrillation, increased solubility, or increased chemical stability while retaining amylin agonist activity.

Thus the skilled person cannot concern themselves solely with altering the physical properties of the molecule. Rather, they must balance the competing demands of improving the physical properties while retaining appropriate agonist activity.

Retention of agonist activity

The Asn21-Asn22 doublet is extensively conserved in mammalian amylin. The alignment in Fig. 2 of D1 (reproduced in our letter of 21 September 2016) shows that it is present in human, cat, dog, rat, mouse and hamster. Thus these residues have clearly been extensively conserved through evolution, which in turn suggests that these residues are very important for amylin's biological function.

Thus, even if the skilled person were to believe that deleting these residues might improve the molecule's physical properties, they could have no realistic expectation of retaining agonist activity.

Furthermore, if (as the Examiner argues) these residues are implicated in fibrillation, it might be expected that they would be the subject of negative selection pressure, since fibrillation appears to be deleterious to the organism, e.g. in the formation of amyloid plaques. The fact that these residues nevertheless remain so highly conserved would further reinforce the conclusion that they are important for function and thus unsuitable for deletion.

Use of hindsight

We believe that the Examiner has inadvertently used hindsight knowledge of the present invention in reaching a conclusion of obviousness.

The Examiner maintains that D4-D8 would lead the skilled person to "*give the skilled person a reasonable expectation that replacement or deletion of the Asn residues 21 and/or 22 will reduce the tendency for fibrillation*".

Although we do not wish to repeat all the arguments from our previous letter, we would emphasise again that not all wild type amylin molecules with the Asn21-Asn22 doublet have a tendency to fibrillate. For example, amylin from rat and hamster do not fibrillate despite possessing this doublet.

Thus, in the context of a full-length amylin analogue (rather than a short peptide derived from it), it is not possible to assert with any confidence that the Asn21-Asn22 doublet is responsible for fibrillation, either in whole or in part.

This is illustrated by a very early study of fibrillation, described in the enclosed paper by Westermarck et al. (1990), discussed in D1 at page 3 lines 27-36. Similar to D5, this paper looks at positions 20-29 of human and cat amylin (which do form fibrils), and introduces modifications from rat and hamster amylin molecules (which do not). However, positions 21 and 22 are not modified because these residues are the same in all of these species. The authors conclude that *"the sequence Ala-Ile-Leu-Ser-Ser, corresponding to positions 25-29 of human IAPP, is strongly amyloidogenic and that a proline-for-serine substitution in position 28, as in several rodents, almost completely inhibits formation of amyloid fibrils"* (Abstract, final sentence.)

Thus different studies have produced different results. Notwithstanding the results in D5 and D6, it seems impossible logically to conclude that a pair of residues present in molecules with completely different fibrillation properties can be the main determinant of fibrillation. Other factors must be involved. At the priority date, the skilled person would be well versed in the literature regarding amylin and would be aware of this.

The difficulty presented by the fibrillation of human amylin has therefore been recognised for many years. Many attempts have been made to produce adequately stable, soluble and active amylin analogues. D1 to D3 represent just a sample of the relevant patent applications.

D4 to D8 date from 2005, 1999, 2000, 2007 and 2004 respectively. Thus, these documents had been available to the skilled person for between 8 and 16 years before the present application's priority date.

Nevertheless, the present application represents the first proposal to delete Asn21 and Asn22 in the context of functional amylin analogues. If the solution were truly obvious, it would surely have been suggested before.

This strongly suggests that the claimed subject matter is inventive when viewed correctly, i.e. through the eyes of the skilled person who is fully informed about the difficulties associated with formulation of amylin analogues but who is not already aware of the solution provided by the present invention.

Problem-solution approach

The Examiner suggests that any of D1 to D3 could be the closest prior art.

D2 does not appear to be appropriate because it is directed specifically to analogues having proline at position 21. Thus the skilled person would not seek to adapt this document by making a completely different change at that precise position.

Beginning from D1 or D3, the proper technical problem could be seen as the provision of alternative amylin analogues having improved solubility or stability, or reduced fibrillation, compared to human amylin, while retaining agonist activity at amylin receptors.

As discussed above, the prior art provides no pointer towards the claimed solution. In particular, even if the skilled person believed that deleting Asn21 and Asn22 might improve the physical properties of the molecule, they could have no reasonable expectation of

retaining agonist activity. Furthermore, by making these deletions in the analogues of D1 or D3, they still would not arrive at the molecules now claimed.

The Examiner's proposed approach of "trial and error" does not amount to the same thing, and at best could be undertaken with an "understandable hope to succeed".

We therefore believe that the claims are inventive.

Problem solved across scope of claim

The Examiner proposes that the claims should include a further functional limitation, reciting the relevant physical properties of the molecules. Although we understand the Examiner's point, we believe this is unnecessary. As a result of the deletion, the claimed compounds display improved physical properties as compared to equivalent compounds possessing the Asn21-Asn22 doublet. The presence of the deletion should necessarily lead to the improved physical properties, and thus there should be no need to recite the improved physical properties in the claim.

We respectfully request that the Examiner reconsider the objections and we look forward to receiving a positive IPRP in due course.

Yours faithfully

/ GRAHAM FORREST /

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Enc. Westermarck et al. (1990)

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