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(54) **Title:** NOVEL USE OF INSULIN DERIVATIVES

(57) **Abstract:** This invention relates to insulin derivatives having long duration of action. The insulin derivatives have been found to be useful for the treatment of diabetes, and in particular for less frequent administration to the diabetic patients, in particular as seldom as about once weekly.



NOVEL USE OF INSULIN DERIVATIVES

FIELD OF THIS INVENTION

This invention relates to insulin derivatives having an extremely long duration of action. Said derivatives can be used to treat diabetes and aspects related thereto. In a preferred aspect, these derivatives are only administered around once weekly to the patients.

BACKGROUND OF THIS INVENTION

Insulin is a polypeptide hormone secreted by β -cells of the pancreas. Insulin consists of two polypeptide chains designated the A and B chains which are linked together by two inter-chain disulphide bridges. In human, porcine and bovine insulin, the A and B chains contains 21 and 30 amino acid residues, respectively. However, from species to species, there are variations among the amino acid residues present in the different positions in the two chains. The widespread use of genetic engineering has made it possible to prepare analogues of natural occurring insulins by exchanging, deleting and adding one of more of the amino acid residues.

Insulin is used for the treatment of diabetes and diseases connected therewith or resulting from it. Insulin is essential in maintaining normal metabolic regulation. Usually, insulin is administered by injections (subcutaneously). Unfortunately, many diabetics are unwilling to undertake intensive therapy due to the discomfort associated with the many injections required to maintain close control of blood glucose levels. In the last decades, it has turned out that it is extremely important for a diabetic patient to maintain close control of the blood glucose level.

For decades, insulin preparations with different duration of action have been developed and put on the market and general examples of such preparations are long-acting insulin preparations, medium acting insulin preparations and fast acting insulin preparations. Many patients take 2-4 injections per day. For example, before a meal, many patients take a fast acting insulin preparation which shall control the glucose level after the meal, such treatments being designated prandial treatment. However, in order to control the glucose level at other moments than close to the moments of eating, diabetics have to take an insulin preparation with a longer duration of action, e.g., before they go to sleep, and this can be designated basal treatment. Hence, many diabetics take one injection every evening before they go to sleep. Even though such insulin preparations are effective in controlling the glucose level for about one night and day, they are not sufficient for controlling the glucose level for more than one night and day. No basal insulin products are approved for other than

daily subcutaneous injection. The discomfort of a large number of daily injections can, for example, be diminished by using insulin derivatives having an extremely long duration of action.

Claim 1 in WO 2010/049488 mentions "administering ... effective dosages of the insulin derivative ... said dosages are administered at intervals longer than 24 hours". According to the abstract in *J. Controlled Release* 104 (2005), 447-60, "When doses [of PEGylated human insulin encapsulated in PLGA] were given [to animals] at 7-day intervals, steady state drug levels were achieved after only 2 doses". Claim 25 in WO 98/05361 mentions "A method wherein ... effective doses of N-(Fmoc)₂-insulin and N-(Fmoc)₃-insulin are administered to the patient at 5-8 day intervals". In example 107 of WO 2011/161125, it is mentioned that acylated insulin derivatives of the invention (insulin derivatives having two or more cysteine substitutions to allow for one or more additional disulphide bonds) are administered to rats, plasma is collected at time points 0-96 hours after dosing and the plasma is assayed for glucose. WO 2009/115469 relates to acylated insulin analogues, that are able to give a satisfactory control of the blood glucose level following once daily administration, see page 2 line 15.

It is very desirable for the diabetics, if insulin preparations which are to be administered only say about once weekly and which would give a satisfactory basal treatment were available.

In 2007, there were 246 million diabetics in the world. In 2025, the number is expected to be about 380 million.

OBJECTS OF THIS INVENTION

The object of this invention is to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

Another aspect of this invention relates to the furnishing of insulin derivatives which have a so long time of action that it is sufficient to administer them with a frequency of about once weekly in order for the diabetic patient to get a sufficient basal administration of insulin.

Another aspect of this invention relates to the furnishing of insulin derivatives which have a long action profile.

Another aspect of this invention relates to the furnishing of insulin derivatives which increases convenience for the patients.

Another aspect of this invention relates to the furnishing of insulin derivatives which have a constant time-action profile for a period of time of about 1 week.

Another aspect of this invention relates to the furnishing of insulin derivatives which

have a flat action profile for a period of time of about 1 week.

Another aspect of this invention relates to the furnishing of insulin derivatives which have increased solubility.

Another aspect of this invention relates to the furnishing of insulin derivatives which have increased solubility in presence of zinc ions.

Another aspect of this invention relates to the furnishing of insulin derivatives which have increased solubility in presence of zinc ions and salt, such as sodium chloride.

DEFINITIONS

As defined herein, the term "diabetes" or "diabetes mellitus" includes type 1 diabetes, type 2 diabetes, gestational diabetes (during pregnancy) and other states that cause hyperglycaemia. The term is used for a metabolic disorder in which the pancreas produces insufficient amounts of insulin, or in which the cells of the body fail to respond appropriately to insulin thus preventing cells from absorbing glucose. As a result, glucose builds up in the blood.

Type 1 diabetes, also called insulin-dependent diabetes mellitus (IDDM) and juvenile-onset diabetes, is caused by B-cell destruction, usually leading to absolute insulin deficiency. Type 2 diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM) and adult-onset diabetes, is associated with predominant insulin resistance and thus relative insulin deficiency and/or a predominantly insulin secretory defect with insulin resistance.

As defined herein, the term "formulation" is used synonymously with the term "composition".

As defined herein, the following abbreviations are used: "gGlu" or "γGlu" for gamma L-glutamyl and "OEG" for the amino acid with the formula $\text{NH}_2-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{O}-\text{CH}_2-\text{COOH}$ corresponding to the group or residue $-\text{NH}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{O}-\text{CH}_2-\text{CO}-$ also designated [2-(2-aminoethoxy)ethoxy]methylcarbonyl.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein (to the maximum extent permitted by law).

The citation and incorporation of patent documents herein is done for convenience only and does not reflect any view of the validity, patentability, and/or enforceability of such patent documents. The mentioning herein of references is no admission that they constitute prior art.

All headings and sub-headings are used herein for convenience only and should not be construed as limiting the invention in any way.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. In the case of inconsistency between the present disclosure and the issued patents, applications and references that are cited herein or elsewhere, the present disclosure will prevail.

The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

Herein, the word "comprise" is to be interpreted broadly meaning "include", "contain" or "comprehend" (*vide*, Guidelines for Examination in the Europe Patent Office, part C, chapter III, 4.21, December 2007).

This invention includes all modifications and equivalents of the subject matter recited in the claims and clauses appended hereto as permitted by applicable law.

DETAILED DESCRIPTION OF THIS INVENTION

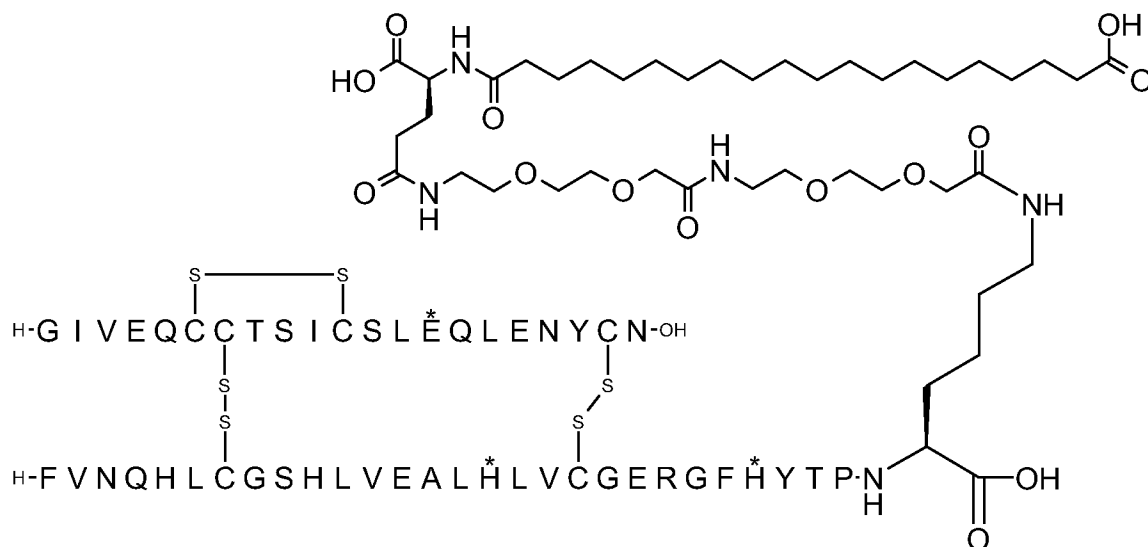
Human insulin consists of two polypeptide chains, interconnected by two cystine disulphide bridges. The primary amino acid sequence for the human insulin A chain (21 amino acids) is n-G I V E Q C C T S I C S L Y Q L E N Y C N-c (SEQ ID NO: 1). The primary amino acid sequence for the human insulin B chain (30 amino acids) is n-F V N Q H L C G D H L V E A L Y L V C G E R G F F Y T P K T-c (SEQ ID NO: 2).

It has, surprisingly, been found that insulin derivatives having the general formula I: Acy-X-Y_n-Ins, have an extremely long duration of action. The insulin derivatives of formula I have a so retarded duration of action that, to many patients, it can be used as the only insulin product for basal administration and that it is sufficient to administer it only about once weekly. In formula I, "Ins" designates an analogue of human insulin, to which insulin analogue a side chain (designated Acy-X-Y_n-) has been attached to the ε amino group present in the B29 lysine amino acid in said insulin analogue. In other words, "Ins" designates an insulin analogue as herein defined; and, according to formula I, a side chain (designated Acy-X-Y_n-) has been attached to said insulin analogue, i.e., attached to the ε amino group present in the B29 lysine amino acid in said insulin analogue. Said insulin analogue is human insulin containing glutamic acid in the A14 position, histidine in the B25

position, optionally histidine in the B16 position and, optionally, the B27 and/or B30 amino acid(s) has/have been removed. In said side chain having the general formula II (and designated Acy-X-Y_n-), Acy is a fatty diacid with 8-24 carbon atoms from which a hydroxyl group has been removed, X is γGlu wherein the amino residue has been connected to "Acy" and - if n is different from zero - the carbonyl group in γGlu has been connected to Y or - if n is zero - the gamma- (γ) carbonyl group in γGlu has been connected to the ε amino group in lysine in the B29 position in the insulin analogue, Y is -NH-(CH₂)₂-O-(CH₂)₂-O-CH₂-CO- wherein the amino residue is connected to X and the carbonyl group is connected to the ε amino group in lysine in the B29 position in the insulin analogue, and n is 0 (zero), 1, 2 or 3.

Hence, this invention relates to insulin derivatives having the general formula I: Acy-X-Y_n-Ins, wherein Ins designates an insulin analogue and a side chain (designated Acy-X-Y_n-) has been attached to the ε amino group present in the B29 lysine amino acid in said insulin analogue, said insulin analogue is human insulin containing glutamic acid in the A14 position, histidine in the B25 position, optionally histidine in the B16 position and, optionally, the B27 and/or B30 amino acid(s) has/have been removed, Acy is a fatty diacid with 8-24 carbon atoms from which a hydroxyl group has been removed, X is γGlu wherein the amino residue has been connected to "Acy" and - if n is different from zero - the carbonyl group in γGlu has been connected to Y or - if n is zero - the gamma-(γ) carbonyl group in γGlu has been connected to the ε amino group in lysine in the B29 position in the insulin analogue, Y is -NH-(CH₂)₂-O-(CH₂)₂-O-CH₂-CO- wherein the amino residue is connected to X and the carbonyl group is connected to the ε amino group in lysine in the B29 position in the insulin analogue, and n is 0 (zero), 1, 2 or 3.

A specific example of such an insulin derivative of formula I is A14E, B16H, B25H, B29K(N^ε-eicosanedioyl-γGlu-[2-(2-{2-[2-(2-aminoethoxy)ethoxy]acetylaminomethoxy}ethoxy)ethoxy]-acetyl), desB30 human insulin (herein designated Compound 1). This compound can also be designated A14E, B16H, B25H, B29K(N^ε-eicosandioyl-γGlu-OEG-OEG), desB30 human insulin, or alternatively A14E, B16H, B25H, B29K(N^ε-eicosandioyl-γGlu-2xOEG), desB30 human insulin, and has the following formula:



The above compound is mentioned in example 33 in WO 2009/115469.

Examples of other specific insulin derivatives of formula I are A14E, B16H, B25H, B29K(N^E-hexadecandioyl-γGlu), desB30 human insulin (herein designated Compound 2);

- 5 A14E, B16H, B25H, B29K(N^E-eicosanedioyl-γGlu), desB30 human insulin (herein designated Compound 3); A14E, B25H, desB27, B29K(N^E-(octadecandioyl-γGlu), desB30 human insulin (herein designated Compound 4); A14E, B25H, desB27, B29K(N^E-octadecandioyl-γGlu-OEG-OEG), desB30 human insulin (herein designated Compound 5); and A14E, B25H, B29K(N^E-octadecandioyl-γGlu-OEG-OEG), desB30 human insulin (herein designated
- 10 Compound 6). The formulae of the five last-mentioned compounds are stated in examples 27, 60, 151, 57 and 9, respectively, in WO 2009/115469.

Some of the compounds of formula I are known compounds and the remaining compounds of formula I can be prepared in a manner known *per se*, e.g., as analogously as described in WO 2009/115469.

- 15 Biophysics studies show that Compound 1 has different behaviour than ordinary insulin molecules and, similarly, this is expected to apply for the other insulin derivatives of formula I.

The *in vivo* potency of Compound 1 in pigs and dogs was estimated to be approximately 200% relative to insulin glargine.

- 20 *In vivo* pharmacology of Compound 1 in pigs has shown that dosing of a 4.2 mM solution, the absolute bioavailability is 90% relative to intravenously administration of the same compound.

Pharmaceutical formulations containing an insulin derivative of formula I can be prepared in a manner known *per se*, i.e., by using the additives usually used in similar insulin formulations.

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The insulin formulations are administered to the patients in a manner known *per se*, e.g., according to the general knowledge of the patient combined with the general knowledge of the physician. This invention is best used at the convenience of the patient. Therefore, specific administration intervals will be explored for each patient where dosages are administered less than daily. The final mode of use thus depends both on the product's capabilities and on the disposition and preference of the patient. This is due to the fact that the effect of any insulin product depends on the insulin need of the individual patient and the sensitivity to the pharmacodynamic actions of said insulin and lastly also to the preferences of the patient in a given situation. These conditions may change over time, both in terms of longer periods (years) and from day to day. The optimal dose level for any patient will depend on a variety of factors including the age, body weight, physical activity, and diet of the patient, on a possible combination with other drugs, and on the severity of the state to be treated. It is recommended that the dosage regimen be determined for each individual patient by those skilled in the art in a similar way as for known insulin formulations, however taking into consideration the present teachings concerning dosage intervals.

For the convenience of the patients, it is presumed that they prefer that the time interval (time lag) from the administration of one derivative of formula I to the next administration of a derivative of formula I has the same length, or approximately the same length, counted in number of days. It can even be expected that the patients will prefer that the administration of a derivative of formula I takes place only once weekly, i.e., on the same day in the week, e.g. on every Sunday. This will be an administration of a derivative of formula I every 7th day and not more frequently on an average calculated for a period of time of 1 month, 6 months or 1 year. For some patients, it may be desirable to administer a derivative of formula I every 6th day or approximately every 6th day and not more frequently on an average calculated for a period of time of 1 month, 6 months or 1 year. For other patients, it may be desirable to administer a derivative of formula I every 5th day or approximately every 5th day and not more frequently on an average calculated for a period of time of 1 month, 6 months or 1 year. For other patients, it may be desirable to administer a derivative of formula I every 4th day or approximately every 4th day and not more frequently on an average calculated for a period of time of 1 month, 6 months or 1 year. Even other patients may find it advantageous to administer a derivative of formula I only twice weekly, e.g., with an interval of about 3-4 days between each administration and not more frequently on an average calculated for a period of time of 1 month, 6 months or 1 year. For some patients, it may be desirable to administer a derivative of formula I every 3rd day or approximately every 3rd day and not more frequently on an average calculated for a period of

time of 1 month, 6 months or 1 year. For other patients, it may be desirable to administer a derivative of formula I every 2nd day or approximately every 2nd day and not more frequently on an average calculated for a period of time of 1 month, 6 months or 1 year. For some patients, it may be desirable to administer a derivative of formula I every 8th day or approximately every 8th day and not more frequently on an average calculated for a period of time of 1 month, 6 months or 1 year. Even other patients may not administer the derivative of formula I with a time interval of precisely the same length (counted in days), week after week, month after month or year after year. Some patients may administer a derivative of formula I sometime in the time interval from every 6th to every 8th day and not more frequently on an average calculated for a period of time of 1 month, 6 months or 1 year. Other patients may administer a derivative of formula I sometime in the time interval from every 5th to every 7th day and not more frequently on an average calculated for a period of time of 1 month, 6 months or 1 year. Even other patients may administer a derivative of formula I sometime in the time interval from every 4th to every 8th day and not more frequently on an average calculated for a period of time of 1 month, 6 months or 1 year. The time intervals mentioned here are to be understood as average time intervals within a period of time of say weeks, months or years. Here, it is intended that the term "day" covers 24 hours (i.e., a day and night) and, for the sake of easiness, a number of hours which is not divisible by 24 is to be rounded up to a whole number of days. Hence, e.g., 30 hours corresponds to 1 day and 40 hours corresponds to 2 days. Obviously, the above intervals of administration are to be calculated for each person.

The patients may have a daily basal insulin requirement of above about 0.2 IU/kg/day and below about 1 IU/kg/day and, furthermore, the patients may have a total (i.e., basal plus prandial) daily insulin requirement of above about 1 IU/kg/day. However, these ranges may vary considerably from patient to patient and may for several patients be somewhat outside the ranges mentioned here.

Diseases and conditions which are the primary targets for this invention are diabetes mellitus (type 1 or 2) or other conditions characterized by hyperglycaemia, but also metabolic diseases and conditions in general where the metabolic effects of insulin has a clinical relevance or are of interest, such as pre-diabetes, impaired glucose tolerance, metabolic syndrome, obesity, cachexia, *in vivo* beta-cell loss/death, excessive appetite, and inflammation. All these types of conditions are known to or believed to benefit from a stable metabolic state in the subject who has the disease or condition. At any rate, any therapeutic regimen where administration of insulin is included may be modified by implementing the

current teachings, meaning that such therapies will include administration of prolonged-profile-of-action insulins according to the teachings provided herein.

In order to exercise this invention, an insulin preparation may be administered parenterally to patients in need of such a treatment. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump. Further options are to administer the insulin composition nasally or pulmonary, preferably in compositions, powders or liquids, specifically designed for the purpose.

Embodiments of the method of this invention include those wherein administration of an insulin derivative of formula I is supplemented with more frequent administrations of a fast-acting naturally occurring insulin, insulin analogue or insulin derivative and/or administration of a non-insulin anti-diabetic drug. In one embodiment of this invention, administration of an insulin derivative of formula I is supplemented with administration of a non-insulin anti-diabetic drug, such as metformin.

PREFERRED FEATURES OF THIS INVENTION

To sum up and supplement the above statements, the features and clauses of this invention are as follows:

1. An insulin derivative of formula I: $\text{Acy-X-Y}_n\text{-Ins}$, wherein Ins designates an insulin analogue and a side chain (designated Acy-X-Y_n) has been attached to the ϵ amino group present in the B29 lysine amino acid in said insulin analogue, said insulin analogue is human insulin containing glutamic acid in the A14 position, histidine in the B25 position, optionally histidine in the B16 position and, optionally, the B27 and/or B30 amino acid(s) has/have been removed, Acy is a fatty diacid with 8-24 carbon atoms from which a hydroxyl group has been removed, X is γGlu wherein the amino residue has been connected to "Acy" and - if n is different from zero - the carbonyl group in γGlu has been connected to Y or - if n is zero - the gamma-(γ) carbonyl group in γGlu has been connected to the ϵ amino group in lysine in the B29 position in the insulin analogue, Y is $-\text{NH}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{O}-\text{CH}_2-\text{CO}-$ wherein the amino residue is connected to X and the carbonyl group is connected to the ϵ amino group in lysine in the B29 position in the insulin analogue, and n is 0 (zero), 1, 2 or 3; for use in treating diabetes said derivative being administered to the same patient every 2nd day or less frequently and, on average, during a period of time of at least 1 month, 6 months or 1 year, said derivative is not administered more frequently to the same patient.

2. The insulin derivative of formula I according to the preceding clause for use in treating diabetes which derivative is administered every 3rd day or less frequently and, on average, during a period of time of at least 1 month, 6 months or 1 year, said derivative is not administered more frequently to the same patient.

5 3. The insulin derivative of formula I according to the preceding clause for use in treating diabetes which derivative is administered twice a week or less frequently and, on average, during a period of time of at least 1 month, 6 months or 1 year, said derivative is not administered more frequently to the same patient.

10 4. The insulin derivative of formula I according to the preceding clause for use in treating diabetes which derivative is administered every 4th day or less frequently and, on average, during a period of time of at least 1 month, 6 months or 1 year, said derivative is not administered more frequently to the same patient.

15 5. The insulin derivative of formula I according to the preceding clause for use in treating diabetes which derivative is administered every 5th day or less frequently and, on average, during a period of time of at least 1 month, 6 months or 1 year, said derivative is not administered more frequently to the same patient.

20 6. The insulin derivative of formula I according to the preceding clause for use in treating diabetes which derivative is administered every 6th day or less frequently and, on average, during a period of time of at least 1 month, 6 months or 1 year, said derivative is not administered more frequently to the same patient.

7. The insulin derivative of formula I according to the preceding clause for use in treating diabetes which derivative is administered every 7th day and, on average, during a period of time of at least 1 month, 6 months or 1 year, said derivative is not administered more frequently to the same patient.

25 8. The insulin derivative of formula I according to any one of the preceding clauses for use in treating diabetes which derivative is administered every 11th day or more frequently on average, during a period of time of at least 1 month, 6 months or 1 year.

30 9. The insulin derivative of formula I according to the preceding clause for use in treating diabetes which derivative is administered every 10th day or more frequently on average, during a period of time of at least 1 month, 6 months or 1 year.

10. The insulin derivative of formula I according to the preceding clause for use in treating diabetes which derivative is administered every 9th day or more frequently on average, during a period of time of at least 1 month, 6 months or 1 year.

11. The insulin derivative of formula I according to the preceding clause for use in treating diabetes which derivative is administered every 8th day or more frequently on average, during a period of time of at least 1 month, 6 months or 1 year.

12. The insulin derivative of formula I according to any one of the preceding clauses for use in treating diabetes which derivative is A14E, B16H, B25H, B29K(N^E-eicosanedioyl-gGlu-[2-(2-{2-[2-(2-aminoethoxy)ethoxy]acetyl-amino}ethoxy)ethoxy]acetyl), desB30 human insulin (Compound 1).

13. The insulin derivative of formula I according to any one of the preceding clauses, to the extent possible, for use in treating diabetes which derivative is A14E, B16H, B25H, B29K(N^E-hexadecandioyl-γGlu), desB30 human insulin (Compound 2).

14. The insulin derivative of formula I according to any one of the preceding clauses, to the extent possible, for use in treating diabetes which derivative is A14E, B16H, B25H, B29K(N^E-eicosanedioyl-γGlu), desB30 human insulin (Compound 3).

15. The insulin derivative of formula I according to any one of the preceding clauses, to the extent possible, for use in treating diabetes which derivative is A14E, B25H, desB27, B29K(N^E-octadecandioyl-γGlu), desB30 human insulin (Compound 4).

16. The insulin derivative of formula I according to any one of the preceding clauses, to the extent possible, for use in treating diabetes which derivative is A14E, B25H, desB27, B29K(N^E-octadecanedioyl-γGlu-OEG-OEG), desB30 human insulin (Compound 5).

17. The insulin derivative of formula I according to any one of the preceding clauses, to the extent possible, for use in treating diabetes which derivative is A14E, B25H, B29K(N^E-octadecandioyl-γGlu-OEG-OEG), desB30 human insulin (Compound 6).

18. The insulin derivative of formula I according to any one of the preceding clauses wherein the currently or repeatedly treatment for diabetes with a compound of formula I lasts for more than 1 month.

19. The insulin derivative of formula I according to the preceding clause wherein the currently or repeatedly treatment for diabetes lasts for more than 2 months.

20. The insulin derivative of formula I according to any one of the preceding clauses wherein the currently or repeatedly treatment for diabetes lasts for more than 3 months.

21. The insulin derivative of formula I according to any one of the preceding clauses wherein the currently or repeatedly treatment for diabetes lasts for more than 1 year.

22. The insulin derivative of formula I according to any one of the preceding clauses for use in treating diabetes which derivative is administered parenterally.

23. The insulin derivative of formula I according to the preceding clauses for use in treating diabetes which derivative is administered subcutaneously, intramuscularly or intravenously, preferably subcutaneously.

24. The use of an insulin derivative of formula I for treating diabetes said derivative being administered to the same patient with a frequency in the range from every 2nd day to every 11th day.

25. A pharmaceutical formulation containing an insulin derivative of formula I for treating diabetes said formulation being administered to the same patient with a frequency in the range from every 2nd day to every 11th day.

26. A pharmaceutical formulation as defined in any one of ten above clauses relating to a compound of formula I for use in treating diabetes.

27. A method for treatment of diabetes, the method comprising administering to a subject in need thereof a therapeutically effective amount of an insulin derivative of formula I with a frequency in the range from every 2nd day to every 11th day.

28. A method for treatment of diabetes, as defined in any one of the above clauses relating to a compound of formula I for use in treating diabetes.

29. Any novel product, apparatus, method or use defined by a feature and or a claim and/or a combination of features and/or claims described herein.

Combining one or more of the clauses and embodiments described herein, optionally also with one or more of the claims below, results in further embodiments and the present invention relates to all possible combinations of said clauses, embodiments and claims.

The following examples are offered by way of illustration, not by limitation.

Example 1

Effect of subcutaneously administered insulin analogue of the invention on blood glucose, C-peptide, and HbA1c versus NPH insulin and vehicle in Sprague Dawley rats

Rats were allowed free access to food and water prior to the experiment. At time 0 min, 200 µL tongue blood was drawn. The rats (groups of 6 animals) were injected either with vehicle, NPH insulin (12 nmol/animal), and A14E, B16H, B25H, B29K(N^E-eicosanedioyl-γGlu-[2-(2-{2-[2-(2-aminoethoxy)ethoxy]acetylaminomethoxy}ethoxy)acetyl]), desB30 human insulin (Compound 1) (50, 100, and 200 nmol/animal) s.c in the neck skin. At following time points, blood samples were drawn: 2, 4, 6, 8, 24, 32, 48, 72, and 96 hours. Blood samples were analysed for insulin exposure, C-peptide, plasma glucose, and HbA1c (HbA1c only 96 h time point). The results are presented in Figures 1-4:

Fig. 1 shows the plasma concentration levels following dosing of 3 different doses of Compound 1 (50, 100 and 200 nmol/animal) to rats within the time interval of 1-4 days.

Fig. 2 shows the blood glucose levels following dosing of NPH insulin (12 nmol/animal), of 3 different doses of Compound 1 (50, 100, and 200 nmol/animal) and of vehicle to rats within the time interval of 1-4 days.

Fig. 3 shows the C-peptide levels following dosing of NPH insulin (12 nmol/animal) and of 3 different doses of Compound 1 (50, 100, and 200 nmol/animal) to rats within the time interval of 1-4 days.

Fig. 4 shows the level of HbA1c 4 days after administration of NPH insulin (12 nmol/animal) and of 3 different doses of Compound 1 (50, 100, and 200 nmol/animal) to rats 4 days after administration.

The conclusion from these figures is that one single dosing of Compound 1 to normal non-diabetic rats is enough to:

- Lower blood glucose for 2-3 days
- Lower C-peptide for at least 4 days
- Significantly lower HbA1c in non-diabetic rats.

The importance of the data given for the compound of this invention is illustrated by comparison with the data for the NPH insulin which is, generally, considered a long-acting preparation.

Example 2

Pharmacokinetic profiles after intravenously (i.v.) dosing were made in Beagle dogs (weighing approximately 12 kg) to evaluate the pharmacokinetic properties of insulin degludec (Insulin degludec is a once-daily basal insulin analogue with an ultra-long duration of action described in e.g. WO 2005/012347), and to evaluate the pharmacokinetic properties of a compound of formula 1, i.e., A14E, B16H, B25H, B29K(N^E-eicosanedioyl-γGlu-[2-(2-{2-[2-(2-aminoethoxy)ethoxy]acetylamino}ethoxy)ethoxy]acetyl), desB30 human insulin (Compound 1). It was also desirable to be able to calculate the bioavailability after extravascular dosing. The animals were dosed i.v., 1.0 or 1.6 nmol/kg of insulin degludec or Compound 1, respectively, blood samples were collected and plasma analysed using sandwich immunoassay.

Pharmacokinetic profiles after subcutaneous (s.c.) profile were made in Beagle dogs (approximately 12 kg), to evaluate the pharmacokinetic properties after s.c. dosing. 4.1 or 17 nmol/kg of insulin degludec or Compound 1, respectively, were injected subcutaneously.

Blood samples were drawn and the plasma concentration of insulin degludec and of Compound 1, respectively, were measured.

All studies were single dose studies. The calculations were performed using the software WinNonlin Professional 5.3 (Pharsight Inc., Mountain View, CA, USA). The data obtained are presented in Tables 1-2 below.

As can be deduced from the data obtained from MRT after s.c. dosing (7.7 hours versus 92 hours), it indicates that in dog the duration of action of Compound 1 is at least 7 times longer than the duration of action of insulin degludec, which in turn has been shown to be a true once daily insulin in humans.

Table 1

Mean Dog PK data after i.v. dosing of insulin degludec and Compound 1, respectively

Analogue	Dose		AUC/D	AUC % extrap	Vz	CL	MR T	T _½ *
	nmol/kg		pM*min/ (nmol/kg)		ml/kg	ml/kg /min	h	h
Insulin degludec (n=5)	1	Mean	3397	8	75	0.30	3.8	2.9
		SD	446	1	13	0.04	0.4	0.2
Compound 1 (n=4)	1.6	Mean	67787	13	78	0.015	78	60
		SD	9506	0	12	0.002	2	1

* T_½ given as harmonic mean±pseudoSD

Table 2

Mean Dog PK data after i.v. dosing of insulin degludec and Compound 1, respectively

Analogue	Dose		T _{max} *	C _{max} /D	MRT	T _½ **	F
	nmol/kg		H	pM/(nmol/kg)	H	h	%
Insulin degludec (n=5)	4.1	Mean	4	5495	7.7	6.1	80
		SD	1.1	1920	1.5	2.3	15
Compound 1 (n=6)	17	Mean	24	6218	92	56	64
		SD	5	1250	2	2	13

* T_{max} given as median±SD

** T_½ given as harmonic mean±pseudoSD

Name	Explanation
AUC	The area under the concentration-time curve from zero to infinity and the mean was calculated (WinNonlin name: AUCinf_pred) [Unit: pM*min]
AUC/D	The area under the concentration-time curve from zero to infinity divided with dose and the mean was calculated (WinNonlin name: AUCinf_pred/D) [Unit: pM*min/(pmol/kg)]
AUC %extrap	The percentage of the AUC from zero to infinity which was extrapolated from the last data point to infinity and the mean was calculated (WinNonlin name: AUC_%Extrap_pred) [Unit: %]
CL	The total body clearance and the mean was calculated (WinNonlin name: Cl_pred) [Unit: ml/(kg*min)]
C _{max}	Plasma concentrations of the compound were measured and plotted against the time in a semi-logarithmic plot, and the time to reach peak or maximum concentration following a single dose is read directly from concentration-time profile. C _{max} is always associated with T _{max} . [Unit: pM]
C _{max} /Dose	Plasma concentrations of the compound were measured and plotted against the time in a semi-logarithmic plot, and the maximum (peak) plasma concentration after a single dose is read directly from concentration-time profile. C _{max} is always associated with T _{max} . [Unit: ml/(kg*min)]
D	Dose [Unit: nmol/kg]
F	The fraction sc bioavailable = $((AUC_{sc}/D_{sc})/(AUC_{iv}/D_{iv})) * 100$ [Unit: %]
MRT	MRT = mean residence time extrapolated to infinity. The average time the number of molecules introduced into the body, resides in the body. $MRT = AUMC_{inf_pred} / AUC_{inf_pred}$ and AUMC: Area under the first moment curve extrapolated to infinity was based on the last observed concentration and calculated as $AUMC_{last} + C_{last} / \lambda_z^2 + (T_{last} + C_{last}) / \lambda_z$ (WinNonlin name: MRTinf_pred) [Unit: Hrs]
T _½	The elimination phase can be described by the elimination half-life which expresses the time in which half of the compound disappears from plasma following administration and the harmonic mean was calculated (WinNonlin name: HL_lambda_z) [Unit: Hrs]
T _{max}	Plasma concentrations of the compound were measured and plotted against the time in a semi-logarithmic plot, and the time to reach peak or maximum concentration following a single dose is read directly from concentration-time profile. T _{max} is always associated with C _{max} and the median was given. [Unit: Minutes]
V _z	Volume of distribution based on the terminal phase = $D / (\lambda_z * AUC)$. The mean was calculated (WinNonlin name: Vz_pred) [Unit: Vz]

Example 3

- 5 Pharmacokinetic simulation was performed to show that A14E, B25H, B29K(N^ε-octadecandioyl-γGlu-2xOEG), desB30 human insulin (Compound 6) could be injected twice

weekly to humans with similar flat steady state plasma concentration profile as insulin degludec injected every day.

The simulation was performed using the software WinNonlin Professional 5.3 (Pharsight Inc., Mountain View, CA, USA). A simple one compartment model with first order elimination and absorption rate was used to simulate insulin degludec dosing once daily (every 24 hour) and Compound 6, dosing once daily (every 24 hour) and in addition twice weekly (every 84 h). Average pharmacokinetic parameters from human studies were used for insulin degludec (absorption rate constant = 0.031 h^{-1} and elimination rate constant = 0.25 h^{-1} corresponding to absorption half-life of 22 hours and elimination half-life of 2.8 hours). For Compound 6, average parameters from human studies were used for the elimination rate constant, but as the absorption rate constant after subcutaneous dosing was not known for humans, the absorption rate constant for insulin degludec was used instead (elimination rate constant = 0.013 h^{-1} corresponding to elimination half-life of 52 hours).

From the simulated steady state levels of both insulin analogues the maximum plasma concentration and the minimum plasma concentration achieved from plasma concentration vs time profiles was recorded. The fluctuation at steady state was then calculated as the maximum plasma concentration divided by the minimum plasma concentration.

The fluctuations were estimated to be:

Insulin analogue	Dosing interval	Fluctuation rate
Insulin degludec	24 hours	1.5
Compound 6	24 hours	1.1
Compound 6	84 hours	1.5

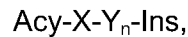
Based on simulated results, Compound 6 given once daily would be expected to provide a more flat plasma concentration vs time profile than that insulin degludec as judged by the lowering in fluctuations rate. Also, Compound 6 injected twice weekly would be expected to give the same fluctuations in the plasma concentration profile as that of insulin degludec once daily based on similar fluctuation rates.

A14E, B25H, desB27, B29K(N^{E} -(octadecandioyl- γ Glu), desB30 human insulin (Compound 4) has been shown to have almost the same terminal half-life, and thus similar elimination rates, in humans as Compound 6. Also, A14E, B25H, desB27, B29K(N^{E} -octadecanedioyl- γ Glu-2xOEG), desB30 human insulin (Compound 5) is expected to show

the same terminal half-life as that of Compound 6 in man (as the elimination half-lives are very similar to that of Compound 6 in dogs). Therefore a flat steady state plasma concentration profile with lower fluctuations than that of insulin degludec should be expected for these insulin analogues.

What is claimed is:

1. An insulin derivative of the general formula I:



wherein Ins designates an insulin analogue, to which Ins a side chain (designated Acy-X-Y_n-) has been attached to the ε amino group present in the B29 lysine amino acid in said insulin analogue, which insulin analogue is human insulin containing

glutamic acid in the A14 position;

histidine in the B25 position;

optionally histidine in the B16 position; and,

optionally, the B27 and/or B30 amino acid(s) has/have been removed;

Acy is a fatty diacid with 8-24 carbon atoms, from which a hydroxyl group has been removed;

X is γGlu, wherein the amino residue has been connected to "Acy", and - if n is different from zero - the carbonyl group in γGlu has been connected to Y, or - if n is zero - the gamma-(γ) carbonyl group in γGlu has been connected to the ε amino group in lysine in the B29 position in the insulin analogue;

Y is -NH-(CH₂)₂-O-(CH₂)₂-O-CH₂-CO-, wherein the amino residue is connected to X, and the carbonyl group is connected to the ε amino group in lysine in the B29 position in the insulin analogue, and

n is 0 (zero), 1, 2 or 3;

for use as a medicament for the treatment of diabetes, said compound being administered to the same patient with a frequency in the range from every 2nd day to every 11th day, on average, during a period of time of at least 1 month, of at least 6 months, or of at least 1 year, and within said period of time no administration of said derivative takes place to the same patient more frequently than every 2nd day or less frequently than every 11th day.

2. The insulin derivative according to claim 1, for use as herein described, which insulin derivative is selected from the group consisting of

A14E, B16H, B25H, B29K(N^ε-eicosanedioyl-γGlu-[2-(2-{2-[2-(2-aminoethoxy)-ethoxy]acetylaminomethoxy}ethoxy)acetyl]), desB30 human insulin;

A14E, B16H, B25H, B29K(N^ε-hexadecandioyl-γGlu), desB30 human insulin;

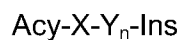
A14E, B16H, B25H, B29K(N^ε-eicosanedioyl-γGlu), desB30 human insulin;

A14E, B25H, desB27, B29K(N^ε-(octadecandioyl-γGlu), desB30 human insulin;

A14E, B25H, desB27, B29K(N^{ϵ} -octadecanedioyl- γ Glu-2xOEG), desB30 human insulin; and

A14E, B25H, B29K(N^{ϵ} -octadecandioyl- γ Glu-2xOEG), desB30 human insulin.

- 5 3. A pharmaceutical formulation comprising an insulin derivative of the general formula I:



wherein Ins designates an insulin analogue, to which Ins a side chain (designated Acy-X-Y_n-) has been attached to the ϵ amino group present in the B29 lysine amino acid in
10 said insulin analogue, which insulin analogue is human insulin containing

glutamic acid in the A14 position;

histidine in the B25 position;

optionally histidine in the B16 position; and,

optionally, the B27 and/or B30 amino acid(s) has/have been removed;

15 Acy is a fatty diacid with 8-24 carbon atoms, from which a hydroxyl group has been removed;

X is γ Glu, wherein the amino residue has been connected to "Acy", and - if n is different from zero - the carbonyl group in γ Glu has been connected to Y, or - if n is zero - the gamma-(γ) carbonyl group in γ Glu has been connected to the ϵ amino group in lysine in the
20 B29 position in the insulin analogue;

Y is $-\text{NH}(\text{CH}_2)_2\text{-O}(\text{CH}_2)_2\text{-O-CH}_2\text{-CO-}$, wherein the amino residue is connected to X, and the carbonyl group is connected to the ϵ amino group in lysine in the B29 position in the insulin analogue, and

n is 0 (zero), 1, 2 or 3;

25 for use in the treatment of diabetes, wherein said formulation is being administered to the same patient with a frequency in the range from every 2nd day to every 11th day.

4. The pharmaceutical formulation according to claim 3, wherein the insulin derivative is selected from the group consisting of

30 A14E, B16H, B25H, B29K(N^{ϵ} -eicosanedioyl- γ Glu-[2-(2-{2-[2-(2-aminoethoxy)-ethoxy]acetyl-amino}ethoxy)ethoxy]acetyl), desB30 human insulin;

A14E, B16H, B25H, B29K(N^{ϵ} -hexadecandioyl- γ Glu), desB30 human insulin;

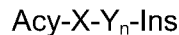
A14E, B16H, B25H, B29K(N^{ϵ} -eicosanedioyl- γ Glu), desB30 human insulin;

A14E, B25H, desB27, B29K(N^{ϵ} -(octadecandioyl- γ Glu), desB30 human insulin;

A14E, B25H, desB27, B29K(N^{ϵ} -octadecanedioyl- γ Glu-2xOEG), desB30 human insulin; and

A14E, B25H, B29K(N^{ϵ} -octadecandioyl- γ Glu-2xOEG), desB30 human insulin.

- 5 5. A method for treatment of diabetes, the method comprising administering to a subject in need thereof a therapeutically effective amount of an insulin derivative of the general formula I



10 wherein Ins designates an insulin analogue, to which Ins a side chain (designated Acy-X-Y_n-) has been attached to the ϵ amino group present in the B29 lysine amino acid in said insulin analogue, which insulin analogue is human insulin containing

glutamic acid in the A14 position;

histidine in the B25 position;

optionally histidine in the B16 position; and,

15 optionally, the B27 and/or B30 amino acid(s) has/have been removed;

Acy is a fatty diacid with 8-24 carbon atoms, from which a hydroxyl group has been removed;

20 X is γ Glu, wherein the amino residue has been connected to "Acy", and - if n is different from zero - the carbonyl group in γ Glu has been connected to Y, or - if n is zero - the gamma-(γ) carbonyl group in γ Glu has been connected to the ϵ amino group in lysine in the B29 position in the insulin analogue;

Y is -NH-(CH₂)₂-O-(CH₂)₂-O-CH₂-CO-, wherein the amino residue is connected to X, and the carbonyl group is connected to the ϵ amino group in lysine in the B29 position in the insulin analogue, and

25 n is 0 (zero), 1, 2 or 3;

with a frequency in the range from every 2nd day to every 11th day.

6. The method according to claim 5, wherein the insulin derivative is selected from the group consisting of

30 A14E, B16H, B25H, B29K(N^{ϵ} -eicosanedioyl- γ Glu-[2-(2-{2-[2-(2-aminoethoxy)-ethoxy]acetyl}amino}ethoxy)ethoxy]acetyl), desB30 human insulin;

A14E, B16H, B25H, B29K(N^{ϵ} -hexadecandioyl- γ Glu), desB30 human insulin;

A14E, B16H, B25H, B29K(N^{ϵ} -eicosanedioyl- γ Glu), desB30 human insulin;

A14E, B25H, desB27, B29K(N^{ϵ} -(octadecandioyl- γ Glu), desB30 human insulin;

A14E, B25H, desB27, B29K(*N*^ε-octadecanedioyl- γ Glu-2xOEG), desB30 human insulin; and

A14E, B25H, B29K(*N*^εoctadecandioyl- γ Glu-2xOEG), desB30 human insulin.

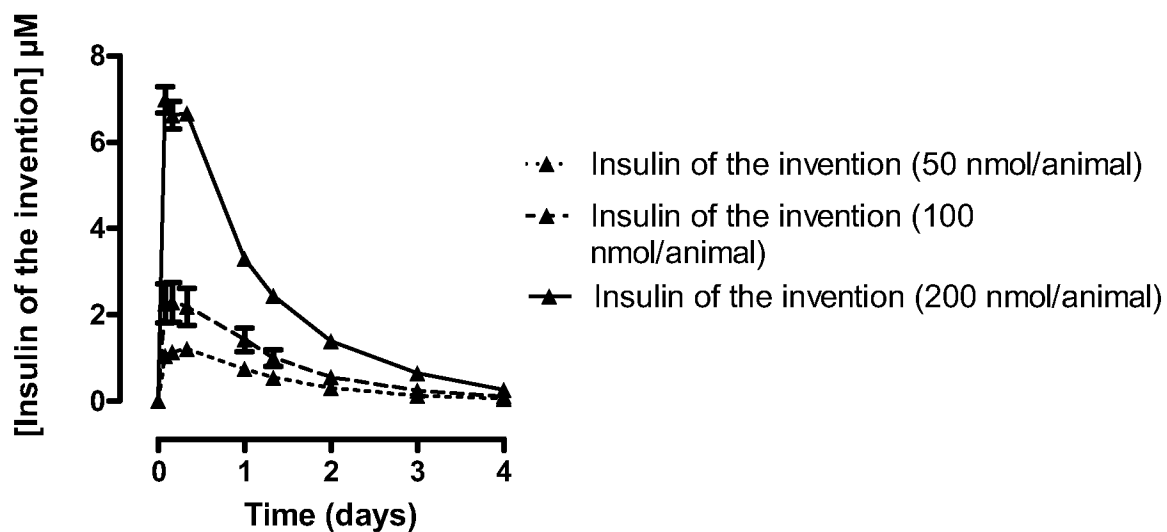


Fig. 1/4

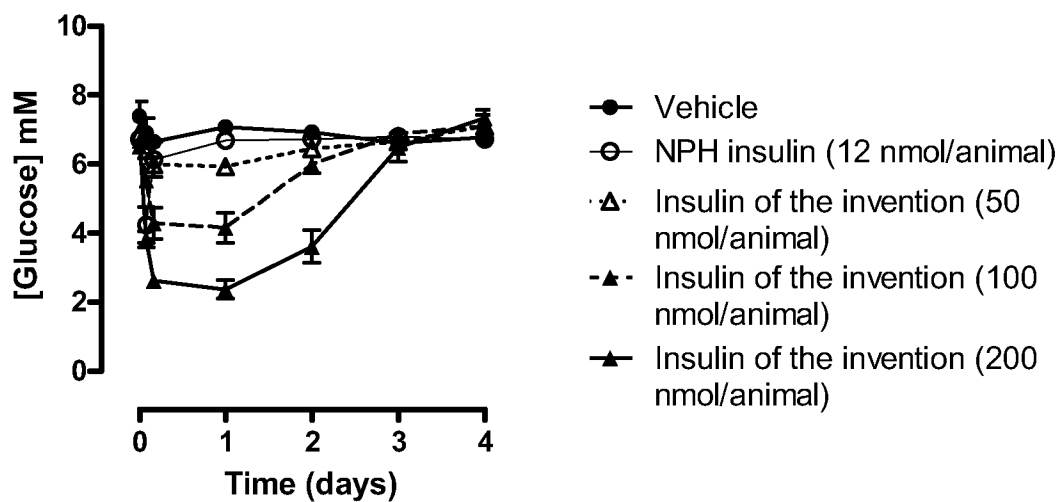


Fig. 2/4

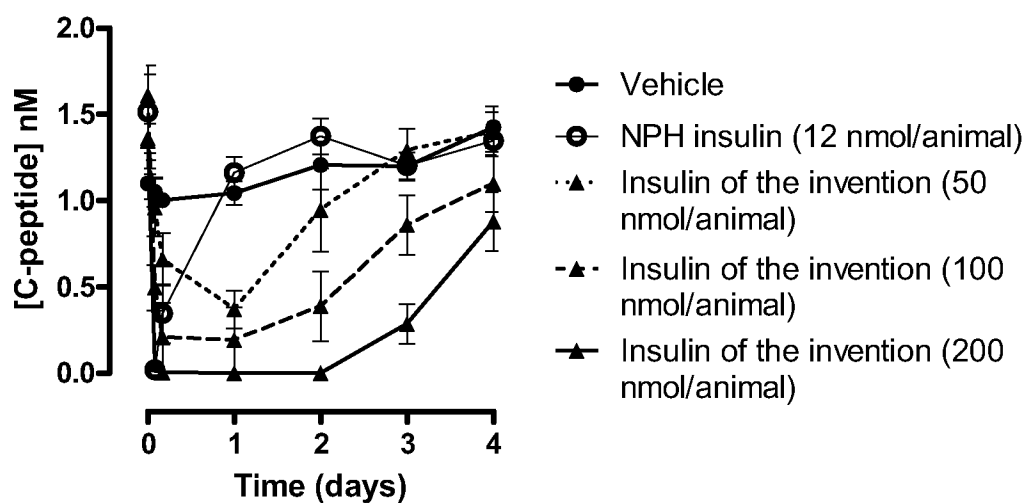


Fig. 3/4

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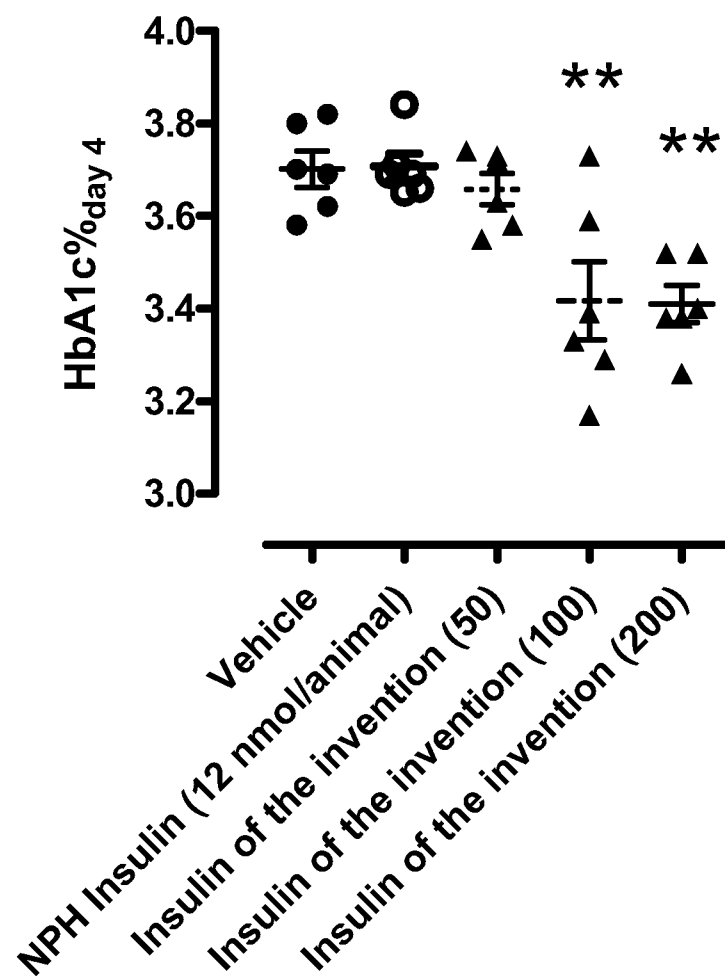


Fig. 4/4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/064392

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/28 A61P3/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2009/115469 A1 (NOVO NORDISK AS [DK]; MADSEN PETER [DK]; KJELDEN THOMAS BOERGLUM [DK]) 24 September 2009 (2009-09-24) cited in the application examples 27, 33, 60, 151 the whole document	1-6
X	WO 2011/161125 A1 (NOVO NORDISK AS [DK]; MADSEN PETER [DK]; HUBALEK FRANTISEK [DK]; KJELD) 29 December 2011 (2011-12-29) the whole document example 107	1-6



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

24 September 2013

Date of mailing of the international search report

02/10/2013

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/064392

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