Docket No.: 8545US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Christine Bjoern Jensen et al.

Application No.: Not Yet Assigned | Confirmation No.: N/A

Filed: Concurrently Herewith | Art Unit: N/A

For: Use of Logn-Acting GLP-1 Peptides | Examiner: Not Yet Assigned

UTILITY PATENT APPLICATION TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This is a request for filing a Continuation application under 37 C.F.R. 1.53(b).

Applicant: Novo Nordisk A/S

Title: Use of Long-Acting GLP-1 Peptides

Applicants enclose a duly filled in Application Data Sheet with all relevant priority information.

Direct all future correspondence to Customer Number 23650.

Please charge the required fee associated with this application and credit any overpayments to Novo Nordisk, Inc., Deposit Account No. 14-1447, under Order No. 8545US02 from which the undersigned is authorized to draw. Please charge any additional fees, should they be required, to Deposit Account No. 14-1447.

Dated: July 20, 2017

Respectfully submitted,

Electronic signature: /Leon Y. Lum/
Leon Y. Lum
Registration No.: 62,124
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536
(609) 987-5800
Attorney For Applicant

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0001

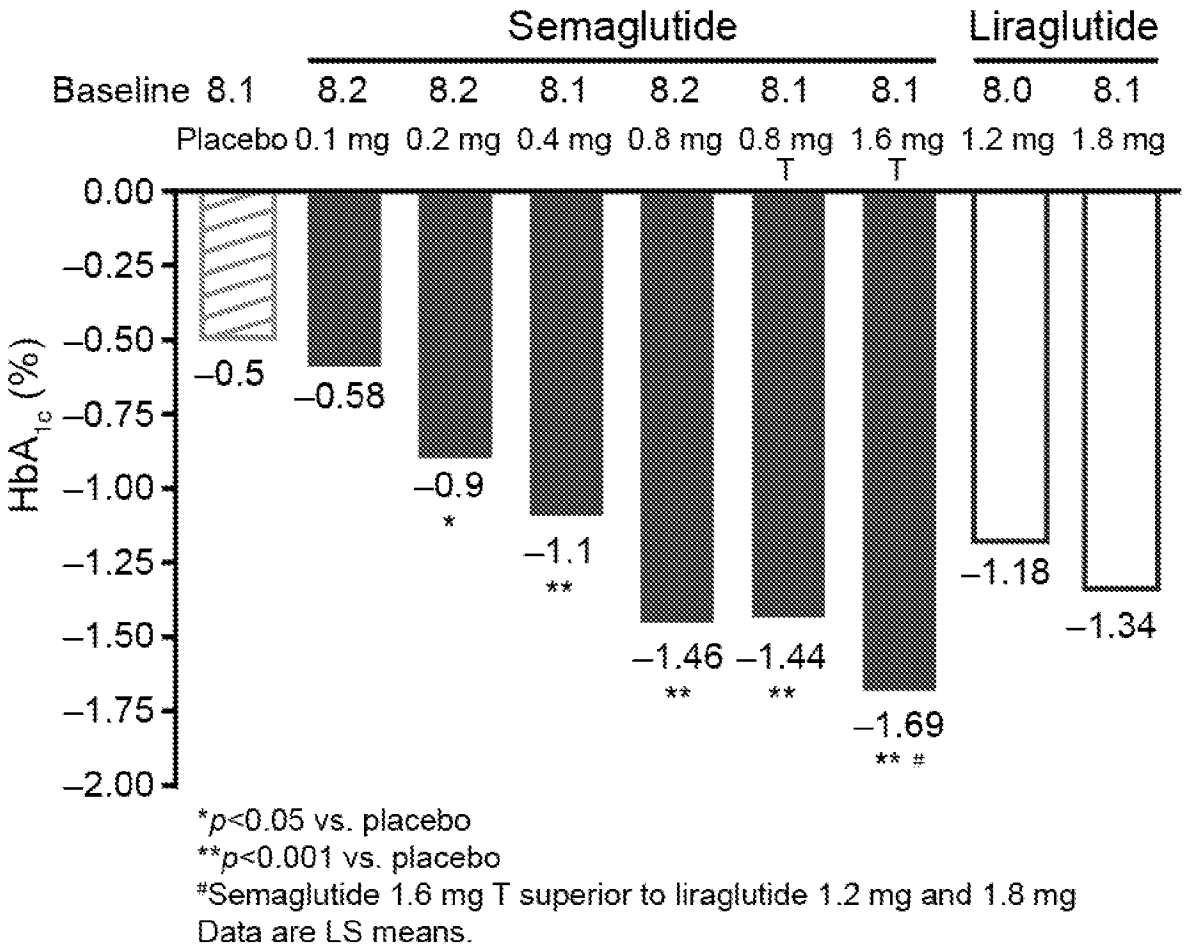
Semaglutide
Liraglutide
Baseline 8.1
8.2
8.2
8.1
8.2
8.1
8.1
8.0
8.1
Placebo
0.1 mg
0.2 mg
0.4 mg
0.8 mg
0.8 mg T
1.6 mg T
1.2 mg
1.8 mg
HbA1c (%)
0.00
–0.25
–0.50
–0.75
–1.00
–1.25
–1.50
–1.75
–2.00
–0.5
–0.58
–0.9 *
–1.1 **
–1.46 **
–1.44 **
–1.69 ** #
–1.18
–1.34
*p<0.05 vs. placebo
**p<0.001 vs. placebo
#Semaglutide 1.6 mg T superior to liraglutide 1.2 mg and 1.8 mg
Data are LS means.

Fig. 1

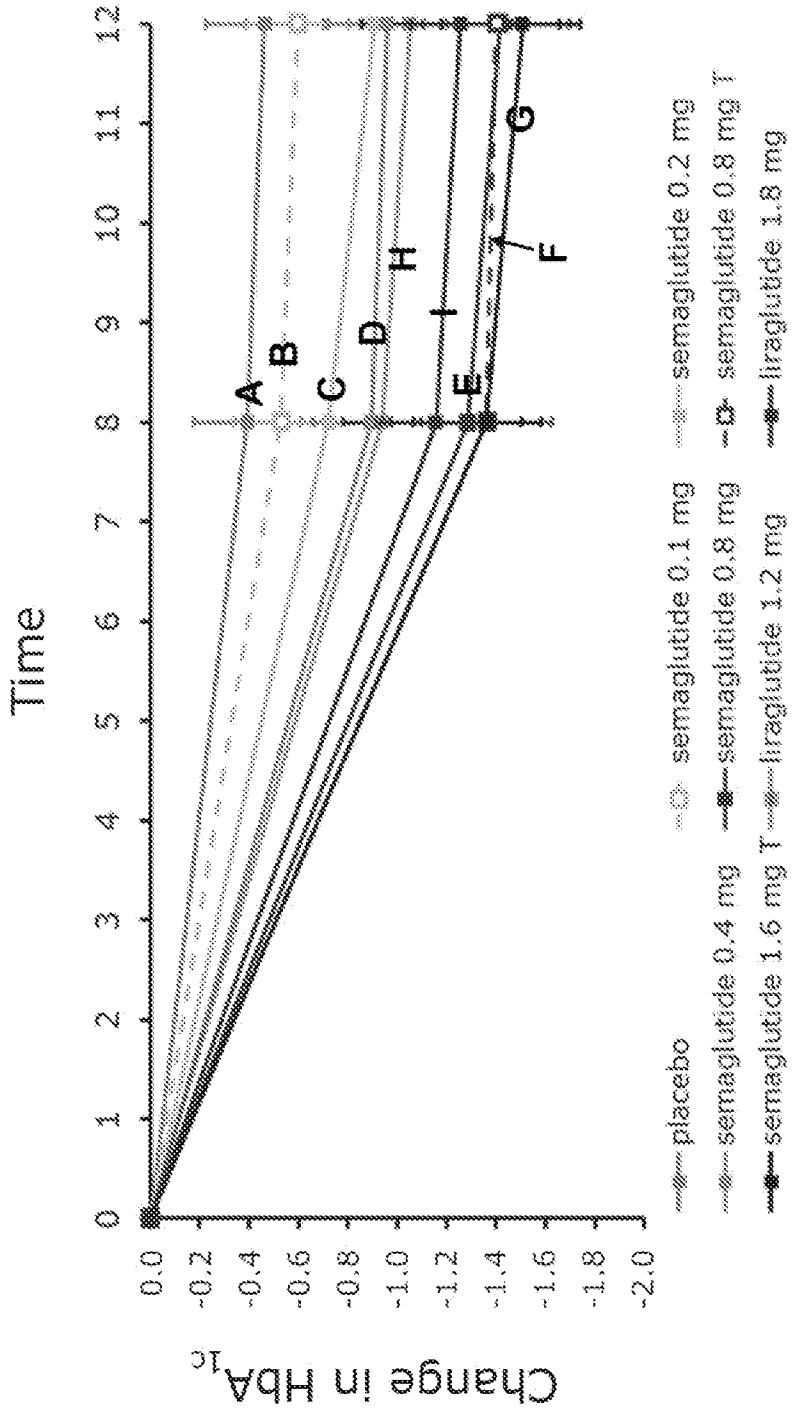

Fig. 2

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Petitioner Apotex Exhibit 1002-0003

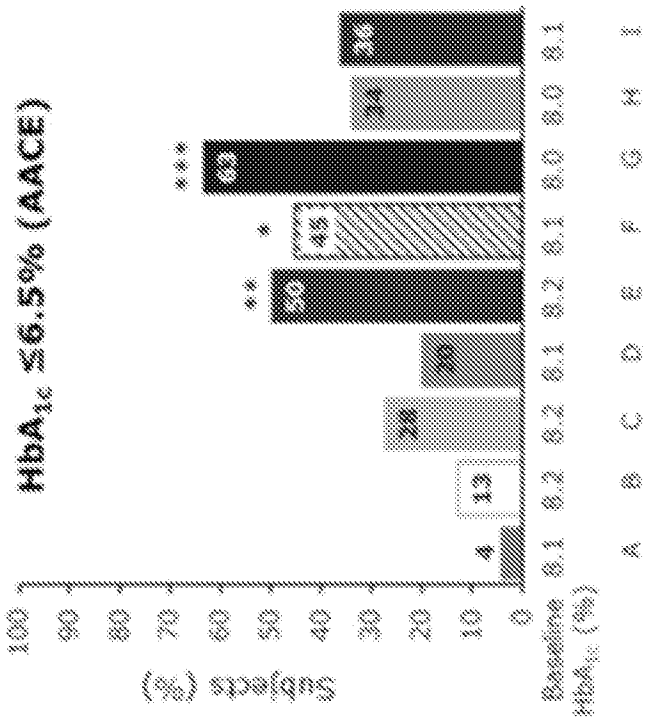
HbA1c ≤6.5% (AACE)
Subjects (%)
100
90
80
70
60
50
40
30
20
10
0
Baseline HbA1c (%)
8.1
8.2
8.2
8.1
8.2
8.1
8.0
8.0
8.1
4
13
28
30
50
45
63
34
36
A
B
C
D
E
F
G
H
I

Fig. 3A

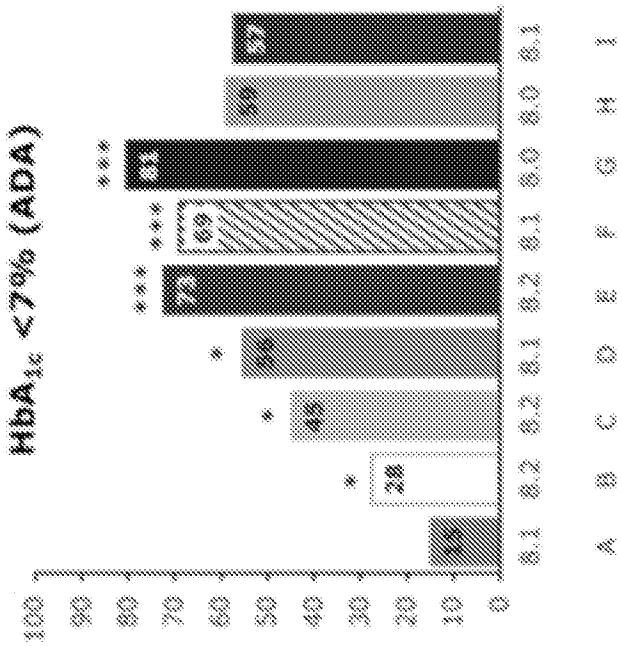
HbA1c <7% (ADA)
100
90
80
70
60
50
40
30
20
10
0
8.1
8.2
8.2
8.1
8.2
8.1
8.0
8.0
8.1
A
B
C
D
E
F
G
H
I
28
45
73
69
81
59
57

Fig. 3 B

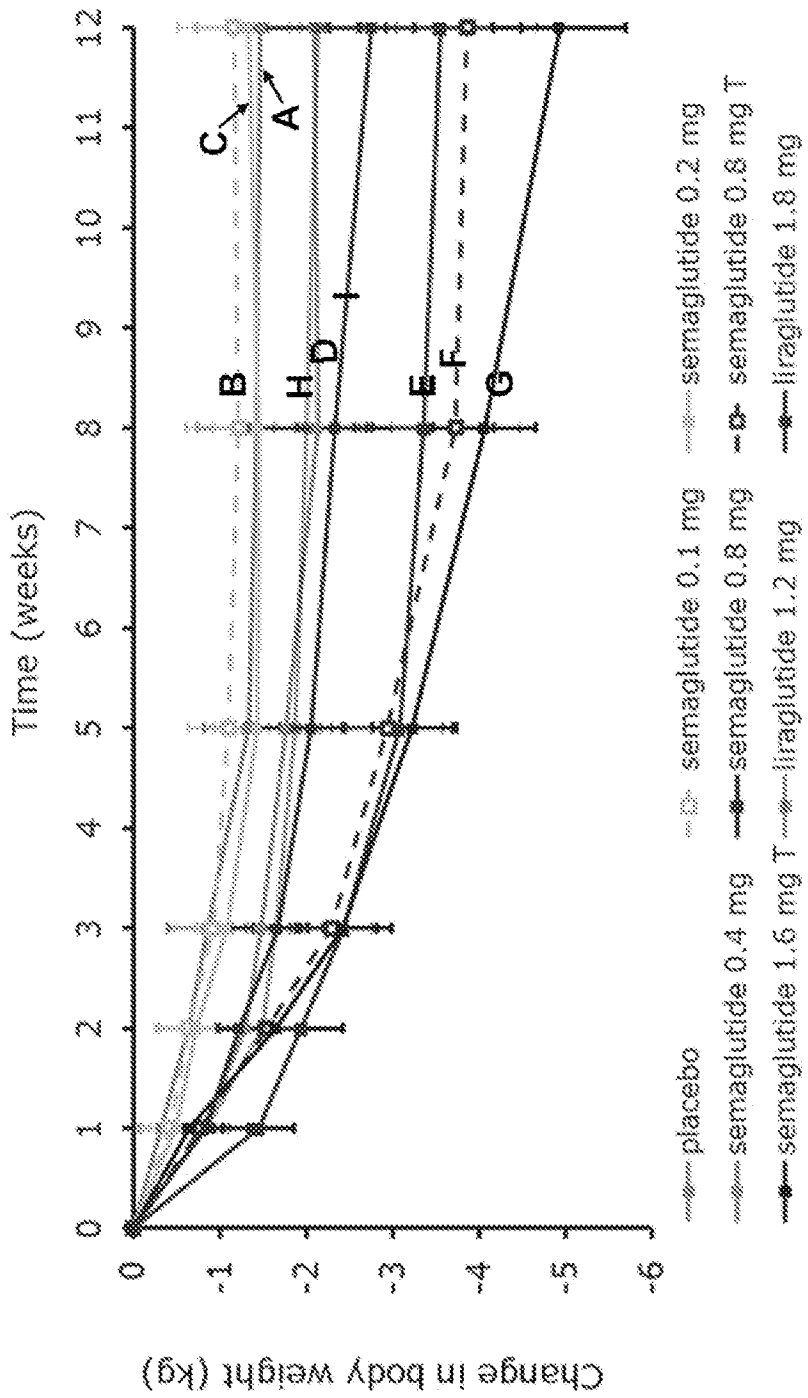

Fig. 4

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Petitioner Apotex Exhibit 1002-0006

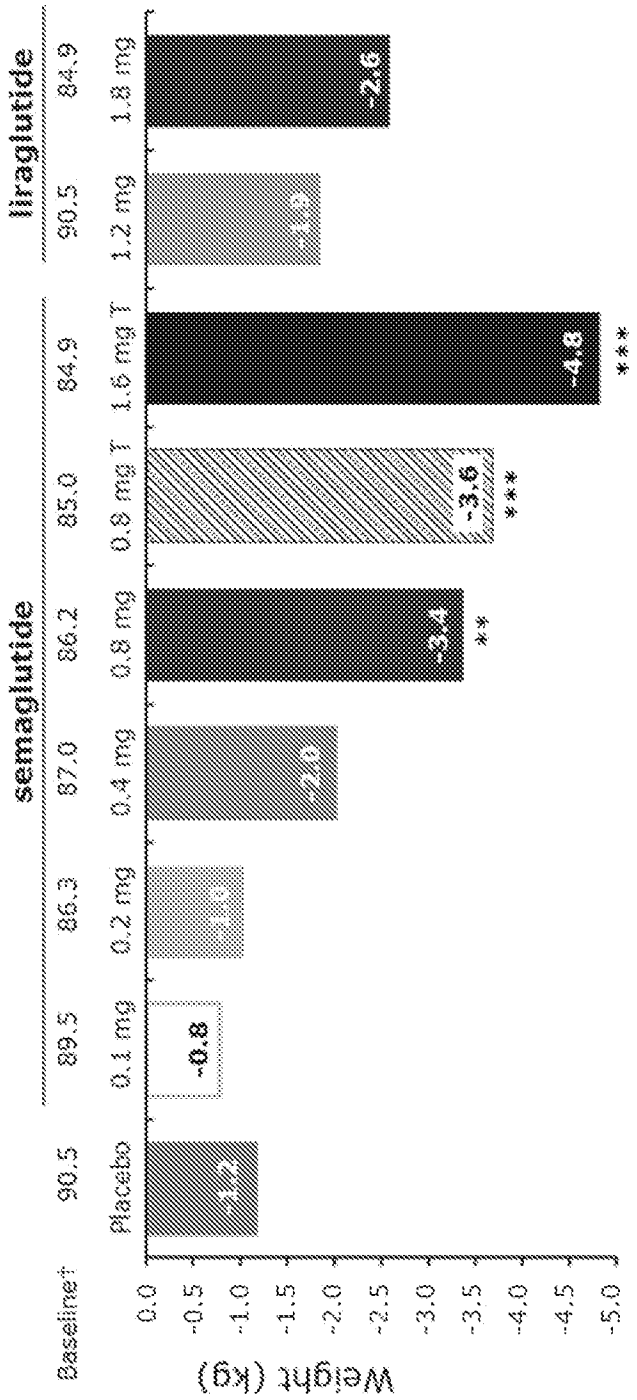
semaglutide
liraglutide
Baseline†
90.5
Placebo
-1.7
89.5
0.1 mg
-0.8
86.3
0.2 mg
-1.9
87.0
0.4 mg
-2.0
86.2
0.8 mg
-3.1
**
85.0
0.8 mg T
-3.6
***
84.9
1.6 mg T
-4.0
***
90.5
1.2 mg
-1.5
84.9
1.8 mg
-2.0
Weight (kg)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0

Fig. 5

Claims

1. A method for

a) reduction of HbA1c;

b) treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or

c) treatment of obesity, reducing body weight and/or food intake, or inducing satiety;

wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof,

wherein said GLP-1 agonist

i) has a half-life of at least 72 hours;

ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and

iii) is administered once weekly or less often.

2. The method according to claim 1, wherein said GLP-1 agonist has a half-life of at least 96 hours.

3. The method according to claim 1, wherein the GLP-1 agonist has an EC_{50} at or below 3000pM.

4. The method according to claim 1, wherein said GLP-1 agonist is administered in an amount of

i) at least 0.8 mg per week; or

ii) in an amount equivalent to at least 0.8 mg semaglutide per week.

5. The method according to claim 1, wherein the GLP-1 agonist is a GLP-1 peptide.

6. The method according to claim 5, wherein said GLP-1 peptide comprises no more than 6 amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

7. The method according to claim 1, wherein said GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

8. The method according to claim 1, wherein said GLP-1 agonist is administered by parenteral administration.

9. The method according to claim 1, wherein said GLP-1 agonist is administered simultaneously or sequentially with another therapeutic agent.

10. The method according to claim 1, wherein the method comprises treatment, reduction or induction in one or more diseases or conditions selected from a) and b), a) and c), b) and c), or a), b) and c) as defined in claim 1.

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	8545US02
	Application Number	
Title of Invention	Use of Long-Acting GLP-1 Peptides	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Christine	Bjoern	Jensen	

Residence Information (Select One) US Residency ● Non US Residency Active US Military Service

City	Charlottenlund	Country of Residence i	DK

Mailing Address of Inventor:

Address 1	c/o Novo Nordisk A/S		
Address 2	Novo Alle		
City	Bagsvaerd	State/Province	
Postal Code	DK-2880	Country i	DK

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Mads	Frederik	Rasmussen	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Copenhagen OE	Country of Residence i	DK

Mailing Address of Inventor:

Address 1	c/o Novo Nordisk A/S		
Address 2	Novo Alle		
City	Bagsvaerd	State/Province	
Postal Code	DK-2880	Country i	DK

Inventor 3 Remove

Legal Name

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Petitioner Apotex Exhibit 1002-0010

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	8545US02
	Application Number	
Title of Invention	Use of Long-Acting GLP-1 Peptides	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Milan		Zdravkovic	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Holte	Country of Residence i	DK

Mailing Address of Inventor:

Address 1	c/o Novo Nordisk A/S
Address 2	Novo Alle
City	Bagsvaerd
State/Province	
Postal Code	DK-2880
Country i	DK

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Peter		Kristensen	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Broenshoej	Country of Residence i	DK

Mailing Address of Inventor:

Address 1	c/o Novo Nordisk A/S
Address 2	Novo Alle
City	Bagsvaerd
State/Province	
Postal Code	DK-2880
Country i	DK

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	23650	
Email Address	nnipatent@novonordisk.com	Add Email / Remove Email

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	8545US02
	Application Number	
Title of Invention	Use of Long-Acting GLP-1 Peptides	

Application Information:

Title of the Invention	Use of Long-Acting GLP-1 Peptides		
Attorney Docket Number	8545US02	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	6	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	23650		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	8545US02
	Application Number	
Title of Invention	Use of Long-Acting GLP-1 Peptides	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	14/409493	2014-12-19
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/409493	a 371 of international	PCT/EP2013/063004	2013-06-21
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/EP2013/063004	Claims benefit of provisional	61/708162	2012-10-01
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/EP2013/063004	Claims benefit of provisional	61/694837	2012-08-30

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
12186781.6	EP	2012-10-01	

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Petitioner Apotex Exhibit 1002-0013

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	8545US02
	Application Number	
Title of Invention	Use of Long-Acting GLP-1 Peptides	

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
12174535.0	EP	2012-07-01	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Petitioner Apotex Exhibit 1002-0014

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	8545US02
	Application Number	
Title of Invention	Use of Long-Acting GLP-1 Peptides	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	8545US02
	Application Number	
Title of Invention	Use of Long-Acting GLP-1 Peptides	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Novo Nordisk A/S		
Mailing Address Information For Applicant:			
Address 1	Novo Alle		
Address 2			
City	Bagsvaerd	**State/Province**	
Country	DK	Postal Code	DK-2880
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Petitioner Apotex Exhibit 1002-0016

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	8545US02
	Application Number	
Title of Invention	Use of Long-Acting GLP-1 Peptides	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Leon Y. Lum/			Date (YYYY-MM-DD)	2017-07-20
First Name	Leon Y.	Last Name	Lum	Registration Number	62,124

Additional Signature may be generated within this form by selecting the Add button. Add

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Petitioner Apotex Exhibit 1002-0017

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	8545US02
	Application Number	
Title of Invention	Use of Long-Acting GLP-1 Peptides	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2017-07-21
First Named Inventor	Christine Bjoern Jensen
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	8545US02

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	1	8536122	A1	2013-09-17	Lau et al.	
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	1	20110301080		2011-12-08	Bush et al.	
	2	20100292133		2010-11-18	Spetzler et al.	
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Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0019

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	
	Filing Date	2017-07-21
	First Named Inventor	Christine Bjoern Jensen
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	8545US02

	1	12136790	WO	A1	2012-10-11	Glaxo Group Ltd		
	2	12130136	WO	A1	2012-10-04	Tianjin Inst Pharm Research		
	3	12016419	WO	A1	2012-02-09	Zhejiang Beta Pharma Inc		
	4	102229668	CN	A	2011-11-02	Zhejiang Beta Pharma Co.,ltd		X
	5	2010/092163	WO	A2	2010-08-19	Boehringer Ingelheim Int		☐
	6	2011138421	WO	A1	2011-11-10	Boehringer Ingelheim Int		☐
	7	2012177929	WO	A2	2012-12-27	Amylin Pharmaceuticals, Inc		☐
	8	2012107476	WO	A1	2012-08-16	Boehringer Ingelheim Int		☐
	9	2011/080103	WO	A1	2011-07-07	Novo Nordisk As		☐
	10	2006/097537	WO	A2	2006-09-21	Novo Nordisk As		☐
	11	2012080471	WO	A1	2012-06-21	Novo Nordisk As		☐

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	1	Madsbad S et al. An Overview of once-weekly glucagon-like peptide-1 receptor agonists available efficacy and safety data and perspectives for the future, 'Diabetes, Obesity and Metabolism" Year 2011, Vol 13, No 5, Pages 394-407	
	2	BUSE B. J. et al., Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study, Lancet, 2013, Vol. 381, pages 117-124	
	3	Kim et al. "Effects of Once-Weekly Dosing of a Long-Acting Release Formulation of Exentide on Glucose Control and Body Weight in Subjects with Type 2 Diabetes." Diabetes care (2007) Vol 30 pgs 1487-1493.	
	4	Bydureon NDA 022200/S-008 Package Information pages 1-179 (February 2014).	
	5	Clinical Trial NCT00696657 entitled "A Randomized Controlled Clinical Trial in Type 2 Diabetes Comparing Semaglutide to Placebo and Liraglutide." pages 1-5 March 2015. Accessed September 24, 2015 at clinicaltrials.gov/archive/NCT00696657/2011_03_25.	
	6	Lau et al. "Discovery of the Once-WEekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide." J. Med. Chem. (2015) Vol 58 pgs 7370-7380	
	7	Eperzan Assessment Report. Euro. Med. Agency. pages 1-124 (2014) accessed September 24, 2015 at URL ema.europa.ed/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002735/WC500165119.pdf	
	8	Trulicity Assessment Report. Euro. Med. Agency. pages 1-172 (2014) accessed September 24, 2015 at URL ema.europa.ed/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002825/WC500179473.pdf	
	9	Mizuta et al. "The Role for GLP-1 in Regulation of Body Weight." Progress in Medicine 2008 Vol 28 No 8 pgs 1909-1912	

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	Examiner Name	Not Yet Assigned
	Attorney Docket Number	8545US02

	10	CDC, "National Health and Nutrition Examination Survey: Healthy Weight, Overweight and Obesity among U.S. adults" 03-0260 pp 1-2 (July 2003), accessed 5/10/2016 at URL cdc.gov/nchs/data/nhanes/databriefs/adultweight.pdf

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Examiner Signature		Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0022

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	
	Filing Date	2017-07-21
	First Named Inventor	Christine Bjoern Jensen
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	8545US02

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Leon Y. Lum/	Date (YYYY-MM-DD)	2017-07-20
Name/Print	Leon Y. Lum	Registration Number	62,124

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Sequence Listing (Text File)	8545US02_SeqListing_ST25.txt	7975	no	-
Warnings:					
Information:					
2	Specification	8545US02_Spec.pdf	202570 0cc53be9d51ef47b4f97c025b5c042aaec936dfb	no	37
Warnings:					
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3	Transmittal Letter	InformationDisclosureStatement_02.pdf	19170 d99d8388e7f6e00a76738808943eb2f68b08f277	no	2
Warnings:					
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4	Miscellaneous Incoming Letter	RequestforReconsiderationOf.pdf	96809 8b9b405cf844325dd736cc925d93b22948630a1a	no	2
Warnings:					
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5	Transmittal Letter	StatementtoSupportFilinganSubmissioninAccordance.pdf	19377 9bcd4316cf344a8d807316bb20af3e2d32bd6e58	no	2
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6	Transmittal of New Application	UtilityPatentApplicationTransmittal.pdf	84987 0ae544909f1712df7e32d2701412efce102db3fd	no	1
Warnings:					
Information:					

7	Drawings-only black and white line drawings	8545US02_Drawings.pdf	473213 4e7f693c70d1fb3b4302509a756207ce7686045c	no	6
Warnings:					
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8	Claims	8545US02_Claims.pdf	62172 1527c8ca5d0b9f56039393102c4d549c06c9e97f	no	2
Warnings:					
Information:					
9	Application Data Sheet	ApplicationDataSheetFillablePDF.pdf	1822890 f90553a071d1fd62e4e7098167f266e3c42e4b21	no	10
Warnings:					
Information:					
10	Information Disclosure Statement (IDS) Form (SB08)	InformationDisclosureStatementFillablePDF.pdf	1036597 dc19663e6c6268553d80bb02e32b8f00ae0137fb	no	6
Warnings:					
Information:					
11	Fee Worksheet (SB06)	fee-info.pdf	37167 6b6b2b5ff23b937f7a3071d82b50ce5fca6bc652	no	2
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12	Abstract	ABSTRACT.docx	13558 5792e5f95b89c35b633a6c8f27cdebe5c40007bc41de8928d56094fb51bbb97ffcfb338f3567c54a299cabab1234ce81857b469493cd54ab8e271e8e0d5e54c2	no	-
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13	Abstract	c03b823c-fb4f-4f8b-a68c-62a02c215ea8.pdf	83216 94a178bb09615ec21de98208a774d3f89fd4419c	no	1
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USE OF LONG-ACTING GLP-1 PEPTIDES

The present invention relates to improved uses of GLP-1 peptides in therapy.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of US Application 14/409,493, filed December 19, 2014, which is a 35 U.S.C. § 371 National Stage application of International Application PCT/EP2013/063004 (WO 2014/005858), filed JUNE 21, 2013, which claimed priority of European Patent Application 12174535.0, filed JULY 1, 2012 and European Patent Application 12186781.6, filed OCTOBER 1, 2012; this application claims priority under 35 U.S.C. § 119 of U.S. Provisional Application 61/694,837; filed AUGUST 30, 2012 and U.S. Provisional Application 61/708,162; filed OCTOBER 1, 2012.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 17, 2013 and amended on July 12, 2017, is named 8545US02_SeqList.txt and is 7,975 bytes in size.

SUMMARY

In one embodiment the invention relates to a method for a) reduction of HbA1c; b) prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) prevention or treatment of obesity, reducing body weight and/or food intake, or inducing satiety; wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof, wherein said GLP-1 agonist i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and iii) is administered once weekly or less often.

In one embodiment the invention relates to a GLP-1 agonist for use in a) the reduction of HbA1c; b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety; wherein said use comprises administration of said GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week, and wherein said GLP-1 agonist and/or administration optionally is as defined herein.

In one embodiment the invention relates to a composition comprising a GLP-1 agonist for use in a) the reduction of HbA1c; b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety; wherein said GLP-1 agonist i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); and ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and wherein said composition is administered once weekly or less often, and wherein said GLP-1 agonist and/or administration optionally is as defined herein.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows change in HbA1c following subcutaneous administration of placebo, semaglutide, or liraglutide to human subjects. *p<0.05 vs. placebo; **p<0.001 vs. placebo (based on adjusted means). Baseline values are for information only: data are model-adjusted for baseline HbA1c. Data are model-adjusted LS means, FAS LOCF. The estimates are from an ANOVA model with treatment, country and previous treatment as fixed effects and baseline HbA1c as covariate.

Fig. 2 shows mean change in HbA1c from baseline versus time; data are mean (1.96SE), FAS LOCF. The treatments are placebo (A); semaglutide 0.1 mg (B, dashed line), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F, dashed line), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I).

Fig. 3 shows subjects reaching the AACE or ADA criteria for glycaemic control. The number of patients reaching the criteria per treatment is indicated in each bar. The treatments are placebo (A); semaglutide 0.1 mg (B), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I). *p<0.05 vs. placebo; **p<0.001 vs. placebo; ***p<0.0001 vs. placebo (based on adjusted means). Data are FAS LOCF. The estimates are from a logistic regression model treatment, country and previous treatment as fixed effects and baseline HbA1c as covariate. ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists.

Fig. 4 shows mean body weight change versus time; data are mean (1.96SE), FAS LOCF. The treatments are placebo (A); semaglutide 0.1 mg (B, dashed line), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F, dashed line), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I).

Fig. 5 shows body weight change from baseline at week 12. **p<0.001 vs. placebo; ***p<0.0001 vs. placebo (based on adjusted means. †: Baseline values for information only:

data are model-adjusted for baseline weight. Data are model-adjusted LS means, FAS LOCF. The estimates are from an ANOVA model with treatment, country and previous treatment as fixed effects and baseline weight as covariate.

SE: Standard error. FAS: Full analysis set. LOCF: Last observation carried forward.

DESCRIPTION

The present invention relates to an improved use of GLP-1 agonists in therapy. In one embodiment the invention relates to certain dosage regimes of GLP-1 agonists which provide improved effect in diseases or conditions, such as prevention and/or treatment of type 2 diabetes and obesity. In one embodiment the methods of the present invention provides surprisingly showed improved reduction of HbA1c and reduction of body weight. In one embodiment the GLP-1 agonist is administered in an amount which provides an improved a) reduction in HbA1c or b) reduction in body weight compared to administration of 1.8 mg liraglutide or less, such as 0.8 mg liraglutide or less, per day.

In one embodiment the invention relates to a method for reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the method is for reduction of HbA1c. In one embodiment the method is for prevention or treatment of type 2 diabetes. In one embodiment the method is for prevention or treatment of hyperglycemia. In one embodiment the method is for prevention or treatment of impaired glucose tolerance. In one embodiment the method is for prevention or treatment of non-insulin dependent diabetes. In one embodiment the method of the invention comprises delaying or preventing diabetic disease progression. In one embodiment a HbA1c level below 7% is achieved. In one embodiment the level of HbA1c is determined according to the method defined by the Diabetes Control and Complications Trial (DCCT). In one embodiment the level of HbA1c is determined according to the method defined by the International Federation of Clinical Chemistry (IFCC).

In one embodiment the invention relates to a method for treating or preventing obesity, for reducing body weight and/or food intake, or for inducing satiety, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the method is for prevention or treatment of obesity. In one embodiment the

method is for reducing body weight and/or food intake. In one embodiment the method is for inducing satiety.

In one embodiment the GLP-1 agonist has a half-life of at least 24 hours, such as at least 48 hours, at least 60 hours, or at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours, or optionally at least 120 hours, at least 132 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

In one embodiment the GLP-1 agonist is administered twice weekly or less often, once weekly or less often, or once weekly or less often. In one embodiment the GLP-1 agonist is administered once every secondly week or less often, once every third week or less often, or once a month or less often.

In one embodiment the GLP-1 agonist is administered in an amount per week of at least 0.8 mg, at least 0.9 mg, or at least 1.0 mg. In one embodiment the GLP-1 agonist is administered in an amount per week of at least 1.1 mg, at least 1.2 mg, or at least 1.3 mg. In one embodiment the GLP-1 agonist is administered in an amount per week of at least 1.4 mg, at least 1.5 mg, or at least 1.6 mg.

In one embodiment the GLP-1 agonist is administered in an amount per week equivalent to at least 0.8 mg, at least 0.9 mg, or at least 1.0 mg semaglutide. In one embodiment the GLP-1 agonist is administered in an amount per week equivalent to at least 1.1 mg, at least 1.2 mg, or at least 1.3 mg semaglutide. In one embodiment the GLP-1 agonist is administered in an amount per week equivalent to at least 1.4 mg, at least 1.5 mg, or at least 1.6 mg semaglutide.

In one embodiment the GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

In one embodiment the GLP-1 agonist is administered by parenteral administration, such as subcutaneous injection.

In one embodiment the GLP-1 agonist is a GLP-1 peptide. In one embodiment the GLP-1 peptide comprises no more than 5, such as no more than 4 or no more than 3, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37). In one embodiment the GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code.

In one embodiment the GLP-1 peptide is a DPPIV protected GLP-1 peptide. In one embodiment the GLP-1 peptide is DPPIV stabilised.

In one embodiment the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100 pM, optionally determined by Assay (I).

In one embodiment the invention relates to a GLP-1 agonist for use in the reduction of HbA1c or for use in the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to a GLP-1 agonist for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to a composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to a composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the GLP-1 agonist is administered with another therapeutic agent. Administration with another therapeutic agent may be carried out as administration of the GLP-1 agonist and the other therapeutic agent within the same therapeutic window (e.g. withinin a period of two weeks, a period of one week, or in a 96, 72, or 48 hour period, etc.). The treatment with a GLP-1 agonist according to the present invention may be combined with one or more additional therapeutic agents, e.g. selected from antidiabetic agents, antiobesity agents, appetite regulating agents, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity; examples of these therapeutic agents are: sulphonylureas, thiazolidinediones, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists, and DPP-IV (dipeptidyl peptidase-IV) inhibitors.

In one embodiment, as used herein, an “amount equivalent to” when used in relation to GLP-1 agonists refers to amounts of a first GLP-1 agonist and a second GLP-1 agonist having GLP-1 receptor potency (i.e. EC_{50}) within ±30%, such as within ±20% or within ±10%, of each other optionally determined by Assay (I) described herein and having a half-life within ±30%, such as within ±20% or within ±10%, of each other optionally determined by Assay (II) described herein.

In one embodiment an "effective amount" of a GLP-1 agonist as used herein means an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease or state and its complications. An amount adequate to accomplish this is defined as "effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary.

In one embodiment the term "treatment" or "treating" as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. In one embodiment the term "treatment" or "treating" is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications; to delay the progression of the disease, disorder, or condition; to alleviate or relieve the symptoms and complications; and/or, to cure or eliminate the disease, disorder, or condition as well as to prevent the condition. In one embodiment prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications.

In one embodiment the term "hydrophilic spacer" as used herein means a spacer that separates a peptide and an albumin binding residue with a chemical moiety which comprises at least 5 non- hydrogen atoms where 30-50% of these are either N or O.

In one embodiment the term "analogue" as used herein referring to a polypeptide means a modified peptide wherein one or more amino acid residues of the peptide have been substituted by other amino acid residues and/or wherein one or more amino acid residues have been deleted from the peptide and or wherein one or more amino acid residues have been added to the peptide. Such addition or deletion of amino acid residues can take place at the N-terminal of the peptide and/or at the C-terminal of the peptide. A simple system is used to

describe analogues: For example Arg^{34}GLP-1 (7-37) Lys designates a GLP-1 analogue wherein the naturally occurring lysine at position 34 has been substituted with arginine and a lysine residue has been added to the C-terminal (position 38).

In one embodiment the term "GLP-1 peptide" as used herein means GLP-1 (7-37), a GLP-1 analogue, a GLP-1 derivative or a derivative of a GLP-1 analogue.

In one embodiment the term "exendin-4 peptide" as used herein means exendin-4 (1-39), an exendin-4 analogue, an exendin-4 derivative or a derivative of an exendin-4 analogue.

In one embodiment the term “DPP-IV protected” as used herein referring to a polypeptide means a polypeptide which has been chemically modified in order to render said compound resistant to the plasma peptidase dipeptidyl aminopeptidase-4 (DPP-IV). The DPP-IV enzyme in plasma is known to be involved in the degradation of several peptide hormones, e.g. GLP-1, Exendin-4 etc. Thus a considerable effort is being made to develop GLP-1 agonists less susceptible to DPP-IV mediated hydrolysis in order to reduce the rate of degradation by DPP-IV.

The present invention also relates to a GLP-1 agonist of the invention, for use as a medicament. In particular embodiments, the GLP-1 agonist of the invention may be used for the following medical treatments:

(i) prevention and/or treatment of all forms of diabetes, such as hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, non-insulin dependent diabetes, MODY (maturity onset diabetes of the young), gestational diabetes, and/or for reduction of HbA1c;

(ii) delaying or preventing diabetic disease progression, such as progression in type 2 diabetes, delaying the progression of impaired glucose tolerance (IGT) to insulin requiring type 2 diabetes, and/or delaying the progression of non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes;

(iii) prevention and/or treatment of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; and/or delaying gastric emptying.

In another particular embodiment, the indication is (i). In a further particular embodiment the indication is (ii). In a still further particular embodiment the indication is (iii). In one embodiment the indication is type 2 diabetes and/or obesity.

In one embodiment the method comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions defined herein. In one embodiment the indication is (i) and (iii). In one embodiment the indication is (ii) and (iii). In one embodiment the

method comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions selected from a) and b), a) and c), b) and c), or a), b) and c) as defined in claim 1.

In one embodiment the invention relates to administration of an effective amount of a GLP-1 agonist.

In one embodiment as used herein, specific values given in relation to numbers or intervals may be understood as the specific value or as about the specific value.

FUNCTIONAL PROPERTIES

In a first functional aspect, the GLP-1 agonists of the invention have a good potency. Also, or alternatively, in a second functional aspect, the GLP-1 agonists of the invention have a protracted pharmacokinetic profile. Also, or alternatively, in a third functional aspect, the GLP-1 agonists of the invention are stable against degradation by gastro intestinal enzymes.

Biological activity (potency)

According to the first functional aspect, the GLP-1 agonists of the invention are biologically active, or potent. In a particular embodiment, “potency” and/or “activity” refers to in vitro potency, i.e. performance in a functional GLP-1 receptor assay, more in particular to the capability of stimulating cAMP formation in a cell line expressing the cloned human GLP-1 receptor.

The stimulation of the formation of cAMP in a medium containing the human GLP-1 receptor may preferably be determined using a stable transfected cell-line such as BHK467-12A (tk-ts13), and/or using for the determination of cAMP a functional receptor assay, e.g. based on competition between endogenously formed cAMP and exogenously added biotin-labelled cAMP, in which assay cAMP is more preferably captured using a specific antibody, and/or wherein an even more preferred assay is the AlphaScreen cAMP Assay, such as the one described in Assay (I).

In one embodiment the term half maximal effective concentration (EC_{50}) generally refers to the concentration which induces a response halfway between the baseline and maximum, by reference to the dose response curve. EC_{50} is used as a measure of the potency of a compound and represents the concentration where 50% of its maximal effect is observed.

The in vitro potency of the GLP-1 agonists of the invention may be determined as described above, and the EC_{50} of the GLP-1 agonist in question determined. The lower the EC_{50}, the better the potency.

In a particular embodiment, the medium has the following composition (final in-assay

concentrations): 50 mM TRIS-HCl; 5 mM HEPES; 10 mM $MgCl_2$, $6H_2O$; 150 mM NaCl; 0.01% Tween; 0.1% BSA ; 0.5 mM IBMX; 1 mM ATP; 1 μM GTP; pH 7.4.

In a further particular embodiment, the GLP-1 agonist of the invention has an in vitro potency corresponding to an EC_{50} at or below 3000pM, such as below 2000pM, below 1000pM, or below 500pM, or such as below 200 pM or below 100 pM.

In another particular embodiment the GLP-1 agonist of the invention are potent in vivo, which may be determined as is known in the art in any suitable animal model, as well as in clinical trials.

The diabetic db/db mouse is one example of a suitable animal model, and the blood glucose lowering effect may be determined in such mice in vivo, e.g. as described in Assay (III), or as described in Example 43 of WO09/030738.

Also, or alternatively, the effect on food intake in vivo may be determined in pharmacodynamic studies in pigs, e.g. as described in Assay (IV).

Protraction - half life in vivo in minipigs

According to the second functional aspect, the GLP-1 agonists of the invention are protracted. In a particular embodiment protraction may be determined as half-life ($T_{½}$) in vivo in minipigs after i.v. administration. In additional embodiments, the half-life is at least 24 hours, such as at least 48 hours, at least 60 hours, at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours.

A suitable assay for determining half-life in vivo in minipigs after i.v. administration is disclosed in Assay (II).

Degradation by gastro intestinal enzymes

According to the third functional aspect, the GLP-1 agonists of the invention are stable, or stabilised, against degradation by one or more gastro intestinal enzymes.

Gastro intestinal enzymes include, without limitation, exo and endo peptidases, such as pepsin, trypsin, chymotrypsin, elastases, and carboxypeptidases. The stability may be tested against these gastro intestinal enzymes in the form of purified enzymes, or in the form of extracts from the gastrointestinal system.

In a particular embodiment, the GLP-1 agonist of the invention has an in vitro half-life ($T_{½}$), in an extract of rat small intestines, divided by the corresponding half-life ($T_{½}$) of GLP-1(7-37), of at least 1, such as above 1.0, at least 1.2, at least 2.0, or such as at least 3.0, or at least 4.0. In other words, a ratio(SI) may be defined for each GLP-1 agonist, viz. as the in vitro half-

life ($T_{½}$) of the GLP-1 agonist in question, in an extract of rat small intestines, divided by the corresponding half-life ($T_{½}$) of GLP-1(7-37).

A suitable assay for determining in vitro half-life in an extract of rat small intestines is disclosed in Assay (V).

GLP-1 AGONISTS

In one embodiment the GLP-1 peptide comprises an Aib residue in position 8.

In one embodiment the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

In one embodiment the GLP-1 peptide is attached to a hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

In one embodiment the GLP-1 peptide is exendin-4, an exendin-4-analogue, or a derivative of exendin-4.

In one embodiment the GLP-1 agonist peptide comprises the amino acid sequence of the following formula:
H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 (SEQ ID NO: 2).

In one embodiment the GLP-1 agonist comprises an albumin binding residue attached via a hydrophilic spacer to the C-terminal amino acid residue of said GLP-1 peptide.

In one embodiment the GLP-1 agonist comprises a second albumin binding residue is attached to an amino acid residue which is not the C-terminal amino acid residue.

In one embodiment the GLP-1 peptide is selected from the group consisting of semaglutide, albiglutide and dulaglitide.

In one embodiment the GLP-1 peptide has the following structure:
His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg (SEQ ID NO: 3).

In one embodiment the GLP-1 peptide has the following structure:
(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2 (SEQ ID NO: 4)–genetically fused to human albumin.

In one embodiment the GLP-1 peptide is dulaglitide.

In one embodiment the GLP-1 agonists of the invention have GLP-1 activity. In one embodiment "a GLP-1 agonist" is understood to refer to any compound, including peptides and non-peptide compounds, which fully or partially activate the human GLP-1 receptor. In one embodiment the "GLP-1 agonist" is any peptide or non-peptide small molecule that binds to a GLP-1 receptor, preferably with an affinity constant (K_D) or a potency (EC_{50}) of below 1 μM, e. g. below 100 nM as measured by methods known in the art (see e. g., WO 98/08871). In one embodiment methods for identifying GLP-1 agonists are described in WO 93/19175 (Novo Nordisk A/S) and examples of suitable GLP-1 agonists which can be used according to the present invention includes those referred to in WO 2005/027978 (Novo Nordisk A/S), the teachings of which are both incorporated by reference herein. “GLP-1 activity” refers to the ability to bind to the GLP-1 receptor and initiate a signal transduction pathway resulting in insulinotropic action or other physiological effects as is known in the art. For example, the GLP-1 agonists of the invention can be tested for GLP-1 activity using the assay described in Assay (I) herein.

In yet another embodiment the GLP-1 agonist is a stable GLP-1 agonist. As used herein a "stable GLP-1 agonist" means a GLP-1agonist which exhibits an in vivo plasma elimination half-life of at least 24 hours in man, optionally determined by the method described below. Examples of stable GLP-1 agonists can be found in WO2006/097537.

In one embodiment the method for determination of plasma elimination half-life of a compound in man may be carried out as follows: The compound is dissolved in an isotonic buffer, pH 7.4, PBS or any other suitable buffer. The dose is injected peripherally, preferably in the abdominal or upper thigh. Blood samples for determination of active compound are taken at frequent intervals, and for a sufficient duration to cover the terminal elimination part (e. g., Pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24 (day 2), 36 (day 2), 48 (day 3), 60 (day 3), 72 (day 4) and 84 (day 4) hours post dose). Determination of the concentration of active compound is performed as described in Wilken *et al.*, Diabetologia 43 (51), 2000. Derived pharmacokinetic parameters are calculated from the concentration-time data for each individual subject by use of non-compartmental methods, using the commercially available software WinNonlin Version 2.1 (Pharsight, Cary, NC, USA). The terminal elimination rate constant is estimated by log-linear regression on the terminal log-linear part of the concentration-time curve, and used for calculating the elimination half-life.

In one embodiment the GLP-1 agonist is formulated so as to have a half-life in man of at least 48 hours. This may be obtained by sustained release formulations known in the art.

In one embodiment the GLP-1 agonist is a GLP-1 peptide. In one embodiment the GLP-1 peptide is selected from GLP-1 (7-35), GLP-1 (7-36), GLP-1 (7-36)-amide, GLP-1 (7-37), GLP-1 (7-38), GLP-1 (7-39), GLP-1 (7-40), GLP-1 (7-41) or an analogue or derivative thereof. In one embodiment the GLP-1 peptide comprises no more than 15, such as no more than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37). In one embodiment the GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code. In yet another embodiment, the GLP-1 agonist is exendin-4 or exendin-3, an exendin-4 or exendin-3 analogue, or a derivative of any of these.

In one embodiment the GLP-1 peptide is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglitide. In one embodiment the GLP-1 peptide is semaglutide. WO 06/097537 discloses semaglutide (Example 4), a mono-acylated GLP-1 agonist for once weekly administration. In one embodiment the GLP-1 peptide is exenatide. In one embodiment the GLP-1 peptide comprises the amino acid sequence of the formula: H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 (SEQ ID NO: 2). Exenatide is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. Exenatide displays biological properties similar to GLP-1. In some embodiments the composition is BYDUREON® (a long acting release formula of exenatide in PLGA particles). In one embodiment the “Bydureon® composition” refer to a powder comprising exenatide, poly (D,L-lactide-co-glycolide), and sucrose which immediately prior to injection is reconstituted in a solvent comprising carmellose sodium, sodium chloride, polysorbate 20, monobasic sodium phosphate (e.g. its monohydrate), dibasic sodium phosphate (e.g. its heptahydrate), and water for injections. In one embodiment the GLP-1 peptide has the structure (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2 (SEQ ID NO: 4)–genetically fused to human albumin. Albiglutide is a recombinant human serum albumin (HSA)-GLP-1 hybrid protein, likely a GLP-1 dimer fused to HSA. The constituent GLP-1 peptide is analogue, in which Ala at position 8 has been substituted by Glu. In one embodiment the GLP-1 peptide is dulaglitide. Dulaglutide is a GLP-1-Fc construct (GLP-1 - linker - Fc from IgG4). In one embodiment the GLP-1 peptide has the structure His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg (SEQ ID NO: 3). Liraglutide is a mono-acylated GLP-1 agonist for once daily administration which is marketed as of 2009 by Novo Nordisk A/S, is disclosed in WO 98/08871 Example 37.

In one embodiment the present invention encompasses pharmaceutically acceptable salts of the GLP-1 agonists. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium, and alkylated ammonium salts. Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present GLP-1 agonists are able to form.

In one embodiment the route of administration of GLP-1 agonists may be any route which effectively transports the active compound to the appropriate or desired site of action, such as parenteral. In one embodiment medicaments or pharmaceutical compositions comprising a GLP-1 agonist, such as semaglutide, may be administered parenterally to a patient in need thereof. In one embodiment 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. A further option is a composition which may be a powder or a liquid for the administration of a GLP-1 agonist in the form of a nasal or pulmonal spray. As a still further option, the GLP-1 agonist can also be administered transdermally, e.g., from a patch, optionally an iontophoretic patch, or transmucosally, e.g., bucally. The above-mentioned possible ways to administer GLP-1 agonists are not considered as limiting the scope of the invention.

In one embodiment the GLP-1 agonist is co-administered together with a further therapeutically active agent used in the treatments defined herein.

In one embodiment the GLP-1 peptide comprises the amino acid sequence of the formula (I) (SEQ ID NO: 5):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa_{16}-Ser-Xaa_{18}-$Xaa_{19}Xaa_{20}$GluXaa_{22}-Xaa_{23}-Ala-Xaa_{25}-Xaa_{26}-Xaa_{27}-Phe-Ile-Xaa_{30}-Trp-Leu-Xaa_{33}-Xaa_{34}-Xaa_{35}-Xaa_{36}-Xaa_{37}-Xaa_{38}-Xaa_{39}-Xaa_{40}-Xaa_{41}-Xaa_{42}-Xaa_{43}-Xaa_{44}-Xaa_{45}-Xaa_{46}

Formula (I)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{25} is Ala or Val;

Xaa_{26} is Lys, Glu or Arg;

Xaa_{27} is Glu or Leu;

Xaa_{30} is Ala, Glu or Arg;

Xaa_{33} is Val or Lys;

Xaa_{34} is Lys, Glu, Asn or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg, Gly or Lys;

Xaa_{37} is Gly, Ala, Glu, Pro, Lys, amide or is absent;

Xaa_{38} is Lys, Ser, amide or is absent;

Xaa_{39} is Ser, Lys, amide or is absent;

Xaa_{40} is Gly, amide or is absent;

Xaa_{41} is Ala, amide or is absent;

Xaa_{42} is Pro, amide or is absent;

Xaa_{43} is Pro, amide or is absent;

Xaa_{44} is Pro, amide or is absent;

Xaa_{45} is Ser, amide or is absent;

Xaa_{46} is amide or is absent;

provided that if Xaa_{38}, Xaa_{39}, Xaa_{40}, Xaa_{41}, Xaa_{42}, Xaa_{43}, Xaa_{44}, Xaa_{45} or Xaa_{46} is absent then each amino acid residue downstream is also absent.

In one embodiment the GLP-1 peptide comprises the amino acid sequence of formula (II) (SEQ ID NO: 6):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Xaa_{18}-Tyr-Leu-Glu-Xaa22-Xaa_{23}-Ala-Ala-Xaa_{26}-Glu-Phe-Ile-Xaa_{3o}-Trp-Leu-Val-Xaa_{34}-Xaa_{35}-Xaa_{36}-$Xaa_{37}Xaa_{38}$

Formula (II)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine,-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-

pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{26} is Lys, Glu or Arg; Xaa30 is Ala, Glu or Arg;

Xaa_{34} is Lys, Glu or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg or Lys;

Xaa_{37} is Gly, Ala, Glu or Lys;

Xaa_{38} is Lys, amide or is absent.

In one embodiment the GLP-1 peptide is a DPPIV protected GLP-1 peptide.

In one embodiment the GLP-1 peptide is DPPIV stabilised.

In one embodiment the GLP-1 peptide comprises an Aib residue in position 8.

In one embodiment the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

In one embodiment the GLP-1 peptide comprises Arg^{34}GLP-1 (7-37) or [Aib8,Arg34]GLP-1-(7-37).

In one embodiment the GLP-1 agonist comprises an albumin binding residue which is covalently attached, optionally via a hydrophilic spacer. In one embodiment said albumin binding residue is covalently attached, optionally via a hydrophilic spacer, to the C-terminal amino acid residue of said GLP-1 peptide or an amino acid residue which is not the C-terminal amino acid residue. In one embodiment the GLP-1 peptide is attached to a hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

Human Glucagon-Like Peptide-1 is GLP-1(7-37) and has the sequence HAEGTFTSDVSSYLEGQAAKEFI AWLVKGRG (SEQ ID NO: 1). GLP-1(7-37) may also be designated "native" GLP-1. In the sequence listing, the first amino acid residue of SEQ ID NO: 1

(histidine) is assigned no. 1. However, in what follows - according to established practice in the art - this histidine residue is referred to as no. 7, and subsequent amino acid residues are numbered accordingly, ending with glycine no. 37. Therefore, generally, any reference herein to an amino acid residue number or a position number of the GLP-1(7-37) sequence is to the sequence starting with His at position 7 and ending with Gly at position 37. A non-limiting example of a suitable analogue nomenclature is [Aib^{8},Arg^{34},Lys^{37}]GLP-1(7-37), which designates a GLP-1(7-37) analogue, in which the alanine at position 8 has been substituted with α-aminoisobutyric acid (Aib), the lysine at position 34 has been substituted with arginine, and the glycine at position 37 has been substituted with lysine.

In one embodiment the GLP-1 agonist exhibits at least 60%, 65%, 70%, 80% or 90% sequence identity to GLP-1(7-37) over the entire length of GLP-1(7-37). As an example of a method for determination of sequence identity between two analogues the two peptides [Aib8]GLP-1(7-37) and GLP-1(7-37) are aligned. The sequence identity of [Aib8]GLP-1(7-37) relative to GLP-1(7-37) is given by the number of aligned identical residues minus the number of different residues divided by the total number of residues in GLP-1(7-37). Accordingly, in said example the sequence identity is (31-1)/31. In one embodiment non-peptide moieties of the GLP-1 agonist are not included when determining sequence identity.

In one embodiment the GLP-1 agonist is a derivative. In one embodiment the term “derivative” as used herein in the context of a GLP-1 agonist, peptide or analogue means a chemically modified GLP-1 agonist, peptide or analogue, in which one or more substituents have been covalently attached to the agonist, peptide or analogue. The substituent may also be referred to as a side chain. Typical modifications are amides, carbohydrates, alkyl groups, acyl groups, esters and the like. An example of a derivative of GLP-1(7-37) is N$^{\varepsilon 26}$-(γ-Glu(N$^{\alpha}$-hexadecanoyl)) - [Arg^{34}, Lys^{25}]) GLP-1 (7- 37).

In a particular embodiment, the side chain is capable of forming non-covalent aggregates with albumin, thereby promoting the circulation of the GLP-1 agonist with the blood stream, and also having the effect of protracting the time of action of the GLP-1 agonist, due to the fact that the aggregate of the GLP-1 agonist and albumin is only slowly disintegrated to release the active pharmaceutical ingredient. Thus, the substituent, or side chain, as a whole may be referred to as an albumin binding moiety.

In particular embodiments, the side chain has at least 10 carbon atoms, or at least 15, 20, 25, 30, 35, or at least 40 carbon atoms. In further particular embodiments, the side chain may further include at least 5 hetero atoms, in particular O and N, for example at least 7, 9, 10, 12, 15, 17, or at least 20 hetero atoms, such as at least 1, 2, or 3 N-atoms, and/or at least 3, 6,

9, 12, or 15 O-atoms.

In another particular embodiment the albumin binding moiety comprises a portion which is particularly relevant for the albumin binding and thereby the protraction, which portion may accordingly be referred to as a protracting moiety. The protracting moiety may be at, or near, the opposite end of the albumin binding moiety, relative to its point of attachment to the peptide.

In a still further particular embodiment the albumin binding moiety comprises a portion in between the protracting moiety and the point of attachment to the peptide, which portion may be referred to as a linker, linker moiety, spacer, or the like. The linker may be optional, and hence in that case the albumin binding moiety may be identical to the protracting moiety.

In particular embodiments, the albumin binding moiety and/or the protracting moiety is lipophilic, and/or negatively charged at physiological pH (7.4).

The albumin binding moiety, the protracting moiety, or the linker may be covalently attached to a lysine residue of the GLP-1 peptide by acylation. Additional or alternative conjugation chemistry includes alkylation, ester formation, or amide formation, or coupling to a cysteine residue, such as by maleimide or haloacetamide (such as bromo-/fluoro-/iodo-) coupling.

In one embodiment an active ester of the albumin binding moiety, e.g. comprising a protracting moiety and a linker, is covalently linked to an amino group of a lysine residue, e.g. the epsilon amino group thereof, under formation of an amide bond (this process being referred to as acylation).

Unless otherwise stated, when reference is made to an acylation of a lysine residue, it is understood to be to the epsilon-amino group thereof.

For the present purposes, the terms "albumin binding moiety", "protracting moiety", and "linker" may include the unreacted as well as the reacted forms of these molecules. Whether or not one or the other form is meant is clear from the context in which the term is used.

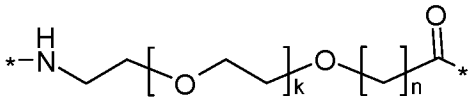
For the attachment to the GLP-1 agonist, the acid group of the fatty acid, or one of the acid groups of the fatty diacid, forms an amide bond with the epsilon amino group of a lysine residue in the GLP-1 peptide, e.g. via a linker.

In one embodiment the term "fatty acid" refers to aliphatic monocarboxylic acids having from 4 to 28 carbon atoms, it is optionally unbranched, and/or even numbered, and it may be saturated or unsaturated.

In one embodiment the term "fatty diacid" refers to fatty acids as defined above but with an additional carboxylic acid group in the omega position. Thus, fatty diacids are dicarboxylic acids.

Each of the two linkers of the GLP-1 agonist of the invention may comprise the following first linker element:

Chem. 5:



,

wherein k is an integer in the range of 1-5, and n is an integer in the range of 1-5.

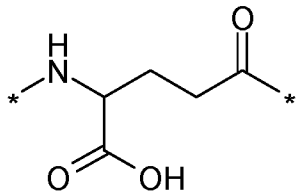
In a particular embodiment, when k=1 and n= 1, this linker element may be designated OEG, or a di-radical of 8-amino-3,6-dioxaoctanic acid, and/or it may be represented by the following formula:

Chem. 5a:

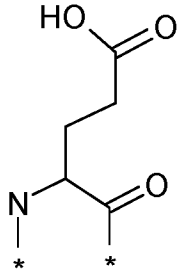
-NH-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-.

In another particular embodiment, each linker of the GLP-1 agonist of the invention may further comprise, independently, a second linker element, e.g. a Glu di-radical, such as Chem. 6 and/or Chem. 7:

Chem. 6:



Chem. 7:



,

wherein the Glu di-radical may be included p times, where p is an integer in the range of 1-3.

Chem. 6 may also be referred to as gamma-Glu, or briefly gGlu, due to the fact that it is the gamma carboxy group of the amino acid glutamic acid which is here used for connection to another linker element, or to the epsilon-amino group of lysine. As explained above, the other

linker element may, for example, be another Glu residue, or an OEG molecule. The amino group of Glu in turn forms an amide bond with the carboxy group of the protracting moiety, or with the carboxy group of, e.g., an OEG molecule, if present, or with the gamma-carboxy group of, e.g., another Glu, if present.

Chem. 7 may also be referred to as alpha-Glu, or briefly aGlu, or simply Glu, due to the fact that it is the alpha carboxy group of the amino acid glutamic acid which is here used for connection to another linker element, or to the epsilon-amino group of lysine.

The above structures of Chem. 6 and Chem. 7 cover the L-form, as well as the D-form of Glu. In particular embodiments, Chem. 6 and/or Chem. 7 is/are, independently, a) in the L-form, or b) in the D-form.

In still further particular embodiments the linker has a) from 5 to 41 C-atoms; and/or b) from 4 to 28 hetero atoms.

The concentration in plasma of the GLP-1 agonists of the invention may be determined using any suitable method. For example, LC-MS (Liquid Chromatography Mass Spectroscopy) may be used, or immunoassays such as RIA (Radio Immuno Assay), ELISA (Enzyme-Linked Immuno Sorbent Assay), and LOCI (Luminescence Oxygen Channeling Immunoasssay). General protocols for suitable RIA and ELISA assays are found in, e.g., WO09/030738 on p. 116-118. A preferred assay is the LOCI (Luminescent Oxygen Channeling Immunoassay), generally as described for the determination of insulin by Poulsen and Jensen in Journal of Biomolecular Screening 2007, vol. 12, p. 240-247 - briefly blood samples may be collected at desired intervals, plasma separated, immediately frozen, and kept at -20°C until analyzed for plasma concentration of the respective GLP-1 agonist; the donor beads are coated with streptavidin, while acceptor beads are conjugated with a monoclonal antibody recognising a mid-/C-terminal epitope of the peptide; another monoclonal antibody, specific for the N-terminus, is biotinylated; the three reactants are combined with the analyte and formed a two-sited immuno-complex; illumination of the complex releases singlet oxygen atoms from the donor beads, which are channeled into the acceptor beads and triggered chemiluminescence which may be measured in an Envision plate reader; the amount of light is proportional to the concentration of the compound.

In one embodiment the term “Aib” as used herein refers to α-aminoisobutyric acid.

PHARMACEUTICAL COMPOSITIONS

An administered dose may contain from 5 mg - 100 mg of the GLP-1 agonist, or from

5-50 mg, or from 5-20 mg, or from 5-10 mg of the GLP-1 agonist.

In one embodiment the composition is BYDUREON® (a long acting release formula of exenatide in PLGA particles).

Pharmaceutical compositions comprising a GLP-1 agonist of the invention or a pharmaceutically acceptable salt, amide, or ester thereof, and a pharmaceutically acceptable excipient may be prepared as is known in the art.

In one embodiment the term "excipient" broadly refers to any component other than the active therapeutic ingredient(s). The excipient may be an inert substance, an inactive substance, and/or a not medicinally active substance. The formulation of pharmaceutically active ingredients with various excipients is known in the art, see e.g. Remington: The Science and Practice of Pharmacy (e.g. 19th edition (1995), and any later editions). Non-limiting examples of excipients are: solvents, diluents, buffers, preservatives, tonicity regulating agents (e.g isotonic agents), chelating agents, stabilisers (e.g. oxidation inhibitors, aggregation inhibitors, surfactants, and/or protease inhibitors).

Examples of formulations include liquid formulations, i.e. aqueous formulations comprising water. A liquid formulation may be a solution, or a suspension. An aqueous formulation typically comprises at least 50% w/w water, or at least 60%, 70%, 80%, or even at least 90% w/w of water.

Alternatively, a pharmaceutical composition may be a solid formulation, e.g. a freeze-dried or spray-dried composition, which may be used as is, or whereto the physician or the patient adds solvents, and/or diluents prior to use.

The pH in an aqueous formulation may be anything between pH 3 and pH 10, for example from about 7.0 to about 9.5; or from about 3.0 to about 7.0.

Still further, a pharmaceutical composition may be formulated as is known in the art of oral formulations of insulinotropic compounds, e.g. using any one or more of the formulations described in WO 2008/145728.

A composition may be administered in several dosage forms, for example as a solution; a suspension; an emulsion; a microemulsion; multiple emulsions; a foam; a salve; a paste; a plaster; an ointment; a tablet; a coated tablet; a chewing gum; a rinse; a capsule such as hard or soft gelatine capsules; a suppositorium; a rectal capsule; drops; a gel; a spray; a powder; an aerosol; an inhalant; eye drops; an ophthalmic ointment; an ophthalmic rinse; a vaginal pessary; a vaginal ring; a vaginal ointment; an injection solution; an in situ transforming solution such as in situ gelling, setting, precipitating, and in situ crystallisation; an infusion solution; or as an implant.

A composition may further be compounded in a drug carrier or drug delivery system, e.g. in order to improve stability, bioavailability, and/or solubility. In a particular embodiment a composition may be attached to such system through covalent, hydrophobic, and/or electrostatic interactions. The purpose of such compounding may be, e.g., to decrease adverse effects, achieve chronotherapy, and/or increase patient compliance.

A composition may also be used in the formulation of controlled, sustained, protracting, retarded, and/or slow release drug delivery systems.

The composition may be administered by parenteral administration. Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal, or intravenous injection by means of a syringe, optionally a pen-like syringe, or by means of an infusion pump.

PRODUCTION PROCESSES

In one embodiment GLP-1 peptides can be produced by appropriate derivatisation of an appropriate peptide backbone which has been produced by recombinant DNA technology or by peptide synthesis (e.g., Merrifield-type solid phase synthesis) as known in the art of peptide synthesis and peptide chemistry.

In one embodiment the production of peptides like GLP-1(7-37) and GLP-1 analogues is well known in the art. The GLP-1 moiety of the GLP-1 peptide of the invention (or fragments thereof) may for instance be produced by classical peptide synthesis, e.g., solid phase peptide synthesis using t-Boc or Fmoc chemistry or other well established techniques, see, e.g., Greene and Wuts, “Protective Groups in Organic Synthesis”, John Wiley & Sons, 1999, Florencio Zaragoza Dörwald, “Organic Synthesis on solid Phase”, Wiley-VCH Verlag GmbH, 2000, and “Fmoc Solid Phase Peptide Synthesis”, Edited by W.C. Chan and P.D. White, Oxford University Press, 2000.

In one embodiment GLP-1 agonists may be produced by recombinant methods, viz. by culturing a host cell containing a DNA sequence encoding the GLP-1 agonist and capable of expressing the peptide in a suitable nutrient medium under conditions permitting the expression of the peptide. Non-limiting examples of host cells suitable for expression of these peptides are: Escherichia coli, Saccharomyces cerevisiae, as well as mammalian BHK or CHO cell lines.

In one embodiment GLP-1 agonists of the invention which include non-natural amino acids and/or a covalently attached N-terminal mono- or dipeptide mimetic may e.g. be produced as described in the experimental part. Or see e.g., Hodgson et al: "The synthesis of peptides and proteins containing non-natural amino acids", Chemical Society Reviews, vol. 33, no. 7

(2004), p. 422-430; and WO 2009/083549 A1 entitled "Semi-recombinant preparation of GLP-1 analogues".

EMBODIMENTS

The following are non-limiting embodiments of the invention:

1. A method for reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

2. A method for treating or preventing obesity, for reducing body weight and/or food intake, or for inducing satiety, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

3. The method according to any one of the preceding embodiments, wherein said method comprises delaying or preventing diabetic disease progression.

4. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist has a half-life of at least 24 hours, such as at least 48 hours, at least 60 hours, or at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours, or optionally at least 120 hours, at least 132 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

5. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered twice weekly or less often, once weekly or less often, such as less often than once weekly or once every secondly week or less often, or such as once every third week or less often or once a month or less often.

6. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount of at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, per week.

7. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount equivalent to at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, semaglutide per week.

8. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount which provides an improved a) reduction in HbA1c or b) reduction in body weight compared to administration of 1.8 mg liraglutide or less, such as 0.8 mg liraglutide or less, per day.

9. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

10. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered by parenteral administration, such as subcutaneous injection.

11. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered simultaneously or sequentially with another therapeutic agent.

12. The method according to any one of any one of the preceding embodiments, wherein the GLP-1 agonist is a GLP-1 peptide.

13. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide comprises the amino acid sequence of the formula (I) (SEQ ID NO: 5):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa_{16}-Ser-Xaa_{18}-$Xaa_{19}Xaa_{20}$GluXaa_{22}-Xaa_{23}-Ala-Xaa_{25}-Xaa_{26}-Xaa_{27}-Phe-Ile-Xaa_{3}o-Trp-Leu-Xaa_{33}-Xaa_{34}-Xaa_{35}-Xaa_{36}-Xaa_{37}-Xaa_{38}-Xaa_{39}-Xaa_{4}o-Xaa_{41}-Xaa_{42}-Xaa_{43}-Xaa_{44}-Xaa_{45}-Xaa_{46}

Formula (I)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3- pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{25} is Ala or Val;

Xaa_{26} is Lys, Glu or Arg;

Xaa_{27} is Glu or Leu;

Xaa_{30} is Ala, Glu or Arg;

Xaa_{33} is Val or Lys;

Xaa_{34} is Lys, Glu, Asn or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg, Gly or Lys;

Xaa_{37} is Gly, Ala, Glu, Pro, Lys, amide or is absent;

Xaa_{38} is Lys, Ser, amide or is absent;

Xaa_{39} is Ser, Lys, amide or is absent;

Xaa_{40} is Gly, amide or is absent;

Xaa_{41} is Ala, amide or is absent;

Xaa_{42} is Pro, amide or is absent;

Xaa_{43} is Pro, amide or is absent;

Xaa_{44} is Pro, amide or is absent;

Xaa_{45} is Ser, amide or is absent;

Xaa_{46} is amide or is absent;

provided that if Xaa_{38}, Xaa_{39}, Xaa_{40}, Xaa_{41}, Xaa_{42}, Xaa_{43}, Xaa_{44}, Xaa_{45} or Xaa_{46} is absent then each amino acid residue downstream is also absent.

14. The method according to any one of the preceding embodiments, wherein said polypeptide is a GLP-1 peptide comprising the amino acid sequence of formula (II) (SEQ ID NO: 6):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Xaa_{18}-Tyr-Leu-Glu-Xaa22-Xaa_{23}-Ala-Ala-Xaa_{26}-Glu-Phe-Ile-Xaa_{3o}-Trp-Leu-Val-Xaa_{34}-Xaa_{35}-Xaa_{36}-$Xaa_{37}Xaa_{38}$

Formula (II)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine,-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{26} is Lys, Glu or Arg; Xaa30 is Ala, Glu or Arg;

Xaa_{34} is Lys, Glu or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg or Lys;

Xaa_{37} is Gly, Ala, Glu or Lys;

Xaa_{38} is Lys, amide or is absent.

15. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide is selected from GLP-1 (7-35), GLP-1 (7-36), GLP-1 (7-36)-amide, GLP-1 (7-37), GLP-1 (7-38), GLP-1 (7-39), GLP-1 (7-40), GLP-1 (7-41) or an analogue or derivative thereof.

16. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 15, such as no more than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

17. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 5 amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

18. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code.

19. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide is a DPPIV protected GLP-1 peptide.

20. The method according to any one of the preceding embodiments, wherein GLP-1 peptide is DPPIV stabilised.

21. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises an Aib residue in position 8.

22. The method according to any one of the preceding embodiments, wherein the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4-pyridylalanine.

23. The method according to any one of embodiments 7 to 16, wherein said GLP-1 peptide is attached to said hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

24. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide is exendin-4, an exendin-4-analogue, or a derivative of exendin-4.

25. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide comprises the amino acid sequence of the following formula:

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu

Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 (SEQ ID NO: 2).

26. The method according to any one of the preceding embodiments wherein one albumin binding residue via said hydrophilic spacer is attached to the C-terminal amino acid residue of said GLP-1 peptide.

27. The method according to any one of the preceding embodiments, wherein a second albumin binding residue is attached to an amino acid residue which is not the C-terminal amino acid residue.

28. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide is selected from the group consisting of semaglutide, albiglutide and dulaglitide.

29. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide has the following structure:
His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg (SEQ ID NO: 3).

30. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide has the following structure:
(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-
Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2 (SEQ ID NO: 4)–
genetically fused to human albumin.

31. The method according to any one of the preceding embodiments wherein the GLP-1 peptide is dulaglitide.

32. The method according to any one of the preceding embodiments wherein the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100 pM, optionally determined by Assay (I).

33. A GLP-1 agonist for use in the reduction of HbA1c or for use in the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

34. A GLP-1 agonist for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

35. A GLP-1 agonist for use according to embodiment 33 or 34, wherein the GLP-1 agonist and/or administration is as defined in any of embodiments 1-32 or 40.

36. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

37. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

38. A composition for use according to any one of the preceding embodiments, wherein said GLP-1 agonist and/or administration is as defined in any one of embodiments 1-32 or 40.

39. A composition for use according to any one of the preceding embodiments, wherein said composition comprises the Bydureon® composition.

40. The method according to any one of the preceding claims, wherein the method comprises prevention, treatment, reduction or induction in one or more diseases or conditions defined in any one of the previous embodiments.

EXAMPLES

Abbreviations

The following abbreviations are used in the following, in alphabetical order:

ADA: American Diabetes Association

Example 1: The Glp-1 Peptide Semaglutide Provides Reduced HbA1c and Body Weight

Semaglutide is a unique acylated GLP-1 peptide with a half-life of 160 hours. The aim was to investigate HbA1c dose-response of once-weekly doses of semaglutide (five dose-levels) in subjects with type 2 diabetes. Safety, tolerability and pharmacodynamics of semaglutide versus placebo and open-label once-daily liraglutide were also investigated.

Materials and methods

Liraglutide may be prepared as described in Example 37 of WO98/08871. Semaglutide may be prepared as described in Example 4 of WO2006/097537. The composition of the GLP-1 agonists administered may be formulated as isotonic aqueous solutions with a phosphate

buffer, such as a sodium dihydrogen phosphate buffer, having a pH in the range 7.0-9.0, such as pH 7.4 or pH 8.15, for example further comprising the excipients propylene glycol and phenol. The composition of the GLP-1 agonists administered may be as described in WO2003/002136 or WO2005/049061. The placebo composition may be identical to the composition of the GLP-1 agonists, but not containing a GLP-1 agonist.

In a 12-week, randomised, double-blind, placebo-controlled trial, 411 human subjects (n=43–50 per group) with type 2 diabetes were exposed. Participants (male/female 65/35%; baseline HbA1c (mean±SD) 8.1±0.8%; baseline body weight 87.5±13.8 kg; duration of diabetes 2.6±3.1 years; metformin only/diet and exercise alone 80/20%) received subcutaneous injection of one of five semaglutide doses (0.1–1.6 mg) once weekly, open-label liraglutide (1.2 mg, 1.8 mg) once daily, or placebo once weekly. Two of the semaglutide doses were titrated (T) in weekly increments of 0.4 mg. The primary endpoint was change in HbA1c from baseline. Secondary efficacy endpoints included proportion of subjects reaching ADA HbA1c target (<7%) and change in body weight. Change and percentage to target were analysed by ANOVA and logistic regression, respectively. Comparisons between semaglutide and liraglutide were not corrected for multiplicity. Baseline characteristics of the subjects are shown in Table 1.

Table 1. Baseline characteristics of subjects

	Placebo	Semaglutide						Liraglutide	
		0.1 mg	0.2 mg	0.4 mg	0.8 mg	0.8 mg T	1.6 mg T	1.2 mg	1.8 mg
Exposed* subjects	46	47	43	48	42	43	47	45	50
D&E: metformin (%)	22:78	23:77	14:86	23:77	19:81	16:84	19:81	18:82	24:76
Female: male (%)	39:61	34:66	30:70	23:77	48:52	37:63	45:55	31:69	30:70
Age (years)	55.3 (10.6)	55.2 (10 .1)	54.7 (10.0)	53.8 (10.2)	55.0 (9.7)	55.9 (7.9)	56.4 (10.5)	54.8 (9.2)	54.3 (10.1)
Duration of diabetes (years)	2.4 (3.3)	3.6 (5.0)	2.3 (2.7)	2.0 (2.3)	3.0 (3.0)	2.6 (2.1)	1.8 (2.0)	3.3 (3.4)	2.5 (2.6)

HbA1c (%)	8.1 (0.8)	8.2 (0.9)	8.2 (0.9)	8.1 (0.9)	8.2 (0.9)	8.0 (0.8)	8.0 (0.7)	8.0 (0.8)	8.1 (0.7)
FPG (mmol/L)	8.9 (1.5)	9.8 (2.7)	9.5 (2.5)	9.3 (2.1)	9.5 (2.4)	9.6 (2.1)	9.0 (1.9)	9.0 (2.3)	9.3 (2.0)
Weight (kg)	90.5 (13.0)	89.5 (14.2)	86.3 (15.1)	87.0 (14.0)	85.9 (15.1)	85.7 (12.6)	84.5 (14.0)	90.5 (13.5)	87.2 (13.1)
BMI (kg/m^2)	31.7 (3.8)	31.5 (4.6)	30.4 (3.9)	29.7 (4.5)	30.7 (4.5)	31.2 (4.2)	30.9 (4.7)	31.0 (4.6)	30.9 (4.6)

Data are mean (SD) unless otherwise stated. *: Number of subjects exposed to actual treatment. D&E: Diet and exercise. FPG: Fasting plasma glucose. BMI: Body mass index.

Results

In the full analysis set, semaglutide (≥0.2 mg) dose-dependently reduced HbA1c from baseline (Fig. 1), and increased the likelihood of achieving HbA1c <7% ($p<0.05$ vs. placebo for doses ≥0.2 mg). The results with respect to change in HbA1c are shown in Fig. 1. The change in HbA1c in fig. 1 is from baseline at week 12. Fig. 2 shows the change in HbA1c over time with the different treatments. Treatment with semaglutide ≥0.8 mg numerically brought more patients to target than liraglutide 1.8 mg (0.8 mg T 69%, 0.8 mg 73%, 1.6 mg T 81% vs. liraglutide 1.8 mg 57%).The results (see e.g. Fig. 1) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T improved reduction of HbA1c compared to treatment with liraglutide 1.2 mg or 1.8 mg; furthermore, treatment with semaglutide 1.6 mg T was statistically superior to treatment with liraglutide 1.2 mg or 1.8 mg with respect to reduction of HbA1c (based on unadjusted means). Fig. 3 shows the percentage and the number of subjects reaching the AACE or ADA criteria for glycaemic control with the different treatments. The results (see Fig. 3) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T improved the percentage and the number of subjects reaching the AACE or ADA criteria for glycaemic control compared to treatment with liraglutide 1.2 mg or 1.8 mg.

Body weight was dose-dependently reduced from baseline by up to 4.8 kg vs. placebo 1.2 kg ($p<0.01$ for doses ≥0.8 mg). Fig. 4 and 5 shows mean body weight change versus time and body weight change from baseline at week 12, respectively, with the different treatments. The results (see e.g. Fig. 5) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T increased reduction of body weight compared to treatment with liraglutide 1.2 mg or 1.8 mg. Furthermore, the results (see e.g. Fig. 5) shows that treatment with semaglutide 0.8 mg T or 1.6 mg T was statistically superior to treatment with liraglutide 1.8 mg with respect to reduction of

body weight; and that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T was statistically superior to liraglutide 1.2 mg with respect to reduction of body weight (based on unadjusted means).

There were no reports of pancreatitis or treatment-related changes in blood calcitonin. Proportion of subjects with nausea and vomiting increased with dose, but were generally mild or moderate and ameliorated by titration. Withdrawals due to gastrointestinal adverse events were 4.7%-27.7% for semaglutide and 2.2%-10% for liraglutide. Few subjects reported minor hypoglycaemia (semaglutide n=5, liraglutide n=3); no major hypoglycaemia. Injection site reactions were reported by 7 subjects: semaglutide n=2; liraglutide n=5. One subject (semaglutide 1.6 mg T) developed low titre non-neutralising anti-semaglutide antibodies (no cross-reaction to native GLP-1).

Conclusion

Over 12 weeks, semaglutide dose-dependently reduced HbA1c and body weight. The effect of semaglutide 0.4 mg on glycaemic control and body weight was comparable to that of liraglutide 1.2 mg, while semaglutide ≥0.8 mg appeared to bring more subjects to target and provided better weight loss than liraglutide 1.8 mg. No semaglutide safety concerns were identified. Dose escalation was not a major focus of this trial and it will be optimised in future clinical trials.

Pharmacological Methods

Assay (I): In Vitro Potency

The purpose of this example is to test the activity, or potency, of GLP-1 agonists in vitro. The potencies of GLP-1 agonists may be determined as described below, i.e. as the stimulation of the formation of cyclic AMP (cAMP) in a medium containing membranes expressing the human GLP-1 receptor.

Principle

Purified plasma membranes from a stable transfected cell line, BHK467-12A (tk-ts13), expressing the human GLP-1 receptor are stimulated with the GLP-1 agonist in question, and the potency of cAMP production is measured using the AlphaScreenTM cAMP Assay Kit from Perkin Elmer Life Sciences. The basic principle of The AlphaScreen Assay is a competition between endogenous cAMP and exogenously added biotin-cAMP. The capture of cAMP is

achieved by using a specific antibody conjugated to acceptor beads.

Cell culture and preparation of membranes

A stable transfected cell line and a high expressing clone are selected for screening. The cells are grown at 5% CO_2 in DMEM, 5% FCS, 1% Pen/Strep (Penicillin/Streptomycin) and 0.5 mg/ml of the selection marker G418.

Cells at approximate 80% confluence are washed 2X with PBS and harvested with Versene (aqueous solution of the tetrasodium salt of ethylenediaminetetraacetic acid), centrifuged 5 min at 1000 rpm and the supernatant removed. The additional steps are all made on ice. The cell pellet is homogenised by the Ultrathurax for 20-30 sec. in 10 ml of Buffer 1 (20 mM Na-HEPES, 10 mM EDTA, pH=7.4), centrifuged 15 min at 20,000 rpm and the pellet resuspended in 10 ml of Buffer 2 (20 mM Na-HEPES, 0.1 mM EDTA, pH=7.4). The suspension is homogenised for 20-30 sec and centrifuged 15 min at 20,000 rpm. Suspension in Buffer 2, homogenisation and centrifugation is repeated once and the membranes are resuspended in Buffer 2. The protein concentration is determined and the membranes stored at -80°C until use.

The assay is performed in ½-area 96-well plates, flat bottom (e.g. Costar cat. no:3693). The final volume per well is 50 µl.

Solutions and reagents

Exemplary solutions and reagents are given below.

AlphaScreen cAMP Assay Kit from Perkin Elmer Life Sciences (cat. No: 6760625M); containing Anti-cAMP Acceptor beads (10 U/µl), Streptavidin Donor beads (10 U/µl) and Biotinylated-cAMP (133 U/µl).

AlphaScreen Buffer, pH=7.4: 50 mM TRIS-HCl (Sigma, cat.no: T3253); 5 mM HEPES (Sigma, cat.no: H3375); 10 mM $MgCl_2$, $6H_2O$ (Merck, cat.no: 5833); 150 mM NaCl (Sigma, cat.no: S9625); 0.01% Tween (Merck, cat.no: 822184). The following was added to the AlphaScreen Buffer prior to use (final concentrations indicated): BSA (Sigma, cat. no. A7906): 0.1%; IBMX (Sigma, cat. no. I5879): 0.5 mM; ATP (Sigma, cat. no. A7699): 1 mM; GTP (Sigma, cat. no. G8877): 1 µM.

cAMP standard (dilution factor in assay = 5): cAMP Solution: 5 µL of a 5 mM cAMP-stock + 495 µL AlphaScreen Buffer.

Suitable dilution series in AlphaScreen Buffer are prepared of the cAMP standard as well as the GLP-1 agonist to be tested, e.g. the following eight concentrations of the GLP-1 agonist: 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} and 10^{-14}M, and a series from, e.g., 10^{-6} to $3x10^{-11}$ of cAMP.

Membrane/Acceptor beads

Use hGLP-1/ BHK 467-12A membranes; 6 µg/well corresponding to 0.6 mg/ml (the amount of membranes used pr. well may vary)

"No membranes": Acceptor Beads (15µg/ml final) in AlphaScreen buffer

"6 µg/well membranes": membranes + Acceptor Beads (15µg/ml final) in AlphaScreen buffer

Add 10 µl "No membranes" to the cAMP standard (per well in duplicates) and the positive and negative controls

Add 10 µl "6 µg/well membranes" to GLP-1 and GLP-1 agonists (per well in duplicates/triplicates)

Pos. Control: 10 µl "no membranes" + 10 µl AlphaScreen Buffer

Neg. Control: 10 µl "no membranes" + 10 µl cAMP Stock Solution (50µM)

As the beads are sensitive to direct light, any handling is in the dark (as dark as possible), or in green light. All dilutions are made on ice.

Procedure

1. Make the AlphaScreen Buffer.
2. Dissolve and dilute the GLP-1 agonists/cAMP standard in AlphaScreen Buffer.
3. Make the Donor Beads solution and incubate 30 min. at RT.
4. Add the cAMP/GLP-1 agonists to the plate: 10 µl per well.
5. Prepare membrane/Acceptor Beads solution and add this to the plates: 10 µl per well.
6. Add the Donor Beads: 30 µl per well.
7. Wrap the plate in aluminum foil and incubate on the shaker for 3 hours (very slowly) at RT.
8. Count on AlphaScreen – each plate pre incubates in the AlphaScreen for 3 minutes before counting.

The EC_{50} [pM] values may be calculated using the Graph-Pad Prism software (version 5). If desired, the fold variation in relation to GLP-1 may be calculated as EC_{50} (GLP-1)/ EC_{50} (analogue) – 3693.2.

Assay (II): Half-life in Minipigs

The purpose of this study is to determine the protraction in vivo of GLP-1 agonists after i.v. administration to minipigs, i.e. the prolongation of their time of action. This is done in a pharmacokinetic (PK) study, where the terminal half-life of the GLP-1 agonist in question is determined. By terminal half-life is generally meant the period of time it takes to halve a certain plasma concentration, measured after the initial distribution phase.

Male Göttingen minipigs are obtained from Ellegaard Göttingen Minipigs (Dalmose, Denmark) approximately 7-14 months of age and weighing from approximately 16-35 kg are used in the studies. The minipigs are housed individually and fed restrictedly once or twice daily with SDS minipig diet (Special Diets Services, Essex, UK). After at least 2 weeks of acclimatisation two permanent central venous catheters are implanted in vena cava caudalis or cranialis in each animal. The animals are allowed 1 week recovery after the surgery, and are then used for repeated pharmacokinetic studies with a suitable wash-out period between dosings.

The animals are fasted for approximately 18 h before dosing and for at least 4 h after dosing, but have ad libitum access to water during the whole period.

The GLP-1 agonist is dissolved in 50 mM sodium phosphate, 145 mM sodium chloride, 0.05% tween 80, pH 7.4 to a concentration of usually from 20-60 nmol/ml. Intravenous injections (the volume corresponding to usually 1-2 nmol/kg, for example 0.033ml/kg) of the compounds are given through one catheter, and blood is sampled at predefined time points for up till 13 days post dosing (preferably through the other catheter). Blood samples (for example 0.8 ml) are collected in EDTA buffer (8mM) and then centrifuged at 4°C and 1942G for 10 minutes. Plasma is pippetted into Micronic tubes on dry ice, and kept at -20°C until analyzed for plasma concentration of the respective GLP-1 compound using ELISA or a similar antibody based assay or LC-MS. Individual plasma concentration-time profiles are analyzed by a non-compartmental model in WinNonlin v. 5.0 (Pharsight Inc., Mountain View, CA, USA), and the resulting terminal half-lives (harmonic mean) determined.

Assay (III): Effect on Blood Glucose and Body Weight

The purpose of the study is to verify the effect of GLP-1 agonists on blood glucose (BG) and body weight (BW) in a diabetic setting. GLP-1 agonists may be tested in a dose-response study in an obese, diabetic mouse model (db/db mice) as described in the following.

Fifty db/db mice (Taconic, Denmark), fed from birth with the diet NIH31 (NIH 31M Rodent Diet, commercially available from Taconic Farms, Inc., US, see www.taconic.com), are enrolled for the study at the age of 7-9 weeks The mice are given free access to standard chow (e.g. Altromin 1324, Brogaarden, Gentofte, Denmark) and tap water and kept at 24°C. After 1-2 weeks of acclimatisation, the basal blood glucose is assessed twice on two consecutive days (i.e. at 9 am). The 8 mice with the lowest blood glucose values may be excluded from the experiments. Based on the mean blood glucose values, the remaining 42 mice may be selected for further experimentation and allocated to 7 groups (n=6) with matching blood glucose levels.

The mice may be used in experiments with duration of 5 days for up to 4 times. After the last experiment the mice are euthanised.

The seven groups may receive treatment as follows:

1: Vehicle, subcutaneous
2: GLP-1 agonist, 0.3 nmol/kg, subcutaneous
3: GLP-1 agonist, 1.0 nmol/kg, subcutaneous
4: GLP-1 agonist, 3.0 nmol/kg, subcutaneous
5: GLP-1 agonist, 10 nmol/kg, subcutaneous
6: GLP-1 agonist, 30 nmol/kg, subcutaneous
7: GLP-1 agonist, 100 nmol/kg, subcutaneous

Vehicle: 50mM sodium phosphate, 145 mM sodium chloride, 0.05% tween 80, pH 7.4.

The GLP-1 agonist is dissolved in the vehicle, e.g. to concentrations of 0.05, 0.17, 0.5, 1.7, 5.0 and 17.0 nmol/ml. Animals are dosed subcutaneous with a dose-volume of 6 ml/kg (i.e. 300 µl per 50 g mouse).

On the day of dosing, blood glucose is assessed at time -½h (8.30 am), where after the mice are weighed. The GLP-1 agonist is dosed at approximately 9 am (time 0). On the day of dosing, blood glucose is assessed e.g. at times 1, 2, 4 and 8 h (10 am, 11 am, 1 pm and 5 pm).

On the following days, the blood glucose is assessed e.g. at time 24, 48, 72, and 96h after dosing (i.e. at 9 am on day 2, 3, 4, 5). On each day, the mice are weighed following blood glucose sampling.

The mice are weighed individually on a digital weight.

Samples for the measurement of blood glucose are obtained from the tail tip capillary of conscious mice. Blood, 10 µl, is collected into heparinised capillaries and transferred to 500 µl glucose buffer (EKF system solution, Eppendorf, Germany). The glucose concentration is measured using the glucose oxidase method (glucose analyser Biosen 5040, EKF Diagnostic, GmbH, Barleben, Germany). The samples are kept at room temperature for up to 1 h until analysis. If analysis has to be postponed, samples are kept at 4°C for a maximum of 24 h.

ED_{50} is the dose giving rise to half-maximal effect in nmol /kg. This value is calculated on the basis of the ability of the GLP-1 agonists to lower body weight as well as the ability to lower blood glucose, as explained below.

ED_{50} for body weight is calculated as the dose giving rise to half-maximum effect on delta BW 24 hours following the subcutaneous administration of the GLP-1 agonist. For example, if the maximum decrease in body weight after 24 hours is 4.0 g, then ED_{50} bodyweight would be that dose in nmol/kg which gives rise to a decrease in body weight after 24 hours of

2.0 g. This dose (ED_{50} body weight) may be read from the dose-response curve.

ED_{50} for blood glucose is calculated as the dose giving rise to half-maximum effect on AUC delta BG 8 hours following the subcutaneous administration of the GLP-1 agonist.

The ED_{50} value may only be calculated if a proper sigmoidal dose-response relationship exists with a clear definition of the maximum response. Thus, if this would not be the case the GLP-1 agonist in question is re-tested in a different range of doses until the sigmoidal dose-response relationship is obtained.

Assay (IV): Effect on Food Intake

The purpose of this experiment is to investigate the effect of GLP-1 agonists on food intake in pigs. This is done in a pharmacodynamic (PD) study as described below, in which food intake is measured 1, 2, 3, and 4 days after administration of a single dose of the GLP-1 agonist, as compared to a vehicle-treated control group.

Female Landrace Yorkshire Duroc (LYD) pigs, approximately 3 months of age, weighing approximately 30-35 kg are used (n=3-4 per group). The animals are housed in a group for 1-2 weeks during acclimatisation to the animal facilities. During the experimental period the animals are placed in individual pens from Monday morning to Friday afternoon for measurement of individual food intake. The animals are fed ad libitum with pig fodder (Svinefoder, Antonio) at all times both during the acclimatisation and the experimental period. Food intake is monitored on line by logging the weight of fodder every 15 minutes. The system used is Mpigwin (Ellegaard Systems, Faaborg, Denmark).

The GLP-1 agonists are dissolved in a phosphate buffer (50 mM phosphate, 0.05% tween 80, pH 8) e.g. at concentrations of 12, 40, 120, 400 or 1200 nmol/ml corresponding to doses of 0.3, 1, 3, 10, or 30 nmol/kg. The phosphate buffer served as vehicle. Animals are dosed with a single subcutaneous dose of the GLP-1 agonist or vehicle (dose volume 0.025 ml/kg) on the morning of day 1, and food intake is measured for 4 days after dosing. On the last day of each study, 4 days after dosing, a blood sample for measurement of plasma exposure of the GLP-1 agonist is taken from the heart in anaesthetised animals. The animals are thereafter euthanised with an intra-cardial overdose of pentobarbitone. Plasma content of the GLP-1 agonist is analysed using ELISA or a similar antibody based assay.

Food intake is calculated as mean ± SEM 24 h food intake on the 4 days. Statistical comparisons of the 24 hour food intake in the vehicle vs. GLP-1 agonist group on the 4 days are done using one-way or two-way-ANOVA repeated measures, followed by Bonferroni post-test.

Assay (V): Stability against Degradation by Intestinal Enzymes

The purpose of this example is to test the stability against degradation by intestinal enzymes. GLP-1(7-37) may be used in the assay as a comparative compound. The strongest proteolytic activities in the intestine are of pancreatic origin and include the serine endopeptidases trypsin, chymotrypsin, and elastase as well as several types of carboxypeptidases. An assay with small intestine extract from rats was developed and used as described in the following.

Extracts from rat small intestine

Small intestines are prepared from rats and flushed with 8 ml of 150 mM NaCl, 20 mM Hepes pH 7.4. The solutions are centrifuged for 15 min at 4,600 rpm in a Heraeus Multifuge 3 S-R centrifuge with a 75006445 rotor. The supernatants are removed and filtered through a 0.22 µm Millipore Millex GV PVDF membrane. Filtrates of several animals are pooled to average out individual differences.

The protein content of the obtained extracts is determined by Bradford Assay (see e.g. Analytical Biochemistry (1976), vol. 72, p. 248-254, and Analytical Biochemistry (1996), vol. 236 p. 302-308).

Degradation assay

2.5 nmol of the GLP-1 agonists to be tested are incubated with the intestinal extract in a volume of 250 µl at 37°C over a period of one hour. Intestinal samples are assayed in presence of 20 mM Hepes at pH 7.4. The concentration of the intestinal extract is titrated in pilot experiments so that the half-life (t½) of GLP-1(7-37) is in the range of 10-20 minutes. The small intestine extract is used at a concentration of 1.4 µg/ml. All components except for the intestinal extract are mixed and pre-warmed for ten minutes at 37°C. Immediately after addition of the intestinal extract a sample of 50 µl is taken and mixed with the same volume of 1% trifluoroacetic acid (TFA). Further samples are taken accordingly after 15, 30, and 60 minutes.

Sample analysis

UPLC analysis: 10 µl of the samples are analysed by UPLC using a Waters Acquity system with a BEH C18 1.7 µm 2.1 x 50 mm column and a 30 to 65% gradient of 0.1% TFA and 0.07% TFA in acetonitrile over 5 minutes at a flow rate of 0.6 ml/min. After baseline subtraction the peak integrals of the intact compounds in the HPLC chromatogram recorded at a wavelength of 214 nm are determined.

MALDI-TOF analysis: 1 µl of each sample is transferred to a Bruker/Eppendorf PAC HCCA 384 MALDI target. Analysis is performed with a Bruker Autoflex matrix-assisted laser desorption and ionisation - time of flight (MALDI-TOF) mass spectrometer using the pre-defined

method “PAC_measure” with an extended detection range of 500 to 5000 Da and the pre-defined calibration method “PAC_calibrate”.

Data analysis: The peak integrals of the HPLC chromatograms are plotted against time. The half-life of the respective compound is calculated by fitting the data using SigmaPlot 9.0 software and an equation for a 2-parameter exponential decay. For each GLP-1 agonist tested, the relative half-life (relative $T_{½}$) is calculated as the half-life ($T_{½}$) of the compound in question, divided by the half-life ($T_{½}$) of GLP-1(7-37), determined in the same way.

While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

Docket No.: 8545US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christine Bjoern Jensen et al.

Application No.: Not Yet Assigned | Confirmation No.: N/A

Filed: Concurrently Herewith | Art Unit: N/A

For: Use of Logn-Acting GLP-1 Peptides | Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement accompanies the new patent application submitted herewith.

In accordance with 37 C.F.R. § 1.98(d)(1), the references are not supplied because they were previously cited by or submitted to the Office in prior application number 14/409,493 filed December 19, 2014 and relied on in the above-identified application for an earlier effective filing date under 35 U.S.C. § 120.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0063

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 14-1447, under Order No. 8545US02 from which the undersigned is authorized to draw.

Dated: July 20, 2017

Respectfully submitted,

Electronic signature: /Leon Y. Lum/
Leon Y. Lum
Registration No.: 62,124
NOVO NORDISK INC
800 Scudders Mill Road
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(609) 987-5800
Attorney For Applicant

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0064

Docket No.: 8545US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christine Bjoern Jensen et al.

Application No.: Not Yet Assigned | Confirmation No.: N/A

Filed: Concurrently Herewith | Art Unit: N/A

For: Use of Long-Acting GLP-1 Peptides | Examiner: Not Yet Assigned

HAKIM STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This application is a continuation of U.S. Patent Application No. 14/409,493 (the "parent application"). The scope of the claims of this application may be broader or narrower from those of the parent application. Except as otherwise explicitly stated herein, Applicant hereby rescinds any disclaimer of claim scope (perceived or actual) made in the parent application (by amendment, argument, or both).

Accordingly, Applicant hereby requests the Examiner that she/he to revisit and reconsider any prior art that the Office considered to be overcome or avoided by amendments and/or arguments made in the parent application and/or any prior art searches that were performed in the parent application. *See*, *e.g.*, Hakim v. Cannon Avent Group, PLC et al., 479 F.3d 1313, 1317-1318 (Fed. Cir. 2007).

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0065

Applicant believes no additional fee is due with this response. However, if an additional fee is due, please charge our Deposit Account No. 14-1447, under Order No. 8545US02 from which the undersigned is authorized to draw.

Dated: July 20, 2017

Respectfully submitted,

Electronic signature: /Leon Y. Lum/
Leon Y. Lum
Registration No.: 62,124
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536
(609) 987-5800
Attorney For Applicant

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0066

Docket No.: 8545US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christine Bjoern Jensen et al.

Application No.: Not Yet Assigned | Confirmation No.: N/A

Filed: Concurrently Herewith | Art Unit: N/A

For: Use of Long-Acting GLP-1 Peptides | Examiner: Not Yet Assigned

STATEMENT TO SUPPORT FILING AND SUBMISSION IN ACCORDANCE WITH 37 C.F.R. §§ 1.821-1.825

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In connection with a Sequence Listing submitted concurrently herewith, the undersigned hereby states that:

1. the submission, filed herewith in accordance with 37 C.F.R. § 1.821(b), does not include new matter;

2. the content of the electronically filed Sequence Listing is submitted in accordance with 37 C.F.R. § 1.821(e).

No new matter is added.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this response or application.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0067

Applicant believes no additional fee is due with this response. However, if an additional fee is due, please charge our Deposit Account No. 14-1447, under Order No. 8545US02 from which the undersigned is authorized to draw.

Dated: July 20, 2017

Respectfully submitted,

Electronic signature: /Leon Y. Lum/
Leon Y. Lum
Registration No.: 62,124
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536
(609) 987-5800
Attorney For Applicant

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0068

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 15656042 Document Date: 07/21/2017

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Sequence Listing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0069

SCORE Placeholder Sheet for IFW Content

Application Number: 15656042 Document Date: 07/21/2017

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Drawings – Other than Black and White Line Drawings

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

To access the documents in the SCORE database, refer to instructions below.

At the time of document entry (noted above):

- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://Score.uspto.gov/ScoreAccessWeb/).
- External customers may access SCORE content via the Public and Private PAIR interfaces.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0070

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Sequence Listing was accepted.
If you need help call the Patent Electronic Business Center at (866) 217-9197 (toll free).
Reviewer: Anjum, Durreshwar
Timestamp: [year=2017; month=7; day=27; hr=12; min=21; sec=59; ms=624;]
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Validated By CRFValidator v 1.0.5

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02

CONFIRMATION NO. 9712

FORMALITIES LETTER

23650
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

OC000000093174404

Date Mailed: 08/02/2017

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings are not in compliance with 37 CFR 1.84 because figures 2-5 contain figure or view numbers that have incorrect orientation. Reference characters, sheet numbers, and view numbers must be oriented in the same direction as the view. See 37 CFR 1.84(p)(1).

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Christine Bjoern Jensen
  Mads Frederik Rasmussen
  Milan Zdravkovic
  Peter Kristensen

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0080

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/erimando/

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0081

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/656,042	07/21/2017	1629	1740	8545US02	10	1

CONFIRMATION NO. 9712

FILING RECEIPT

23650
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

OC000000093174403

Date Mailed: 08/02/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Christine Bjoern Jensen, Charlottenlund, DENMARK;
Mads Frederik Rasmussen, Copenhagen OE, DENMARK;
Milan Zdravkovic, Holte, DENMARK;
Peter Kristensen, Broenshoej, DENMARK;

Applicant(s)

Novo Nordisk A/S, Bagsvaerd, DENMARK;

Power of Attorney: The patent practitioners associated with Customer Number 23650

Domestic Priority data as claimed by applicant

This application is a CON of 14/409,493 12/19/2014
which is a 371 of PCT/EP2013/063004 06/21/2013
which claims benefit of 61/708,162 10/01/2012
and claims benefit of 61/694,837 08/30/2012

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
EUROPEAN PATENT OFFICE (EPO) 12186781.6 10/01/2012
EUROPEAN PATENT OFFICE (EPO) 12174535.0 07/01/2012

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0082

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

Request to Retrieve - This application either claims priority to one or more applications filed in an intellectual property Office that participates in the Priority Document Exchange (PDX) program or contains a proper **Request to Retrieve Electronic Priority Application(s)** (PTO/SB/38 or its equivalent). Consequently, the USPTO will attempt to electronically retrieve these priority documents.

If Required, Foreign Filing License Granted: 08/01/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/656,042**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No

Title

Use of Long-Acting GLP-1 Peptides

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0083

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15656042
Filing Date	2017-07-21
First Named Inventor	Christine Bjoern Jensen
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	8545US02

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2409349	RU	C2	2011-01-20	Mannkajnd Corp	corresponds to US7,799,344	☒
	2	2413530	RU	C2	2011-03-10	Novo Nordiks As	corresponds to US8,748,376	☒

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0084

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15656042
	Filing Date	2017-07-21
	First Named Inventor	Christine Bjoern Jensen
	Art Unit	1629
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	8545US02

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0085

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15656042
	Filing Date	2017-07-21
	First Named Inventor	Christine Bjoern Jensen
	Art Unit	1629
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	8545US02

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Leon Y. Lum/	Date (YYYY-MM-DD)	2017-09-29
Name/Print	Leon Y. Lum	Registration Number	62,124

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0086

Docket No.: 8545US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christine Bjoern Jensen et al.

Application No.: 15/656,042 | Confirmation No.: 9712

Filed: July 21, 2017 | Art Unit: 1629

For: Use of Long-Acting GLP-1 Peptides | Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits (37 C.F.R. § 1.97(b)(3)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0087

with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

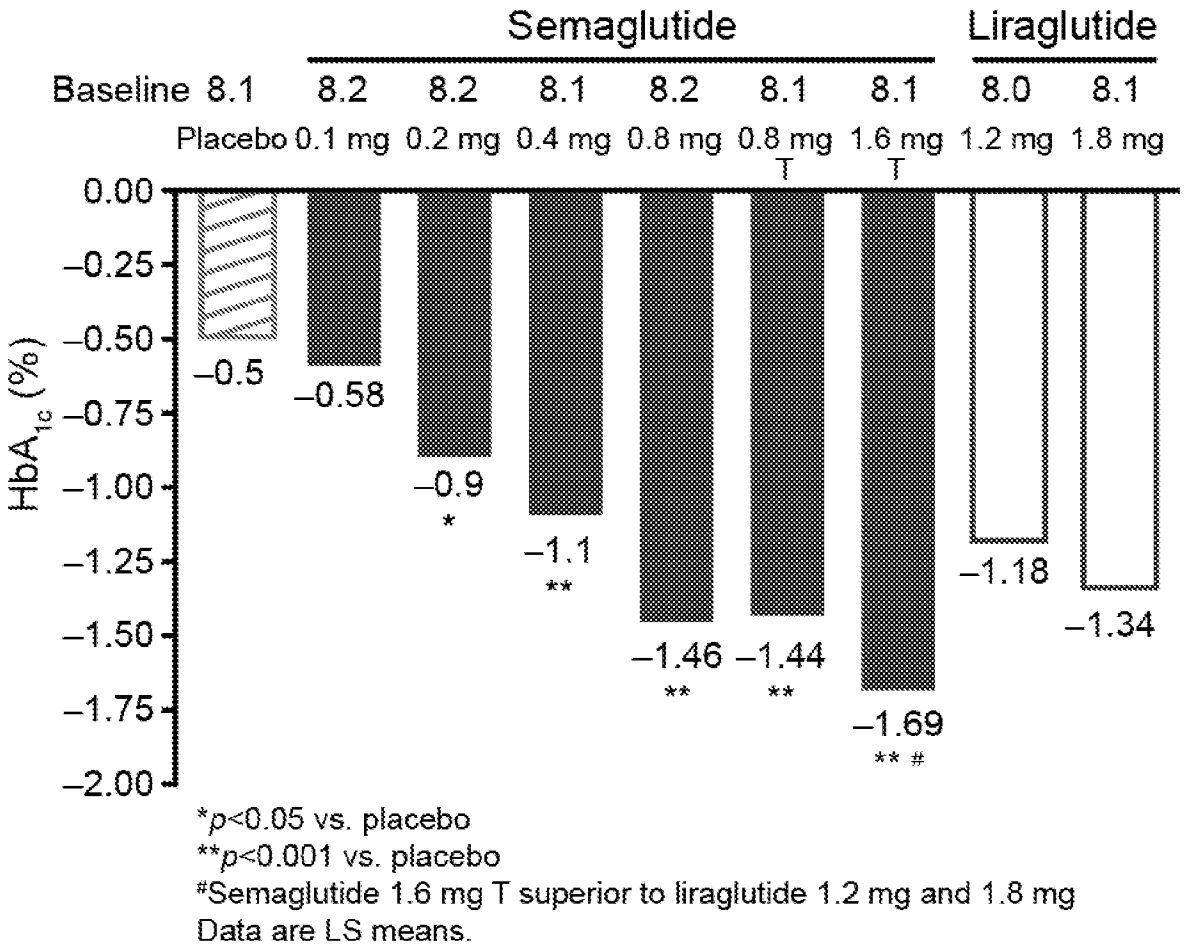
Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 14-1447, under Order No. 8545US02 from which the undersigned is authorized to draw.

Dated: September 29, 2017

Respectfully submitted,

Electronic signature: /Leon Y. Lum/
Leon Y. Lum
Registration No.: 62,124
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536
(609) 987-5800
Attorney For Applicant

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0088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Liraglutide
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8.2
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0.2 mg
0.4 mg
0.8 mg
0.8 mg T
1.6 mg T
1.2 mg
1.8 mg
HbA1c (%)
0.00
–0.25
–0.50
–0.75
–1.00
–1.25
–1.50
–1.75
–2.00
–0.5
–0.58
–0.9 *
–1.1 **
–1.46 **
–1.44 **
–1.69 ** #
–1.18
–1.34
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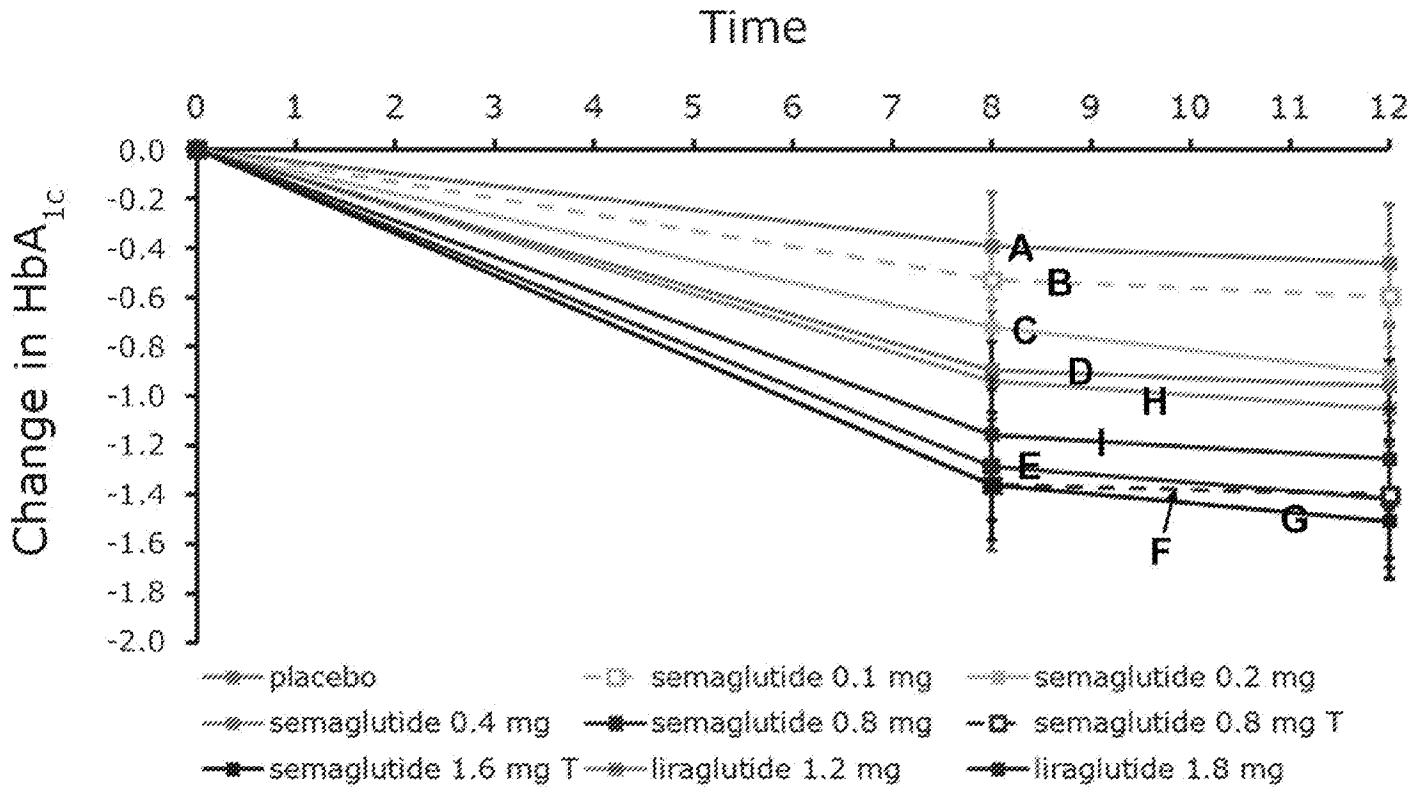
Fig. 1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4
5
6
7
8
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-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
-2.0
A
B
C
D
H
I
E
F
G
placebo
semaglutide 0.1 mg
semaglutide 0.2 mg
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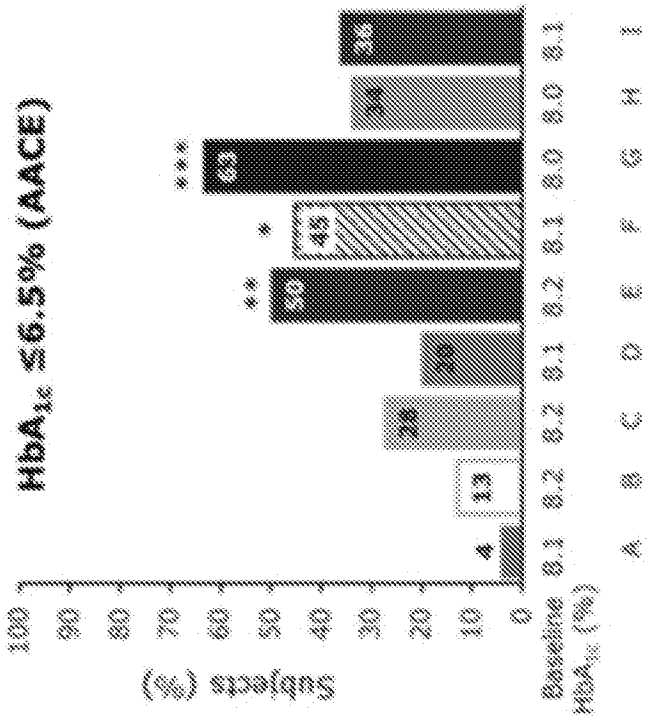
Fig. 2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8.2
8.2
8.1
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8.1
A
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Fig. 3A

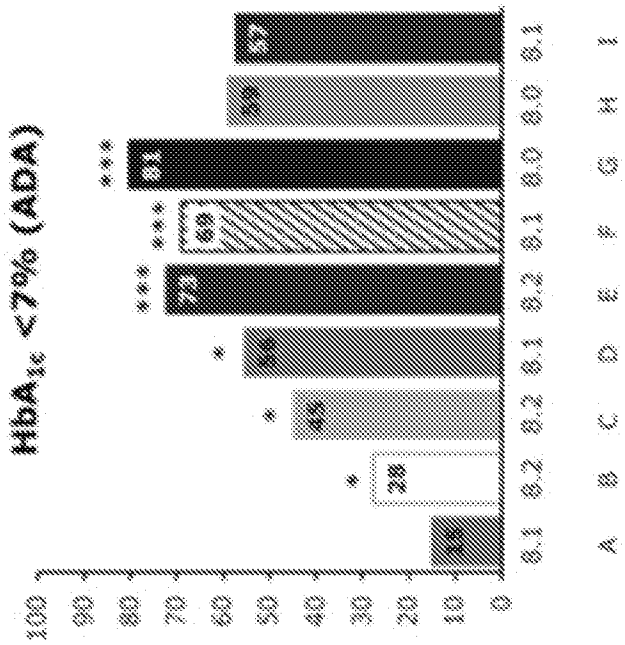
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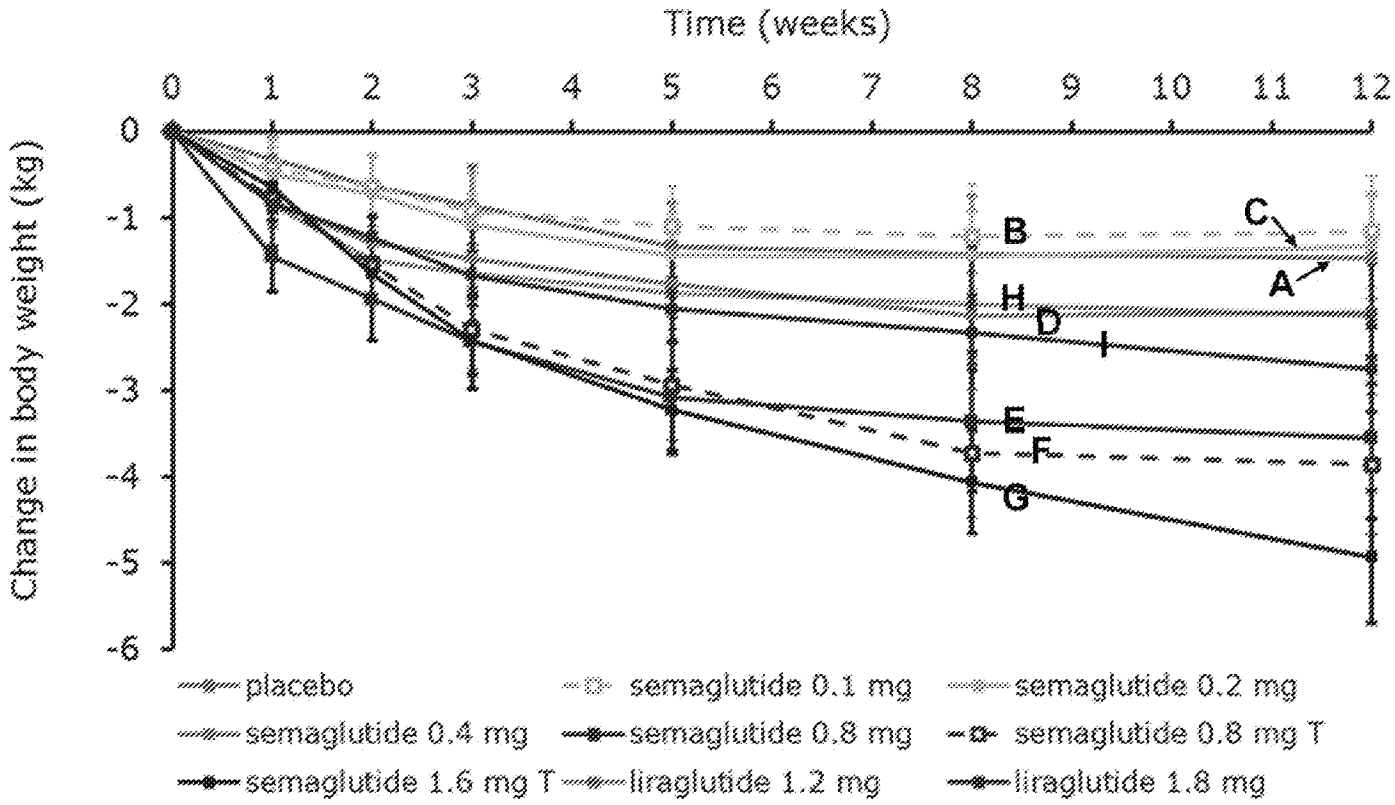
Fig. 3 B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0
1
2
3
4
5
6
7
8
9
10
11
12
Change in body weight (kg)
0
-1
-2
-3
-4
-5
-6
A
B
C
D
E
F
G
H
I
placebo
semaglutide 0.1 mg
semaglutide 0.2 mg
semaglutide 0.4 mg
semaglutide 0.8 mg
semaglutide 0.8 mg T
semaglutide 1.6 mg T
liraglutide 1.2 mg
liraglutide 1.8 mg

Fig. 4

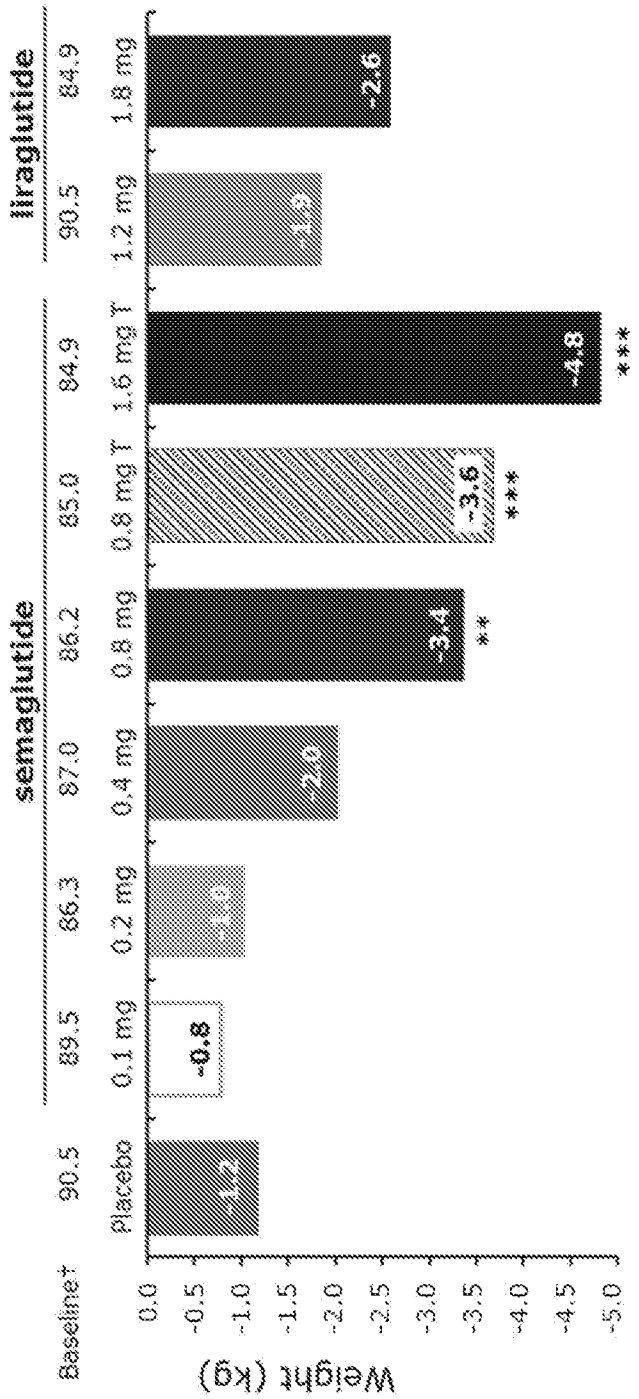
Weight (kg)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
Baseline†
90.5
Placebo
-1.2
89.5
0.1 mg
-0.8
86.3
0.2 mg
-1.9
87.0
0.4 mg
-2.0
semaglutide
86.2
0.8 mg
-3.4
**
85.0
0.8 mg T
-3.6
***
84.9
1.6 mg T
-4.8
***
liraglutide
90.5
1.2 mg
-1.6
84.9
1.8 mg
-2.6

Fig. 5

Docket No.: 8545US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christine Bjoern Jensen et al.

Application No.: 15/656,042 | Confirmation No.: 9712

Filed: July 21, 2017 | Art Unit: 1629

For: Use of Long-Acting GLP-1 Peptides | Examiner: Not Yet Assigned

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Drawings begin on page 2 of this paper and include an attached replacement sheet .

Remarks/Arguments begin on page 3 of this paper.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0095

AMENDMENTS TO THE DRAWINGS

The Notice to File Corrected Application Papers mailed August 2, 2017 objected to the orientation of the figure numbers in figures 2 – 5. Applicants have re-oriented the figure numbers to comply with 37 CFR 1.84 as per the Office Action request.

No New Matter is Added.

Attachment: Replacement sheets

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0096

REMARKS

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 14-1447, under Order No. 8545US02 from which the undersigned is authorized to draw.

Dated: September 29, 2017

Respectfully submitted,

Electronic signature: /Leon Y. Lum/
Leon Y. Lum
Registration No.: 62,124
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536
(609) 987-5800
Attorney For Applicant

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0097

DocCode – SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 15656042 Document Date: 10/02/2017

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0098

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02

CONFIRMATION NO. 9712

FORMALITIES LETTER

23650
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

OC000000094505862

Date Mailed: 10/04/2017

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The application contains drawings and the specification contains a brief description of the drawings. However, the specification does not contain a brief description of the several views of the drawings as required by 37 CFR 1.74 and 37 CFR 1.77(b)(7) and/or a drawing(s) has not been labeled in accordance with 37 CFR 1.84(u)(1). If each figure is not labeled "Fig." with a consecutive Arabic numeral (1, 2, etc.) or an Arabic numeral and capital letter in the English alphabet (A, B, etc.), then the drawing(s) must be relabeled in accordance with 37 CFR 1.84(u)(1). In addition, if the brief description of the several views of the drawings does not refer to the figure(s) as properly labeled, then the specification must be amended to correspond to the figure(s) as properly labeled and a substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Christine Bjoern Jensen
  Mads Frederik Rasmussen
  Milan Zdravkovic

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0099

Peter Kristensen

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/zretta/

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0100

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02

CONFIRMATION NO. 9712

23650
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

WITHDRAWAL NOTICE

OC000000094505803

Date Mailed: 10/04/2017

Letter Regarding a New Notice and/or the Status of the Application

If a new notice or Filing Receipt is enclosed, applicant may disregard the previous notice mailed on 08/02/2017. The time period for reply runs from the mail date of the new notice. Within the time period for reply, applicant is required to file a reply in compliance with the requirements set forth in the new notice to avoid abandonment of the application.

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web. https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If the reply is not filed electronically via EFS-Web, the reply must be accompanied by a copy of the new notice.

If the Office previously granted a petition to withdraw the holding of abandonment or a petition to revive under 37 CFR 1.137, the status of the application has been returned to pending status.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/zretta/

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/656,042	07/21/2017	1629	1740	8545US02	10	1

CONFIRMATION NO. 9712

FILING RECEIPT

23650
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

OC000000094505861

Date Mailed: 10/04/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Christine Bjoern Jensen, Charlottenlund, DENMARK;
Mads Frederik Rasmussen, Copenhagen OE, DENMARK;
Milan Zdravkovic, Holte, DENMARK;
Peter Kristensen, Broenshoej, DENMARK;

Applicant(s)

Novo Nordisk A/S, Bagsvaerd, DENMARK;

Power of Attorney: The patent practitioners associated with Customer Number 23650

Domestic Priority data as claimed by applicant

This application is a CON of 14/409,493 12/19/2014 PAT 9764003
which is a 371 of PCT/EP2013/063004 06/21/2013
which claims benefit of 61/708,162 10/01/2012
and claims benefit of 61/694,837 08/30/2012

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
EUROPEAN PATENT OFFICE (EPO) 12186781.6 10/01/2012
EUROPEAN PATENT OFFICE (EPO) 12174535.0 07/01/2012

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0102

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

Request to Retrieve - This application either claims priority to one or more applications filed in an intellectual property Office that participates in the Priority Document Exchange (PDX) program or contains a proper **Request to Retrieve Electronic Priority Application(s)** (PTO/SB/38 or its equivalent). Consequently, the USPTO will attempt to electronically retrieve these priority documents.

If Required, Foreign Filing License Granted: 08/01/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/656,042**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No

Title

Use of Long-Acting GLP-1 Peptides

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0103

Docket No.: 8545US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christine Bjoern Jensen et al.

Application No.: 15/656,042 | Confirmation No.: 9712

Filed: July 21, 2017 | Art Unit: 1629

For: Use of Long-Acting GLP-1 Peptides | Examiner: Not Yet Assigned

DECLARATION TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Applicant submits a Declaration signed and dated by Inventors for the above-captioned application. Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 14-1447, under Order No. 8545US02 from which the undersigned is authorized to draw.

Dated: November 30, 2017

Respectfully submitted,

Electronic signature: /Leon Y. Lum/
Leon Y. Lum
Registration No.: 62,124
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536
(609) 987-5800
Attorney For Applicant

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0104

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention: USE OF LONG-ACTING GLP-1 PEPTIDES

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 14/409,493

filed on December 19, 2014.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: CHRISTINE B. JENSEN Date (Optional): 22-Jan-2015

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2

PTO/AIA/01 (08-12)
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LEGAL NAME OF INVENTOR

Inventor: MADS F. RASMUSSEN Date (Optional): 22-JAN-2015

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

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LEGAL NAME OF INVENTOR

Inventor: MILAN ZDRAVKOVIC Date (Optional): 26 Jan 2015

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/01 (08-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention: USE OF LONG-ACTING GLP-1 PEPTIDES

As the below named inventor, I hereby declare that:

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☒ United States application or PCT international application number 14/409,493 filed on December 19, 2014.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: PETER KRISTENSEN Date (Optional): 2-FEB-2015

Signature: Peter Kristensen

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Docket No.: 8545US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christine Bjoern Jensen et al.

Application No.: 15/656,042 | Confirmation No.: 9712

Filed: July 21, 2017 | Art Unit: 1629

For: Use of Long-Acting GLP-1 Peptides | Examiner: Not Yet Assigned

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

INTRODUCTORY COMMENTS

In response to the Notice to File Corrected Application Papers dated October 4, 2017 ("Notice") and prior to examination on the merits, please amend the above-identified U.S. patent application as follows and consider the Remarks herein:

Amendments to the Drawings begin on page 2 of this paper and include an attached replacement sheet.

Amendments to the Specification begin on page 3 of this paper.

Remarks begin on page 4 of this paper.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0109

AMENDMENTS TO THE DRAWINGS

Replacement Drawings were filed on October 2, 2017, addressing an "incorrect orientation" issue presented in an earlier Notice to File Corrected Application Papers, mailed August 2, 2017. The current Notice, objecting to the drawings/specification and stating that "drawings submitted are not acceptable," was mailed thereafter. Because the current Notice appears to base the objection not on "incorrect orientation," but on a discrepancy between the Drawings and Specification, it is believed that the Replacement Drawings filed on October 2, 2017 were proper and sufficiently addressed the "incorrect orientation" issue. However, to the extent that the Replacement Drawings were not entered due to the discrepancy issue, the Replacement Drawings are hereby submitted again for entry, along with an amendment to the specification to address the discrepancy issue.

No new matter is added.

Attachment: Replacement sheets

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0110

AMENDMENTS TO THE SPECIFICATION

The Notice objected to a discrepancy between the specification and drawings, in an apparent reference to the Drawings reciting "Fig. 3A" and "Fig. 3B," but the specification reciting only "Fig. 3" on page 2. In response to this objection, please amend the specification as indicated below. No new matter is added.

At page 2, line 21, please amend the specification as follows:

Fig. 3 shows subjects reaching the AACE (Fig. 3A) or ADA (Fig. 3B) criteria for glycaemic control. The number of patients reaching the criteria per treatment is indicated in each bar. The treatments are placebo (A); semaglutide 0.1 mg (B), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I). *$p<0.05$ vs. placebo; **$p<0.001$ vs. placebo; ***$p<0.0001$ vs. placebo (based on adjusted means). Data are FAS LOCF. The estimates are from a logistic regression model treatment, country and previous treatment as fixed effects and baseline HbA1c as covariate. ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0111

REMARKS

In view of the foregoing amendment to the Specification and concurrent submission of Replacement Drawings, Applicant respectfully requests withdrawal of any objection to the Drawings and Specification. Further, Applicant believes the application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 14-1447, under Order No. 8545US02 from which the undersigned is authorized to draw.

Dated: November 30, 2017

Respectfully submitted,

Electronic signature: /Leon Y. Lum/
Leon Y. Lum
Registration No.: 62,124
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536
(609) 987-5800
Attorney For Applicant

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0112

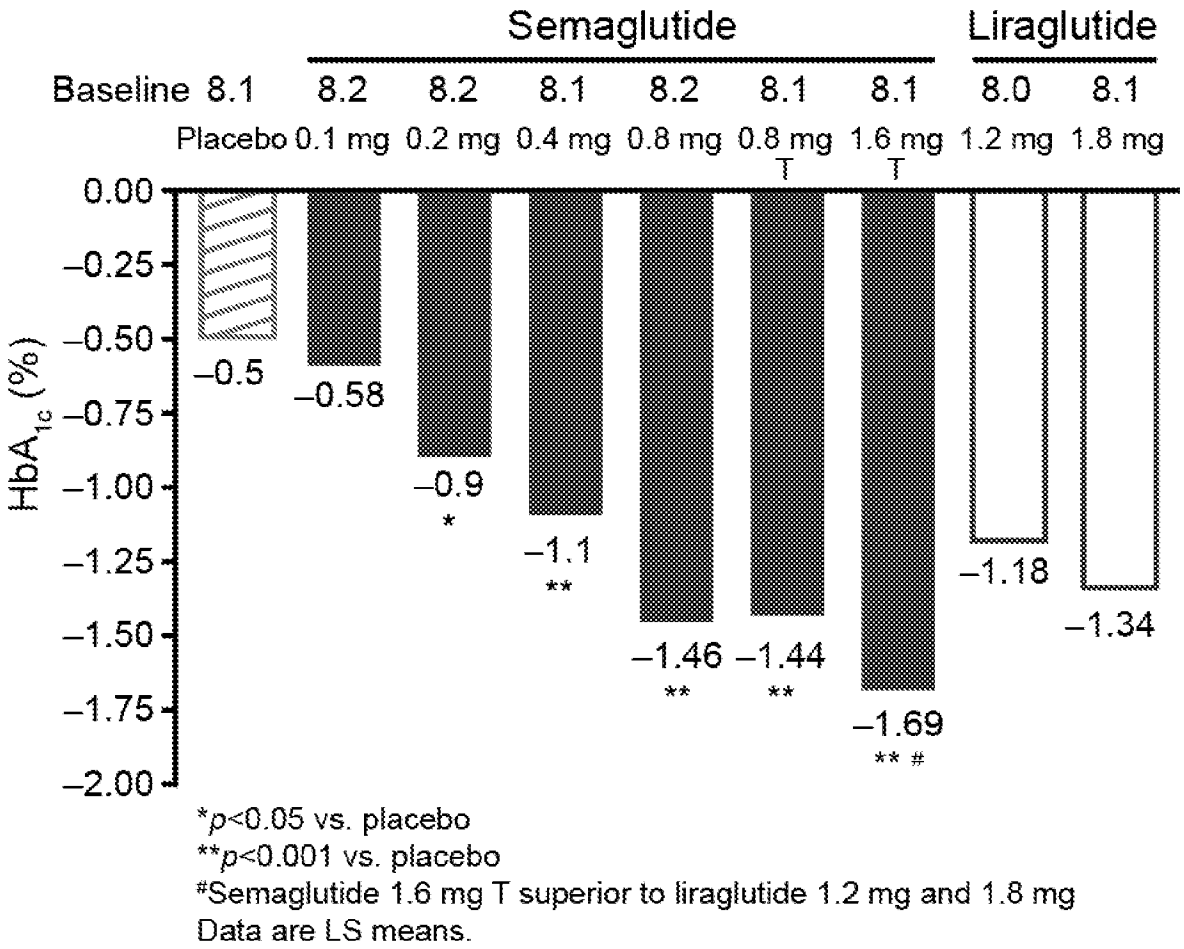
Semaglutide
Liraglutide
Baseline 8.1
8.2
8.2
8.1
8.2
8.1
8.1
8.0
8.1
Placebo
0.1 mg
0.2 mg
0.4 mg
0.8 mg
0.8 mg T
1.6 mg T
1.2 mg
1.8 mg
HbA1c (%)
0.00
–0.25
–0.50
–0.75
–1.00
–1.25
–1.50
–1.75
–2.00
–0.5
–0.58
–0.9 *
–1.1 **
–1.46 **
–1.44 **
–1.69 ** #
–1.18
–1.34
*p<0.05 vs. placebo
**p<0.001 vs. placebo
#Semaglutide 1.6 mg T superior to liraglutide 1.2 mg and 1.8 mg
Data are LS means.

Fig. 1

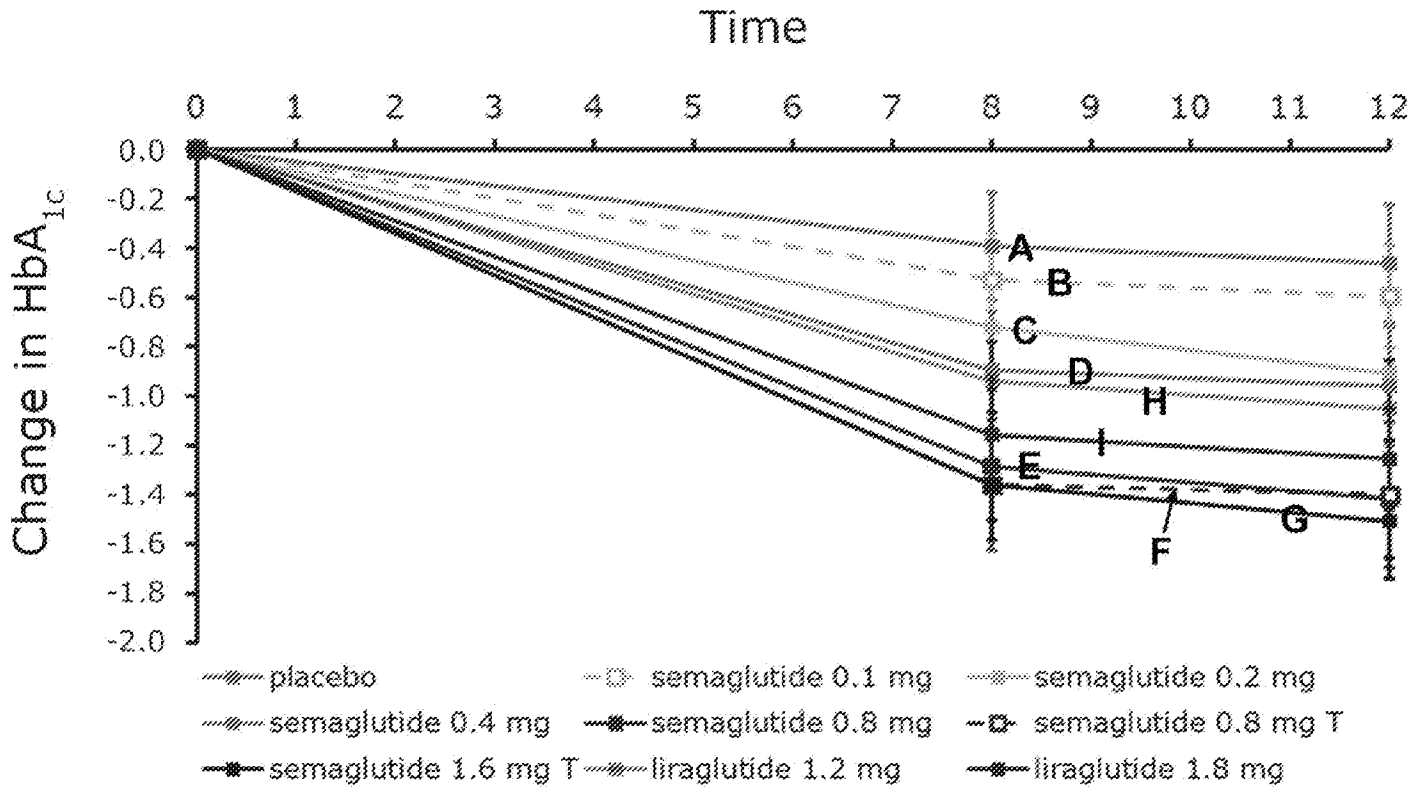
Time
0
1
2
3
4
5
6
7
8
9
10
11
12
Change in HbA1c
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
-2.0
A
B
C
D
H
I
E
F
G
placebo
semaglutide 0.1 mg
semaglutide 0.2 mg
semaglutide 0.4 mg
semaglutide 0.8 mg
semaglutide 0.8 mg T
semaglutide 1.6 mg T
liraglutide 1.2 mg
liraglutide 1.8 mg

Fig. 2

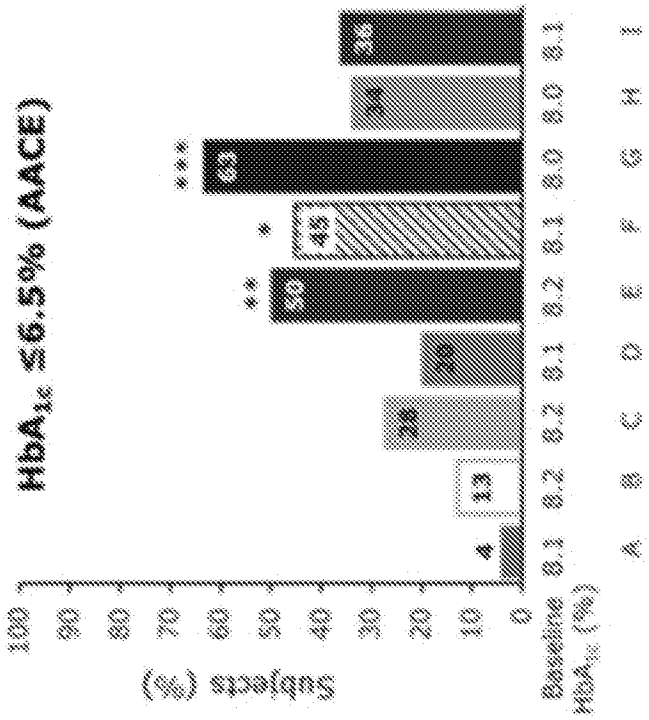
HbA1c ≤6.5% (AACE)
Subjects (%)
100
90
80
70
60
50
40
30
20
10
0
Baseline HbA1c (%)
8.1
8.2
8.2
8.1
8.2
8.1
8.0
8.0
8.1
A
B
C
D
E
F
G
H
I
4
13
28
20
50
45
63
34
35
**
*
***

Fig. 3A

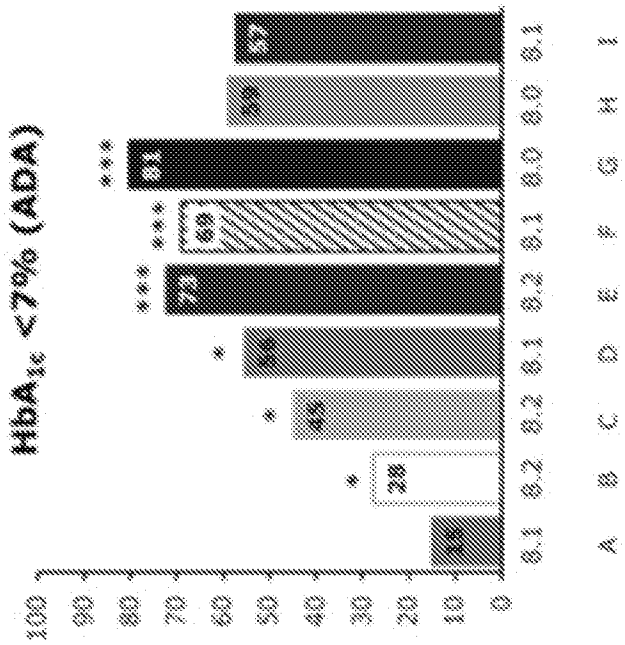
HbA1c <7% (ADA)
100
90
80
70
60
50
40
30
20
10
0
28
45
78
69
81
59
57
8.1
8.2
8.2
8.1
8.2
8.1
8.0
8.0
8.1
A
B
C
D
E
F
G
H
I

Fig. 3 B

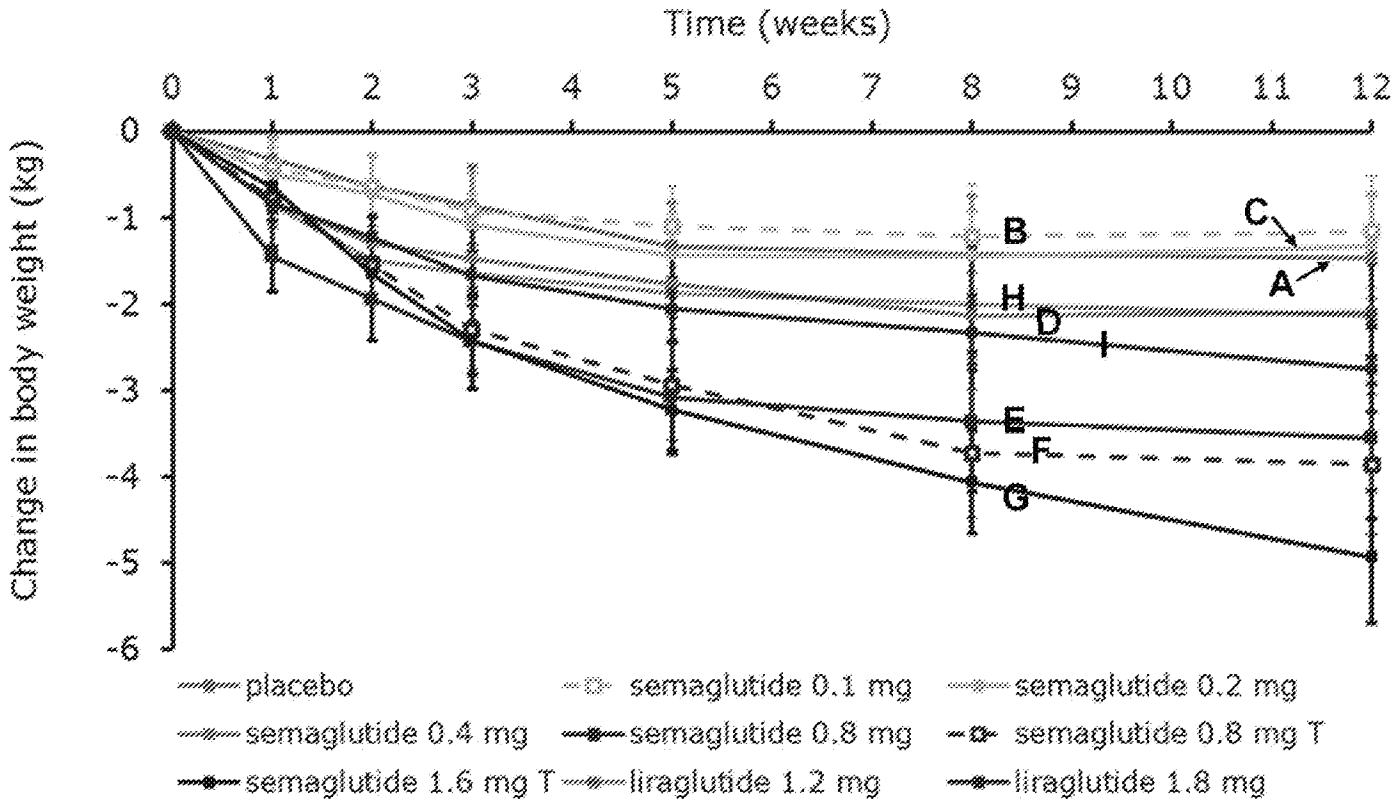
Time (weeks)
0
1
2
3
4
5
6
7
8
9
10
11
12
Change in body weight (kg)
0
-1
-2
-3
-4
-5
-6
A
B
C
D
E
F
G
H
I
placebo
semaglutide 0.1 mg
semaglutide 0.2 mg
semaglutide 0.4 mg
semaglutide 0.8 mg
semaglutide 0.8 mg T
semaglutide 1.6 mg T
liraglutide 1.2 mg
liraglutide 1.8 mg

Fig. 4

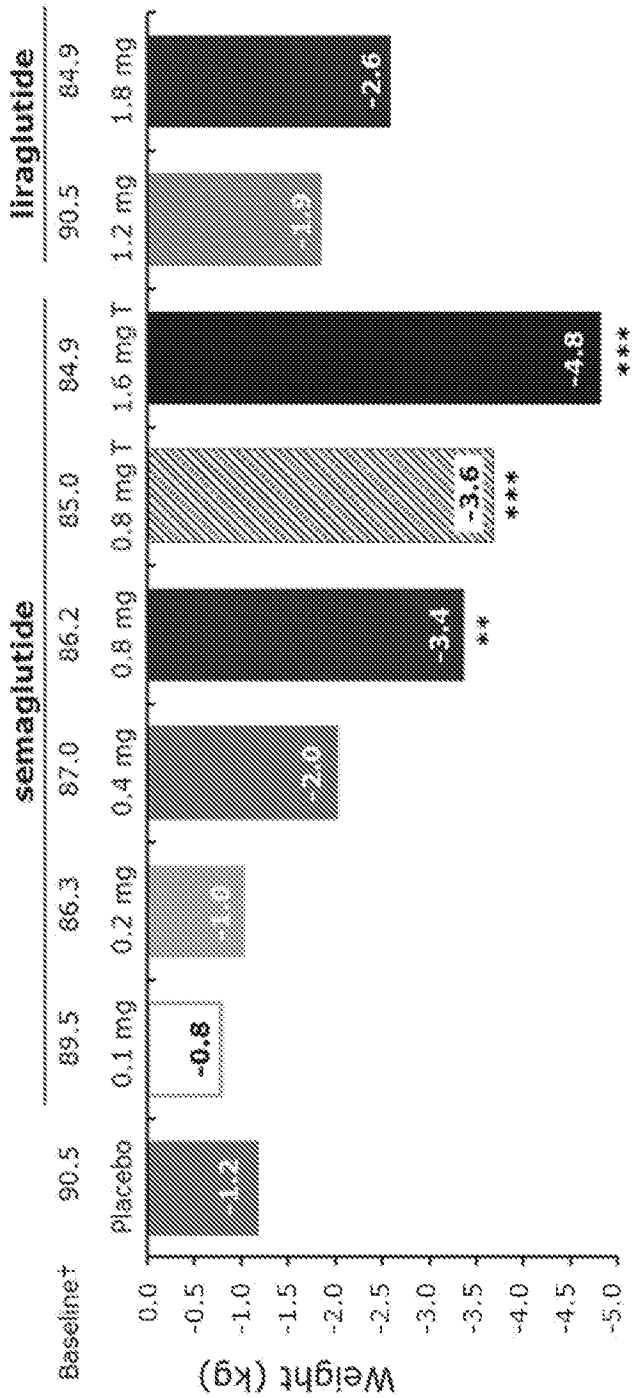
semaglutide
liraglutide
Baseline†
90.5
Placebo
89.5
0.1 mg
86.3
0.2 mg
87.0
0.4 mg
86.2
0.8 mg
85.0
0.8 mg T
84.9
1.6 mg T
90.5
1.2 mg
84.9
1.8 mg
Weight (kg)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
-1.2
-0.8
-2.0
-3.1
**
-3.6
***
-4.8
***
-2.6

Fig. 5

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02

CONFIRMATION NO. 9712

MISCELLANEOUS NOTICE

23650
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

OC000000095850704

Date Mailed: 12/05/2017

A communication which cannot be delivered in electronic form has been mailed to the applicant.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0119

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02

CONFIRMATION NO. 9712

FORMALITIES LETTER

OC000000095850823

23650
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

Date Mailed: 12/05/2017

NOTICE OF INCOMPLETE REPLY (NONPROVISIONAL)

Filing Date Granted

The U.S. Patent and Trademark Office has received your reply on 12/01/2017 to the Notice to File Missing Parts (Notice) mailed 10/04/2017 and it has been entered into the nonprovisional application. The reply, however, does not include the following items required in the Notice. A complete reply must be timely filed to prevent ABANDONMENT of the above-identified application. Replies should be mailed to: Mail Stop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450.

Applicant is given **TWO MONTHS** from the date of the Notice to File Missing Parts (Notice) mailed 10/04/2017 within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

Items Required to Avoid Abandonment:

The required items noted below SHOULD be filed along with any items required above. The filing date of this nonprovisional application will be the date of receipt of the items required above.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The application contains drawings and the specification contains a brief description of the drawings. However, the specification does not contain a brief description of the several views of the drawings as required by 37 CFR 1.74 and 37 CFR 1.77(b)(7) and/or a drawing(s) has not been labeled in accordance with 37 CFR 1.84(u)(1). If each figure is not labeled "Fig." with a consecutive Arabic numeral (1, 2, etc.) or an Arabic numeral and capital letter in the English alphabet (A, B, etc.), then the drawing(s) must be relabeled in accordance with 37 CFR 1.84(u)(1). In addition, if the brief description of the several views of the drawings does not refer to the figure(s) as properly labeled, then the specification must be amended to correspond to the figure(s) as properly labeled and a substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0120

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02

CONFIRMATION NO. 9712

OC000000095850704

23650
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

Date Mailed: 12/5/2017

NOTICE OF INCOMPLETE REPLY

Filing Date Granted

Applicant's reply to the Notice mailed on 10/4/2017 was received in the U.S. Patent and Trademark Office on 12/1/2017 and has been entered into the application. The reply, however, does not include the following item(s) required in the Notice.

The period for reply continues to run from the mailing date of the prior Notice. The item(s) listed below must be timely filed to avoid abandonment of the application. No new time period for reply is provided in this communication. If the period for reply set forth in the prior Notice has expired, this application will become abandoned unless applicant: (1) submits the following checked item(s), **and** (2) obtains an extension of time under 37 CFR 1. 136(a) (including the appropriate fee (37 CFR 1.17(a)). In no case may an applicant obtain an extension of time for more than FIVE (5) MONTHS beyond the date for reply set forth in the prior Notice.

A complete reply which includes the following checked item(s) must be timely filed to prevent ABANDONMENT of the above-identified application:

- ☒ A substitute specification.
- ☒ A statement that the substitute specification contains no new matter.
- ☐ A replacement abstract commencing on a separate sheet in compliance with 37 CFR 1.72(b) and 1.121 (deleting the drawings or flow diagrams).
- ☐ New and replacement drawing sheets.
- ☐ Replacement drawing sheets with the figures renumbered.
- ☐ A complete claim listing or a replacement claim listing with the claims renumbered.
- ☐ An amendment to the claims in compliance with 37 CFR 1.121 (deleting the drawings or flow diagrams).
- ☐ A replacement transmittal letter listing all of the files except the missing or unreadable file.
- ☐ A duplicate copy of the CD.
- ☐ A statement that the replacement CD contains no new matter.

Rev. 12/2008

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

Replies should be mailed to: Mail Stop Missing Parts

Commissioner for Patents

P.O. Box 1450

Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web. https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web, please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

Application Assistance Unit (571) 272-4200

Rev. 12/2008

DocCode – SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 15656042 Document Date: 12/13/2017

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0123

Docket No.: 8545US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christine Bjoern Jensen et al.

Application No.: 15/656,042 | Confirmation No.: 9712

Filed: July 21, 2017 | Art Unit: 1629

For: Use of Long-Acting GLP-1 Peptides | Examiner: Not Yet Assigned

RESPONSE TO INCOMPLETE REPLY

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

INTRODUCTORY COMMENTS

In response to the Notice of Incomplete Reply dated December 5, 2017 ("Notice") and prior to examination on the merits, please amend the above-identified U.S. patent application as follows and consider the Remarks herein:

Amendments to the Drawings begin on page 2 of this paper and include an attached replacement sheet.

Amendments to the Specification begin on page 3 of this paper.

Remarks begin on page 4 of this paper.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0124

AMENDMENTS TO THE DRAWINGS

To the extent that the concurrently amended Specification does not cure the Office's objection to the specification and drawings, Replacement Drawings are hereby filed. These drawings are the same drawings filed in the previous response on December 1, 2017, which were filed in an overabundance of caution for the reasons presented in that response.

No new matter is added.

Attachment: Replacement sheets

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0125

AMENDMENTS TO THE SPECIFICATION

The Notice objected to a discrepancy between the specification and drawings, in an apparent reference to the Specification reciting a single "Fig. 3" and the drawings reciting "Fig. 3A" and "Fig. 3B". Although Applicant disagrees with the objection, because the Specification does, in fact, recite "Fig. 3A" and "Fig. 3B," Applicant hereby amends the specification as indicated in the marked-up and clean version of the specification, for greater clarity.

No new matter is added.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0126

REMARKS

In view of the foregoing amendment to the Specification and concurrent submission of Replacement Drawings, Applicant respectfully requests withdrawal of any objection to the Drawings and Specification. Further, Applicant believes the application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 14-1447, under Order No. 8545US02 from which the undersigned is authorized to draw.

Dated: December 11, 2017

Respectfully submitted,

Electronic signature: /Leon Y. Lum/
Leon Y. Lum
Registration No.: 62,124
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536
(609) 987-5800
Attorney For Applicant

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0127

USE OF LONG-ACTING GLP-1 PEPTIDES

The present invention relates to improved uses of GLP-1 peptides in therapy.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of US Application 14/409,493, filed December 19, 2014, which is a 35 U.S.C. § 371 National Stage application of International Application PCT/EP2013/063004 (WO 2014/005858), filed JUNE 21, 2013, which claimed priority of European Patent Application 12174535.0, filed JULY 1, 2012 and European Patent Application 12186781.6, filed OCTOBER 1, 2012; this application claims priority under 35 U.S.C. § 119 of U.S. Provisional Application 61/694,837; filed AUGUST 30, 2012 and U.S. Provisional Application 61/708,162; filed OCTOBER 1, 2012.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 17, 2013 and amended on July 12, 2017, is named 8545US02_SeqList.txt and is 7,975 bytes in size.

SUMMARY

In one embodiment the invention relates to a method for a) reduction of HbA1c; b) prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) prevention or treatment of obesity, reducing body weight and/or food intake, or inducing satiety; wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof, wherein said GLP-1 agonist i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and iii) is administered once weekly or less often.

In one embodiment the invention relates to a GLP-1 agonist for use in a) the reduction of HbA1c; b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety; wherein said use comprises administration of said GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week, and wherein said GLP-1 agonist and/or administration optionally is as defined herein.

In one embodiment the invention relates to a composition comprising a GLP-1 agonist for use in a) the reduction of HbA1c; b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety; wherein said GLP-1 agonist i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); and ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and wherein said composition is administered once weekly or less often, and wherein said GLP-1 agonist and/or administration optionally is as defined herein.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows change in HbA1c following subcutaneous administration of placebo, semaglutide, or liraglutide to human subjects. *p<0.05 vs. placebo; **p<0.001 vs. placebo (based on adjusted means). Baseline values are for information only: data are model-adjusted for baseline HbA1c. Data are model-adjusted LS means, FAS LOCF. The estimates are from an ANOVA model with treatment, country and previous treatment as fixed effects and baseline HbA1c as covariate.

Fig. 2 shows mean change in HbA1c from baseline versus time; data are mean (1.96SE), FAS LOCF. The treatments are placebo (A); semaglutide 0.1 mg (B, dashed line), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F, dashed line), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I).

Fig. 3A and Fig. 3B show subjects reaching the AACE (Fig. 3A) or ADA (Fig. 3B) criteria for glycaemic control. The number of patients reaching the criteria per treatment is indicated in each bar. The treatments are placebo (A); semaglutide 0.1 mg (B), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I). *p<0.05 vs. placebo; **p<0.001 vs. placebo; ***p<0.0001 vs. placebo (based on adjusted means). Data are FAS LOCF. The estimates are from a logistic regression model treatment, country and previous treatment as fixed effects and baseline HbA1c as covariate. ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists.

Fig. 4 shows mean body weight change versus time; data are mean (1.96SE), FAS LOCF. The treatments are placebo (A); semaglutide 0.1 mg (B, dashed line), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F, dashed line), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I).

Fig. 5 shows body weight change from baseline at week 12. **p<0.001 vs. placebo; ***p<0.0001 vs. placebo (based on adjusted means. †: Baseline values for information only:

data are model-adjusted for baseline weight. Data are model-adjusted LS means, FAS LOCF. The estimates are from an ANOVA model with treatment, country and previous treatment as fixed effects and baseline weight as covariate.

SE: Standard error. FAS: Full analysis set. LOCF: Last observation carried forward.

DESCRIPTION

The present invention relates to an improved use of GLP-1 agonists in therapy. In one embodiment the invention relates to certain dosage regimes of GLP-1 agonists which provide improved effect in diseases or conditions, such as prevention and/or treatment of type 2 diabetes and obesity. In one embodiment the methods of the present invention provides surprisingly showed improved reduction of HbA1c and reduction of body weight. In one embodiment the GLP-1 agonist is administered in an amount which provides an improved a) reduction in HbA1c or b) reduction in body weight compared to administration of 1.8 mg liraglutide or less, such as 0.8 mg liraglutide or less, per day.

In one embodiment the invention relates to a method for reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the method is for reduction of HbA1c. In one embodiment the method is for prevention or treatment of type 2 diabetes. In one embodiment the method is for prevention or treatment of hyperglycemia. In one embodiment the method is for prevention or treatment of impaired glucose tolerance. In one embodiment the method is for prevention or treatment of non-insulin dependent diabetes. In one embodiment the method of the invention comprises delaying or preventing diabetic disease progression. In one embodiment a HbA1c level below 7% is achieved. In one embodiment the level of HbA1c is determined according to the method defined by the Diabetes Control and Complications Trial (DCCT). In one embodiment the level of HbA1c is determined according to the method defined by the International Federation of Clinical Chemistry (IFCC).

In one embodiment the invention relates to a method for treating or preventing obesity, for reducing body weight and/or food intake, or for inducing satiety, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the method is for prevention or treatment of obesity. In one embodiment the

method is for reducing body weight and/or food intake. In one embodiment the method is for inducing satiety.

In one embodiment the GLP-1 agonist has a half-life of at least 24 hours, such as at least 48 hours, at least 60 hours, or at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours, or optionally at least 120 hours, at least 132 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

In one embodiment the GLP-1 agonist is administered twice weekly or less often, once weekly or less often, or once weekly or less often. In one embodiment the GLP-1 agonist is administered once every secondly week or less often, once every third week or less often, or once a month or less often.

In one embodiment the GLP-1 agonist is administered in an amount per week of at least 0.8 mg, at least 0.9 mg, or at least 1.0 mg. In one embodiment the GLP-1 agonist is administered in an amount per week of at least 1.1 mg, at least 1.2 mg, or at least 1.3 mg. In one embodiment the GLP-1 agonist is administered in an amount per week of at least 1.4 mg, at least 1.5 mg, or at least 1.6 mg.

In one embodiment the GLP-1 agonist is administered in an amount per week equivalent to at least 0.8 mg, at least 0.9 mg, or at least 1.0 mg semaglutide. In one embodiment the GLP-1 agonist is administered in an amount per week equivalent to at least 1.1 mg, at least 1.2 mg, or at least 1.3 mg semaglutide. In one embodiment the GLP-1 agonist is administered in an amount per week equivalent to at least 1.4 mg, at least 1.5 mg, or at least 1.6 mg semaglutide.

In one embodiment the GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

In one embodiment the GLP-1 agonist is administered by parenteral administration, such as subcutaneous injection.

In one embodiment the GLP-1 agonist is a GLP-1 peptide. In one embodiment the GLP-1 peptide comprises no more than 5, such as no more than 4 or no more than 3, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37). In one embodiment the GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code.

In one embodiment the GLP-1 peptide is a DPPIV protected GLP-1 peptide. In one embodiment the GLP-1 peptide is DPPIV stabilised.

In one embodiment the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100 pM, optionally determined by Assay (I).

In one embodiment the invention relates to a GLP-1 agonist for use in the reduction of HbA1c or for use in the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to a GLP-1 agonist for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to a composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to a composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the GLP-1 agonist is administered with another therapeutic agent. Administration with another therapeutic agent may be carried out as administration of the GLP-1 agonist and the other therapeutic agent within the same therapeutic window (e.g. withinin a period of two weeks, a period of one week, or in a 96, 72, or 48 hour period, etc.). The treatment with a GLP-1 agonist according to the present invention may be combined with one or more additional therapeutic agents, e.g. selected from antidiabetic agents, antiobesity agents, appetite regulating agents, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity; examples of these therapeutic agents are: sulphonylureas, thiazolidinediones, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists, and DPP-IV (dipeptidyl peptidase-IV) inhibitors.

In one embodiment, as used herein, an “amount equivalent to” when used in relation to GLP-1 agonists refers to amounts of a first GLP-1 agonist and a second GLP-1 agonist having GLP-1 receptor potency (i.e. EC_{50}) within ±30%, such as within ±20% or within ±10%, of each other optionally determined by Assay (I) described herein and having a half-life within ±30%, such as within ±20% or within ±10%, of each other optionally determined by Assay (II) described herein.

In one embodiment an "effective amount" of a GLP-1 agonist as used herein means an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease or state and its complications. An amount adequate to accomplish this is defined as "effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary.

In one embodiment the term "treatment" or "treating" as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. In one embodiment the term "treatment" or "treating" is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications; to delay the progression of the disease, disorder, or condition; to alleviate or relieve the symptoms and complications; and/or, to cure or eliminate the disease, disorder, or condition as well as to prevent the condition. In one embodiment prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications.

In one embodiment the term "hydrophilic spacer" as used herein means a spacer that separates a peptide and an albumin binding residue with a chemical moiety which comprises at least 5 non- hydrogen atoms where 30-50% of these are either N or O.

In one embodiment the term "analogue" as used herein referring to a polypeptide means a modified peptide wherein one or more amino acid residues of the peptide have been substituted by other amino acid residues and/or wherein one or more amino acid residues have been deleted from the peptide and or wherein one or more amino acid residues have been added to the peptide. Such addition or deletion of amino acid residues can take place at the N-terminal of the peptide and/or at the C-terminal of the peptide. A simple system is used to

describe analogues: For example Arg^{34}GLP-1 (7-37) Lys designates a GLP-1 analogue wherein the naturally occurring lysine at position 34 has been substituted with arginine and a lysine residue has been added to the C-terminal (position 38).

In one embodiment the term "GLP-1 peptide" as used herein means GLP-1 (7-37), a GLP-1 analogue, a GLP-1 derivative or a derivative of a GLP-1 analogue.

In one embodiment the term "exendin-4 peptide" as used herein means exendin-4 (1-39), an exendin-4 analogue, an exendin-4 derivative or a derivative of an exendin-4 analogue.

In one embodiment the term “DPP-IV protected” as used herein referring to a polypeptide means a polypeptide which has been chemically modified in order to render said compound resistant to the plasma peptidase dipeptidyl aminopeptidase-4 (DPP-IV). The DPP-IV enzyme in plasma is known to be involved in the degradation of several peptide hormones, e.g. GLP-1, Exendin-4 etc. Thus a considerable effort is being made to develop GLP-1 agonists less susceptible to DPP-IV mediated hydrolysis in order to reduce the rate of degradation by DPP-IV.

The present invention also relates to a GLP-1 agonist of the invention, for use as a medicament. In particular embodiments, the GLP-1 agonist of the invention may be used for the following medical treatments:

(i) prevention and/or treatment of all forms of diabetes, such as hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, non-insulin dependent diabetes, MODY (maturity onset diabetes of the young), gestational diabetes, and/or for reduction of HbA1c;

(ii) delaying or preventing diabetic disease progression, such as progression in type 2 diabetes, delaying the progression of impaired glucose tolerance (IGT) to insulin requiring type 2 diabetes, and/or delaying the progression of non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes;

(iii) prevention and/or treatment of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; and/or delaying gastric emptying.

In another particular embodiment, the indication is (i). In a further particular embodiment the indication is (ii). In a still further particular embodiment the indication is (iii). In one embodiment the indication is type 2 diabetes and/or obesity.

In one embodiment the method comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions defined herein. In one embodiment the indication is (i) and (iii). In one embodiment the indication is (ii) and (iii). In one embodiment the

method comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions selected from a) and b), a) and c), b) and c), or a), b) and c) as defined in claim 1.

In one embodiment the invention relates to administration of an effective amount of a GLP-1 agonist.

In one embodiment as used herein, specific values given in relation to numbers or intervals may be understood as the specific value or as about the specific value.

FUNCTIONAL PROPERTIES

In a first functional aspect, the GLP-1 agonists of the invention have a good potency. Also, or alternatively, in a second functional aspect, the GLP-1 agonists of the invention have a protracted pharmacokinetic profile. Also, or alternatively, in a third functional aspect, the GLP-1 agonists of the invention are stable against degradation by gastro intestinal enzymes.

Biological activity (potency)

According to the first functional aspect, the GLP-1 agonists of the invention are biologically active, or potent. In a particular embodiment, “potency” and/or “activity” refers to in vitro potency, i.e. performance in a functional GLP-1 receptor assay, more in particular to the capability of stimulating cAMP formation in a cell line expressing the cloned human GLP-1 receptor.

The stimulation of the formation of cAMP in a medium containing the human GLP-1 receptor may preferably be determined using a stable transfected cell-line such as BHK467-12A (tk-ts13), and/or using for the determination of cAMP a functional receptor assay, e.g. based on competition between endogenously formed cAMP and exogenously added biotin-labelled cAMP, in which assay cAMP is more preferably captured using a specific antibody, and/or wherein an even more preferred assay is the AlphaScreen cAMP Assay, such as the one described in Assay (I).

In one embodiment the term half maximal effective concentration (EC_{50}) generally refers to the concentration which induces a response halfway between the baseline and maximum, by reference to the dose response curve. EC_{50} is used as a measure of the potency of a compound and represents the concentration where 50% of its maximal effect is observed.

The in vitro potency of the GLP-1 agonists of the invention may be determined as described above, and the EC_{50} of the GLP-1 agonist in question determined. The lower the EC_{50}, the better the potency.

In a particular embodiment, the medium has the following composition (final in-assay

concentrations): 50 mM TRIS-HCl; 5 mM HEPES; 10 mM $MgCl_2$, $6H_2O$; 150 mM NaCl; 0.01% Tween; 0.1% BSA ; 0.5 mM IBMX; 1 mM ATP; 1 µM GTP; pH 7.4.

In a further particular embodiment, the GLP-1 agonist of the invention has an in vitro potency corresponding to an EC_{50} at or below 3000pM, such as below 2000pM, below 1000pM, or below 500pM, or such as below 200 pM or below 100 pM.

In another particular embodiment the GLP-1 agonist of the invention are potent in vivo, which may be determined as is known in the art in any suitable animal model, as well as in clinical trials.

The diabetic db/db mouse is one example of a suitable animal model, and the blood glucose lowering effect may be determined in such mice in vivo, e.g. as described in Assay (III), or as described in Example 43 of WO09/030738.

Also, or alternatively, the effect on food intake in vivo may be determined in pharmacodynamic studies in pigs, e.g. as described in Assay (IV).

Protraction - half life in vivo in minipigs

According to the second functional aspect, the GLP-1 agonists of the invention are protracted. In a particular embodiment protraction may be determined as half-life ($T_{½}$) in vivo in minipigs after i.v. administration. In additional embodiments, the half-life is at least 24 hours, such as at least 48 hours, at least 60 hours, at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours.

A suitable assay for determining half-life in vivo in minipigs after i.v. administration is disclosed in Assay (II).

Degradation by gastro intestinal enzymes

According to the third functional aspect, the GLP-1 agonists of the invention are stable, or stabilised, against degradation by one or more gastro intestinal enzymes.

Gastro intestinal enzymes include, without limitation, exo and endo peptidases, such as pepsin, trypsin, chymotrypsin, elastases, and carboxypeptidases. The stability may be tested against these gastro intestinal enzymes in the form of purified enzymes, or in the form of extracts from the gastrointestinal system.

In a particular embodiment, the GLP-1 agonist of the invention has an in vitro half-life ($T_{½}$), in an extract of rat small intestines, divided by the corresponding half-life ($T_{½}$) of GLP-1(7-37), of at least 1, such as above 1.0, at least 1.2, at least 2.0, or such as at least 3.0, or at least 4.0. In other words, a ratio(SI) may be defined for each GLP-1 agonist, viz. as the in vitro half-

life ($T_{½}$) of the GLP-1 agonist in question, in an extract of rat small intestines, divided by the corresponding half-life ($T_{½}$) of GLP-1(7-37).

A suitable assay for determining in vitro half-life in an extract of rat small intestines is disclosed in Assay (V).

GLP-1 AGONISTS

In one embodiment the GLP-1 peptide comprises an Aib residue in position 8.

In one embodiment the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

In one embodiment the GLP-1 peptide is attached to a hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

In one embodiment the GLP-1 peptide is exendin-4, an exendin-4-analogue, or a derivative of exendin-4.

In one embodiment the GLP-1 agonist peptide comprises the amino acid sequence of the following formula:
H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 (SEQ ID NO: 2).

In one embodiment the GLP-1 agonist comprises an albumin binding residue attached via a hydrophilic spacer to the C-terminal amino acid residue of said GLP-1 peptide.

In one embodiment the GLP-1 agonist comprises a second albumin binding residue is attached to an amino acid residue which is not the C-terminal amino acid residue.

In one embodiment the GLP-1 peptide is selected from the group consisting of semaglutide, albiglutide and dulaglitide.

In one embodiment the GLP-1 peptide has the following structure:
His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg (SEQ ID NO: 3).

In one embodiment the GLP-1 peptide has the following structure:
(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2 (SEQ ID NO: 4)–genetically fused to human albumin.

In one embodiment the GLP-1 peptide is dulaglitide.

In one embodiment the GLP-1 agonists of the invention have GLP-1 activity. In one embodiment "a GLP-1 agonist" is understood to refer to any compound, including peptides and non-peptide compounds, which fully or partially activate the human GLP-1 receptor. In one embodiment the "GLP-1 agonist" is any peptide or non-peptide small molecule that binds to a GLP-1 receptor, preferably with an affinity constant (K_D) or a potency (EC_{50}) of below 1 μM, e. g. below 100 nM as measured by methods known in the art (see e. g., WO 98/08871). In one embodiment methods for identifying GLP-1 agonists are described in WO 93/19175 (Novo Nordisk A/S) and examples of suitable GLP-1 agonists which can be used according to the present invention includes those referred to in WO 2005/027978 (Novo Nordisk A/S), the teachings of which are both incorporated by reference herein. “GLP-1 activity” refers to the ability to bind to the GLP-1 receptor and initiate a signal transduction pathway resulting in insulinotropic action or other physiological effects as is known in the art. For example, the GLP-1 agonists of the invention can be tested for GLP-1 activity using the assay described in Assay (I) herein.

In yet another embodiment the GLP-1 agonist is a stable GLP-1 agonist. As used herein a "stable GLP-1 agonist" means a GLP-1agonist which exhibits an in vivo plasma elimination half-life of at least 24 hours in man, optionally determined by the method described below. Examples of stable GLP-1 agonists can be found in WO2006/097537.

In one embodiment the method for determination of plasma elimination half-life of a compound in man may be carried out as follows: The compound is dissolved in an isotonic buffer, pH 7.4, PBS or any other suitable buffer. The dose is injected peripherally, preferably in the abdominal or upper thigh. Blood samples for determination of active compound are taken at frequent intervals, and for a sufficient duration to cover the terminal elimination part (e. g., Pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24 (day 2), 36 (day 2), 48 (day 3), 60 (day 3), 72 (day 4) and 84 (day 4) hours post dose). Determination of the concentration of active compound is performed as described in Wilken *et al.*, Diabetologia 43 (51), 2000. Derived pharmacokinetic parameters are calculated from the concentration-time data for each individual subject by use of non-compartmental methods, using the commercially available software WinNonlin Version 2.1 (Pharsight, Cary, NC, USA). The terminal elimination rate constant is estimated by log-linear regression on the terminal log-linear part of the concentration-time curve, and used for calculating the elimination half-life.

In one embodiment the GLP-1 agonist is formulated so as to have a half-life in man of at least 48 hours. This may be obtained by sustained release formulations known in the art.

In one embodiment the GLP-1 agonist is a GLP-1 peptide. In one embodiment the GLP-1 peptide is selected from GLP-1 (7-35), GLP-1 (7-36), GLP-1 (7-36)-amide, GLP-1 (7-37), GLP-1 (7-38), GLP-1 (7-39), GLP-1 (7-40), GLP-1 (7-41) or an analogue or derivative thereof. In one embodiment the GLP-1 peptide comprises no more than 15, such as no more than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37). In one embodiment the GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code. In yet another embodiment, the GLP-1 agonist is exendin-4 or exendin-3, an exendin-4 or exendin-3 analogue, or a derivative of any of these.

In one embodiment the GLP-1 peptide is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglitide. In one embodiment the GLP-1 peptide is semaglutide. WO 06/097537 discloses semaglutide (Example 4), a mono-acylated GLP-1 agonist for once weekly administration. In one embodiment the GLP-1 peptide is exenatide. In one embodiment the GLP-1 peptide comprises the amino acid sequence of the formula: H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 (SEQ ID NO: 2). Exenatide is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. Exenatide displays biological properties similar to GLP-1. In some embodiments the composition is BYDUREON® (a long acting release formula of exenatide in PLGA particles). In one embodiment the “Bydureon® composition” refer to a powder comprising exenatide, poly (D,L-lactide-co-glycolide), and sucrose which immediately prior to injection is reconstituted in a solvent comprising carmellose sodium, sodium chloride, polysorbate 20, monobasic sodium phosphate (e.g. its monohydrate), dibasic sodium phosphate (e.g. its heptahydrate), and water for injections. In one embodiment the GLP-1 peptide has the structure (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2 (SEQ ID NO: 4)–genetically fused to human albumin. Albiglutide is a recombinant human serum albumin (HSA)-GLP-1 hybrid protein, likely a GLP-1 dimer fused to HSA. The constituent GLP-1 peptide is analogue, in which Ala at position 8 has been substituted by Glu. In one embodiment the GLP-1 peptide is dulaglitide. Dulaglutide is a GLP-1-Fc construct (GLP-1 - linker - Fc from IgG4). In one embodiment the GLP-1 peptide has the structure His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg (SEQ ID NO: 3). Liraglutide is a mono-acylated GLP-1 agonist for once daily administration which is marketed as of 2009 by Novo Nordisk A/S, is disclosed in WO 98/08871 Example 37.

In one embodiment the present invention encompasses pharmaceutically acceptable salts of the GLP-1 agonists. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium, and alkylated ammonium salts. Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present GLP-1 agonists are able to form.

In one embodiment the route of administration of GLP-1 agonists may be any route which effectively transports the active compound to the appropriate or desired site of action, such as parenteral. In one embodiment medicaments or pharmaceutical compositions comprising a GLP-1 agonist, such as semaglutide, may be administered parenterally to a patient in need thereof. In one embodiment 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. A further option is a composition which may be a powder or a liquid for the administration of a GLP-1 agonist in the form of a nasal or pulmonal spray. As a still further option, the GLP-1 agonist can also be administered transdermally, e.g., from a patch, optionally an iontophoretic patch, or transmucosally, e.g., bucally. The above-mentioned possible ways to administer GLP-1 agonists are not considered as limiting the scope of the invention.

In one embodiment the GLP-1 agonist is co-administered together with a further therapeutically active agent used in the treatments defined herein.

In one embodiment the GLP-1 peptide comprises the amino acid sequence of the formula (I) (SEQ ID NO: 5):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa_{16}-Ser-Xaa_{18}-$Xaa_{19}Xaa_{20}$GluXaa_{22}-Xaa_{23}-Ala-Xaa_{25}-Xaa_{26}-Xaa_{27}-Phe-Ile-Xaa_{30}-Trp-Leu-Xaa_{33}-Xaa_{34}-Xaa_{35}-Xaa_{36}-Xaa_{37}-Xaa_{38}-Xaa_{39}-Xaa_{40}-Xaa_{41}-Xaa_{42}-Xaa_{43}-Xaa_{44}-Xaa_{45}-Xaa_{46}

Formula (I)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{25} is Ala or Val;

Xaa_{26} is Lys, Glu or Arg;

Xaa_{27} is Glu or Leu;

Xaa_{30} is Ala, Glu or Arg;

Xaa_{33} is Val or Lys;

Xaa_{34} is Lys, Glu, Asn or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg, Gly or Lys;

Xaa_{37} is Gly, Ala, Glu, Pro, Lys, amide or is absent;

Xaa_{38} is Lys, Ser, amide or is absent;

Xaa_{39} is Ser, Lys, amide or is absent;

Xaa_{40} is Gly, amide or is absent;

Xaa_{41} is Ala, amide or is absent;

Xaa_{42} is Pro, amide or is absent;

Xaa_{43} is Pro, amide or is absent;

Xaa_{44} is Pro, amide or is absent;

Xaa_{45} is Ser, amide or is absent;

Xaa_{46} is amide or is absent;

provided that if Xaa_{38}, Xaa_{39}, Xaa_{40}, Xaa_{41}, Xaa_{42}, Xaa_{43}, Xaa_{44}, Xaa_{45} or Xaa_{46} is absent then each amino acid residue downstream is also absent.

In one embodiment the GLP-1 peptide comprises the amino acid sequence of formula (II) (SEQ ID NO: 6):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Xaa_{18}-Tyr-Leu-Glu-Xaa22-Xaa_{23}-Ala-Ala-Xaa_{26}-Glu-Phe-Ile-Xaa_{3o}-Trp-Leu-Val-Xaa_{34}-Xaa_{35}-Xaa_{36}-$Xaa_{37}Xaa_{38}$

Formula (II)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine,-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-

pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{26} is Lys, Glu or Arg; Xaa30 is Ala, Glu or Arg;

Xaa_{34} is Lys, Glu or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg or Lys;

Xaa_{37} is Gly, Ala, Glu or Lys;

Xaa_{38} is Lys, amide or is absent.

In one embodiment the GLP-1 peptide is a DPPIV protected GLP-1 peptide.

In one embodiment the GLP-1 peptide is DPPIV stabilised.

In one embodiment the GLP-1 peptide comprises an Aib residue in position 8.

In one embodiment the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

In one embodiment the GLP-1 peptide comprises Arg^{34}GLP-1 (7-37) or [Aib8,Arg34]GLP-1-(7-37).

In one embodiment the GLP-1 agonist comprises an albumin binding residue which is covalently attached, optionally via a hydrophilic spacer. In one embodiment said albumin binding residue is covalently attached, optionally via a hydrophilic spacer, to the C-terminal amino acid residue of said GLP-1 peptide or an amino acid residue which is not the C-terminal amino acid residue. In one embodiment the GLP-1 peptide is attached to a hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

Human Glucagon-Like Peptide-1 is GLP-1(7-37) and has the sequence HAEGTFTSDVSSYLEGQAAKEFI AWLVKGRG (SEQ ID NO: 1). GLP-1(7-37) may also be designated "native" GLP-1. In the sequence listing, the first amino acid residue of SEQ ID NO: 1

(histidine) is assigned no. 1. However, in what follows - according to established practice in the art - this histidine residue is referred to as no. 7, and subsequent amino acid residues are numbered accordingly, ending with glycine no. 37. Therefore, generally, any reference herein to an amino acid residue number or a position number of the GLP-1(7-37) sequence is to the sequence starting with His at position 7 and ending with Gly at position 37. A non-limiting example of a suitable analogue nomenclature is [Aib^8,Arg^{34},Lys^{37}]GLP-1(7-37), which designates a GLP-1(7-37) analogue, in which the alanine at position 8 has been substituted with α-aminoisobutyric acid (Aib), the lysine at position 34 has been substituted with arginine, and the glycine at position 37 has been substituted with lysine.

In one embodiment the GLP-1 agonist exhibits at least 60%, 65%, 70%, 80% or 90% sequence identity to GLP-1(7-37) over the entire length of GLP-1(7-37). As an example of a method for determination of sequence identity between two analogues the two peptides [Aib8]GLP-1(7-37) and GLP-1(7-37) are aligned. The sequence identity of [Aib8]GLP-1(7-37) relative to GLP-1(7-37) is given by the number of aligned identical residues minus the number of different residues divided by the total number of residues in GLP-1(7-37). Accordingly, in said example the sequence identity is (31-1)/31. In one embodiment non-peptide moieties of the GLP-1 agonist are not included when determining sequence identity.

In one embodiment the GLP-1 agonist is a derivative. In one embodiment the term “derivative” as used herein in the context of a GLP-1 agonist, peptide or analogue means a chemically modified GLP-1 agonist, peptide or analogue, in which one or more substituents have been covalently attached to the agonist, peptide or analogue. The substituent may also be referred to as a side chain. Typical modifications are amides, carbohydrates, alkyl groups, acyl groups, esters and the like. An example of a derivative of GLP-1(7-37) is $N^{\varepsilon 26}$-(γ-Glu(N^{α}-hexadecanoyl)) - [Arg^{34}, Lys^{25}]) GLP-1 (7- 37).

In a particular embodiment, the side chain is capable of forming non-covalent aggregates with albumin, thereby promoting the circulation of the GLP-1 agonist with the blood stream, and also having the effect of protracting the time of action of the GLP-1 agonist, due to the fact that the aggregate of the GLP-1 agonist and albumin is only slowly disintegrated to release the active pharmaceutical ingredient. Thus, the substituent, or side chain, as a whole may be referred to as an albumin binding moiety.

In particular embodiments, the side chain has at least 10 carbon atoms, or at least 15, 20, 25, 30, 35, or at least 40 carbon atoms. In further particular embodiments, the side chain may further include at least 5 hetero atoms, in particular O and N, for example at least 7, 9, 10, 12, 15, 17, or at least 20 hetero atoms, such as at least 1, 2, or 3 N-atoms, and/or at least 3, 6,

9, 12, or 15 O-atoms.

In another particular embodiment the albumin binding moiety comprises a portion which is particularly relevant for the albumin binding and thereby the protraction, which portion may accordingly be referred to as a protracting moiety. The protracting moiety may be at, or near, the opposite end of the albumin binding moiety, relative to its point of attachment to the peptide.

In a still further particular embodiment the albumin binding moiety comprises a portion in between the protracting moiety and the point of attachment to the peptide, which portion may be referred to as a linker, linker moiety, spacer, or the like. The linker may be optional, and hence in that case the albumin binding moiety may be identical to the protracting moiety.

In particular embodiments, the albumin binding moiety and/or the protracting moiety is lipophilic, and/or negatively charged at physiological pH (7.4).

The albumin binding moiety, the protracting moiety, or the linker may be covalently attached to a lysine residue of the GLP-1 peptide by acylation. Additional or alternative conjugation chemistry includes alkylation, ester formation, or amide formation, or coupling to a cysteine residue, such as by maleimide or haloacetamide (such as bromo-/fluoro-/iodo-) coupling.

In one embodiment an active ester of the albumin binding moiety, e.g. comprising a protracting moiety and a linker, is covalently linked to an amino group of a lysine residue, e.g. the epsilon amino group thereof, under formation of an amide bond (this process being referred to as acylation).

Unless otherwise stated, when reference is made to an acylation of a lysine residue, it is understood to be to the epsilon-amino group thereof.

For the present purposes, the terms "albumin binding moiety", "protracting moiety", and "linker" may include the unreacted as well as the reacted forms of these molecules. Whether or not one or the other form is meant is clear from the context in which the term is used.

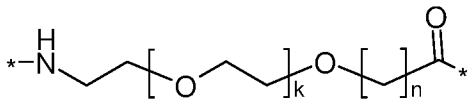
For the attachment to the GLP-1 agonist, the acid group of the fatty acid, or one of the acid groups of the fatty diacid, forms an amide bond with the epsilon amino group of a lysine residue in the GLP-1 peptide, e.g. via a linker.

In one embodiment the term "fatty acid" refers to aliphatic monocarboxylic acids having from 4 to 28 carbon atoms, it is optionally unbranched, and/or even numbered, and it may be saturated or unsaturated.

In one embodiment the term "fatty diacid" refers to fatty acids as defined above but with an additional carboxylic acid group in the omega position. Thus, fatty diacids are dicarboxylic acids.

Each of the two linkers of the GLP-1 agonist of the invention may comprise the following first linker element:

Chem. 5:



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wherein k is an integer in the range of 1-5, and n is an integer in the range of 1-5.

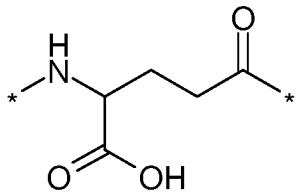
In a particular embodiment, when k=1 and n= 1, this linker element may be designated OEG, or a di-radical of 8-amino-3,6-dioxaoctanic acid, and/or it may be represented by the following formula:

Chem. 5a:

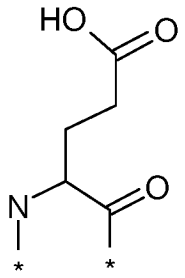
-NH-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-.

In another particular embodiment, each linker of the GLP-1 agonist of the invention may further comprise, independently, a second linker element, e.g. a Glu di-radical, such as Chem. 6 and/or Chem. 7:

Chem. 6:



Chem. 7:



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wherein the Glu di-radical may be included p times, where p is an integer in the range of 1-3.

Chem. 6 may also be referred to as gamma-Glu, or briefly gGlu, due to the fact that it is the gamma carboxy group of the amino acid glutamic acid which is here used for connection to another linker element, or to the epsilon-amino group of lysine. As explained above, the other

linker element may, for example, be another Glu residue, or an OEG molecule. The amino group of Glu in turn forms an amide bond with the carboxy group of the protracting moiety, or with the carboxy group of, e.g., an OEG molecule, if present, or with the gamma-carboxy group of, e.g., another Glu, if present.

Chem. 7 may also be referred to as alpha-Glu, or briefly aGlu, or simply Glu, due to the fact that it is the alpha carboxy group of the amino acid glutamic acid which is here used for connection to another linker element, or to the epsilon-amino group of lysine.

The above structures of Chem. 6 and Chem. 7 cover the L-form, as well as the D-form of Glu. In particular embodiments, Chem. 6 and/or Chem. 7 is/are, independently, a) in the L-form, or b) in the D-form.

In still further particular embodiments the linker has a) from 5 to 41 C-atoms; and/or b) from 4 to 28 hetero atoms.

The concentration in plasma of the GLP-1 agonists of the invention may be determined using any suitable method. For example, LC-MS (Liquid Chromatography Mass Spectroscopy) may be used, or immunoassays such as RIA (Radio Immuno Assay), ELISA (Enzyme-Linked Immuno Sorbent Assay), and LOCI (Luminescence Oxygen Channeling Immunoasssay). General protocols for suitable RIA and ELISA assays are found in, e.g., WO09/030738 on p. 116-118. A preferred assay is the LOCI (Luminescent Oxygen Channeling Immunoassay), generally as described for the determination of insulin by Poulsen and Jensen in Journal of Biomolecular Screening 2007, vol. 12, p. 240-247 - briefly blood samples may be collected at desired intervals, plasma separated, immediately frozen, and kept at -20°C until analyzed for plasma concentration of the respective GLP-1 agonist; the donor beads are coated with streptavidin, while acceptor beads are conjugated with a monoclonal antibody recognising a mid-/C-terminal epitope of the peptide; another monoclonal antibody, specific for the N-terminus, is biotinylated; the three reactants are combined with the analyte and formed a two-sited immuno-complex; illumination of the complex releases singlet oxygen atoms from the donor beads, which are channeled into the acceptor beads and triggered chemiluminescence which may be measured in an Envision plate reader; the amount of light is proportional to the concentration of the compound.

In one embodiment the term “Aib” as used herein refers to α-aminoisobutyric acid.

PHARMACEUTICAL COMPOSITIONS

An administered dose may contain from 5 mg - 100 mg of the GLP-1 agonist, or from

5-50 mg, or from 5-20 mg, or from 5-10 mg of the GLP-1 agonist.

In one embodiment the composition is BYDUREON® (a long acting release formula of exenatide in PLGA particles).

Pharmaceutical compositions comprising a GLP-1 agonist of the invention or a pharmaceutically acceptable salt, amide, or ester thereof, and a pharmaceutically acceptable excipient may be prepared as is known in the art.

In one embodiment the term "excipient" broadly refers to any component other than the active therapeutic ingredient(s). The excipient may be an inert substance, an inactive substance, and/or a not medicinally active substance. The formulation of pharmaceutically active ingredients with various excipients is known in the art, see e.g. Remington: The Science and Practice of Pharmacy (e.g. 19th edition (1995), and any later editions). Non-limiting examples of excipients are: solvents, diluents, buffers, preservatives, tonicity regulating agents (e.g isotonic agents), chelating agents, stabilisers (e.g. oxidation inhibitors, aggregation inhibitors, surfactants, and/or protease inhibitors).

Examples of formulations include liquid formulations, i.e. aqueous formulations comprising water. A liquid formulation may be a solution, or a suspension. An aqueous formulation typically comprises at least 50% w/w water, or at least 60%, 70%, 80%, or even at least 90% w/w of water.

Alternatively, a pharmaceutical composition may be a solid formulation, e.g. a freeze-dried or spray-dried composition, which may be used as is, or whereto the physician or the patient adds solvents, and/or diluents prior to use.

The pH in an aqueous formulation may be anything between pH 3 and pH 10, for example from about 7.0 to about 9.5; or from about 3.0 to about 7.0.

Still further, a pharmaceutical composition may be formulated as is known in the art of oral formulations of insulinotropic compounds, e.g. using any one or more of the formulations described in WO 2008/145728.

A composition may be administered in several dosage forms, for example as a solution; a suspension; an emulsion; a microemulsion; multiple emulsions; a foam; a salve; a paste; a plaster; an ointment; a tablet; a coated tablet; a chewing gum; a rinse; a capsule such as hard or soft gelatine capsules; a suppositorium; a rectal capsule; drops; a gel; a spray; a powder; an aerosol; an inhalant; eye drops; an ophthalmic ointment; an ophthalmic rinse; a vaginal pessary; a vaginal ring; a vaginal ointment; an injection solution; an in situ transforming solution such as in situ gelling, setting, precipitating, and in situ crystallisation; an infusion solution; or as an implant.

A composition may further be compounded in a drug carrier or drug delivery system, e.g. in order to improve stability, bioavailability, and/or solubility. In a particular embodiment a composition may be attached to such system through covalent, hydrophobic, and/or electrostatic interactions. The purpose of such compounding may be, e.g., to decrease adverse effects, achieve chronotherapy, and/or increase patient compliance.

A composition may also be used in the formulation of controlled, sustained, protracting, retarded, and/or slow release drug delivery systems.

The composition may be administered by parenteral administration. Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal, or intravenous injection by means of a syringe, optionally a pen-like syringe, or by means of an infusion pump.

PRODUCTION PROCESSES

In one embodiment GLP-1 peptides can be produced by appropriate derivatisation of an appropriate peptide backbone which has been produced by recombinant DNA technology or by peptide synthesis (e.g., Merrifield-type solid phase synthesis) as known in the art of peptide synthesis and peptide chemistry.

In one embodiment the production of peptides like GLP-1(7-37) and GLP-1 analogues is well known in the art. The GLP-1 moiety of the GLP-1 peptide of the invention (or fragments thereof) may for instance be produced by classical peptide synthesis, e.g., solid phase peptide synthesis using t-Boc or Fmoc chemistry or other well established techniques, see, e.g., Greene and Wuts, “Protective Groups in Organic Synthesis”, John Wiley & Sons, 1999, Florencio Zaragoza Dörwald, “Organic Synthesis on solid Phase”, Wiley-VCH Verlag GmbH, 2000, and “Fmoc Solid Phase Peptide Synthesis”, Edited by W.C. Chan and P.D. White, Oxford University Press, 2000.

In one embodiment GLP-1 agonists may be produced by recombinant methods, viz. by culturing a host cell containing a DNA sequence encoding the GLP-1 agonist and capable of expressing the peptide in a suitable nutrient medium under conditions permitting the expression of the peptide. Non-limiting examples of host cells suitable for expression of these peptides are: Escherichia coli, Saccharomyces cerevisiae, as well as mammalian BHK or CHO cell lines.

In one embodiment GLP-1 agonists of the invention which include non-natural amino acids and/or a covalently attached N-terminal mono- or dipeptide mimetic may e.g. be produced as described in the experimental part. Or see e.g., Hodgson et al: "The synthesis of peptides and proteins containing non-natural amino acids", Chemical Society Reviews, vol. 33, no. 7

(2004), p. 422-430; and WO 2009/083549 A1 entitled "Semi-recombinant preparation of GLP-1 analogues".

EMBODIMENTS

The following are non-limiting embodiments of the invention:

1. A method for reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

2. A method for treating or preventing obesity, for reducing body weight and/or food intake, or for inducing satiety, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

3. The method according to any one of the preceding embodiments, wherein said method comprises delaying or preventing diabetic disease progression.

4. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist has a half-life of at least 24 hours, such as at least 48 hours, at least 60 hours, or at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours, or optionally at least 120 hours, at least 132 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

5. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered twice weekly or less often, once weekly or less often, such as less often than once weekly or once every secondly week or less often, or such as once every third week or less often or once a month or less often.

6. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount of at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, per week.

7. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount equivalent to at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, semaglutide per week.

8. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount which provides an improved a) reduction in HbA1c or b) reduction in body weight compared to administration of 1.8 mg liraglutide or less, such as 0.8 mg liraglutide or less, per day.

9. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

10. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered by parenteral administration, such as subcutaneous injection.

11. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered simultaneously or sequentially with another therapeutic agent.

12. The method according to any one of any one of the preceding embodiments, wherein the GLP-1 agonist is a GLP-1 peptide.

13. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide comprises the amino acid sequence of the formula (I) (SEQ ID NO: 5):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa_{16}-Ser-Xaa_{18}-$Xaa_{19}Xaa_{20}$GluXaa_{22}-Xaa_{23}-Ala-Xaa_{25}-Xaa_{26}-Xaa_{27}-Phe-Ile-Xaa_3o-Trp-Leu-Xaa_{33}-Xaa_{34}-Xaa_{35}-Xaa_{36}-Xaa_{37}-Xaa_{38}-Xaa_{39}-Xaa_4o-Xaa_{41}-Xaa_{42}-Xaa_{43}-Xaa_{44}-Xaa_{45}-Xaa_{46}

Formula (I)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3- pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{25} is Ala or Val;

Xaa_{26} is Lys, Glu or Arg;

Xaa_{27} is Glu or Leu;

Xaa_{30} is Ala, Glu or Arg;

Xaa_{33} is Val or Lys;

Xaa_{34} is Lys, Glu, Asn or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg, Gly or Lys;

Xaa_{37} is Gly, Ala, Glu, Pro, Lys, amide or is absent;

Xaa_{38} is Lys, Ser, amide or is absent;

Xaa_{39} is Ser, Lys, amide or is absent;

Xaa_{40} is Gly, amide or is absent;

Xaa_{41} is Ala, amide or is absent;

Xaa_{42} is Pro, amide or is absent;

Xaa_{43} is Pro, amide or is absent;

Xaa_{44} is Pro, amide or is absent;

Xaa_{45} is Ser, amide or is absent;

Xaa_{46} is amide or is absent;

provided that if Xaa_{38}, Xaa_{39}, Xaa_{40}, Xaa_{41}, Xaa_{42}, Xaa_{43}, Xaa_{44}, Xaa_{45} or Xaa_{46} is absent then each amino acid residue downstream is also absent.

14. The method according to any one of the preceding embodiments, wherein said polypeptide is a GLP-1 peptide comprising the amino acid sequence of formula (II) (SEQ ID NO: 6):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Xaa_{18}-Tyr-Leu-Glu-Xaa22-Xaa_{23}-Ala-Ala-Xaa_{26}-Glu-Phe-Ile-Xaa_{3o}-Trp-Leu-Val-Xaa_{34}-Xaa_{35}-Xaa_{36}-$Xaa_{37}Xaa_{38}$

Formula (II)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine,-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{26} is Lys, Glu or Arg; Xaa30 is Ala, Glu or Arg;

Xaa_{34} is Lys, Glu or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg or Lys;

Xaa_{37} is Gly, Ala, Glu or Lys;

Xaa_{38} is Lys, amide or is absent.

15. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide is selected from GLP-1 (7-35), GLP-1 (7-36), GLP-1 (7-36)-amide, GLP-1 (7-37), GLP-1 (7-38), GLP-1 (7-39), GLP-1 (7-40), GLP-1 (7-41) or an analogue or derivative thereof.

16. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 15, such as no more than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

17. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 5 amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

18. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code.

19. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide is a DPPIV protected GLP-1 peptide.

20. The method according to any one of the preceding embodiments, wherein GLP-1 peptide is DPPIV stabilised.

21. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises an Aib residue in position 8.

22. The method according to any one of the preceding embodiments, wherein the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4-pyridylalanine.

23. The method according to any one of embodiments 7 to 16, wherein said GLP-1 peptide is attached to said hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

24. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide is exendin-4, an exendin-4-analogue, or a derivative of exendin-4.

25. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide comprises the amino acid sequence of the following formula:

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu

Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 (SEQ ID NO: 2).

26. The method according to any one of the preceding embodiments wherein one albumin binding residue via said hydrophilic spacer is attached to the C-terminal amino acid residue of said GLP-1 peptide.

27. The method according to any one of the preceding embodiments, wherein a second albumin binding residue is attached to an amino acid residue which is not the C-terminal amino acid residue.

28. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide is selected from the group consisting of semaglutide, albiglutide and dulaglitide.

29. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide has the following structure:
His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg (SEQ ID NO: 3).

30. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide has the following structure:
(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-
Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2 (SEQ ID NO: 4)–
genetically fused to human albumin.

31. The method according to any one of the preceding embodiments wherein the GLP-1 peptide is dulaglitide.

32. The method according to any one of the preceding embodiments wherein the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100 pM, optionally determined by Assay (I).

33. A GLP-1 agonist for use in the reduction of HbA1c or for use in the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

34. A GLP-1 agonist for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

35. A GLP-1 agonist for use according to embodiment 33 or 34, wherein the GLP-1 agonist and/or administration is as defined in any of embodiments 1-32 or 40.

36. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

37. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

38. A composition for use according to any one of the preceding embodiments, wherein said GLP-1 agonist and/or administration is as defined in any one of embodiments 1-32 or 40.

39. A composition for use according to any one of the preceding embodiments, wherein said composition comprises the Bydureon® composition.

40. The method according to any one of the preceding claims, wherein the method comprises prevention, treatment, reduction or induction in one or more diseases or conditions defined in any one of the previous embodiments.

EXAMPLES

Abbreviations

The following abbreviations are used in the following, in alphabetical order:

ADA: American Diabetes Association

Example 1: The Glp-1 Peptide Semaglutide Provides Reduced HbA1c and Body Weight

Semaglutide is a unique acylated GLP-1 peptide with a half-life of 160 hours. The aim was to investigate HbA1c dose-response of once-weekly doses of semaglutide (five dose-levels) in subjects with type 2 diabetes. Safety, tolerability and pharmacodynamics of semaglutide versus placebo and open-label once-daily liraglutide were also investigated.

Materials and methods

Liraglutide may be prepared as described in Example 37 of WO98/08871. Semaglutide may be prepared as described in Example 4 of WO2006/097537. The composition of the GLP-1 agonists administered may be formulated as isotonic aqueous solutions with a phosphate

buffer, such as a sodium dihydrogen phosphate buffer, having a pH in the range 7.0-9.0, such as pH 7.4 or pH 8.15, for example further comprising the excipients propylene glycol and phenol. The composition of the GLP-1 agonists administered may be as described in WO2003/002136 or WO2005/049061. The placebo composition may be identical to the composition of the GLP-1 agonists, but not containing a GLP-1 agonist.

In a 12-week, randomised, double-blind, placebo-controlled trial, 411 human subjects (n=43–50 per group) with type 2 diabetes were exposed. Participants (male/female 65/35%; baseline HbA1c (mean±SD) 8.1±0.8%; baseline body weight 87.5±13.8 kg; duration of diabetes 2.6±3.1 years; metformin only/diet and exercise alone 80/20%) received subcutaneous injection of one of five semaglutide doses (0.1–1.6 mg) once weekly, open-label liraglutide (1.2 mg, 1.8 mg) once daily, or placebo once weekly. Two of the semaglutide doses were titrated (T) in weekly increments of 0.4 mg. The primary endpoint was change in HbA1c from baseline. Secondary efficacy endpoints included proportion of subjects reaching ADA HbA1c target (<7%) and change in body weight. Change and percentage to target were analysed by ANOVA and logistic regression, respectively. Comparisons between semaglutide and liraglutide were not corrected for multiplicity. Baseline characteristics of the subjects are shown in Table 1.

Table 1. Baseline characteristics of subjects

	Placebo	Semaglutide						Liraglutide	
		0.1 mg	0.2 mg	0.4 mg	0.8 mg	0.8 mg T	1.6 mg T	1.2 mg	1.8 mg
Exposed* subjects	46	47	43	48	42	43	47	45	50
D&E: metformin (%)	22:78	23:77	14:86	23:77	19:81	16:84	19:81	18:82	24:76
Female: male (%)	39:61	34:66	30:70	23:77	48:52	37:63	45:55	31:69	30:70
Age (years)	55.3 (10.6)	55.2 (10 .1)	54.7 (10.0)	53.8 (10.2)	55.0 (9.7)	55.9 (7.9)	56.4 (10.5)	54.8 (9.2)	54.3 (10.1)
Duration of diabetes (years)	2.4 (3.3)	3.6 (5.0)	2.3 (2.7)	2.0 (2.3)	3.0 (3.0)	2.6 (2.1)	1.8 (2.0)	3.3 (3.4)	2.5 (2.6)

HbA1c (%)	8.1 (0.8)	8.2 (0.9)	8.2 (0.9)	8.1 (0.9)	8.2 (0.9)	8.0 (0.8)	8.0 (0.7)	8.0 (0.8)	8.1 (0.7)
FPG (mmol/L)	8.9 (1.5)	9.8 (2.7)	9.5 (2.5)	9.3 (2.1)	9.5 (2.4)	9.6 (2.1)	9.0 (1.9)	9.0 (2.3)	9.3 (2.0)
Weight (kg)	90.5 (13.0)	89.5 (14.2)	86.3 (15.1)	87.0 (14.0)	85.9 (15.1)	85.7 (12.6)	84.5 (14.0)	90.5 (13.5)	87.2 (13.1)
BMI (kg/m^2)	31.7 (3.8)	31.5 (4.6)	30.4 (3.9)	29.7 (4.5)	30.7 (4.5)	31.2 (4.2)	30.9 (4.7)	31.0 (4.6)	30.9 (4.6)

Data are mean (SD) unless otherwise stated. *: Number of subjects exposed to actual treatment. D&E: Diet and exercise. FPG: Fasting plasma glucose. BMI: Body mass index.

Results

In the full analysis set, semaglutide (≥0.2 mg) dose-dependently reduced HbA1c from baseline (Fig. 1), and increased the likelihood of achieving HbA1c <7% ($p<0.05$ vs. placebo for doses ≥0.2 mg). The results with respect to change in HbA1c are shown in Fig. 1. The change in HbA1c in fig. 1 is from baseline at week 12. Fig. 2 shows the change in HbA1c over time with the different treatments. Treatment with semaglutide ≥0.8 mg numerically brought more patients to target than liraglutide 1.8 mg (0.8 mg T 69%, 0.8 mg 73%, 1.6 mg T 81% vs. liraglutide 1.8 mg 57%).The results (see e.g. Fig. 1) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T improved reduction of HbA1c compared to treatment with liraglutide 1.2 mg or 1.8 mg; furthermore, treatment with semaglutide 1.6 mg T was statistically superior to treatment with liraglutide 1.2 mg or 1.8 mg with respect to reduction of HbA1c (based on unadjusted means). Fig. 3 shows the percentage and the number of subjects reaching the AACE or ADA criteria for glycaemic control with the different treatments. The results (see Fig. 3) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T improved the percentage and the number of subjects reaching the AACE or ADA criteria for glycaemic control compared to treatment with liraglutide 1.2 mg or 1.8 mg.

Body weight was dose-dependently reduced from baseline by up to 4.8 kg vs. placebo 1.2 kg ($p<0.01$ for doses ≥0.8 mg). Fig. 4 and 5 shows mean body weight change versus time and body weight change from baseline at week 12, respectively, with the different treatments. The results (see e.g. Fig. 5) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T increased reduction of body weight compared to treatment with liraglutide 1.2 mg or 1.8 mg. Furthermore, the results (see e.g. Fig. 5) shows that treatment with semaglutide 0.8 mg T or 1.6 mg T was statistically superior to treatment with liraglutide 1.8 mg with respect to reduction of

body weight; and that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T was statistically superior to liraglutide 1.2 mg with respect to reduction of body weight (based on unadjusted means).

There were no reports of pancreatitis or treatment-related changes in blood calcitonin. Proportion of subjects with nausea and vomiting increased with dose, but were generally mild or moderate and ameliorated by titration. Withdrawals due to gastrointestinal adverse events were 4.7%-27.7% for semaglutide and 2.2%-10% for liraglutide. Few subjects reported minor hypoglycaemia (semaglutide n=5, liraglutide n=3); no major hypoglycaemia. Injection site reactions were reported by 7 subjects: semaglutide n=2; liraglutide n=5. One subject (semaglutide 1.6 mg T) developed low titre non-neutralising anti-semaglutide antibodies (no cross-reaction to native GLP-1).

Conclusion

Over 12 weeks, semaglutide dose-dependently reduced HbA1c and body weight. The effect of semaglutide 0.4 mg on glycaemic control and body weight was comparable to that of liraglutide 1.2 mg, while semaglutide ≥0.8 mg appeared to bring more subjects to target and provided better weight loss than liraglutide 1.8 mg. No semaglutide safety concerns were identified. Dose escalation was not a major focus of this trial and it will be optimised in future clinical trials.

Pharmacological Methods

Assay (I): In Vitro Potency

The purpose of this example is to test the activity, or potency, of GLP-1 agonists in vitro. The potencies of GLP-1 agonists may be determined as described below, i.e. as the stimulation of the formation of cyclic AMP (cAMP) in a medium containing membranes expressing the human GLP-1 receptor.

Principle

Purified plasma membranes from a stable transfected cell line, BHK467-12A (tk-ts13), expressing the human GLP-1 receptor are stimulated with the GLP-1 agonist in question, and the potency of cAMP production is measured using the AlphaScreenTM cAMP Assay Kit from Perkin Elmer Life Sciences. The basic principle of The AlphaScreen Assay is a competition between endogenous cAMP and exogenously added biotin-cAMP. The capture of cAMP is

achieved by using a specific antibody conjugated to acceptor beads.

Cell culture and preparation of membranes

A stable transfected cell line and a high expressing clone are selected for screening. The cells are grown at 5% CO_2 in DMEM, 5% FCS, 1% Pen/Strep (Penicillin/Streptomycin) and 0.5 mg/ml of the selection marker G418.

Cells at approximate 80% confluence are washed 2X with PBS and harvested with Versene (aqueous solution of the tetrasodium salt of ethylenediaminetetraacetic acid), centrifuged 5 min at 1000 rpm and the supernatant removed. The additional steps are all made on ice. The cell pellet is homogenised by the Ultrathurax for 20-30 sec. in 10 ml of Buffer 1 (20 mM Na-HEPES, 10 mM EDTA, pH=7.4), centrifuged 15 min at 20,000 rpm and the pellet resuspended in 10 ml of Buffer 2 (20 mM Na-HEPES, 0.1 mM EDTA, pH=7.4). The suspension is homogenised for 20-30 sec and centrifuged 15 min at 20,000 rpm. Suspension in Buffer 2, homogenisation and centrifugation is repeated once and the membranes are resuspended in Buffer 2. The protein concentration is determined and the membranes stored at -80°C until use.

The assay is performed in ½-area 96-well plates, flat bottom (e.g. Costar cat. no:3693). The final volume per well is 50 µl.

Solutions and reagents

Exemplary solutions and reagents are given below.

AlphaScreen cAMP Assay Kit from Perkin Elmer Life Sciences (cat. No: 6760625M); containing Anti-cAMP Acceptor beads (10 U/µl), Streptavidin Donor beads (10 U/µl) and Biotinylated-cAMP (133 U/µl).

AlphaScreen Buffer, pH=7.4: 50 mM TRIS-HCl (Sigma, cat.no: T3253); 5 mM HEPES (Sigma, cat.no: H3375); 10 mM $MgCl_2$, $6H_2O$ (Merck, cat.no: 5833); 150 mM NaCl (Sigma, cat.no: S9625); 0.01% Tween (Merck, cat.no: 822184). The following was added to the AlphaScreen Buffer prior to use (final concentrations indicated): BSA (Sigma, cat. no. A7906): 0.1%; IBMX (Sigma, cat. no. I5879): 0.5 mM; ATP (Sigma, cat. no. A7699): 1 mM; GTP (Sigma, cat. no. G8877): 1 µM.

cAMP standard (dilution factor in assay = 5): cAMP Solution: 5 µL of a 5 mM cAMP-stock + 495 µL AlphaScreen Buffer.

Suitable dilution series in AlphaScreen Buffer are prepared of the cAMP standard as well as the GLP-1 agonist to be tested, e.g. the following eight concentrations of the GLP-1 agonist: 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} and 10^{-14}M, and a series from, e.g., 10^{-6} to $3x10^{-11}$ of cAMP.

Membrane/Acceptor beads

Use hGLP-1/ BHK 467-12A membranes; 6 µg/well corresponding to 0.6 mg/ml (the amount of membranes used pr. well may vary)

"No membranes": Acceptor Beads (15µg/ml final) in AlphaScreen buffer

"6 µg/well membranes": membranes + Acceptor Beads (15µg/ml final) in AlphaScreen buffer

Add 10 µl "No membranes" to the cAMP standard (per well in duplicates) and the positive and negative controls

Add 10 µl "6 µg/well membranes" to GLP-1 and GLP-1 agonists (per well in duplicates/triplicates)

Pos. Control: 10 µl "no membranes" + 10 µl AlphaScreen Buffer

Neg. Control: 10 µl "no membranes" + 10 µl cAMP Stock Solution (50µM)

As the beads are sensitive to direct light, any handling is in the dark (as dark as possible), or in green light. All dilutions are made on ice.

Procedure

1. Make the AlphaScreen Buffer.
2. Dissolve and dilute the GLP-1 agonists/cAMP standard in AlphaScreen Buffer.
3. Make the Donor Beads solution and incubate 30 min. at RT.
4. Add the cAMP/GLP-1 agonists to the plate: 10 µl per well.
5. Prepare membrane/Acceptor Beads solution and add this to the plates: 10 µl per well.
6. Add the Donor Beads: 30 µl per well.
7. Wrap the plate in aluminum foil and incubate on the shaker for 3 hours (very slowly) at RT.
8. Count on AlphaScreen – each plate pre incubates in the AlphaScreen for 3 minutes before counting.

The EC_{50} [pM] values may be calculated using the Graph-Pad Prism software (version 5). If desired, the fold variation in relation to GLP-1 may be calculated as EC_{50} (GLP-1)/ EC_{50} (analogue) – 3693.2.

Assay (II): Half-life in Minipigs

The purpose of this study is to determine the protraction in vivo of GLP-1 agonists after i.v. administration to minipigs, i.e. the prolongation of their time of action. This is done in a pharmacokinetic (PK) study, where the terminal half-life of the GLP-1 agonist in question is determined. By terminal half-life is generally meant the period of time it takes to halve a certain plasma concentration, measured after the initial distribution phase.

Male Göttingen minipigs are obtained from Ellegaard Göttingen Minipigs (Dalmose, Denmark) approximately 7-14 months of age and weighing from approximately 16-35 kg are used in the studies. The minipigs are housed individually and fed restrictedly once or twice daily with SDS minipig diet (Special Diets Services, Essex, UK). After at least 2 weeks of acclimatisation two permanent central venous catheters are implanted in vena cava caudalis or cranialis in each animal. The animals are allowed 1 week recovery after the surgery, and are then used for repeated pharmacokinetic studies with a suitable wash-out period between dosings.

The animals are fasted for approximately 18 h before dosing and for at least 4 h after dosing, but have ad libitum access to water during the whole period.

The GLP-1 agonist is dissolved in 50 mM sodium phosphate, 145 mM sodium chloride, 0.05% tween 80, pH 7.4 to a concentration of usually from 20-60 nmol/ml. Intravenous injections (the volume corresponding to usually 1-2 nmol/kg, for example 0.033ml/kg) of the compounds are given through one catheter, and blood is sampled at predefined time points for up till 13 days post dosing (preferably through the other catheter). Blood samples (for example 0.8 ml) are collected in EDTA buffer (8mM) and then centrifuged at 4°C and 1942G for 10 minutes. Plasma is pippetted into Micronic tubes on dry ice, and kept at -20°C until analyzed for plasma concentration of the respective GLP-1 compound using ELISA or a similar antibody based assay or LC-MS. Individual plasma concentration-time profiles are analyzed by a non-compartmental model in WinNonlin v. 5.0 (Pharsight Inc., Mountain View, CA, USA), and the resulting terminal half-lives (harmonic mean) determined.

Assay (III): Effect on Blood Glucose and Body Weight

The purpose of the study is to verify the effect of GLP-1 agonists on blood glucose (BG) and body weight (BW) in a diabetic setting. GLP-1 agonists may be tested in a dose-response study in an obese, diabetic mouse model (db/db mice) as described in the following.

Fifty db/db mice (Taconic, Denmark), fed from birth with the diet NIH31 (NIH 31M Rodent Diet, commercially available from Taconic Farms, Inc., US, see www.taconic.com), are enrolled for the study at the age of 7-9 weeks The mice are given free access to standard chow (e.g. Altromin 1324, Brogaarden, Gentofte, Denmark) and tap water and kept at 24°C. After 1-2 weeks of acclimatisation, the basal blood glucose is assessed twice on two consecutive days (i.e. at 9 am). The 8 mice with the lowest blood glucose values may be excluded from the experiments. Based on the mean blood glucose values, the remaining 42 mice may be selected for further experimentation and allocated to 7 groups (n=6) with matching blood glucose levels.

The mice may be used in experiments with duration of 5 days for up to 4 times. After the last experiment the mice are euthanised.

The seven groups may receive treatment as follows:

1: Vehicle, subcutaneous
2: GLP-1 agonist, 0.3 nmol/kg, subcutaneous
3: GLP-1 agonist, 1.0 nmol/kg, subcutaneous
4: GLP-1 agonist, 3.0 nmol/kg, subcutaneous
5: GLP-1 agonist, 10 nmol/kg, subcutaneous
6: GLP-1 agonist, 30 nmol/kg, subcutaneous
7: GLP-1 agonist, 100 nmol/kg, subcutaneous

Vehicle: 50mM sodium phosphate, 145 mM sodium chloride, 0.05% tween 80, pH 7.4.

The GLP-1 agonist is dissolved in the vehicle, e.g. to concentrations of 0.05, 0.17, 0.5, 1.7, 5.0 and 17.0 nmol/ml. Animals are dosed subcutaneous with a dose-volume of 6 ml/kg (i.e. 300 µl per 50 g mouse).

On the day of dosing, blood glucose is assessed at time -½h (8.30 am), where after the mice are weighed. The GLP-1 agonist is dosed at approximately 9 am (time 0). On the day of dosing, blood glucose is assessed e.g. at times 1, 2, 4 and 8 h (10 am, 11 am, 1 pm and 5 pm).

On the following days, the blood glucose is assessed e.g. at time 24, 48, 72, and 96h after dosing (i.e. at 9 am on day 2, 3, 4, 5). On each day, the mice are weighed following blood glucose sampling.

The mice are weighed individually on a digital weight.

Samples for the measurement of blood glucose are obtained from the tail tip capillary of conscious mice. Blood, 10 µl, is collected into heparinised capillaries and transferred to 500 µl glucose buffer (EKF system solution, Eppendorf, Germany). The glucose concentration is measured using the glucose oxidase method (glucose analyser Biosen 5040, EKF Diagnostic, GmbH, Barleben, Germany). The samples are kept at room temperature for up to 1 h until analysis. If analysis has to be postponed, samples are kept at 4°C for a maximum of 24 h.

ED_{50} is the dose giving rise to half-maximal effect in nmol /kg. This value is calculated on the basis of the ability of the GLP-1 agonists to lower body weight as well as the ability to lower blood glucose, as explained below.

ED_{50} for body weight is calculated as the dose giving rise to half-maximum effect on delta BW 24 hours following the subcutaneous administration of the GLP-1 agonist. For example, if the maximum decrease in body weight after 24 hours is 4.0 g, then ED_{50} bodyweight would be that dose in nmol/kg which gives rise to a decrease in body weight after 24 hours of

2.0 g. This dose (ED_{50} body weight) may be read from the dose-response curve.

ED_{50} for blood glucose is calculated as the dose giving rise to half-maximum effect on AUC delta BG 8 hours following the subcutaneous administration of the GLP-1 agonist.

The ED_{50} value may only be calculated if a proper sigmoidal dose-response relationship exists with a clear definition of the maximum response. Thus, if this would not be the case the GLP-1 agonist in question is re-tested in a different range of doses until the sigmoidal dose-response relationship is obtained.

Assay (IV): Effect on Food Intake

The purpose of this experiment is to investigate the effect of GLP-1 agonists on food intake in pigs. This is done in a pharmacodynamic (PD) study as described below, in which food intake is measured 1, 2, 3, and 4 days after administration of a single dose of the GLP-1 agonist, as compared to a vehicle-treated control group.

Female Landrace Yorkshire Duroc (LYD) pigs, approximately 3 months of age, weighing approximately 30-35 kg are used (n=3-4 per group). The animals are housed in a group for 1-2 weeks during acclimatisation to the animal facilities. During the experimental period the animals are placed in individual pens from Monday morning to Friday afternoon for measurement of individual food intake. The animals are fed ad libitum with pig fodder (Svinefoder, Antonio) at all times both during the acclimatisation and the experimental period. Food intake is monitored on line by logging the weight of fodder every 15 minutes. The system used is Mpigwin (Ellegaard Systems, Faaborg, Denmark).

The GLP-1 agonists are dissolved in a phosphate buffer (50 mM phosphate, 0.05% tween 80, pH 8) e.g. at concentrations of 12, 40, 120, 400 or 1200 nmol/ml corresponding to doses of 0.3, 1, 3, 10, or 30 nmol/kg. The phosphate buffer served as vehicle. Animals are dosed with a single subcutaneous dose of the GLP-1 agonist or vehicle (dose volume 0.025 ml/kg) on the morning of day 1, and food intake is measured for 4 days after dosing. On the last day of each study, 4 days after dosing, a blood sample for measurement of plasma exposure of the GLP-1 agonist is taken from the heart in anaesthetised animals. The animals are thereafter euthanised with an intra-cardial overdose of pentobarbitone. Plasma content of the GLP-1 agonist is analysed using ELISA or a similar antibody based assay.

Food intake is calculated as mean ± SEM 24 h food intake on the 4 days. Statistical comparisons of the 24 hour food intake in the vehicle vs. GLP-1 agonist group on the 4 days are done using one-way or two-way-ANOVA repeated measures, followed by Bonferroni post-test.

Assay (V): Stability against Degradation by Intestinal Enzymes

The purpose of this example is to test the stability against degradation by intestinal enzymes. GLP-1(7-37) may be used in the assay as a comparative compound. The strongest proteolytic activities in the intestine are of pancreatic origin and include the serine endopeptidases trypsin, chymotrypsin, and elastase as well as several types of carboxypeptidases. An assay with small intestine extract from rats was developed and used as described in the following.

Extracts from rat small intestine

Small intestines are prepared from rats and flushed with 8 ml of 150 mM NaCl, 20 mM Hepes pH 7.4. The solutions are centrifuged for 15 min at 4,600 rpm in a Heraeus Multifuge 3 S-R centrifuge with a 75006445 rotor. The supernatants are removed and filtered through a 0.22 µm Millipore Millex GV PVDF membrane. Filtrates of several animals are pooled to average out individual differences.

The protein content of the obtained extracts is determined by Bradford Assay (see e.g. Analytical Biochemistry (1976), vol. 72, p. 248-254, and Analytical Biochemistry (1996), vol. 236 p. 302-308).

Degradation assay

2.5 nmol of the GLP-1 agonists to be tested are incubated with the intestinal extract in a volume of 250 µl at 37°C over a period of one hour. Intestinal samples are assayed in presence of 20 mM Hepes at pH 7.4. The concentration of the intestinal extract is titrated in pilot experiments so that the half-life (t½) of GLP-1(7-37) is in the range of 10-20 minutes. The small intestine extract is used at a concentration of 1.4 µg/ml. All components except for the intestinal extract are mixed and pre-warmed for ten minutes at 37°C. Immediately after addition of the intestinal extract a sample of 50 µl is taken and mixed with the same volume of 1% trifluoroacetic acid (TFA). Further samples are taken accordingly after 15, 30, and 60 minutes.

Sample analysis

UPLC analysis: 10 µl of the samples are analysed by UPLC using a Waters Acquity system with a BEH C18 1.7 µm 2.1 x 50 mm column and a 30 to 65% gradient of 0.1% TFA and 0.07% TFA in acetonitrile over 5 minutes at a flow rate of 0.6 ml/min. After baseline subtraction the peak integrals of the intact compounds in the HPLC chromatogram recorded at a wavelength of 214 nm are determined.

MALDI-TOF analysis: 1 µl of each sample is transferred to a Bruker/Eppendorf PAC HCCA 384 MALDI target. Analysis is performed with a Bruker Autoflex matrix-assisted laser desorption and ionisation - time of flight (MALDI-TOF) mass spectrometer using the pre-defined

method “PAC_measure” with an extended detection range of 500 to 5000 Da and the pre-defined calibration method “PAC_calibrate”.

Data analysis: The peak integrals of the HPLC chromatograms are plotted against time. The half-life of the respective compound is calculated by fitting the data using SigmaPlot 9.0 software and an equation for a 2-parameter exponential decay. For each GLP-1 agonist tested, the relative half-life (relative $T_{½}$) is calculated as the half-life ($T_{½}$) of the compound in question, divided by the half-life ($T_{½}$) of GLP-1(7-37), determined in the same way.

While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

USE OF LONG-ACTING GLP-1 PEPTIDES

The present invention relates to improved uses of GLP-1 peptides in therapy.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of US Application 14/409,493, filed December 19, 2014, which is a 35 U.S.C. § 371 National Stage application of International Application PCT/EP2013/063004 (WO 2014/005858), filed JUNE 21, 2013, which claimed priority of European Patent Application 12174535.0, filed JULY 1, 2012 and European Patent Application 12186781.6, filed OCTOBER 1, 2012; this application claims priority under 35 U.S.C. § 119 of U.S. Provisional Application 61/694,837; filed AUGUST 30, 2012 and U.S. Provisional Application 61/708,162; filed OCTOBER 1, 2012.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 17, 2013 and amended on July 12, 2017, is named 8545US02_SeqList.txt and is 7,975 bytes in size.

SUMMARY

In one embodiment the invention relates to a method for a) reduction of HbA1c; b) prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) prevention or treatment of obesity, reducing body weight and/or food intake, or inducing satiety; wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof, wherein said GLP-1 agonist i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and iii) is administered once weekly or less often.

In one embodiment the invention relates to a GLP-1 agonist for use in a) the reduction of HbA1c; b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety; wherein said use comprises administration of said GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week, and wherein said GLP-1 agonist and/or administration optionally is as defined herein.

In one embodiment the invention relates to a composition comprising a GLP-1 agonist for use in a) the reduction of HbA1c; b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety; wherein said GLP-1 agonist i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); and ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and wherein said composition is administered once weekly or less often, and wherein said GLP-1 agonist and/or administration optionally is as defined herein.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows change in HbA1c following subcutaneous administration of placebo, semaglutide, or liraglutide to human subjects. *p<0.05 vs. placebo; **p<0.001 vs. placebo (based on adjusted means). Baseline values are for information only: data are model-adjusted for baseline HbA1c. Data are model-adjusted LS means, FAS LOCF. The estimates are from an ANOVA model with treatment, country and previous treatment as fixed effects and baseline HbA1c as covariate.

Fig. 2 shows mean change in HbA1c from baseline versus time; data are mean (1.96SE), FAS LOCF. The treatments are placebo (A); semaglutide 0.1 mg (B, dashed line), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F, dashed line), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I).

Fig. 3A and Fig. 3B show ~~shows~~ subjects reaching the AACE (Fig. 3A) or ADA (Fig. 3B) criteria for glycaemic control. The number of patients reaching the criteria per treatment is indicated in each bar. The treatments are placebo (A); semaglutide 0.1 mg (B), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I). *p<0.05 vs. placebo; **p<0.001 vs. placebo; ***p<0.0001 vs. placebo (based on adjusted means). Data are FAS LOCF. The estimates are from a logistic regression model treatment, country and previous treatment as fixed effects and baseline HbA1c as covariate. ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists.

Fig. 4 shows mean body weight change versus time; data are mean (1.96SE), FAS LOCF. The treatments are placebo (A); semaglutide 0.1 mg (B, dashed line), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F, dashed line), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I).

Fig. 5 shows body weight change from baseline at week 12. **p<0.001 vs. placebo; ***p<0.0001 vs. placebo (based on adjusted means. †: Baseline values for information only:

data are model-adjusted for baseline weight. Data are model-adjusted LS means, FAS LOCF. The estimates are from an ANOVA model with treatment, country and previous treatment as fixed effects and baseline weight as covariate.

SE: Standard error. FAS: Full analysis set. LOCF: Last observation carried forward.

DESCRIPTION

The present invention relates to an improved use of GLP-1 agonists in therapy. In one embodiment the invention relates to certain dosage regimes of GLP-1 agonists which provide improved effect in diseases or conditions, such as prevention and/or treatment of type 2 diabetes and obesity. In one embodiment the methods of the present invention provides surprisingly showed improved reduction of HbA1c and reduction of body weight. In one embodiment the GLP-1 agonist is administered in an amount which provides an improved a) reduction in HbA1c or b) reduction in body weight compared to administration of 1.8 mg liraglutide or less, such as 0.8 mg liraglutide or less, per day.

In one embodiment the invention relates to a method for reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the method is for reduction of HbA1c. In one embodiment the method is for prevention or treatment of type 2 diabetes. In one embodiment the method is for prevention or treatment of hyperglycemia. In one embodiment the method is for prevention or treatment of impaired glucose tolerance. In one embodiment the method is for prevention or treatment of non-insulin dependent diabetes. In one embodiment the method of the invention comprises delaying or preventing diabetic disease progression. In one embodiment a HbA1c level below 7% is achieved. In one embodiment the level of HbA1c is determined according to the method defined by the Diabetes Control and Complications Trial (DCCT). In one embodiment the level of HbA1c is determined according to the method defined by the International Federation of Clinical Chemistry (IFCC).

In one embodiment the invention relates to a method for treating or preventing obesity, for reducing body weight and/or food intake, or for inducing satiety, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the method is for prevention or treatment of obesity. In one embodiment the

method is for reducing body weight and/or food intake. In one embodiment the method is for inducing satiety.

In one embodiment the GLP-1 agonist has a half-life of at least 24 hours, such as at least 48 hours, at least 60 hours, or at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours, or optionally at least 120 hours, at least 132 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

In one embodiment the GLP-1 agonist is administered twice weekly or less often, once weekly or less often, or once weekly or less often. In one embodiment the GLP-1 agonist is administered once every secondly week or less often, once every third week or less often, or once a month or less often.

In one embodiment the GLP-1 agonist is administered in an amount per week of at least 0.8 mg, at least 0.9 mg, or at least 1.0 mg. In one embodiment the GLP-1 agonist is administered in an amount per week of at least 1.1 mg, at least 1.2 mg, or at least 1.3 mg. In one embodiment the GLP-1 agonist is administered in an amount per week of at least 1.4 mg, at least 1.5 mg, or at least 1.6 mg.

In one embodiment the GLP-1 agonist is administered in an amount per week equivalent to at least 0.8 mg, at least 0.9 mg, or at least 1.0 mg semaglutide. In one embodiment the GLP-1 agonist is administered in an amount per week equivalent to at least 1.1 mg, at least 1.2 mg, or at least 1.3 mg semaglutide. In one embodiment the GLP-1 agonist is administered in an amount per week equivalent to at least 1.4 mg, at least 1.5 mg, or at least 1.6 mg semaglutide.

In one embodiment the GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

In one embodiment the GLP-1 agonist is administered by parenteral administration, such as subcutaneous injection.

In one embodiment the GLP-1 agonist is a GLP-1 peptide. In one embodiment the GLP-1 peptide comprises no more than 5, such as no more than 4 or no more than 3, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37). In one embodiment the GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code.

In one embodiment the GLP-1 peptide is a DPPIV protected GLP-1 peptide. In one embodiment the GLP-1 peptide is DPPIV stabilised.

In one embodiment the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100 pM, optionally determined by Assay (I).

In one embodiment the invention relates to a GLP-1 agonist for use in the reduction of HbA1c or for use in the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to a GLP-1 agonist for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to a composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to a composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the GLP-1 agonist is administered with another therapeutic agent. Administration with another therapeutic agent may be carried out as administration of the GLP-1 agonist and the other therapeutic agent within the same therapeutic window (e.g. withinin a period of two weeks, a period of one week, or in a 96, 72, or 48 hour period, etc.). The treatment with a GLP-1 agonist according to the present invention may be combined with one or more additional therapeutic agents, e.g. selected from antidiabetic agents, antiobesity agents, appetite regulating agents, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity; examples of these therapeutic agents are: sulphonylureas, thiazolidinediones, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists, and DPP-IV (dipeptidyl peptidase-IV) inhibitors.

In one embodiment, as used herein, an “amount equivalent to” when used in relation to GLP-1 agonists refers to amounts of a first GLP-1 agonist and a second GLP-1 agonist having GLP-1 receptor potency (i.e. EC_{50}) within ±30%, such as within ±20% or within ±10%, of each other optionally determined by Assay (I) described herein and having a half-life within ±30%, such as within ±20% or within ±10%, of each other optionally determined by Assay (II) described herein.

In one embodiment an "effective amount" of a GLP-1 agonist as used herein means an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease or state and its complications. An amount adequate to accomplish this is defined as "effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary.

In one embodiment the term "treatment" or "treating" as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. In one embodiment the term "treatment" or "treating" is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications; to delay the progression of the disease, disorder, or condition; to alleviate or relieve the symptoms and complications; and/or, to cure or eliminate the disease, disorder, or condition as well as to prevent the condition. In one embodiment prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications.

In one embodiment the term "hydrophilic spacer" as used herein means a spacer that separates a peptide and an albumin binding residue with a chemical moiety which comprises at least 5 non- hydrogen atoms where 30-50% of these are either N or O.

In one embodiment the term "analogue" as used herein referring to a polypeptide means a modified peptide wherein one or more amino acid residues of the peptide have been substituted by other amino acid residues and/or wherein one or more amino acid residues have been deleted from the peptide and or wherein one or more amino acid residues have been added to the peptide. Such addition or deletion of amino acid residues can take place at the N-terminal of the peptide and/or at the C-terminal of the peptide. A simple system is used to

describe analogues: For example Arg^{34}GLP-1 (7-37) Lys designates a GLP-1 analogue wherein the naturally occurring lysine at position 34 has been substituted with arginine and a lysine residue has been added to the C-terminal (position 38).

In one embodiment the term "GLP-1 peptide" as used herein means GLP-1 (7-37), a GLP-1 analogue, a GLP-1 derivative or a derivative of a GLP-1 analogue.

In one embodiment the term "exendin-4 peptide" as used herein means exendin-4 (1-39), an exendin-4 analogue, an exendin-4 derivative or a derivative of an exendin-4 analogue.

In one embodiment the term “DPP-IV protected” as used herein referring to a polypeptide means a polypeptide which has been chemically modified in order to render said compound resistant to the plasma peptidase dipeptidyl aminopeptidase-4 (DPP-IV). The DPP-IV enzyme in plasma is known to be involved in the degradation of several peptide hormones, e.g. GLP-1, Exendin-4 etc. Thus a considerable effort is being made to develop GLP-1 agonists less susceptible to DPP-IV mediated hydrolysis in order to reduce the rate of degradation by DPP-IV.

The present invention also relates to a GLP-1 agonist of the invention, for use as a medicament. In particular embodiments, the GLP-1 agonist of the invention may be used for the following medical treatments:

(i) prevention and/or treatment of all forms of diabetes, such as hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, non-insulin dependent diabetes, MODY (maturity onset diabetes of the young), gestational diabetes, and/or for reduction of HbA1c;

(ii) delaying or preventing diabetic disease progression, such as progression in type 2 diabetes, delaying the progression of impaired glucose tolerance (IGT) to insulin requiring type 2 diabetes, and/or delaying the progression of non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes;

(iii) prevention and/or treatment of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; and/or delaying gastric emptying.

In another particular embodiment, the indication is (i). In a further particular embodiment the indication is (ii). In a still further particular embodiment the indication is (iii). In one embodiment the indication is type 2 diabetes and/or obesity.

In one embodiment the method comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions defined herein. In one embodiment the indication is (i) and (iii). In one embodiment the indication is (ii) and (iii). In one embodiment the

method comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions selected from a) and b), a) and c), b) and c), or a), b) and c) as defined in claim 1.

In one embodiment the invention relates to administration of an effective amount of a GLP-1 agonist.

In one embodiment as used herein, specific values given in relation to numbers or intervals may be understood as the specific value or as about the specific value.

FUNCTIONAL PROPERTIES

In a first functional aspect, the GLP-1 agonists of the invention have a good potency. Also, or alternatively, in a second functional aspect, the GLP-1 agonists of the invention have a protracted pharmacokinetic profile. Also, or alternatively, in a third functional aspect, the GLP-1 agonists of the invention are stable against degradation by gastro intestinal enzymes.

Biological activity (potency)

According to the first functional aspect, the GLP-1 agonists of the invention are biologically active, or potent. In a particular embodiment, “potency” and/or “activity” refers to in vitro potency, i.e. performance in a functional GLP-1 receptor assay, more in particular to the capability of stimulating cAMP formation in a cell line expressing the cloned human GLP-1 receptor.

The stimulation of the formation of cAMP in a medium containing the human GLP-1 receptor may preferably be determined using a stable transfected cell-line such as BHK467-12A (tk-ts13), and/or using for the determination of cAMP a functional receptor assay, e.g. based on competition between endogenously formed cAMP and exogenously added biotin-labelled cAMP, in which assay cAMP is more preferably captured using a specific antibody, and/or wherein an even more preferred assay is the AlphaScreen cAMP Assay, such as the one described in Assay (I).

In one embodiment the term half maximal effective concentration (EC_{50}) generally refers to the concentration which induces a response halfway between the baseline and maximum, by reference to the dose response curve. EC_{50} is used as a measure of the potency of a compound and represents the concentration where 50% of its maximal effect is observed.

The in vitro potency of the GLP-1 agonists of the invention may be determined as described above, and the EC_{50} of the GLP-1 agonist in question determined. The lower the EC_{50}, the better the potency.

In a particular embodiment, the medium has the following composition (final in-assay

concentrations): 50 mM TRIS-HCl; 5 mM HEPES; 10 mM $MgCl_2$, $6H_2O$; 150 mM NaCl; 0.01% Tween; 0.1% BSA ; 0.5 mM IBMX; 1 mM ATP; 1 µM GTP; pH 7.4.

In a further particular embodiment, the GLP-1 agonist of the invention has an in vitro potency corresponding to an EC_{50} at or below 3000pM, such as below 2000pM, below 1000pM, or below 500pM, or such as below 200 pM or below 100 pM.

In another particular embodiment the GLP-1 agonist of the invention are potent in vivo, which may be determined as is known in the art in any suitable animal model, as well as in clinical trials.

The diabetic db/db mouse is one example of a suitable animal model, and the blood glucose lowering effect may be determined in such mice in vivo, e.g. as described in Assay (III), or as described in Example 43 of WO09/030738.

Also, or alternatively, the effect on food intake in vivo may be determined in pharmacodynamic studies in pigs, e.g. as described in Assay (IV).

Protraction - half life in vivo in minipigs

According to the second functional aspect, the GLP-1 agonists of the invention are protracted. In a particular embodiment protraction may be determined as half-life ($T_{½}$) in vivo in minipigs after i.v. administration. In additional embodiments, the half-life is at least 24 hours, such as at least 48 hours, at least 60 hours, at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours.

A suitable assay for determining half-life in vivo in minipigs after i.v. administration is disclosed in Assay (II).

Degradation by gastro intestinal enzymes

According to the third functional aspect, the GLP-1 agonists of the invention are stable, or stabilised, against degradation by one or more gastro intestinal enzymes.

Gastro intestinal enzymes include, without limitation, exo and endo peptidases, such as pepsin, trypsin, chymotrypsin, elastases, and carboxypeptidases. The stability may be tested against these gastro intestinal enzymes in the form of purified enzymes, or in the form of extracts from the gastrointestinal system.

In a particular embodiment, the GLP-1 agonist of the invention has an in vitro half-life ($T_{½}$), in an extract of rat small intestines, divided by the corresponding half-life ($T_{½}$) of GLP-1(7-37), of at least 1, such as above 1.0, at least 1.2, at least 2.0, or such as at least 3.0, or at least 4.0. In other words, a ratio(SI) may be defined for each GLP-1 agonist, viz. as the in vitro half-

life ($T_{½}$) of the GLP-1 agonist in question, in an extract of rat small intestines, divided by the corresponding half-life ($T_{½}$) of GLP-1(7-37).

A suitable assay for determining in vitro half-life in an extract of rat small intestines is disclosed in Assay (V).

GLP-1 AGONISTS

In one embodiment the GLP-1 peptide comprises an Aib residue in position 8.

In one embodiment the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

In one embodiment the GLP-1 peptide is attached to a hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

In one embodiment the GLP-1 peptide is exendin-4, an exendin-4-analogue, or a derivative of exendin-4.

In one embodiment the GLP-1 agonist peptide comprises the amino acid sequence of the following formula:

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 (SEQ ID NO: 2).

In one embodiment the GLP-1 agonist comprises an albumin binding residue attached via a hydrophilic spacer to the C-terminal amino acid residue of said GLP-1 peptide.

In one embodiment the GLP-1 agonist comprises a second albumin binding residue is attached to an amino acid residue which is not the C-terminal amino acid residue.

In one embodiment the GLP-1 peptide is selected from the group consisting of semaglutide, albiglutide and dulaglitide.

In one embodiment the GLP-1 peptide has the following structure:

His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg (SEQ ID NO: 3).

In one embodiment the GLP-1 peptide has the following structure:

(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2 (SEQ ID NO: 4)–genetically fused to human albumin.

In one embodiment the GLP-1 peptide is dulaglitide.

In one embodiment the GLP-1 agonists of the invention have GLP-1 activity. In one embodiment "a GLP-1 agonist" is understood to refer to any compound, including peptides and non-peptide compounds, which fully or partially activate the human GLP-1 receptor. In one embodiment the "GLP-1 agonist" is any peptide or non-peptide small molecule that binds to a GLP-1 receptor, preferably with an affinity constant (K_D) or a potency (EC_{50}) of below 1 μM, e. g. below 100 nM as measured by methods known in the art (see e. g., WO 98/08871). In one embodiment methods for identifying GLP-1 agonists are described in WO 93/19175 (Novo Nordisk A/S) and examples of suitable GLP-1 agonists which can be used according to the present invention includes those referred to in WO 2005/027978 (Novo Nordisk A/S), the teachings of which are both incorporated by reference herein. “GLP-1 activity” refers to the ability to bind to the GLP-1 receptor and initiate a signal transduction pathway resulting in insulinotropic action or other physiological effects as is known in the art. For example, the GLP-1 agonists of the invention can be tested for GLP-1 activity using the assay described in Assay (I) herein.

In yet another embodiment the GLP-1 agonist is a stable GLP-1 agonist. As used herein a "stable GLP-1 agonist" means a GLP-1agonist which exhibits an in vivo plasma elimination half-life of at least 24 hours in man, optionally determined by the method described below. Examples of stable GLP-1 agonists can be found in WO2006/097537.

In one embodiment the method for determination of plasma elimination half-life of a compound in man may be carried out as follows: The compound is dissolved in an isotonic buffer, pH 7.4, PBS or any other suitable buffer. The dose is injected peripherally, preferably in the abdominal or upper thigh. Blood samples for determination of active compound are taken at frequent intervals, and for a sufficient duration to cover the terminal elimination part (e. g., Pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24 (day 2), 36 (day 2), 48 (day 3), 60 (day 3), 72 (day 4) and 84 (day 4) hours post dose). Determination of the concentration of active compound is performed as described in Wilken *et al.*, Diabetologia 43 (51), 2000. Derived pharmacokinetic parameters are calculated from the concentration-time data for each individual subject by use of non-compartmental methods, using the commercially available software WinNonlin Version 2.1 (Pharsight, Cary, NC, USA). The terminal elimination rate constant is estimated by log-linear regression on the terminal log-linear part of the concentration-time curve, and used for calculating the elimination half-life.

In one embodiment the GLP-1 agonist is formulated so as to have a half-life in man of at least 48 hours. This may be obtained by sustained release formulations known in the art.

In one embodiment the GLP-1 agonist is a GLP-1 peptide. In one embodiment the GLP-1 peptide is selected from GLP-1 (7-35), GLP-1 (7-36), GLP-1 (7-36)-amide, GLP-1 (7-37), GLP-1 (7-38), GLP-1 (7-39), GLP-1 (7-40), GLP-1 (7-41) or an analogue or derivative thereof. In one embodiment the GLP-1 peptide comprises no more than 15, such as no more than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37). In one embodiment the GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code. In yet another embodiment, the GLP-1 agonist is exendin-4 or exendin-3, an exendin-4 or exendin-3 analogue, or a derivative of any of these.

In one embodiment the GLP-1 peptide is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglitide. In one embodiment the GLP-1 peptide is semaglutide. WO 06/097537 discloses semaglutide (Example 4), a mono-acylated GLP-1 agonist for once weekly administration. In one embodiment the GLP-1 peptide is exenatide. In one embodiment the GLP-1 peptide comprises the amino acid sequence of the formula: H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 (SEQ ID NO: 2). Exenatide is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. Exenatide displays biological properties similar to GLP-1. In some embodiments the composition is BYDUREON® (a long acting release formula of exenatide in PLGA particles). In one embodiment the “Bydureon® composition” refer to a powder comprising exenatide, poly (D,L-lactide-co-glycolide), and sucrose which immediately prior to injection is reconstituted in a solvent comprising carmellose sodium, sodium chloride, polysorbate 20, monobasic sodium phosphate (e.g. its monohydrate), dibasic sodium phosphate (e.g. its heptahydrate), and water for injections. In one embodiment the GLP-1 peptide has the structure (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2 (SEQ ID NO: 4)–genetically fused to human albumin. Albiglutide is a recombinant human serum albumin (HSA)-GLP-1 hybrid protein, likely a GLP-1 dimer fused to HSA. The constituent GLP-1 peptide is analogue, in which Ala at position 8 has been substituted by Glu. In one embodiment the GLP-1 peptide is dulaglitide. Dulaglutide is a GLP-1-Fc construct (GLP-1 - linker - Fc from IgG4). In one embodiment the GLP-1 peptide has the structure His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg (SEQ ID NO: 3). Liraglutide is a mono-acylated GLP-1 agonist for once daily administration which is marketed as of 2009 by Novo Nordisk A/S, is disclosed in WO 98/08871 Example 37.

In one embodiment the present invention encompasses pharmaceutically acceptable salts of the GLP-1 agonists. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium, and alkylated ammonium salts. Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present GLP-1 agonists are able to form.

In one embodiment the route of administration of GLP-1 agonists may be any route which effectively transports the active compound to the appropriate or desired site of action, such as parenteral. In one embodiment medicaments or pharmaceutical compositions comprising a GLP-1 agonist, such as semaglutide, may be administered parenterally to a patient in need thereof. In one embodiment 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. A further option is a composition which may be a powder or a liquid for the administration of a GLP-1 agonist in the form of a nasal or pulmonal spray. As a still further option, the GLP-1 agonist can also be administered transdermally, e.g., from a patch, optionally an iontophoretic patch, or transmucosally, e.g., bucally. The above-mentioned possible ways to administer GLP-1 agonists are not considered as limiting the scope of the invention.

In one embodiment the GLP-1 agonist is co-administered together with a further therapeutically active agent used in the treatments defined herein.

In one embodiment the GLP-1 peptide comprises the amino acid sequence of the formula (I) (SEQ ID NO: 5):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa_{16}-Ser-Xaa_{18}-$Xaa_{19}Xaa_{20}$GluXaa_{22}-Xaa_{23}-Ala-Xaa_{25}-Xaa_{26}-Xaa_{27}-Phe-Ile-Xaa_{30}-Trp-Leu-Xaa_{33}-Xaa_{34}-Xaa_{35}-Xaa_{36}-Xaa_{37}-Xaa_{38}-Xaa_{39}-Xaa_{40}-Xaa_{41}-Xaa_{42}-Xaa_{43}-Xaa_{44}-Xaa_{45}-Xaa_{46}

Formula (I)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{25} is Ala or Val;

Xaa_{26} is Lys, Glu or Arg;

Xaa_{27} is Glu or Leu;

Xaa_{30} is Ala, Glu or Arg;

Xaa_{33} is Val or Lys;

Xaa_{34} is Lys, Glu, Asn or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg, Gly or Lys;

Xaa_{37} is Gly, Ala, Glu, Pro, Lys, amide or is absent;

Xaa_{38} is Lys, Ser, amide or is absent;

Xaa_{39} is Ser, Lys, amide or is absent;

Xaa_{40} is Gly, amide or is absent;

Xaa_{41} is Ala, amide or is absent;

Xaa_{42} is Pro, amide or is absent;

Xaa_{43} is Pro, amide or is absent;

Xaa_{44} is Pro, amide or is absent;

Xaa_{45} is Ser, amide or is absent;

Xaa_{46} is amide or is absent;

provided that if Xaa_{38}, Xaa_{39}, Xaa_{40}, Xaa_{41}, Xaa_{42}, Xaa_{43}, Xaa_{44}, Xaa_{45} or Xaa_{46} is absent then each amino acid residue downstream is also absent.

In one embodiment the GLP-1 peptide comprises the amino acid sequence of formula (II) (SEQ ID NO: 6):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Xaa_{18}-Tyr-Leu-Glu-Xaa22-Xaa_{23}-Ala-Ala-Xaa_{26}-Glu-Phe-Ile-Xaa_{3o}-Trp-Leu-Val-Xaa_{34}-Xaa_{35}-Xaa_{36}-$Xaa_{37}Xaa_{38}$

Formula (II)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine,-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-

pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{26} is Lys, Glu or Arg; Xaa30 is Ala, Glu or Arg;

Xaa_{34} is Lys, Glu or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg or Lys;

Xaa_{37} is Gly, Ala, Glu or Lys;

Xaa_{38} is Lys, amide or is absent.

In one embodiment the GLP-1 peptide is a DPPIV protected GLP-1 peptide.

In one embodiment the GLP-1 peptide is DPPIV stabilised.

In one embodiment the GLP-1 peptide comprises an Aib residue in position 8.

In one embodiment the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

In one embodiment the GLP-1 peptide comprises Arg^{34}GLP-1 (7-37) or [Aib8,Arg34]GLP-1-(7-37).

In one embodiment the GLP-1 agonist comprises an albumin binding residue which is covalently attached, optionally via a hydrophilic spacer. In one embodiment said albumin binding residue is covalently attached, optionally via a hydrophilic spacer, to the C-terminal amino acid residue of said GLP-1 peptide or an amino acid residue which is not the C-terminal amino acid residue. In one embodiment the GLP-1 peptide is attached to a hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

Human Glucagon-Like Peptide-1 is GLP-1(7-37) and has the sequence HAEGTFTSDVSSYLEGQAAKEFI AWLVKGRG (SEQ ID NO: 1). GLP-1(7-37) may also be designated "native" GLP-1. In the sequence listing, the first amino acid residue of SEQ ID NO: 1

(histidine) is assigned no. 1. However, in what follows - according to established practice in the art - this histidine residue is referred to as no. 7, and subsequent amino acid residues are numbered accordingly, ending with glycine no. 37. Therefore, generally, any reference herein to an amino acid residue number or a position number of the GLP-1(7-37) sequence is to the sequence starting with His at position 7 and ending with Gly at position 37. A non-limiting example of a suitable analogue nomenclature is [Aib^8,Arg^{34},Lys^{37}]GLP-1(7-37), which designates a GLP-1(7-37) analogue, in which the alanine at position 8 has been substituted with α-aminoisobutyric acid (Aib), the lysine at position 34 has been substituted with arginine, and the glycine at position 37 has been substituted with lysine.

In one embodiment the GLP-1 agonist exhibits at least 60%, 65%, 70%, 80% or 90% sequence identity to GLP-1(7-37) over the entire length of GLP-1(7-37). As an example of a method for determination of sequence identity between two analogues the two peptides [Aib8]GLP-1(7-37) and GLP-1(7-37) are aligned. The sequence identity of [Aib8]GLP-1(7-37) relative to GLP-1(7-37) is given by the number of aligned identical residues minus the number of different residues divided by the total number of residues in GLP-1(7-37). Accordingly, in said example the sequence identity is (31-1)/31. In one embodiment non-peptide moieties of the GLP-1 agonist are not included when determining sequence identity.

In one embodiment the GLP-1 agonist is a derivative. In one embodiment the term “derivative” as used herein in the context of a GLP-1 agonist, peptide or analogue means a chemically modified GLP-1 agonist, peptide or analogue, in which one or more substituents have been covalently attached to the agonist, peptide or analogue. The substituent may also be referred to as a side chain. Typical modifications are amides, carbohydrates, alkyl groups, acyl groups, esters and the like. An example of a derivative of GLP-1(7-37) is $N^{\varepsilon 26}$-(γ-Glu(N^{α}-hexadecanoyl)) - [Arg^{34}, Lys^{25}]) GLP-1 (7- 37).

In a particular embodiment, the side chain is capable of forming non-covalent aggregates with albumin, thereby promoting the circulation of the GLP-1 agonist with the blood stream, and also having the effect of protracting the time of action of the GLP-1 agonist, due to the fact that the aggregate of the GLP-1 agonist and albumin is only slowly disintegrated to release the active pharmaceutical ingredient. Thus, the substituent, or side chain, as a whole may be referred to as an albumin binding moiety.

In particular embodiments, the side chain has at least 10 carbon atoms, or at least 15, 20, 25, 30, 35, or at least 40 carbon atoms. In further particular embodiments, the side chain may further include at least 5 hetero atoms, in particular O and N, for example at least 7, 9, 10, 12, 15, 17, or at least 20 hetero atoms, such as at least 1, 2, or 3 N-atoms, and/or at least 3, 6,

9, 12, or 15 O-atoms.

In another particular embodiment the albumin binding moiety comprises a portion which is particularly relevant for the albumin binding and thereby the protraction, which portion may accordingly be referred to as a protracting moiety. The protracting moiety may be at, or near, the opposite end of the albumin binding moiety, relative to its point of attachment to the peptide.

In a still further particular embodiment the albumin binding moiety comprises a portion in between the protracting moiety and the point of attachment to the peptide, which portion may be referred to as a linker, linker moiety, spacer, or the like. The linker may be optional, and hence in that case the albumin binding moiety may be identical to the protracting moiety.

In particular embodiments, the albumin binding moiety and/or the protracting moiety is lipophilic, and/or negatively charged at physiological pH (7.4).

The albumin binding moiety, the protracting moiety, or the linker may be covalently attached to a lysine residue of the GLP-1 peptide by acylation. Additional or alternative conjugation chemistry includes alkylation, ester formation, or amide formation, or coupling to a cysteine residue, such as by maleimide or haloacetamide (such as bromo-/fluoro-/iodo-) coupling.

In one embodiment an active ester of the albumin binding moiety, e.g. comprising a protracting moiety and a linker, is covalently linked to an amino group of a lysine residue, e.g. the epsilon amino group thereof, under formation of an amide bond (this process being referred to as acylation).

Unless otherwise stated, when reference is made to an acylation of a lysine residue, it is understood to be to the epsilon-amino group thereof.

For the present purposes, the terms "albumin binding moiety", "protracting moiety", and "linker" may include the unreacted as well as the reacted forms of these molecules. Whether or not one or the other form is meant is clear from the context in which the term is used.

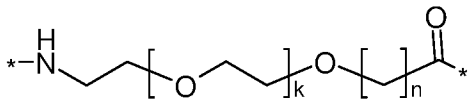
For the attachment to the GLP-1 agonist, the acid group of the fatty acid, or one of the acid groups of the fatty diacid, forms an amide bond with the epsilon amino group of a lysine residue in the GLP-1 peptide, e.g. via a linker.

In one embodiment the term "fatty acid" refers to aliphatic monocarboxylic acids having from 4 to 28 carbon atoms, it is optionally unbranched, and/or even numbered, and it may be saturated or unsaturated.

In one embodiment the term "fatty diacid" refers to fatty acids as defined above but with an additional carboxylic acid group in the omega position. Thus, fatty diacids are dicarboxylic acids.

Each of the two linkers of the GLP-1 agonist of the invention may comprise the following first linker element:

Chem. 5:



,

wherein k is an integer in the range of 1-5, and n is an integer in the range of 1-5.

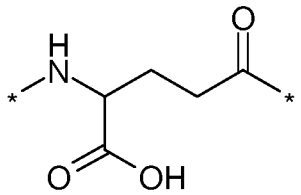
In a particular embodiment, when k=1 and n= 1, this linker element may be designated OEG, or a di-radical of 8-amino-3,6-dioxaoctanic acid, and/or it may be represented by the following formula:

Chem. 5a:

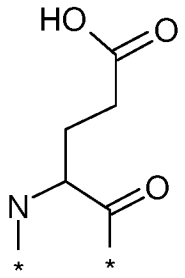
-NH-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-.

In another particular embodiment, each linker of the GLP-1 agonist of the invention may further comprise, independently, a second linker element, e.g. a Glu di-radical, such as Chem. 6 and/or Chem. 7:

Chem. 6:



Chem. 7:



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wherein the Glu di-radical may be included p times, where p is an integer in the range of 1-3.

Chem. 6 may also be referred to as gamma-Glu, or briefly gGlu, due to the fact that it is the gamma carboxy group of the amino acid glutamic acid which is here used for connection to another linker element, or to the epsilon-amino group of lysine. As explained above, the other

linker element may, for example, be another Glu residue, or an OEG molecule. The amino group of Glu in turn forms an amide bond with the carboxy group of the protracting moiety, or with the carboxy group of, e.g., an OEG molecule, if present, or with the gamma-carboxy group of, e.g., another Glu, if present.

Chem. 7 may also be referred to as alpha-Glu, or briefly aGlu, or simply Glu, due to the fact that it is the alpha carboxy group of the amino acid glutamic acid which is here used for connection to another linker element, or to the epsilon-amino group of lysine.

The above structures of Chem. 6 and Chem. 7 cover the L-form, as well as the D-form of Glu. In particular embodiments, Chem. 6 and/or Chem. 7 is/are, independently, a) in the L-form, or b) in the D-form.

In still further particular embodiments the linker has a) from 5 to 41 C-atoms; and/or b) from 4 to 28 hetero atoms.

The concentration in plasma of the GLP-1 agonists of the invention may be determined using any suitable method. For example, LC-MS (Liquid Chromatography Mass Spectroscopy) may be used, or immunoassays such as RIA (Radio Immuno Assay), ELISA (Enzyme-Linked Immuno Sorbent Assay), and LOCI (Luminescence Oxygen Channeling Immunoasssay). General protocols for suitable RIA and ELISA assays are found in, e.g., WO09/030738 on p. 116-118. A preferred assay is the LOCI (Luminescent Oxygen Channeling Immunoassay), generally as described for the determination of insulin by Poulsen and Jensen in Journal of Biomolecular Screening 2007, vol. 12, p. 240-247 - briefly blood samples may be collected at desired intervals, plasma separated, immediately frozen, and kept at -20°C until analyzed for plasma concentration of the respective GLP-1 agonist; the donor beads are coated with streptavidin, while acceptor beads are conjugated with a monoclonal antibody recognising a mid-/C-terminal epitope of the peptide; another monoclonal antibody, specific for the N-terminus, is biotinylated; the three reactants are combined with the analyte and formed a two-sited immuno-complex; illumination of the complex releases singlet oxygen atoms from the donor beads, which are channeled into the acceptor beads and triggered chemiluminescence which may be measured in an Envision plate reader; the amount of light is proportional to the concentration of the compound.

In one embodiment the term “Aib” as used herein refers to α-aminoisobutyric acid.

PHARMACEUTICAL COMPOSITIONS

An administered dose may contain from 5 mg - 100 mg of the GLP-1 agonist, or from

5-50 mg, or from 5-20 mg, or from 5-10 mg of the GLP-1 agonist.

In one embodiment the composition is BYDUREON® (a long acting release formula of exenatide in PLGA particles).

Pharmaceutical compositions comprising a GLP-1 agonist of the invention or a pharmaceutically acceptable salt, amide, or ester thereof, and a pharmaceutically acceptable excipient may be prepared as is known in the art.

In one embodiment the term "excipient" broadly refers to any component other than the active therapeutic ingredient(s). The excipient may be an inert substance, an inactive substance, and/or a not medicinally active substance. The formulation of pharmaceutically active ingredients with various excipients is known in the art, see e.g. Remington: The Science and Practice of Pharmacy (e.g. 19th edition (1995), and any later editions). Non-limiting examples of excipients are: solvents, diluents, buffers, preservatives, tonicity regulating agents (e.g isotonic agents), chelating agents, stabilisers (e.g. oxidation inhibitors, aggregation inhibitors, surfactants, and/or protease inhibitors).

Examples of formulations include liquid formulations, i.e. aqueous formulations comprising water. A liquid formulation may be a solution, or a suspension. An aqueous formulation typically comprises at least 50% w/w water, or at least 60%, 70%, 80%, or even at least 90% w/w of water.

Alternatively, a pharmaceutical composition may be a solid formulation, e.g. a freeze-dried or spray-dried composition, which may be used as is, or whereto the physician or the patient adds solvents, and/or diluents prior to use.

The pH in an aqueous formulation may be anything between pH 3 and pH 10, for example from about 7.0 to about 9.5; or from about 3.0 to about 7.0.

Still further, a pharmaceutical composition may be formulated as is known in the art of oral formulations of insulinotropic compounds, e.g. using any one or more of the formulations described in WO 2008/145728.

A composition may be administered in several dosage forms, for example as a solution; a suspension; an emulsion; a microemulsion; multiple emulsions; a foam; a salve; a paste; a plaster; an ointment; a tablet; a coated tablet; a chewing gum; a rinse; a capsule such as hard or soft gelatine capsules; a suppositorium; a rectal capsule; drops; a gel; a spray; a powder; an aerosol; an inhalant; eye drops; an ophthalmic ointment; an ophthalmic rinse; a vaginal pessary; a vaginal ring; a vaginal ointment; an injection solution; an in situ transforming solution such as in situ gelling, setting, precipitating, and in situ crystallisation; an infusion solution; or as an implant.

A composition may further be compounded in a drug carrier or drug delivery system, e.g. in order to improve stability, bioavailability, and/or solubility. In a particular embodiment a composition may be attached to such system through covalent, hydrophobic, and/or electrostatic interactions. The purpose of such compounding may be, e.g., to decrease adverse effects, achieve chronotherapy, and/or increase patient compliance.

A composition may also be used in the formulation of controlled, sustained, protracting, retarded, and/or slow release drug delivery systems.

The composition may be administered by parenteral administration. Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal, or intravenous injection by means of a syringe, optionally a pen-like syringe, or by means of an infusion pump.

PRODUCTION PROCESSES

In one embodiment GLP-1 peptides can be produced by appropriate derivatisation of an appropriate peptide backbone which has been produced by recombinant DNA technology or by peptide synthesis (e.g., Merrifield-type solid phase synthesis) as known in the art of peptide synthesis and peptide chemistry.

In one embodiment the production of peptides like GLP-1(7-37) and GLP-1 analogues is well known in the art. The GLP-1 moiety of the GLP-1 peptide of the invention (or fragments thereof) may for instance be produced by classical peptide synthesis, e.g., solid phase peptide synthesis using t-Boc or Fmoc chemistry or other well established techniques, see, e.g., Greene and Wuts, “Protective Groups in Organic Synthesis”, John Wiley & Sons, 1999, Florencio Zaragoza Dörwald, “Organic Synthesis on solid Phase”, Wiley-VCH Verlag GmbH, 2000, and “Fmoc Solid Phase Peptide Synthesis”, Edited by W.C. Chan and P.D. White, Oxford University Press, 2000.

In one embodiment GLP-1 agonists may be produced by recombinant methods, viz. by culturing a host cell containing a DNA sequence encoding the GLP-1 agonist and capable of expressing the peptide in a suitable nutrient medium under conditions permitting the expression of the peptide. Non-limiting examples of host cells suitable for expression of these peptides are: Escherichia coli, Saccharomyces cerevisiae, as well as mammalian BHK or CHO cell lines.

In one embodiment GLP-1 agonists of the invention which include non-natural amino acids and/or a covalently attached N-terminal mono- or dipeptide mimetic may e.g. be produced as described in the experimental part. Or see e.g., Hodgson et al: "The synthesis of peptides and proteins containing non-natural amino acids", Chemical Society Reviews, vol. 33, no. 7

(2004), p. 422-430; and WO 2009/083549 A1 entitled "Semi-recombinant preparation of GLP-1 analogues".

EMBODIMENTS

The following are non-limiting embodiments of the invention:

1. A method for reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

2. A method for treating or preventing obesity, for reducing body weight and/or food intake, or for inducing satiety, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

3. The method according to any one of the preceding embodiments, wherein said method comprises delaying or preventing diabetic disease progression.

4. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist has a half-life of at least 24 hours, such as at least 48 hours, at least 60 hours, or at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours, or optionally at least 120 hours, at least 132 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

5. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered twice weekly or less often, once weekly or less often, such as less often than once weekly or once every secondly week or less often, or such as once every third week or less often or once a month or less often.

6. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount of at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, per week.

7. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount equivalent to at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, semaglutide per week.

8. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount which provides an improved a) reduction in HbA1c or b) reduction in body weight compared to administration of 1.8 mg liraglutide or less, such as 0.8 mg liraglutide or less, per day.

9. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

10. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered by parenteral administration, such as subcutaneous injection.

11. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered simultaneously or sequentially with another therapeutic agent.

12. The method according to any one of any one of the preceding embodiments, wherein the GLP-1 agonist is a GLP-1 peptide.

13. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide comprises the amino acid sequence of the formula (I) (SEQ ID NO: 5):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa_{16}-Ser-Xaa_{18}-$Xaa_{19}Xaa_{20}$GluXaa_{22}-Xaa_{23}-Ala-Xaa_{25}-Xaa_{26}-Xaa_{27}-Phe-Ile-Xaa_3o-Trp-Leu-Xaa_{33}-Xaa_{34}-Xaa_{35}-Xaa_{36}-Xaa_{37}-Xaa_{38}-Xaa_{39}-Xaa_4o-Xaa_{41}-Xaa_{42}-Xaa_{43}-Xaa_{44}-Xaa_{45}-Xaa_{46}

Formula (I)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3- pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{25} is Ala or Val;

Xaa_{26} is Lys, Glu or Arg;

Xaa_{27} is Glu or Leu;

Xaa_{30} is Ala, Glu or Arg;

Xaa_{33} is Val or Lys;

Xaa_{34} is Lys, Glu, Asn or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg, Gly or Lys;

Xaa_{37} is Gly, Ala, Glu, Pro, Lys, amide or is absent;

Xaa_{38} is Lys, Ser, amide or is absent;

Xaa_{39} is Ser, Lys, amide or is absent;

Xaa_{40} is Gly, amide or is absent;

Xaa_{41} is Ala, amide or is absent;

Xaa_{42} is Pro, amide or is absent;

Xaa_{43} is Pro, amide or is absent;

Xaa_{44} is Pro, amide or is absent;

Xaa_{45} is Ser, amide or is absent;

Xaa_{46} is amide or is absent;

provided that if Xaa_{38}, Xaa_{39}, Xaa_{40}, Xaa_{41}, Xaa_{42}, Xaa_{43}, Xaa_{44}, Xaa_{45} or Xaa_{46} is absent then each amino acid residue downstream is also absent.

14. The method according to any one of the preceding embodiments, wherein said polypeptide is a GLP-1 peptide comprising the amino acid sequence of formula (II) (SEQ ID NO: 6):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Xaa_{18}-Tyr-Leu-Glu-Xaa22-Xaa_{23}-Ala-Ala-Xaa_{26}-Glu-Phe-Ile-Xaa_{3o}-Trp-Leu-Val-Xaa_{34}-Xaa_{35}-Xaa_{36}-$Xaa_{37}Xaa_{38}$

Formula (II)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine,-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{26} is Lys, Glu or Arg; Xaa30 is Ala, Glu or Arg;

Xaa_{34} is Lys, Glu or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg or Lys;

Xaa_{37} is Gly, Ala, Glu or Lys;

Xaa_{38} is Lys, amide or is absent.

15. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide is selected from GLP-1 (7-35), GLP-1 (7-36), GLP-1 (7-36)-amide, GLP-1 (7-37), GLP-1 (7-38), GLP-1 (7-39), GLP-1 (7-40), GLP-1 (7-41) or an analogue or derivative thereof.

16. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 15, such as no more than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

17. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 5 amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

18. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code.

19. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide is a DPPIV protected GLP-1 peptide.

20. The method according to any one of the preceding embodiments, wherein GLP-1 peptide is DPPIV stabilised.

21. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises an Aib residue in position 8.

22. The method according to any one of the preceding embodiments, wherein the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4-pyridylalanine.

23. The method according to any one of embodiments 7 to 16, wherein said GLP-1 peptide is attached to said hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

24. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide is exendin-4, an exendin-4-analogue, or a derivative of exendin-4.

25. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide comprises the amino acid sequence of the following formula:

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu

Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 (SEQ ID NO: 2).

26. The method according to any one of the preceding embodiments wherein one albumin binding residue via said hydrophilic spacer is attached to the C-terminal amino acid residue of said GLP-1 peptide.

27. The method according to any one of the preceding embodiments, wherein a second albumin binding residue is attached to an amino acid residue which is not the C-terminal amino acid residue.

28. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide is selected from the group consisting of semaglutide, albiglutide and dulaglitide.

29. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide has the following structure:
His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg (SEQ ID NO: 3).

30. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide has the following structure:
(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-
Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2 (SEQ ID NO: 4)–
genetically fused to human albumin.

31. The method according to any one of the preceding embodiments wherein the GLP-1 peptide is dulaglitide.

32. The method according to any one of the preceding embodiments wherein the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100 pM, optionally determined by Assay (I).

33. A GLP-1 agonist for use in the reduction of HbA1c or for use in the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

34. A GLP-1 agonist for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

35. A GLP-1 agonist for use according to embodiment 33 or 34, wherein the GLP-1 agonist and/or administration is as defined in any of embodiments 1-32 or 40.

36. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

37. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

38. A composition for use according to any one of the preceding embodiments, wherein said GLP-1 agonist and/or administration is as defined in any one of embodiments 1-32 or 40.

39. A composition for use according to any one of the preceding embodiments, wherein said composition comprises the Bydureon® composition.

40. The method according to any one of the preceding claims, wherein the method comprises prevention, treatment, reduction or induction in one or more diseases or conditions defined in any one of the previous embodiments.

EXAMPLES

Abbreviations

The following abbreviations are used in the following, in alphabetical order:

ADA: American Diabetes Association

Example 1: The Glp-1 Peptide Semaglutide Provides Reduced HbA1c and Body Weight

Semaglutide is a unique acylated GLP-1 peptide with a half-life of 160 hours. The aim was to investigate HbA1c dose-response of once-weekly doses of semaglutide (five dose-levels) in subjects with type 2 diabetes. Safety, tolerability and pharmacodynamics of semaglutide versus placebo and open-label once-daily liraglutide were also investigated.

Materials and methods

Liraglutide may be prepared as described in Example 37 of WO98/08871. Semaglutide may be prepared as described in Example 4 of WO2006/097537. The composition of the GLP-1 agonists administered may be formulated as isotonic aqueous solutions with a phosphate

buffer, such as a sodium dihydrogen phosphate buffer, having a pH in the range 7.0-9.0, such as pH 7.4 or pH 8.15, for example further comprising the excipients propylene glycol and phenol. The composition of the GLP-1 agonists administered may be as described in WO2003/002136 or WO2005/049061. The placebo composition may be identical to the composition of the GLP-1 agonists, but not containing a GLP-1 agonist.

In a 12-week, randomised, double-blind, placebo-controlled trial, 411 human subjects (n=43–50 per group) with type 2 diabetes were exposed. Participants (male/female 65/35%; baseline HbA1c (mean±SD) 8.1±0.8%; baseline body weight 87.5±13.8 kg; duration of diabetes 2.6±3.1 years; metformin only/diet and exercise alone 80/20%) received subcutaneous injection of one of five semaglutide doses (0.1–1.6 mg) once weekly, open-label liraglutide (1.2 mg, 1.8 mg) once daily, or placebo once weekly. Two of the semaglutide doses were titrated (T) in weekly increments of 0.4 mg. The primary endpoint was change in HbA1c from baseline. Secondary efficacy endpoints included proportion of subjects reaching ADA HbA1c target (<7%) and change in body weight. Change and percentage to target were analysed by ANOVA and logistic regression, respectively. Comparisons between semaglutide and liraglutide were not corrected for multiplicity. Baseline characteristics of the subjects are shown in Table 1.

Table 1. Baseline characteristics of subjects

	Placebo	Semaglutide						Liraglutide	
		0.1 mg	0.2 mg	0.4 mg	0.8 mg	0.8 mg T	1.6 mg T	1.2 mg	1.8 mg
Exposed* subjects	46	47	43	48	42	43	47	45	50
D&E: metformin (%)	22:78	23:77	14:86	23:77	19:81	16:84	19:81	18:82	24:76
Female: male (%)	39:61	34:66	30:70	23:77	48:52	37:63	45:55	31:69	30:70
Age (years)	55.3 (10.6)	55.2 (10 .1)	54.7 (10.0)	53.8 (10.2)	55.0 (9.7)	55.9 (7.9)	56.4 (10.5)	54.8 (9.2)	54.3 (10.1)
Duration of diabetes (years)	2.4 (3.3)	3.6 (5.0)	2.3 (2.7)	2.0 (2.3)	3.0 (3.0)	2.6 (2.1)	1.8 (2.0)	3.3 (3.4)	2.5 (2.6)

HbA1c (%)	8.1 (0.8)	8.2 (0.9)	8.2 (0.9)	8.1 (0.9)	8.2 (0.9)	8.0 (0.8)	8.0 (0.7)	8.0 (0.8)	8.1 (0.7)
FPG (mmol/L)	8.9 (1.5)	9.8 (2.7)	9.5 (2.5)	9.3 (2.1)	9.5 (2.4)	9.6 (2.1)	9.0 (1.9)	9.0 (2.3)	9.3 (2.0)
Weight (kg)	90.5 (13.0)	89.5 (14.2)	86.3 (15.1)	87.0 (14.0)	85.9 (15.1)	85.7 (12.6)	84.5 (14.0)	90.5 (13.5)	87.2 (13.1)
BMI (kg/m^2)	31.7 (3.8)	31.5 (4.6)	30.4 (3.9)	29.7 (4.5)	30.7 (4.5)	31.2 (4.2)	30.9 (4.7)	31.0 (4.6)	30.9 (4.6)

Data are mean (SD) unless otherwise stated. *: Number of subjects exposed to actual treatment. D&E: Diet and exercise. FPG: Fasting plasma glucose. BMI: Body mass index.

Results

In the full analysis set, semaglutide (≥0.2 mg) dose-dependently reduced HbA1c from baseline (Fig. 1), and increased the likelihood of achieving HbA1c <7% ($p<0.05$ vs. placebo for doses ≥0.2 mg). The results with respect to change in HbA1c are shown in Fig. 1. The change in HbA1c in fig. 1 is from baseline at week 12. Fig. 2 shows the change in HbA1c over time with the different treatments. Treatment with semaglutide ≥0.8 mg numerically brought more patients to target than liraglutide 1.8 mg (0.8 mg T 69%, 0.8 mg 73%, 1.6 mg T 81% vs. liraglutide 1.8 mg 57%).The results (see e.g. Fig. 1) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T improved reduction of HbA1c compared to treatment with liraglutide 1.2 mg or 1.8 mg; furthermore, treatment with semaglutide 1.6 mg T was statistically superior to treatment with liraglutide 1.2 mg or 1.8 mg with respect to reduction of HbA1c (based on unadjusted means). Fig. 3 shows the percentage and the number of subjects reaching the AACE or ADA criteria for glycaemic control with the different treatments. The results (see Fig. 3) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T improved the percentage and the number of subjects reaching the AACE or ADA criteria for glycaemic control compared to treatment with liraglutide 1.2 mg or 1.8 mg.

Body weight was dose-dependently reduced from baseline by up to 4.8 kg vs. placebo 1.2 kg ($p<0.01$ for doses ≥0.8 mg). Fig. 4 and 5 shows mean body weight change versus time and body weight change from baseline at week 12, respectively, with the different treatments. The results (see e.g. Fig. 5) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T increased reduction of body weight compared to treatment with liraglutide 1.2 mg or 1.8 mg. Furthermore, the results (see e.g. Fig. 5) shows that treatment with semaglutide 0.8 mg T or 1.6 mg T was statistically superior to treatment with liraglutide 1.8 mg with respect to reduction of

body weight; and that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T was statistically superior to liraglutide 1.2 mg with respect to reduction of body weight (based on unadjusted means).

There were no reports of pancreatitis or treatment-related changes in blood calcitonin. Proportion of subjects with nausea and vomiting increased with dose, but were generally mild or moderate and ameliorated by titration. Withdrawals due to gastrointestinal adverse events were 4.7%-27.7% for semaglutide and 2.2%-10% for liraglutide. Few subjects reported minor hypoglycaemia (semaglutide n=5, liraglutide n=3); no major hypoglycaemia. Injection site reactions were reported by 7 subjects: semaglutide n=2; liraglutide n=5. One subject (semaglutide 1.6 mg T) developed low titre non-neutralising anti-semaglutide antibodies (no cross-reaction to native GLP-1).

Conclusion

Over 12 weeks, semaglutide dose-dependently reduced HbA1c and body weight. The effect of semaglutide 0.4 mg on glycaemic control and body weight was comparable to that of liraglutide 1.2 mg, while semaglutide ≥0.8 mg appeared to bring more subjects to target and provided better weight loss than liraglutide 1.8 mg. No semaglutide safety concerns were identified. Dose escalation was not a major focus of this trial and it will be optimised in future clinical trials.

Pharmacological Methods

Assay (I): In Vitro Potency

The purpose of this example is to test the activity, or potency, of GLP-1 agonists in vitro. The potencies of GLP-1 agonists may be determined as described below, i.e. as the stimulation of the formation of cyclic AMP (cAMP) in a medium containing membranes expressing the human GLP-1 receptor.

Principle

Purified plasma membranes from a stable transfected cell line, BHK467-12A (tk-ts13), expressing the human GLP-1 receptor are stimulated with the GLP-1 agonist in question, and the potency of cAMP production is measured using the AlphaScreenTM cAMP Assay Kit from Perkin Elmer Life Sciences. The basic principle of The AlphaScreen Assay is a competition between endogenous cAMP and exogenously added biotin-cAMP. The capture of cAMP is

achieved by using a specific antibody conjugated to acceptor beads.

Cell culture and preparation of membranes

A stable transfected cell line and a high expressing clone are selected for screening. The cells are grown at 5% CO_2 in DMEM, 5% FCS, 1% Pen/Strep (Penicillin/Streptomycin) and 0.5 mg/ml of the selection marker G418.

Cells at approximate 80% confluence are washed 2X with PBS and harvested with Versene (aqueous solution of the tetrasodium salt of ethylenediaminetetraacetic acid), centrifuged 5 min at 1000 rpm and the supernatant removed. The additional steps are all made on ice. The cell pellet is homogenised by the Ultrathurax for 20-30 sec. in 10 ml of Buffer 1 (20 mM Na-HEPES, 10 mM EDTA, pH=7.4), centrifuged 15 min at 20,000 rpm and the pellet resuspended in 10 ml of Buffer 2 (20 mM Na-HEPES, 0.1 mM EDTA, pH=7.4). The suspension is homogenised for 20-30 sec and centrifuged 15 min at 20,000 rpm. Suspension in Buffer 2, homogenisation and centrifugation is repeated once and the membranes are resuspended in Buffer 2. The protein concentration is determined and the membranes stored at -80°C until use.

The assay is performed in ½-area 96-well plates, flat bottom (e.g. Costar cat. no:3693). The final volume per well is 50 µl.

Solutions and reagents

Exemplary solutions and reagents are given below.

AlphaScreen cAMP Assay Kit from Perkin Elmer Life Sciences (cat. No: 6760625M); containing Anti-cAMP Acceptor beads (10 U/µl), Streptavidin Donor beads (10 U/µl) and Biotinylated-cAMP (133 U/µl).

AlphaScreen Buffer, pH=7.4: 50 mM TRIS-HCl (Sigma, cat.no: T3253); 5 mM HEPES (Sigma, cat.no: H3375); 10 mM $MgCl_2$, $6H_2O$ (Merck, cat.no: 5833); 150 mM NaCl (Sigma, cat.no: S9625); 0.01% Tween (Merck, cat.no: 822184). The following was added to the AlphaScreen Buffer prior to use (final concentrations indicated): BSA (Sigma, cat. no. A7906): 0.1%; IBMX (Sigma, cat. no. I5879): 0.5 mM; ATP (Sigma, cat. no. A7699): 1 mM; GTP (Sigma, cat. no. G8877): 1 µM.

cAMP standard (dilution factor in assay = 5): cAMP Solution: 5 µL of a 5 mM cAMP-stock + 495 µL AlphaScreen Buffer.

Suitable dilution series in AlphaScreen Buffer are prepared of the cAMP standard as well as the GLP-1 agonist to be tested, e.g. the following eight concentrations of the GLP-1 agonist: 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} and 10^{-14}M, and a series from, e.g., 10^{-6} to $3x10^{-11}$ of cAMP.

Membrane/Acceptor beads

Use hGLP-1/ BHK 467-12A membranes; 6 µg/well corresponding to 0.6 mg/ml (the amount of membranes used pr. well may vary)

"No membranes": Acceptor Beads (15µg/ml final) in AlphaScreen buffer

"6 µg/well membranes": membranes + Acceptor Beads (15µg/ml final) in AlphaScreen buffer

Add 10 µl "No membranes" to the cAMP standard (per well in duplicates) and the positive and negative controls

Add 10 µl "6 µg/well membranes" to GLP-1 and GLP-1 agonists (per well in duplicates/triplicates)

Pos. Control: 10 µl "no membranes" + 10 µl AlphaScreen Buffer

Neg. Control: 10 µl "no membranes" + 10 µl cAMP Stock Solution (50µM)

As the beads are sensitive to direct light, any handling is in the dark (as dark as possible), or in green light. All dilutions are made on ice.

Procedure

1. Make the AlphaScreen Buffer.
2. Dissolve and dilute the GLP-1 agonists/cAMP standard in AlphaScreen Buffer.
3. Make the Donor Beads solution and incubate 30 min. at RT.
4. Add the cAMP/GLP-1 agonists to the plate: 10 µl per well.
5. Prepare membrane/Acceptor Beads solution and add this to the plates: 10 µl per well.
6. Add the Donor Beads: 30 µl per well.
7. Wrap the plate in aluminum foil and incubate on the shaker for 3 hours (very slowly) at RT.
8. Count on AlphaScreen – each plate pre incubates in the AlphaScreen for 3 minutes before counting.

The EC_{50} [pM] values may be calculated using the Graph-Pad Prism software (version 5). If desired, the fold variation in relation to GLP-1 may be calculated as EC_{50} (GLP-1)/ EC_{50} (analogue) – 3693.2.

Assay (II): Half-life in Minipigs

The purpose of this study is to determine the protraction in vivo of GLP-1 agonists after i.v. administration to minipigs, i.e. the prolongation of their time of action. This is done in a pharmacokinetic (PK) study, where the terminal half-life of the GLP-1 agonist in question is determined. By terminal half-life is generally meant the period of time it takes to halve a certain plasma concentration, measured after the initial distribution phase.

Male Göttingen minipigs are obtained from Ellegaard Göttingen Minipigs (Dalmose, Denmark) approximately 7-14 months of age and weighing from approximately 16-35 kg are used in the studies. The minipigs are housed individually and fed restrictedly once or twice daily with SDS minipig diet (Special Diets Services, Essex, UK). After at least 2 weeks of acclimatisation two permanent central venous catheters are implanted in vena cava caudalis or cranialis in each animal. The animals are allowed 1 week recovery after the surgery, and are then used for repeated pharmacokinetic studies with a suitable wash-out period between dosings.

The animals are fasted for approximately 18 h before dosing and for at least 4 h after dosing, but have ad libitum access to water during the whole period.

The GLP-1 agonist is dissolved in 50 mM sodium phosphate, 145 mM sodium chloride, 0.05% tween 80, pH 7.4 to a concentration of usually from 20-60 nmol/ml. Intravenous injections (the volume corresponding to usually 1-2 nmol/kg, for example 0.033ml/kg) of the compounds are given through one catheter, and blood is sampled at predefined time points for up till 13 days post dosing (preferably through the other catheter). Blood samples (for example 0.8 ml) are collected in EDTA buffer (8mM) and then centrifuged at 4°C and 1942G for 10 minutes. Plasma is pippetted into Micronic tubes on dry ice, and kept at -20°C until analyzed for plasma concentration of the respective GLP-1 compound using ELISA or a similar antibody based assay or LC-MS. Individual plasma concentration-time profiles are analyzed by a non-compartmental model in WinNonlin v. 5.0 (Pharsight Inc., Mountain View, CA, USA), and the resulting terminal half-lives (harmonic mean) determined.

Assay (III): Effect on Blood Glucose and Body Weight

The purpose of the study is to verify the effect of GLP-1 agonists on blood glucose (BG) and body weight (BW) in a diabetic setting. GLP-1 agonists may be tested in a dose-response study in an obese, diabetic mouse model (db/db mice) as described in the following.

Fifty db/db mice (Taconic, Denmark), fed from birth with the diet NIH31 (NIH 31M Rodent Diet, commercially available from Taconic Farms, Inc., US, see www.taconic.com), are enrolled for the study at the age of 7-9 weeks The mice are given free access to standard chow (e.g. Altromin 1324, Brogaarden, Gentofte, Denmark) and tap water and kept at 24°C. After 1-2 weeks of acclimatisation, the basal blood glucose is assessed twice on two consecutive days (i.e. at 9 am). The 8 mice with the lowest blood glucose values may be excluded from the experiments. Based on the mean blood glucose values, the remaining 42 mice may be selected for further experimentation and allocated to 7 groups (n=6) with matching blood glucose levels.

The mice may be used in experiments with duration of 5 days for up to 4 times. After the last experiment the mice are euthanised.

The seven groups may receive treatment as follows:

1: Vehicle, subcutaneous
2: GLP-1 agonist, 0.3 nmol/kg, subcutaneous
3: GLP-1 agonist, 1.0 nmol/kg, subcutaneous
4: GLP-1 agonist, 3.0 nmol/kg, subcutaneous
5: GLP-1 agonist, 10 nmol/kg, subcutaneous
6: GLP-1 agonist, 30 nmol/kg, subcutaneous
7: GLP-1 agonist, 100 nmol/kg, subcutaneous

Vehicle: 50mM sodium phosphate, 145 mM sodium chloride, 0.05% tween 80, pH 7.4.

The GLP-1 agonist is dissolved in the vehicle, e.g. to concentrations of 0.05, 0.17, 0.5, 1.7, 5.0 and 17.0 nmol/ml. Animals are dosed subcutaneous with a dose-volume of 6 ml/kg (i.e. 300 µl per 50 g mouse).

On the day of dosing, blood glucose is assessed at time -½h (8.30 am), where after the mice are weighed. The GLP-1 agonist is dosed at approximately 9 am (time 0). On the day of dosing, blood glucose is assessed e.g. at times 1, 2, 4 and 8 h (10 am, 11 am, 1 pm and 5 pm).

On the following days, the blood glucose is assessed e.g. at time 24, 48, 72, and 96h after dosing (i.e. at 9 am on day 2, 3, 4, 5). On each day, the mice are weighed following blood glucose sampling.

The mice are weighed individually on a digital weight.

Samples for the measurement of blood glucose are obtained from the tail tip capillary of conscious mice. Blood, 10 µl, is collected into heparinised capillaries and transferred to 500 µl glucose buffer (EKF system solution, Eppendorf, Germany). The glucose concentration is measured using the glucose oxidase method (glucose analyser Biosen 5040, EKF Diagnostic, GmbH, Barleben, Germany). The samples are kept at room temperature for up to 1 h until analysis. If analysis has to be postponed, samples are kept at 4°C for a maximum of 24 h.

ED_{50} is the dose giving rise to half-maximal effect in nmol /kg. This value is calculated on the basis of the ability of the GLP-1 agonists to lower body weight as well as the ability to lower blood glucose, as explained below.

ED_{50} for body weight is calculated as the dose giving rise to half-maximum effect on delta BW 24 hours following the subcutaneous administration of the GLP-1 agonist. For example, if the maximum decrease in body weight after 24 hours is 4.0 g, then ED_{50} bodyweight would be that dose in nmol/kg which gives rise to a decrease in body weight after 24 hours of

2.0 g. This dose (ED_{50} body weight) may be read from the dose-response curve.

ED_{50} for blood glucose is calculated as the dose giving rise to half-maximum effect on AUC delta BG 8 hours following the subcutaneous administration of the GLP-1 agonist.

The ED_{50} value may only be calculated if a proper sigmoidal dose-response relationship exists with a clear definition of the maximum response. Thus, if this would not be the case the GLP-1 agonist in question is re-tested in a different range of doses until the sigmoidal dose-response relationship is obtained.

Assay (IV): Effect on Food Intake

The purpose of this experiment is to investigate the effect of GLP-1 agonists on food intake in pigs. This is done in a pharmacodynamic (PD) study as described below, in which food intake is measured 1, 2, 3, and 4 days after administration of a single dose of the GLP-1 agonist, as compared to a vehicle-treated control group.

Female Landrace Yorkshire Duroc (LYD) pigs, approximately 3 months of age, weighing approximately 30-35 kg are used (n=3-4 per group). The animals are housed in a group for 1-2 weeks during acclimatisation to the animal facilities. During the experimental period the animals are placed in individual pens from Monday morning to Friday afternoon for measurement of individual food intake. The animals are fed ad libitum with pig fodder (Svinefoder, Antonio) at all times both during the acclimatisation and the experimental period. Food intake is monitored on line by logging the weight of fodder every 15 minutes. The system used is Mpigwin (Ellegaard Systems, Faaborg, Denmark).

The GLP-1 agonists are dissolved in a phosphate buffer (50 mM phosphate, 0.05% tween 80, pH 8) e.g. at concentrations of 12, 40, 120, 400 or 1200 nmol/ml corresponding to doses of 0.3, 1, 3, 10, or 30 nmol/kg. The phosphate buffer served as vehicle. Animals are dosed with a single subcutaneous dose of the GLP-1 agonist or vehicle (dose volume 0.025 ml/kg) on the morning of day 1, and food intake is measured for 4 days after dosing. On the last day of each study, 4 days after dosing, a blood sample for measurement of plasma exposure of the GLP-1 agonist is taken from the heart in anaesthetised animals. The animals are thereafter euthanised with an intra-cardial overdose of pentobarbitone. Plasma content of the GLP-1 agonist is analysed using ELISA or a similar antibody based assay.

Food intake is calculated as mean ± SEM 24 h food intake on the 4 days. Statistical comparisons of the 24 hour food intake in the vehicle vs. GLP-1 agonist group on the 4 days are done using one-way or two-way-ANOVA repeated measures, followed by Bonferroni post-test.

Assay (V): Stability against Degradation by Intestinal Enzymes

The purpose of this example is to test the stability against degradation by intestinal enzymes. GLP-1(7-37) may be used in the assay as a comparative compound. The strongest proteolytic activities in the intestine are of pancreatic origin and include the serine endopeptidases trypsin, chymotrypsin, and elastase as well as several types of carboxypeptidases. An assay with small intestine extract from rats was developed and used as described in the following.

Extracts from rat small intestine

Small intestines are prepared from rats and flushed with 8 ml of 150 mM NaCl, 20 mM Hepes pH 7.4. The solutions are centrifuged for 15 min at 4,600 rpm in a Heraeus Multifuge 3 S-R centrifuge with a 75006445 rotor. The supernatants are removed and filtered through a 0.22 µm Millipore Millex GV PVDF membrane. Filtrates of several animals are pooled to average out individual differences.

The protein content of the obtained extracts is determined by Bradford Assay (see e.g. Analytical Biochemistry (1976), vol. 72, p. 248-254, and Analytical Biochemistry (1996), vol. 236 p. 302-308).

Degradation assay

2.5 nmol of the GLP-1 agonists to be tested are incubated with the intestinal extract in a volume of 250 µl at 37°C over a period of one hour. Intestinal samples are assayed in presence of 20 mM Hepes at pH 7.4. The concentration of the intestinal extract is titrated in pilot experiments so that the half-life (t½) of GLP-1(7-37) is in the range of 10-20 minutes. The small intestine extract is used at a concentration of 1.4 µg/ml. All components except for the intestinal extract are mixed and pre-warmed for ten minutes at 37°C. Immediately after addition of the intestinal extract a sample of 50 µl is taken and mixed with the same volume of 1% trifluoroacetic acid (TFA). Further samples are taken accordingly after 15, 30, and 60 minutes.

Sample analysis

UPLC analysis: 10 µl of the samples are analysed by UPLC using a Waters Acquity system with a BEH C18 1.7 µm 2.1 x 50 mm column and a 30 to 65% gradient of 0.1% TFA and 0.07% TFA in acetonitrile over 5 minutes at a flow rate of 0.6 ml/min. After baseline subtraction the peak integrals of the intact compounds in the HPLC chromatogram recorded at a wavelength of 214 nm are determined.

MALDI-TOF analysis: 1 µl of each sample is transferred to a Bruker/Eppendorf PAC HCCA 384 MALDI target. Analysis is performed with a Bruker Autoflex matrix-assisted laser desorption and ionisation - time of flight (MALDI-TOF) mass spectrometer using the pre-defined

method “PAC_measure” with an extended detection range of 500 to 5000 Da and the pre-defined calibration method “PAC_calibrate”.

Data analysis: The peak integrals of the HPLC chromatograms are plotted against time. The half-life of the respective compound is calculated by fitting the data using SigmaPlot 9.0 software and an equation for a 2-parameter exponential decay. For each GLP-1 agonist tested, the relative half-life (relative $T_{½}$) is calculated as the half-life ($T_{½}$) of the compound in question, divided by the half-life ($T_{½}$) of GLP-1(7-37), determined in the same way.

While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

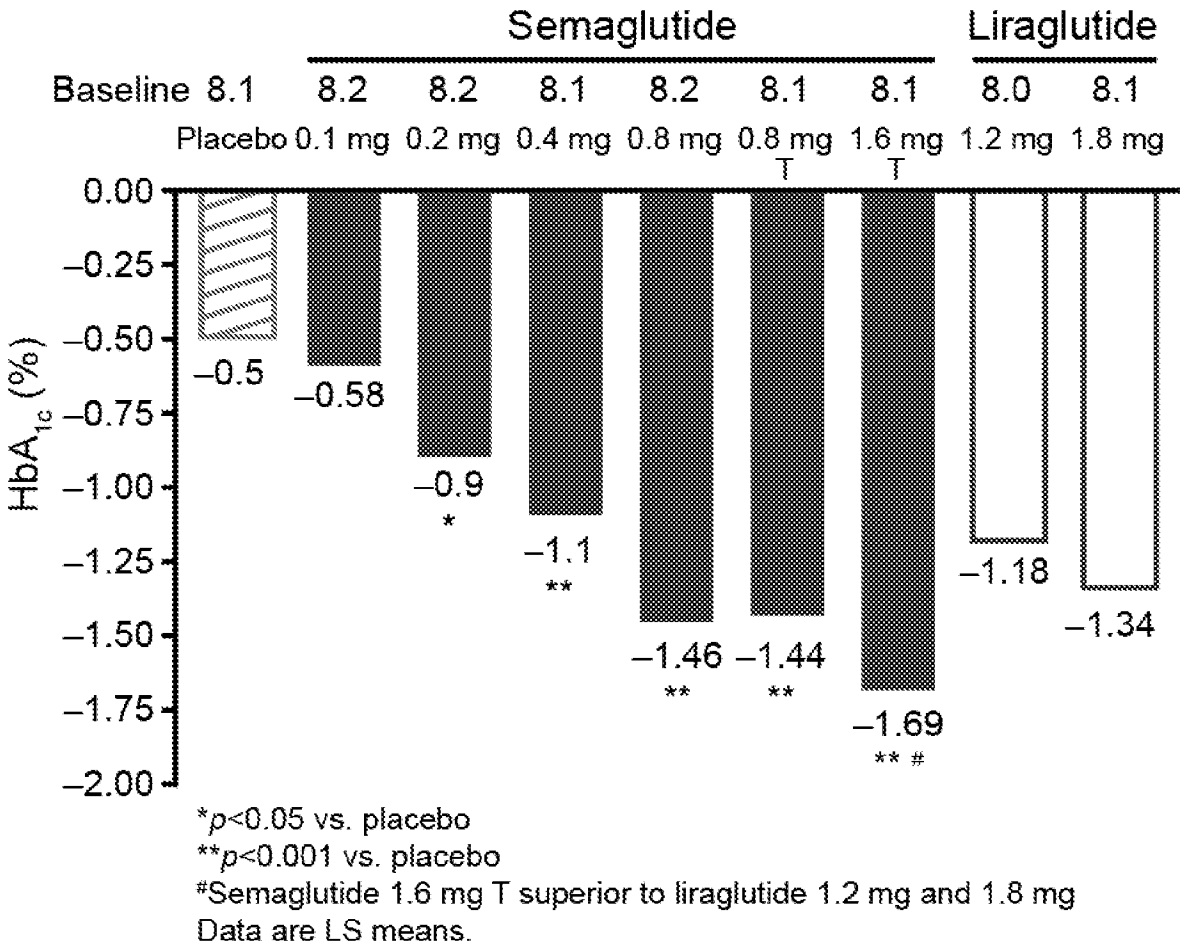
Semaglutide
Liraglutide
Baseline 8.1
8.2
8.2
8.1
8.2
8.1
8.1
8.0
8.1
Placebo
0.1 mg
0.2 mg
0.4 mg
0.8 mg
0.8 mg T
1.6 mg T
1.2 mg
1.8 mg
HbA1c (%)
0.00
–0.25
–0.50
–0.75
–1.00
–1.25
–1.50
–1.75
–2.00
–0.5
–0.58
–0.9 *
–1.1 **
–1.46 **
–1.44 **
–1.69 ** #
–1.18
–1.34
*p<0.05 vs. placebo
**p<0.001 vs. placebo
#Semaglutide 1.6 mg T superior to liraglutide 1.2 mg and 1.8 mg
Data are LS means.

Fig. 1

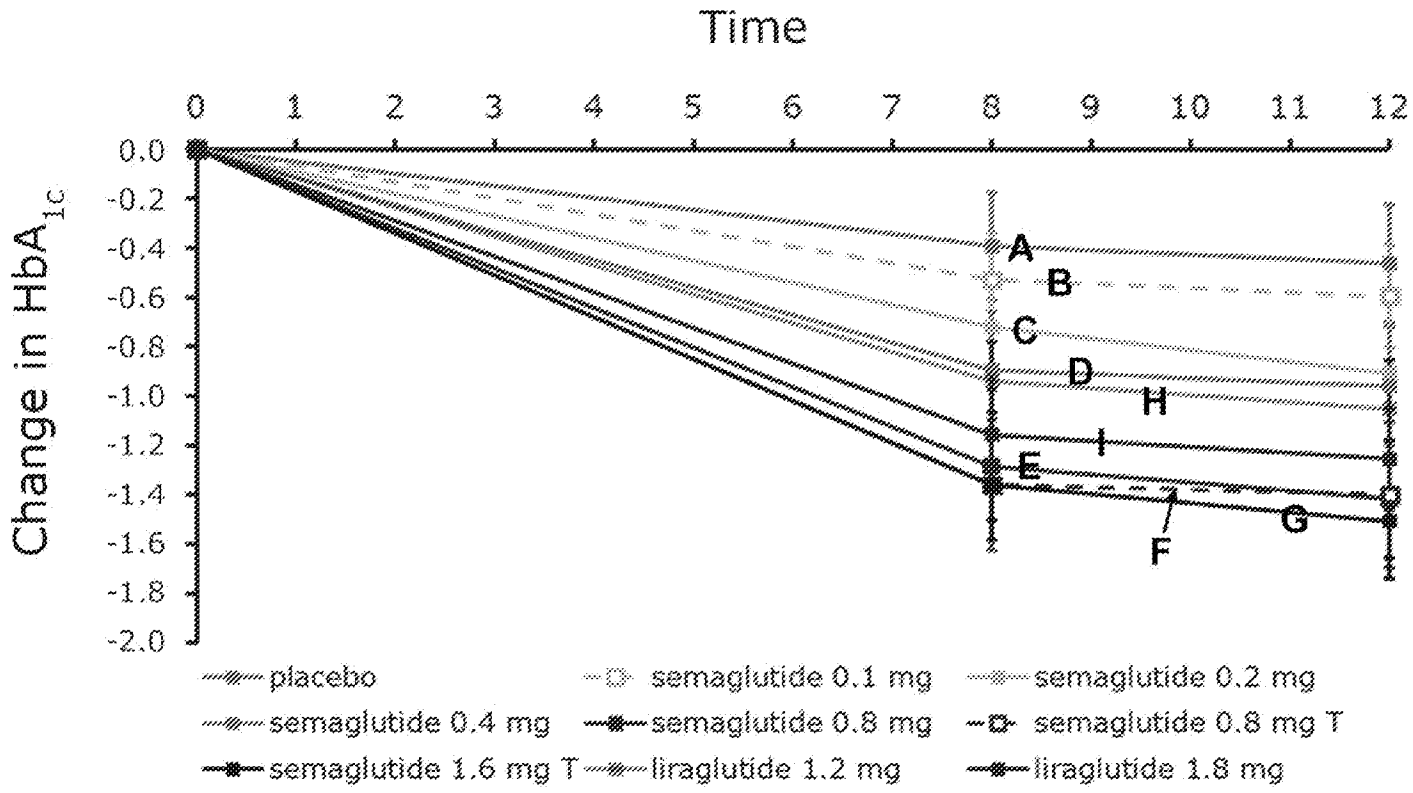
Time
0
1
2
3
4
5
6
7
8
9
10
11
12
Change in HbA1c
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
-2.0
A
B
C
D
H
I
E
F
G
placebo
semaglutide 0.1 mg
semaglutide 0.2 mg
semaglutide 0.4 mg
semaglutide 0.8 mg
semaglutide 0.8 mg T
semaglutide 1.6 mg T
liraglutide 1.2 mg
liraglutide 1.8 mg

Fig. 2

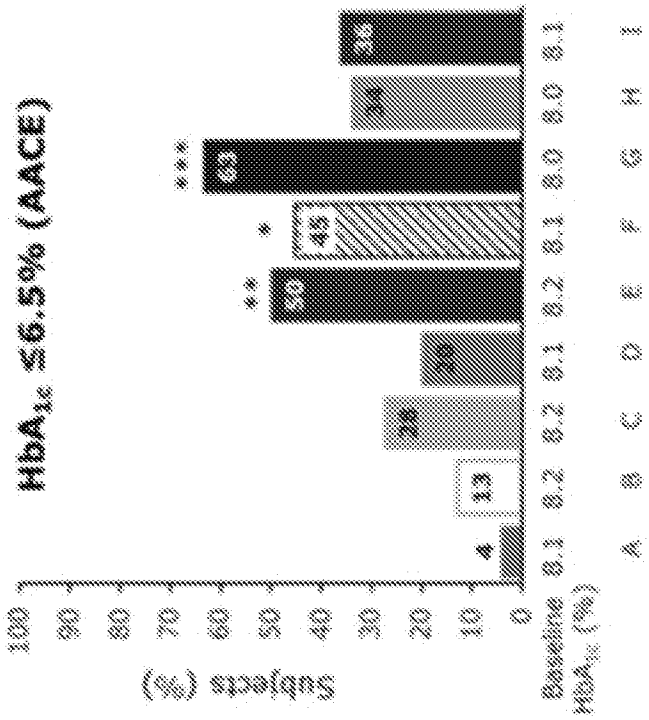
HbA1c ≤6.5% (AACE)
Subjects (%)
100
90
80
70
60
50
40
30
20
10
0
Baseline HbA1c (%)
8.1
8.2
8.2
8.1
8.2
8.1
8.0
8.0
8.1
A
B
C
D
E
F
G
H
I
4
13
28
20
50
45
63
34
35
**
*
***

Fig. 3A

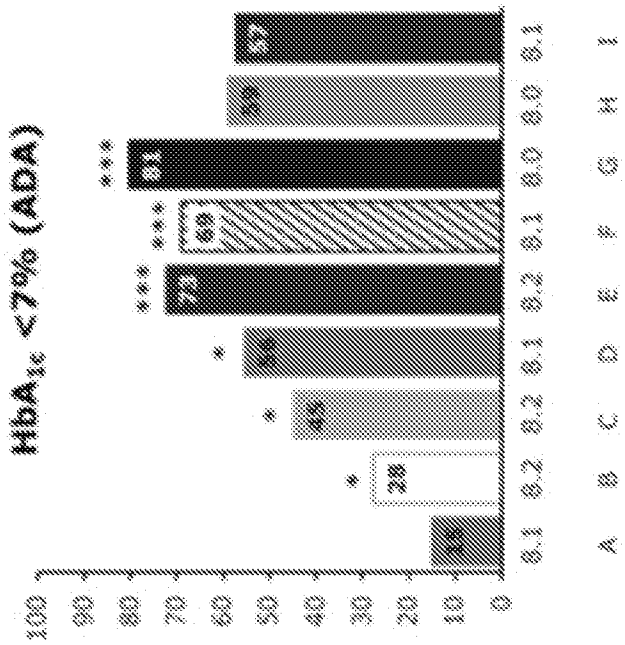
HbA1c <7% (ADA)
100
90
80
70
60
50
40
30
20
10
0
28
45
78
69
81
59
57
8.1
8.2
8.2
8.1
8.2
8.1
8.0
8.0
8.1
A
B
C
D
E
F
G
H
I

Fig. 3 B

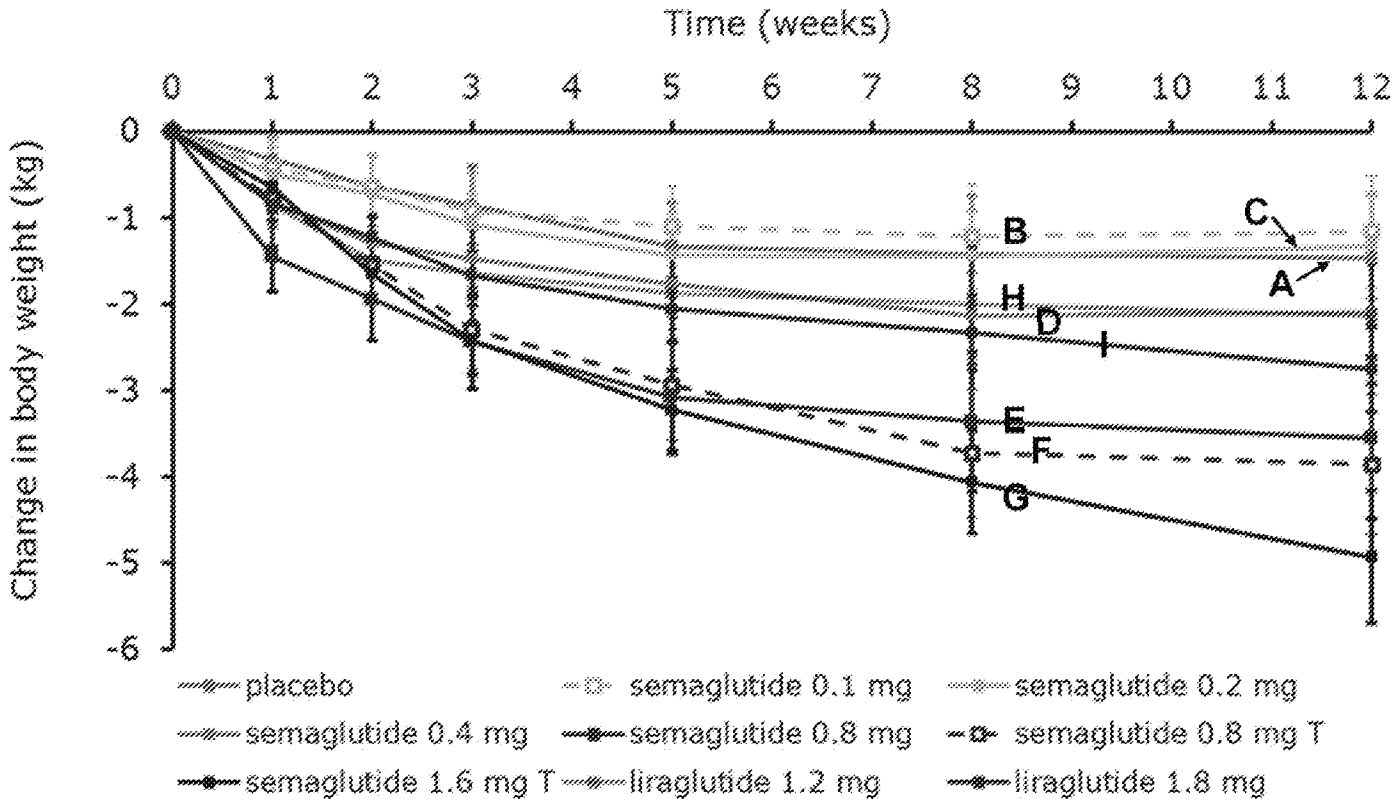
Time (weeks)
0
1
2
3
4
5
6
7
8
9
10
11
12
Change in body weight (kg)
0
-1
-2
-3
-4
-5
-6
A
B
C
D
E
F
G
H
I
placebo
semaglutide 0.1 mg
semaglutide 0.2 mg
semaglutide 0.4 mg
semaglutide 0.8 mg
semaglutide 0.8 mg T
semaglutide 1.6 mg T
liraglutide 1.2 mg
liraglutide 1.8 mg

Fig. 4

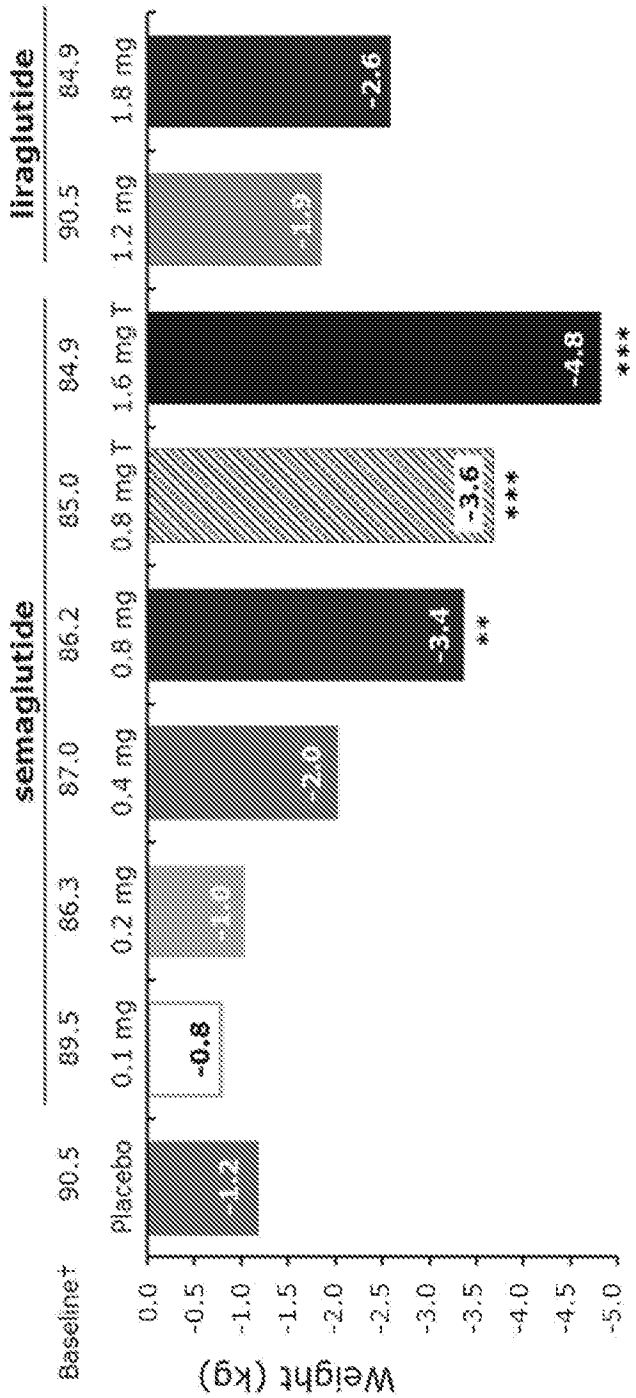
Weight (kg)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
Baseline†
90.5
Placebo
-1.2
89.5
0.1 mg
-0.8
86.3
0.2 mg
-1.9
87.0
0.4 mg
-2.0
semaglutide
86.2
0.8 mg
-3.4
**
85.0
0.8 mg T
-3.6
***
84.9
1.6 mg T
-4.8
***
90.5
1.2 mg
-1.6
liraglutide
84.9
1.8 mg
-2.6

Fig. 5

POWER OF ATTORNEY,

REVOCATION OF PREVIOUSLY GRANTED POWER OF ATTORNEY, AND AUTHORIZATION TO MAKE SUBMISSIONS REGARDING OWNERSHIP

Power of Attorney:

Novo Nordisk A/S (hereinafter "Novo Nordisk"), hereby appoints and acknowledges its appointment of the attorneys of the Novo Nordisk Inc. Intellectual Property Department (the latter including the attorneys and agents associated with U.S. Patent and Trademark Office Customer Number 23650) and any successor entities or appointed agents thereof (hereinafter "NNI Attorneys") to act for Novo Nordisk in all proceedings before the U.S. Patent and Trademark Office ("USPTO").

Such proceedings shall include, without limitation, filing, prosecution, withdrawal, maintenance, and abandonment of such U.S. patent applications (and International (PCT) Patent Applications filed with the USPTO), as well as the initiation and handling of appeal, reexamination, reissue, interference, cancellation, correction, or similar proceedings involving U.S. patents and patent applications and the transaction of all other business associated with such patent applications and patents in the U.S. Patent and Trademark Office. By virtue of this appointment, Novo Nordisk authorizes the NNI Attorneys to receive all communications, official actions, and decisions, of the U.S. Patent and Trademark Office and to lodge and withdraw any legal measures deemed fit by the NNI Attorneys with respect to such patents and patent applications.

Revocation of Previously Granted Power of Attorney:

Immediately upon the filing of this document with USPTO in connection with any patent or patent application, all previously granted powers of attorney in connection with the patent or patent application will be revoked.

Authorization To Make Submissions Regarding Ownership:

Novo Nordisk further hereby authorizes and empowers the NNI attorneys to make any appropriate submissions regarding Novo Nordisk's ownership interest in any such patent applications or patents on behalf of Novo Nordisk A/S with the USPTO in accordance with 37 C.F.R. § 3.73(b) (or any substantially similar successor thereof) and having the application number(s) listed thereon.

The individual whose signature and title is supplied below is authorized to grant this power of attorney and authorization to the NNI Attorneys on behalf of Novo Nordisk.

Lars Kellberg

Vice President – Corporate Patents

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Novo Nordisk A/S

Application No./Patent No.: 15/656,042 Filed/Issue Date: July 21, 2017

Titled: Use of Long-Acting GLP-1 Peptides

Novo Nordisk A/S (Name of Assignee), a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [x] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [x] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 034908, Frame 0221, or for which a copy thereof is attached.

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
   Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
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Petitioner Apotex Exhibit 1002-0209

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STATEMENT UNDER 37 CFR 3.73(c)

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   The document was recorded in the United States Patent and Trademark Office at
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6. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
   Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Leon Y. Lum/	December 13, 2017
Signature	Date
Leon Y. Lum	62,124
Printed or Typed Name	Title or Registration Number

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Petitioner Apotex Exhibit 1002-0210

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/656,042	07/21/2017	1629	1740	8545US02	10	1

CONFIRMATION NO. 9712

UPDATED FILING RECEIPT

OC000000098113528

23650
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

Date Mailed: 12/18/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

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Applicant(s)

Novo Nordisk A/S, Bagsvaerd, DENMARK;

Power of Attorney: The patent practitioners associated with Customer Number 23650

Domestic Priority data as claimed by applicant

This application is a CON of 14/409,493 12/19/2014 PAT 9764003
which is a 371 of PCT/EP2013/063004 06/21/2013
which claims benefit of 61/708,162 10/01/2012
and claims benefit of 61/694,837 08/30/2012

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
EUROPEAN PATENT OFFICE (EPO) 12186781.6 10/01/2012
EUROPEAN PATENT OFFICE (EPO) 12174535.0 07/01/2012

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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Petitioner Apotex Exhibit 1002-0211

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If Required, Foreign Filing License Granted: 08/01/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/656,042**

Projected Publication Date: 03/29/2018

Non-Publication Request: No

Early Publication Request: No

Title

Use of Long-Acting GLP-1 Peptides

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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Petitioner Apotex Exhibit 1002-0212

Europäisches Patentamt
European Patent Office
Office européen des brevets

Bescheinigung	Certificate	Attestation
Die angehefteten Unterlagen stimmen mit der als ursprünglich eingereicht geltenden Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.	The attached documents are exact copies of the text in which the European patent application described on the following page is deemed to have been filed.	Les documents joints à la présente attestation sont conformes au texte, considéré comme initialement déposé, de la demande de brevet européen qui est spécifiée à la page suivante.

Patentanmeldung Nr. **Patent application No.** **Demande de brevet n°**

12174535.0 / EP12174535

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP12174535.

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le President de l'Office européen des brevets
p.o.

U. Ingmann

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0213

Anmeldung Nr:
Application no.: 12174535.0
Demande no :

Anmeldetag:
Date of filing: 01.07.12
Date de dépôt :

Anmelder / Applicant(s) / Demandeur(s):

NOVO NORDISK A/S
Novo Allé
2880 Bagsværd/DK

Bezeichnung der Erfindung / Title of the invention / Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, oder falls die Anmeldung in einer Nicht-Amtssprache des EPA eingereicht wurde, siehe Beschreibung bezüglich ursprünglicher Bezeichnung.
If no title is shown, or if the application has been filed in a non-EPO language, please refer to the description for the original title.
Si aucun titre n'est indiqué, ou si la demande a été déposée dans une langue autre qu'une langue officielle de l'OEB, se référer à la description pour le titre original.)

USE OF LONG-ACTING GLP-1 PEPTIDES

In Anspruch genommene Priorität(en) / Priority(Priorities) claimed / Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

Am Anmeldetag benannte Vertragstaaten / Contracting States designated at date of filing / Etats contractants désignées lors du dépôt:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0214

USE OF LONG-ACTING GLP-1 PEPTIDES

The present invention relates to improved uses of GLP-1 peptides in therapy.

SUMMARY

In one embodiment the invention relates to a method for a) reduction of HbA1c; b) prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) prevention or treatment of obesity, reducing body weight and/or food intake, or inducing satiety; wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof, wherein said GLP-1 agonist i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and iii) is administered once weekly or less often.

In one embodiment the invention relates to a GLP-1 agonist for use in a) the reduction of HbA1c; b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety; wherein said use comprises administration of said GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week, and wherein said GLP-1 agonist and/or administration optionally is as defined herein.

In one embodiment the invention relates to a composition comprising a GLP-1 agonist for use in a) the reduction of HbA1c; b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety; wherein said GLP-1 agonist i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); and ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and wherein said composition is administered once weekly or less often, and wherein said GLP-1 agonist and/or administration optionally is as defined herein.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows change in HbA1c following subcutaneousadministration of placebo, semaglutide, or liraglutide to human subjects.

DESCRIPTION

The present invention relates to an improved use of GLP-1 agonists in therapy. In one embodiment the invention relates to certain dosage regimes of GLP-1 agonists which provide improved effect in diseases or conditions, such as prevention and/or treatment of type 2 diabetes and obesity. In one embodiment the methods of the present invention provides surprisingly showed improved reduction of HbA1c and reduction of body weight. In one embodiment the GLP-1 agonist is administered in an amount which provides an improved a) reduction in HbA1c or b) reduction in body weight compared to administration of 1.8 mg liraglutide or less, such as 0.8 mg liraglutide or less, per day.

In one embodiment the invention relates to a method for reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.In one embodiment the method is for reduction of HbA1c.In one embodiment the method is for prevention or treatment of type 2 diabetes. In one embodiment the method is for prevention or treatment of hyperglycemia. In one embodiment the method is for prevention or treatment of impaired glucose tolerance. In one embodiment the method is for prevention or treatment of non-insulin dependent diabetes. In one embodiment the method of the invention comprises delaying or preventing diabetic disease progression.In one embodiment a HbA1c level below 7% is achieved. In one embodiment the level of HbA1c is determined according to the method defined by the Diabetes Control and Complications Trial (DCCT). In one embodiment the level of HbA1c is determined according to the method defined by the International Federation of Clinical Chemistry (IFCC).

In one embodiment the invention relates to a method for treating or preventing obesity, for reducing body weight and/or food intake, or for inducing satiety, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the method is for prevention or treatment of obesity. In one embodiment the method is for reducing body weight and/or food intake. In one embodiment the method is for inducing satiety.

In one embodiment the GLP-1 agonist has a half-life of at least 24 hours, such as at least 48 hours, at least 60 hours, or at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours, or optionally at least 120 hours, at least 132 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

In one embodiment the GLP-1 agonist is administered twice weekly or less often, once weekly or less often, or once weekly or less often.In one embodiment the GLP-1 agonist is administered once every secondly week or less often, once every third week or less often, or once a month or less often.

In one embodiment the GLP-1 agonist is administered in an amount per weekof at least 0.8 mg, at least 0.9 mg, or at least 1.0 mg. In one embodiment the GLP-1 agonist is administered in an amount per weekofat least 1.1 mg, at least 1.2 mg, or at least 1.3 mg. In one embodiment the GLP-1 agonist is administered in an amount per weekofat least 1.4 mg, at least 1.5 mg, or at least 1.6 mg.

In one embodiment the GLP-1 agonist is administered in an amount per weekequivalent to at least 0.8 mg, at least 0.9 mg, or at least 1.0 mg semaglutide. In one embodiment the GLP-1 agonist is administered in an amount per weekequivalent to at least 1.1 mg, at least 1.2 mg, or at least 1.3 mg semaglutide. In one embodiment the GLP-1 agonist is administered in an amount per weekequivalent to at least 1.4 mg, at least 1.5 mg, or at least 1.6 mg semaglutide.

In one embodiment the GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

In one embodiment the GLP-1 agonist is administered by parenteral administration, such as subcutaneous injection.

In one embodiment the GLP-1 agonist is a GLP-1 peptide.In one embodiment the GLP-1 peptide comprises no more than 5, such as no more than 4 or no more than 3, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37). In one embodiment the GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code.

In one embodiment the GLP-1 peptide is a DPPIV protected GLP-1 peptide. In one embodiment the GLP-1 peptide is DPPIV stabilised.

In one embodiment the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100pM, optionally determined by Assay (I).

In one embodiment the invention relates to a GLP-1 agonist for use in the reduction of HbA1c or for use in the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to a GLP-1 agonist for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to acomposition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to acomposition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the GLP-1 agonist is administered with another therapeutic agent.Administration with another therapeutic agent may be carried out as administration of the GLP-1 agonist and the other therapeutic agent within the same therapeutic window (e.g. withinin a period of two weeks, a period of one week, or in a 96, 72, or 48 hour period, etc.). The treatment with a GLP-1 agonist according to the present invention may be combined with one or more additional therapeutic agents, e.g. selected from antidiabetic agents, antiobesity agents, appetite regulating agents, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity; examples of these therapeutic agents are: sulphonylureas, thiazolidinediones, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists, and DPP-IV (dipeptidyl peptidase-IV) inhibitors.

In one embodiment, as used herein, an “amount equivalent to” when used in relation to GLP-1 agonists refers to amounts of a first GLP-1 agonist and a second GLP-1 agonist having GLP-1 receptor potency (i.e. EC_{50}) within ±30%, such as within ±20% or within ±10%,

of each other optionally determined by Assay (I) described herein and having a half-life within ±30%, such as within ±20% or within ±10%, of each other optionally determined by Assay (II) described herein.

In one embodiment an "effective amount" of a GLP-1 agonist as used herein means an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease or state and its complications. An amount adequate to accomplish this is defined as "effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary.

In one embodiment the term "treatment" or "treating" as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. In one embodiment the term "treatment" or "treating" is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications; to delay the progression of the disease, disorder, or condition; to alleviate or relieve the symptoms and complications; and/or, to cure or eliminate the disease, disorder, or condition as well as to prevent the condition. In one embodiment prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications.

In one embodiment the term "hydrophilic spacer" as used herein means a spacer that separates a peptide and an albumin binding residue with a chemical moiety which comprises at least 5 non- hydrogen atoms where 30-50% of these are either N or O.

In one embodiment the term "analogue" as used herein referring to a polypeptide means a modified peptide wherein one or more amino acid residues of the peptide have been substituted by other amino acid residues and/or wherein one or more amino acid residues have been deleted from the peptide and or wherein one or more amino acid residues have been added to the peptide. Such addition or deletion of amino acid residues can take place at the N-terminal of the peptide and/or at the C-terminal of the peptide. A simple system is used to describe analogues: For example Arg^{34}GLP-1 (7-37) Lys designates a GLP-1 analogue wherein the naturally occurring lysine at position 34 has been substituted with arginine and a lysine residue has been added to the C-terminal (position 38).

In one embodiment the term "GLP-1 peptide" as used herein means GLP-1 (7-37), a GLP-1 analogue, a GLP-1 derivative or a derivative of a GLP-1 analogue.

In one embodiment the term "exendin-4 peptide" as used herein means exendin-4 (1-39), an exendin-4 analogue, an exendin-4 derivative or a derivative of an exendin-4 analogue.

In one embodiment the term “DPP-IV protected” as used herein referring to a polypeptide means a polypeptide which has been chemically modified in order to render said compound resistant to the plasma peptidase dipeptidyl aminopeptidase-4 (DPP-IV). The DPP-IV enzyme in plasma is known to be involved in the degradation of several peptide hormones, e.g. GLP-1, Exendin-4 etc. Thus a considerable effort is being made to develop GLP-1 agonists less susceptible to DPP-IV mediated hydrolysis in order to reduce the rate of degradation by DPP-IV.

The present invention also relates to a GLP-1 agonist of the invention, for use as a medicament. In particular embodiments, the GLP-1 agonist of the invention may be used for the following medical treatments:

(i) prevention and/or treatment of all forms of diabetes, such as hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, non-insulin dependent diabetes, MODY (maturity onset diabetes of the young), gestational diabetes, and/or for reduction of HbA1C;

(ii) delaying or preventing diabetic disease progression, such as progression in type 2 diabetes, delaying the progression of impaired glucose tolerance (IGT) to insulin requiring type 2 diabetes, and/or delaying the progression of non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes;

(iii) prevention and/or treatment of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; and/or delaying gastric emptying.

In another particular embodiment, the indication is (i). In a further particular embodiment the indication is (ii). In a still further particular embodiment the indication is (iii). In one embodiment the indication is type 2 diabetes and/or obesity.

In one embodiment the invention relates to administration of an effective amount of a GLP-1 agonist.

In one embodiment the method comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions defined herein. In one embodiment the

method comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions selected from a) and b), a) and c), b) and c), or a), b) and c) as defined in claim 1.

In one embodiment as used herein, specific values given in relation to numbers or intervals may be understood as the specific value or as about the specific value.

FUNCTIONAL PROPERTIES

In a first functional aspect, the GLP-1 agonists of the invention have a good potency. Also, or alternatively, in a second functional aspect, the GLP-1 agonists of the invention have a protracted pharmacokinetic profile. Also, or alternatively, in a third functional aspect, the GLP-1 agonists of the invention are stable against degradation by gastro intestinal enzymes.

Biological activity (potency)

According to the first functional aspect, the GLP-1 agonists of the invention are biologically active, or potent. In a particular embodiment, “potency” and/or “activity” refers to in vitro potency, i.e. performance in a functional GLP-1 receptor assay, more in particular to the capability of stimulating cAMP formation in a cell line expressing the cloned human GLP-1 receptor.

The stimulation of the formation of cAMP in a medium containing the human GLP-1 receptor may preferably be determined using a stable transfected cell-line such as BHK467-12A (tk-ts13), and/or using for the determination of cAMP a functional receptor assay, e.g. based on competition between endogenously formed cAMP and exogenously added biotin-labelled cAMP, in which assay cAMP is more preferably captured using a specific antibody, and/or wherein an even more preferred assay is the AlphaScreencAMP Assay, such as the one described in Assay (I).

In one embodiment the term half maximal effective concentration (EC_{50}) generally refers to the concentration which induces a response halfway between the baseline and maximum, by reference to the dose response curve. EC_{50} is used as a measure of the potency of a compound and represents the concentration where 50% of its maximal effect is observed.

The in vitro potency of the GLP-1 agonists of the invention may be determined as described above, and the EC_{50} of the GLP-1 agonist in question determined. The lower the EC_{50}, the better the potency.

In a particular embodiment, the medium has the following composition (final in-assay concentrations): 50 mM TRIS-HCl; 5 mM HEPES; 10 mM$MgCl_2$, $6H_2O$; 150 mMNaCl;

0.01% Tween; 0.1% BSA ; 0.5 mM IBMX; 1 mM ATP; 1 μM GTP; pH 7.4.

In a further particular embodiment, the GLP-1 agonist of the invention has an in vitro potency corresponding to an EC_{50} at or below 3000pM, such as below 2000pM, below 1000pM, or below 500pM, or such as below 200 pM or below 100 pM.

In another particular embodiment the GLP-1 agonist of the invention are potent in vivo, which may be determined as is known in the art in any suitable animal model, as well as in clinical trials.

The diabetic db/db mouse is one example of a suitable animal model, and the blood glucose lowering effect may be determined in such mice in vivo, e.g. as described in Assay (III), or as described in Example 43 of WO09/030738.

Also, or alternatively, the effect on food intake in vivo may be determined in pharmacodynamic studies in pigs, e.g. as described in Assay (IV).

Protraction - half life in vivo in minipigs

According to the second functional aspect, the GLP-1 agonists of the invention are protracted. In a particular embodiment protraction may be determined as half-life ($T_{½}$) in vivo in minipigs after i.v. administration. In additional embodiments, the half-life is at least 24 hours, such as at least 48 hours, at least 60 hours, at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours.

A suitable assay for determining half-life in vivo in minipigs after i.v. administration is disclosed in Assay (II).

Degradation by gastro intestinal enzymes

According to the third functional aspect, the GLP-1 agonists of the invention are stable, or stabilised, against degradation by one or more gastro intestinal enzymes.

Gastro intestinal enzymes include, without limitation, exo and endo peptidases, such as pepsin, trypsin, chymotrypsin, elastases, and carboxypeptidases. The stability may be tested against these gastro intestinal enzymes in the form of purified enzymes, or in the form of extracts from the gastrointestinal system.

In a particular embodiment, the GLP-1 agonist of the invention has an in vitro half-life ($T_{½}$), in an extract of rat small intestines, divided by the corresponding half-life ($T_{½}$) of GLP-1(7-37), of at least 1, such as above 1.0, at least 1.2, at least 2.0, or such as at least 3.0, or at least 4.0. In other words, a ratio(SI) may be defined for each GLP-1 agonist, viz. as the in vitro half-life ($T_{½}$) of the GLP-1 agonist in question, in an extract of rat small intestines, divided by the corresponding half-life ($T_{½}$) of GLP-1(7-37).

A suitable assay for determining in vitro half-life in an extract of rat small intestines is disclosed in Assay (V).

GLP-1 AGONISTS

In one embodiment the GLP-1 peptide comprises an Aib residue in position 8.

In one embodiment the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

In one embodiment the GLP-1 peptide is attached to a hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

In one embodiment the GLP-1 peptide is exendin-4, an exendin-4-analogue, or a derivative of exendin-4.

In one embodiment the GLP-1 agonist peptide comprises the amino acid sequence of the following formula:
H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2.

In one embodiment the GLP-1 agonist comprises an albumin binding residue attached via a hydrophilic spacer to the C-terminal amino acid residue of said GLP-1 peptide.

In one embodiment the GLP-1 agonist comprises a second albumin binding residue is attached to an amino acid residue which is not the C-terminal amino acid residue.

In one embodiment the GLP-1 peptide is selected from the group consisting of semaglutide, albiglutide and dulaglitide.

In one embodiment the GLP-1 peptide has the following structure:
His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg.

In one embodiment the GLP-1 peptide has the following structure:
(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-
Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2–
genetically fused to human albumin.

In one embodiment the GLP-1 peptide is dulaglitide.

In one embodiment the GLP-1 agonists of the invention have GLP-1 activity. In one embodiment "a GLP-1 agonist" is understood to refer to any compound, including peptides and non-peptide compounds, which fully or partially activate the human GLP-1 receptor. In

one embodiment the "GLP-1 agonist" is any peptide or non-peptide small molecule that binds to a GLP-1 receptor, preferably with an affinity constant (K_D) or a potency (EC_{50}) of below 1 μM, e. g. below 100 nM as measured by methods known in the art (see e. g., WO 98/08871).In one embodiment methods for identifying GLP-1 agonists are described in WO 93/19175 (Novo Nordisk A/S) and examples of suitable GLP-1 agonists which can be used according to the present invention includes those referred to in WO 2005/027978 (Novo Nordisk A/S), the teachings of which are both incorporated by reference herein.“GLP-1 activity” refers to the ability to bind to the GLP-1 receptor and initiate a signal transduction pathway resulting in insulinotropic action or other physiological effects as is known in the art. For example, the GLP-1 agonists of the invention can be tested for GLP-1 activity using the assay described in Assay (I) herein.

In yet another embodiment the GLP-1 agonist is a stable GLP-1 agonist. As used herein a "stable GLP-1 agonist" means a GLP-1agonist which exhibits an in vivo plasma elimination half-life of at least 24 hours in man, optionally determined by the method described below. Examples of stable GLP-1 agonists can be found in WO2006/097537.

In one embodiment the method for determination of plasma elimination half-life of a compound in man may be carried out as follows: The compound is dissolved in an isotonic buffer, pH 7.4, PBS or any other suitable buffer. The dose is injected peripherally, preferably in the abdominal or upper thigh. Blood samples for determination of active compound are taken at frequent intervals, and for a sufficient duration to cover the terminal elimination part (e. g., Pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24 (day 2), 36 (day 2), 48 (day 3), 60 (day 3), 72 (day 4) and 84 (day 4) hours post dose). Determination of the concentration of active compound is performed as described in Wilken*et al.*, Diabetologia 43 (51), 2000. Derived pharmacokinetic parameters are calculated from the concentration-time data for each individual subject by use of non-compartmental methods, using the commercially available software WinNonlin Version 2.1 (Pharsight, Cary, NC, USA). The terminal elimination rate constant is estimated by log-linear regression on the terminal log-linear part of the concentration-time curve, and used for calculating the elimination half-life.

In one embodiment the GLP-1 agonist is formulated so as to have a half-life in manof at least 48 hours. This may be obtained by sustained release formulations known in the art.

In one embodiment the GLP-1 agonist is a GLP-1 peptide. In one embodiment the GLP-1 peptide is selected from GLP-1 (7-35), GLP-1 (7-36), GLP-1 (7-36)-amide, GLP-1 (7-37), GLP-1 (7-38), GLP-1 (7-39), GLP-1 (7-40), GLP-1 (7-41) or an analogue or derivative thereof. In one embodiment the GLP-1 peptide comprises no more than 15, such as no more

than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37). In one embodiment the GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code. In yet another embodiment, the GLP-1 agonist is exendin-4 or exendin-3, an exendin-4 or exendin-3 analogue, or a derivative of any of these.

In one embodiment the GLP-1 peptide is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglitide. In one embodiment the GLP-1 peptide is semaglutide. WO 06/097537 discloses semaglutide (Example 4), a mono-acylated GLP-1 agonist for once weekly administration. In one embodiment the GLP-1 peptide is exenatide. In one embodiment the GLP-1 peptide comprises the amino acid sequence of the formula: H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2.Exenatide is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. Exenatide displays biological properties similar to GLP-1. In some embodiments the composition is BYDUREON® (a long acting release formula of exenatide in PLGA particles). In one embodiment the “Bydureon® composition” refer to a powder comprising exenatide, poly (D,L-lactide-co-glycolide), and sucrose which immediately prior to injection is reconstituted in a solvent comprising carmellose sodium, sodium chloride, polysorbate 20, monobasic sodium phosphate (e.g. its monohydrate), dibasic sodium phosphate (e.g. itsheptahydrate), and water for injections. In one embodiment the GLP-1 peptide has the structure (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2–genetically fused to human albumin. Albiglutide is a recombinant human serum albumin (HSA)-GLP-1 hybrid protein, likely a GLP-1 dimer fused to HSA. The constituent GLP-1 peptide is analogue, in which Ala at position 8 has been substituted by Glu. In one embodiment the GLP-1 peptide is dulaglitide. Dulaglutide is a GLP-1-Fc construct (GLP-1 - linker - Fc from IgG4). In one embodiment the GLP-1 peptide has the structure His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg. Liraglutide is a mono-acylated GLP-1 agonist for once daily administration which is marketed as of 2009 by Novo Nordisk A/S, is disclosed in WO 98/08871 Example 37.

In one embodiment the present invention encompasses pharmaceutically acceptable salts of the GLP-1 agonists. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium, and alkylated ammonium salts. Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present GLP-1 agonists are able to form.

In one embodiment the route of administration of GLP-1 agonists may be any route which effectively transports the active compound to the appropriate or desired site of action, such as parenteral. In one embodiment medicaments or pharmaceutical compositions comprising a GLP-1 agonist, such as semaglutide, may be administered parenterally to a patient in need thereof. In one embodiment 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. A further option is a composition which may be a powder or a liquid for the administration of a GLP-1 agonist in the form of a nasal or pulmonal spray. As a still further option, the GLP-1 agonist can also be administered transdermally, e.g., from a patch, optionally an iontophoretic patch, or transmucosally, e.g., bucally. The above-mentioned possible ways to administer GLP-1 agonists are not considered as limiting the scope of the invention.

In one embodimentthe GLP-1 agonist is co-administered together with a further therapeutically active agent used in the treatments defined herein.

In one embodiment the GLP-1 peptide comprises the amino acid sequence of the formula (I):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa_{16}-Ser-Xaa_{18}-$Xaa_{19}Xaa_{20}$GluXaa_{22}-Xaa_{23}-Ala-Xaa_{25}-Xaa_{26}-Xaa_{27}-Phe-Ile-Xaa_{30}-Trp-Leu-Xaa_{33}-Xaa_{34}-Xaa_{35}-Xaa_{36}-Xaa_{37}-Xaa_{38}-Xaa_{39}-Xaa_{40}-Xaa_{41}-Xaa_{42}-Xaa_{43}-Xaa_{44}-Xaa_{45}-Xaa_{46}

Formula (I)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3- pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;
Xaa_{25} is Ala or Val;
Xaa_{26} is Lys, Glu or Arg;
Xaa_{27} is Glu or Leu;
Xaa_{30} is Ala, Glu or Arg;
Xaa_{33} is Val or Lys;
Xaa_{34} is Lys, Glu, Asn or Arg;
Xaa_{35} is Gly or Aib;
Xaa_{36} is Arg, Gly or Lys;
Xaa_{37} is Gly, Ala, Glu, Pro, Lys, amide or is absent;
Xaa_{38} is Lys, Ser, amide or is absent;
Xaa_{39} is Ser, Lys, amide or is absent;
Xaa_{40} is Gly, amide or is absent;
Xaa_{41} is Ala, amide or is absent;
Xaa_{42} is Pro, amide or is absent;
Xaa_{43} is Pro, amide or is absent;
Xaa_{44} is Pro, amide or is absent;
Xaa_{45} is Ser, amide or is absent;
Xaa_{46} is amide or is absent;

provided that if Xaa_{38}, Xaa_{39}, Xaa_{40}, Xaa_{41}, Xaa_{42}, Xaa_{43}, Xaa_{44}, Xaa_{45} or Xaa_{46} is absent then each amino acid residue downstream is also absent.

In one embodiment the GLP-1 peptide comprises the amino acid sequence of formula (II):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Xaa_{18}-Tyr-Leu-Glu-Xaa22-Xaa_{23}-Ala-Ala-Xaa_{26}-Glu-Phe-Ile-Xaa_{3o}-Trp-Leu-Val-Xaa_{34}-Xaa_{35}-Xaa_{36}-$Xaa_{37}Xaa_{38}$

Formula (II)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine,-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-

aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{26} is Lys, Glu or Arg; Xaa30 is Ala, Glu or Arg;

Xaa_{34} is Lys, Glu or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg or Lys;

Xaa_{37} is Gly, Ala, Glu or Lys;

Xaa_{38} is Lys, amide or is absent.

In one embodiment the GLP-1 peptide is a DPPIV protected GLP-1 peptide.

In one embodiment the GLP-1 peptide is DPPIV stabilised.

In one embodiment the GLP-1 peptide comprises an Aib residue in position 8.

In one embodiment the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

In one embodiment the GLP-1 peptide comprises Arg^{34}GLP-1 (7-37) or [Aib8,Arg34]GLP-1-(7-37).

In one embodiment the GLP-1 agonist comprises an albumin binding residue which is covalently attached, optionally via a hydrophilic spacer.In one embodiment said albumin binding residue is covalently attached, optionally via a hydrophilic spacer, to the C-terminal amino acid residue of said GLP-1 peptide or an amino acid residue which is not the C-terminal amino acid residue. In one embodiment the GLP-1 peptide is attached to a hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

Human Glucagon-Like Peptide-1 is GLP-1(7-37) and has the sequence HAEGTFTSDVSSYLEGQAAKEFI AWLVKGRG (SEQ ID NO: 1). GLP-1(7-37)may also be designated "native" GLP-1. In the sequence listing, the first amino acid residue of SEQ ID NO: 1 (histidine) is assigned no. 1. However, in what follows - according to established practice in the art - this histidine residue is referred to as no. 7, and subsequent amino acid residues are numbered accordingly, ending with glycine no. 37. Therefore, generally, any reference herein to an amino acid residue number or a position number of the GLP-1(7-37)

sequence is to the sequence starting with His at position 7 and ending with Gly at position 37.A non-limiting example of a suitable analogue nomenclatureis [Aib^8,Arg^{34},Lys^{37}]GLP-1(7-37), which designates a GLP-1(7-37) analogue, in which the alanine at position 8 has been substituted with α-aminoisobutyric acid (Aib), the lysine at position 34 has been substituted with arginine, and the glycine at position 37 has been substituted with lysine.

In one embodiment the GLP-1 agonist exhibits at least 60%, 65%, 70%, 80% or 90% sequence identity to GLP-1(7-37) over the entire length of GLP-1(7-37). As an example of a method for determination of sequence identity between two analogues the two peptides [Aib8]GLP-1(7-37) and GLP-1(7-37) are aligned. The sequence identity of [Aib8]GLP-1(7-37) relative to GLP-1(7-37) is given by the number of aligned identical residues minus the number of different residues divided by the total number of residues in GLP-1(7-37). Accordingly, in said example the sequence identity is (31-1)/31. In one embodiment non-peptide moieties of the GLP-1 agonist are not included when determining sequence identity.

In one embodiment the GLP-1 agonist is a derivative. In one embodiment the term “derivative” as used herein in the context of a GLP-1 agonist, peptide or analogue means a chemically modified GLP-1 agonist, peptide or analogue, in which one or more substituents have been covalently attached to the agonist, peptide or analogue. The substituent may also be referred to as a side chain.Typical modifications are amides, carbohydrates, alkyl groups, acyl groups, esters and the like. An example of a derivative of GLP-1(7-37) is $N^{\varepsilon 26}$-(γ-Glu(N^{α}-hexadecanoyl)) - [Arg^{34}, Lys^{25}]) GLP-1 (7- 37).

In a particular embodiment, the side chain is capable of forming non-covalent aggregates with albumin, thereby promoting the circulation of the GLP-1 agonist with the blood stream, and also having the effect of protracting the time of action of the GLP-1 agonist, due to the fact that the aggregate of the GLP-1 agonist and albumin is only slowly disintegrated to release the active pharmaceutical ingredient. Thus, the substituent, or side chain, as a whole may be referred to as an albumin binding moiety.

In particular embodiments, the side chain has at least 10 carbon atoms, or at least 15, 20, 25, 30, 35, or at least 40 carbon atoms. In further particular embodiments, the side chain may further include at least 5 hetero atoms, in particular O and N, for example at least 7, 9, 10, 12, 15, 17, or at least 20 hetero atoms, such as at least 1, 2, or 3 N-atoms, and/or at least 3, 6, 9, 12, or 15 O-atoms.

In another particular embodiment the albumin binding moiety comprises a portion which is particularly relevant for the albumin binding and thereby the protraction, which portion may accordingly be referred to as a protracting moiety. The protracting moiety may be at, or near, the opposite end of the albumin binding moiety, relative to its point of

attachment to the peptide.

In a still further particular embodiment the albumin binding moiety comprises a portion inbetween the protracting moiety and the point of attachment to the peptide, which portion may be referred to as a linker, linker moiety, spacer, or the like. The linker may be optional, and hence in that case the albumin binding moiety may be identical to the protracting moiety.

In particular embodiments, the albumin binding moiety and/or the protracting moiety is lipophilic, and/or negatively charged at physiological pH (7.4).

The albumin binding moiety, the protracting moiety, or the linker may be covalently attached to a lysine residue of the GLP-1 peptide by acylation. Additional or alternative conjugation chemistry includes alkylation, ester formation, or amide formation, or coupling to a cysteine residue, such as by maleimide or haloacetamide (such as bromo-/fluoro-/iodo-) coupling.

In one embodiment an active ester of the albumin binding moiety, e.g. comprising a protracting moiety and a linker, is covalently linked to an amino group of a lysine residue, e.g. the epsilon amino group thereof, under formation of an amide bond (this process being referred to as acylation).

Unless otherwise stated, when reference is made to an acylation of a lysine residue, it is understood to be to the epsilon-amino group thereof.

For the present purposes, the terms "albumin binding moiety", "protracting moiety", and "linker" may include the unreacted as well as the reacted forms of these molecules. Whether or not one or the other form is meant is clear from the context in which the term is used.

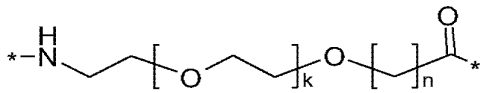
For the attachment to the GLP-1 agonist, the acid group of the fatty acid, or one of the acid groups of the fatty diacid, forms an amide bond with the epsilon amino group of a lysine residue in the GLP-1 peptide, e.g. via a linker.

In one embodiment the term "fatty acid" refers to aliphatic monocarboxylic acids having from 4 to 28 carbon atoms, it is optionally unbranched, and/or even numbered, and it may be saturated or unsaturated.

In one embodiment the term "fatty diacid" refers to fatty acids as defined above but with an additional carboxylic acid group in the omega position. Thus, fatty diacids are dicarboxylic acids.

Each of the twolinkersof the GLP-1 agonist of the invention may comprise the following first linker element:

Chem. 5:



,

wherein k is an integer in the range of 1-5, and n is an integer in the range of 1-5.

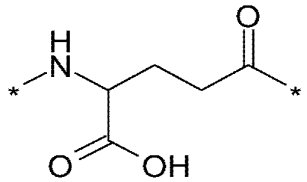
In a particular embodiment, when k=1 and n= 1, this linker element may be designated OEG, or a di-radical of 8-amino-3,6-dioxaoctanic acid, and/or it may be represented by the following formula:

Chem. 5a:

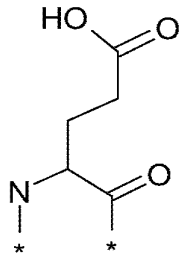
-NH-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-.

In another particular embodiment, each linker of the GLP-1 agonist of the invention may further comprise, independently, a second linker element, e.g. a Glu di-radical, such as Chem. 6 and/or Chem. 7:

Chem. 6:



Chem. 7:



,

wherein the Glu di-radical may be included p times, where p is an integer in the range of 1-3.

Chem. 6 may also be referred to as gamma-Glu, or briefly gGlu, due to the fact that it is the gamma carboxy group of the amino acid glutamic acid which is here used for connection to another linker element, or to the epsilon-amino group of lysine. As explained above, the other linker element may, for example, be another Glu residue, or an OEG molecule. The amino group of Glu in turn forms an amide bond with the carboxy group of the protracting moiety, or with the carboxy group of, e.g., an OEG molecule, if present, or with the gamma-carboxy group of, e.g., another Glu, if present.

Chem. 7 may also be referred to as alpha-Glu, or briefly aGlu, or simply Glu, due to the fact that it is the alpha carboxy group of the amino acid glutamic acid which is here used for connection to another linker element, or to the epsilon-amino group of lysine.

The above structures of Chem. 6 and Chem. 7 cover the L-form, as well as the D-form of Glu. In particular embodiments, Chem. 6 and/or Chem. 7 is/are, independently, a) in the L-form, or b) in the D-form.

In still further particular embodiments the linker has a) from 5 to 41 C-atoms; and/or b) from 4 to 28 hetero atoms.

The concentration in plasma of the GLP-1 agonists of the invention may be determined using any suitable method. For example, LC-MS (Liquid Chromatography Mass Spectroscopy) may be used, or immunoassays such as RIA (Radio Immuno Assay), ELISA (Enzyme-Linked Immuno Sorbent Assay), and LOCI (Luminescence Oxygen ChannelingImmunoasssay). General protocols for suitable RIA and ELISA assays are found in, e.g., WO09/030738 on p. 116-118. A preferred assay is the LOCI (Luminescent Oxygen Channeling Immunoassay), generally as described for the determination of insulin by Poulsen and Jensen in Journal of Biomolecular Screening 2007, vol. 12, p. 240-247 - briefly blood samples may be collected at desired intervals, plasma separated, immediately frozen, and kept at -20°C until analyzed for plasma concentration of the respective GLP-1 agonist;the donor beads are coated with streptavidin, while acceptor beads are conjugated with a monoclonal antibody recognising a mid-/C-terminal epitope of the peptide;another monoclonal antibody, specific for the N-terminus, isbiotinylated;the three reactants are combined with the analyte and formed a two-sited immuno-complex;illumination of the complex releases singlet oxygen atoms from the donor beads, which are channeled into the acceptor beads and triggered chemiluminescence which may be measured in an Envision plate reader;the amount of light is proportional to the concentration of the compound.

In one embodiment the term “Aib” as used herein refers to α-aminoisobutyric acid.

PHARMACEUTICAL COMPOSITIONS

An administered dose may contain from 5 mg - 100 mg of the GLP-1 agonist, or from 5-50 mg, or from 5-20 mg, or from 5-10 mg of the GLP-1 agonist.

In one embodiment the composition is BYDUREON® (a long acting release formula of exenatide in PLGA particles).

Pharmaceutical compositions comprising a GLP-1 agonist of the invention or a pharmaceutically acceptable salt, amide, or ester thereof, and a pharmaceutically acceptable excipient may be prepared as is known in the art.

In one embodiment the term "excipient" broadly refers to any component other than the active therapeutic ingredient(s). The excipient may be an inert substance, an inactive

substance, and/or a not medicinally active substance.The formulation of pharmaceutically active ingredients with various excipients is known in the art, see e.g. Remington: The Science and Practice of Pharmacy (e.g. 19th edition (1995), and any later editions).Non-limiting examples of excipients are: solvents, diluents, buffers, preservatives, tonicity regulating agents (e.gisotonic agents), chelating agents, stabilisers (e.g. oxidation inhibitors, aggregation inhibitors, surfactants, and/or protease inhibitors).

Examples of formulations include liquid formulations, i.e. aqueous formulations comprising water. A liquid formulation may be a solution, or a suspension. An aqueous formulation typically comprises at least 50% w/w water, or at least 60%, 70%, 80%, or even at least 90% w/w of water.

Alternatively, a pharmaceutical composition may be a solid formulation, e.g. a freeze-dried or spray-dried composition, which may be used as is, or whereto the physician or the patient adds solvents, and/or diluents prior to use.

The pH in an aqueous formulation may be anything between pH 3 and pH 10, for example from about 7.0 to about 9.5; or from about 3.0 to about 7.0.

Still further, a pharmaceutical composition may be formulated as is known in the art of oral formulations of insulinotropic compounds, e.g. using any one or more of the formulations described in WO 2008/145728.

A composition may be administered in several dosage forms, for example as a solution; a suspension; an emulsion; a microemulsion; multiple emulsions; a foam; a salve; a paste; a plaster; an ointment; a tablet; a coated tablet; a chewing gum; a rinse; a capsule such as hard or soft gelatine capsules; a suppositorium; a rectal capsule; drops; a gel; a spray; a powder; an aerosol; an inhalant; eye drops; an ophthalmic ointment; an ophthalmic rinse; a vaginal pessary; a vaginal ring; a vaginal ointment; an injection solution; an in situ transforming solution such as in situ gelling, setting, precipitating, and in situ crystallisation; an infusion solution; or as an implant.

A composition may further be compounded in a drug carrier or drug delivery system, e.g. in order to improve stability, bioavailability, and/or solubility. In a particular embodiment a composition may be attached to such system through covalent, hydrophobic, and/or electrostatic interactions. The purpose of such compounding may be, e.g., to decrease adverse effects, achieve chronotherapy, and/or increase patient compliance.

A composition may also be used in the formulation of controlled, sustained, protracting, retarded, and/or slow release drug delivery systems.

The composition may be administered by parenteral administration.Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal, or

intravenous injection by means of a syringe, optionally a pen-like syringe, or by means of an infusion pump.

PRODUCTION PROCESSES

In one embodiment GLP-1 peptides can be produced by appropriate derivatisation of an appropriate peptide backbone which has been produced by recombinant DNA technology or by peptide synthesis (e.g., Merrifield-type solid phase synthesis) as known in the art of peptide synthesis and peptide chemistry.

In one embodiment the production of peptides like GLP-1(7-37) and GLP-1 analogues is well known in the art. The GLP-1 moiety of the GLP-1 peptide of the invention (or fragments thereof) may for instance be produced by classical peptide synthesis, e.g., solid phase peptide synthesis using t-Boc or Fmoc chemistry or other well established techniques, see, e.g., Greene and Wuts, “Protective Groups in Organic Synthesis”, John Wiley & Sons, 1999, Florencio Zaragoza Dörwald, “Organic Synthesis on solid Phase”, Wiley-VCH Verlag GmbH, 2000, and “Fmoc Solid Phase Peptide Synthesis”, Edited by W.C. Chan and P.D. White, Oxford University Press, 2000.

In one embodiment GLP-1 agonists may be produced by recombinant methods, viz. by culturing a host cell containing a DNA sequence encoding the GLP-1 agonist and capable of expressing the peptide in a suitable nutrient medium under conditions permitting the expression of the peptide. Non-limiting examples of host cells suitable for expression of these peptides are: Escherichia coli,Saccharomyces cerevisiae, as well as mammalian BHK or CHO cell lines.

In one embodiment GLP-1 agonists of the invention which include non-natural amino acids and/or a covalently attached N-terminal mono- or dipeptide mimetic may e.g. be produced as described in the experimental part. Or see e.g., Hodgson et al: "The synthesis of peptides and proteins containing non-natural amino acids", Chemical Society Reviews, vol. 33, no. 7 (2004), p. 422-430; and WO 2009/083549 A1 entitled "Semi-recombinant preparation of GLP-1 analogues".

EMBODIMENTS

The following are non-limiting embodiments of the invention:

1. A method for reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, said method comprising administrationof a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

2. A method for treating or preventing obesity, for reducing body weight and/or food intake, or for inducing satiety, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

3. The method according to any one of the preceding embodiments, wherein said method comprises delaying or preventing diabetic disease progression.

4. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist has a half-life of at least 24 hours, such as at least 48 hours, at least 60 hours, or at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours, or optionally at least 120 hours, at least 132 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

5. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered twice weekly or less often, once weekly or less often, such as less often than once weekly or once every secondly week or less often, or such as once every third week or less often or once a month or less often.

6. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount of at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, per week.

7. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount equivalent to at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, semaglutide per week.8. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount which provides an improved a) reduction in HbA1c orb) reduction in body weight compared to administration of 1.8 mg liraglutide or less, such as 0.8 mg liraglutide or less, per day.9. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

10. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered by parenteral administration, such as subcutaneous injection.

11. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered simultaneously or sequentially with another therapeutic agent.

12. The method according to any one of any one of the preceding embodiments, wherein the GLP-1 agonist is a GLP-1 peptide.

13. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide comprises the amino acid sequence of the formula (I):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa_{16}-Ser-Xaa_{18}-$Xaa_{19}Xaa_{20}$GluXaa_{22}-Xaa_{23}-Ala-Xaa_{25}-Xaa_{26}-Xaa_{27}-Phe-Ile-Xaa_{3}o-Trp-Leu-Xaa_{33}-Xaa_{34}-Xaa_{35}-Xaa_{36}-Xaa_{37}-Xaa_{38}-Xaa_{39}-Xaa_{4}o-Xaa_{41}-Xaa_{42}-Xaa_{43}-Xaa_{44}-Xaa_{45}-Xaa_{46}

Formula (I)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3- pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{25} is Ala or Val;

Xaa_{26} is Lys, Glu or Arg;

Xaa_{27} is Glu or Leu;

Xaa_{30} is Ala, Glu or Arg;

Xaa_{33} is Val or Lys;

Xaa_{34} is Lys, Glu, Asn or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg, Gly or Lys;

Xaa_{37} is Gly, Ala, Glu, Pro, Lys, amide or is absent;

Xaa_{38} is Lys, Ser, amide or is absent;

Xaa_{39} is Ser, Lys, amide or is absent;

Xaa_{40} is Gly, amide or is absent;

Xaa_{41} is Ala, amide or is absent;

Xaa_{42} is Pro, amide or is absent;

Xaa_{43} is Pro, amide or is absent;

Xaa_{44} is Pro, amide or is absent;

Xaa_{45} is Ser, amide or is absent;

Xaa_{46} is amide or is absent;

provided that if Xaa_{38}, Xaa_{39}, Xaa_{40}, Xaa_{41}, Xaa_{42}, Xaa_{43}, Xaa_{44}, Xaa_{45} or Xaa_{46} is absent then each amino acid residue downstream is also absent.

14. The method according to any one of the preceding embodiments, wherein said polypeptide is a GLP-1 peptide comprising the amino acid sequence of formula (II):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Xaa_{18}-Tyr-Leu-Glu-Xaa22-Xaa_{23}-Ala-Ala-Xaa_{26}-Glu-Phe-Ile-Xaa_{3o}-Trp-Leu-Val-Xaa_{34}-Xaa_{35}-Xaa_{36}-$Xaa_{37}Xaa_{38}$

Formula (II)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine,-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{26} is Lys, Glu or Arg; Xaa30 is Ala, Glu or Arg;

Xaa_{34} is Lys, Glu or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg or Lys;

Xaa_{37} is Gly, Ala, Glu or Lys;

Xaa_{38} is Lys, amide or is absent.

15. The method according toany one of the preceding embodiments, wherein said GLP-1 peptide is selected from GLP-1 (7-35), GLP-1 (7-36), GLP-1 (7-36)-amide, GLP-1 (7-37), GLP-1 (7-38), GLP-1 (7-39), GLP-1 (7-40), GLP-1 (7-41) or an analogue or derivative thereof.

16. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 15, such as no more than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

17. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 5 amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

18. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code.

19. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide is a DPPIV protected GLP-1 peptide.

20. The method according to any one of the preceding embodiments, wherein GLP-1 peptide is DPPIV stabilised.

21. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises an Aib residue in position 8.

22. The method according to any one of the preceding embodiments, wherein the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

23. The method according to any one of embodiments 7 to 16, wherein said GLP-1 peptide is attached to said hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

24. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide is exendin-4, an exendin-4-analogue, or a derivative of exendin-4.

25. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide comprises the amino acid sequence of the following formula:
H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2.

26. The method according to any one of the preceding embodiments wherein one albumin binding residue via said hydrophilic spacer is attached to the C-terminal amino acid residue of said GLP-1 peptide.

27. The method according to any one of the preceding embodiments, wherein a second albumin binding residue is attached to an amino acid residue which is not the C-terminal amino acid residue.

28. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide is selected from the group consisting of semaglutide, albiglutide and dulaglitide.

29. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide has the following structure:
His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg.

30. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide has the following structure:
(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2–
genetically fused to human albumin.

31. The method according to any one of the preceding embodiments wherein the GLP-1 peptide is dulaglitide.

32. The method according to any one of the preceding embodiments wherein the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100pM, optionally determined by Assay (I).

33. A GLP-1 agonist for use in the reduction of HbA1c or for use in the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

34. A GLP-1 agonist for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

35. A GLP-1 agonist for use according to embodiment 33 or 34, wherein the GLP-1 agonist and/or administration is as defined in any of embodiments 1-32 or 40.

36. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

37. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety, wherein said GLP-1 agonist is administered in

an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

38. A composition for use according to any one of the preceding embodiments, wherein said GLP-1 agonist and/or administration is as defined in any one of embodiments 1-32 or 40.

39. A composition for use according to any one of the preceding embodiments, wherein said composition comprises the Bydureon® composition.

40. The method according to any one of the preceding claims, wherein the method comprises prevention, treatment, reduction or induction in one or more diseases or conditions defined in any one of the previous embodiments.

EXAMPLES

Abbreviations

The following abbreviations are used in the following, in alphabetical order:

ADA: American Diabetes Association

Example 1: The Glp-1 Peptide Semaglutide Provides Reduced HbA1c and Body Weight

Semaglutide is a unique acylated GLP-1 peptide with a half-life of 160 hours. The aim was to investigate HbA1c dose-response of once-weekly doses of semaglutide (five dose-levels) in subjects with type 2 diabetes. Safety, tolerability and pharmacodynamics of semaglutide versus placebo and open-label once-daily liraglutide were also investigated.

Materials and methods

Liraglutide may be prepared as described in Example 37 of WO98/08871. Semaglutide may be prepared as described in Example 4 of WO2006/097537. The composition of the GLP-1 agonists administered may be formulated as isotonic aqueous solutions with a phosphate buffer, such as a sodium dihydrogen phosphate buffer,having a pH in the range 7.0-9.0, such as pH 7.4 or pH8.15, for example further comprising the excipients propylene glycol and phenol. The composition of the GLP-1 agonists administered may be as described in WO2003/002136 or WO2005/049061. The placebo composition may be identical to the composition of the GLP-1 agonists, but not containing a GLP-1 agonist.

In a 12-week, randomised, double-blind, placebo-controlled trial, 411 human subjects (n=43–50 per group) with type 2 diabetes were exposed. Participants (male/female 65/35%; baseline HbA1c (mean±SD) 8.1±0.8%; baseline body weight 87.5±13.8 kg; duration

of diabetes 2.6±3.1 years; metformin only/diet and exercise alone 80/20%) received subcutaneous injection of one of five semaglutide doses (0.1–1.6 mg) once weekly, open-label liraglutide (1.2 mg, 1.8 mg) once daily, or placebo once weekly. Two of the semaglutide doses were titrated (T) in weekly increments of 0.4 mg. The primary endpoint was change in HbA1c from baseline. Secondary efficacy endpoints included proportion of subjects reaching ADA HbA1c target (<7%) and change in body weight. Change and percentage to target were analysed by ANOVA and logistic regression, respectively. Comparisons between semaglutide and liraglutide were not corrected for multiplicity.

Results

In the full analysis set, semaglutide (≥0.2 mg) dose-dependently reduced HbA1c from baseline (Fig. 1), and increased the likelihood of achieving HbA1c <7% ($p<0.05$ vs. placebo for doses ≥0.2 mg). The results with respect to change in HbA1c are shown in Fig. 1. Treatment with semaglutide ≥0.8 mg numerically brought more patients to target than liraglutide 1.8 mg (0.8 mg T 69%, 0.8 mg 73%, 1.6 mg T 81% vs. liraglutide 1.8 mg 57%). Body weight was dose-dependently reduced from baseline by up to 4.8 kg vs placebo 1.2 kg ($p<0.01$ for doses ≥0.8 mg). There were no reports of pancreatitis or treatment-related changes in blood calcitonin. Proportion of subjects with nausea and vomiting increased with dose, but were generally mild or moderate and ameliorated by titration. Withdrawals due to gastrointestinal adverse events were 4.7%-27.7% for semaglutide and 2.2%-10% for liraglutide. Few subjects reported minor hypoglycaemia (semaglutide n=5, liraglutide n=3); no major hypoglycaemia. Injection site reactions were reported by 7 subjects: semaglutide n=2; liraglutide n=5. One subject (semaglutide 1.6 mg T) developed low titre non-neutralising anti-semaglutide antibodies (no cross-reaction to native GLP-1).

Conclusion

Over 12 weeks, semaglutide dose-dependently reduced HbA1c and body weight. The effect of semaglutide 0.4 mg on glycaemic control and body weight was comparable to that of liraglutide 1.2 mg, while semaglutide ≥0.8 mg appeared to bring more subjects to target and provided better weight loss than liraglutide 1.8 mg. No semaglutide safety concerns were identified. Dose escalation was not a major focus of this trial and it will be optimised in future clinical trials.

Pharmacological Methods

Assay (I): In Vitro Potency

The purpose of this example is to test the activity, or potency, of GLP-1 agonists in vitro. The potencies of GLP-1 agonists may be determined as described below, i.e. as the stimulation of the formation of cyclic AMP (cAMP) in a medium containing membranes expressing the human GLP-1 receptor.

Principle

Purified plasma membranes from a stable transfected cell line, BHK467-12A (tk-ts13), expressing the human GLP-1 receptor are stimulated with the GLP-1 agonist in question, and the potency of cAMP production is measured using the AlphaScreenTMcAMP Assay Kit from Perkin Elmer Life Sciences. The basic principle of The AlphaScreen Assay is a competition between endogenous cAMP and exogenously added biotin-cAMP. The capture of cAMP is achieved by using a specific antibody conjugated to acceptor beads.

Cell culture and preparation of membranes

A stable transfected cell line and a high expressing clone are selected for screening. The cells are grown at 5% CO_2 in DMEM, 5% FCS, 1% Pen/Strep (Penicillin/Streptomycin) and 0.5 mg/ml of the selection marker G418. Cells at approximate 80% confluence are washed 2X with PBS and harvested with Versene (aqueous solution of the tetrasodium salt of ethylenediaminetetraacetic acid), centrifuged 5 min at 1000 rpm and the supernatant removed. The additional steps are all made on ice. The cell pellet is homogenised by the Ultrathurax for 20-30 sec. in 10 ml of Buffer 1 (20 mM Na-HEPES, 10 mM EDTA, pH=7.4), centrifuged 15 min at 20,000 rpm and the pellet resuspended in 10 ml of Buffer 2 (20 mM Na-HEPES, 0.1 mM EDTA, pH=7.4). The suspension is homogenised for 20-30 sec and centrifuged 15 min at 20,000 rpm. Suspension in Buffer 2, homogenisation and centrifugation is repeated once and the membranes are resuspended in Buffer 2. The protein concentration is determined and the membranes stored at -80°C until use.

The assay is performed in ½-area 96-well plates, flat bottom (e.g. Costar cat. no:3693). The final volume per well is 50 µl.

Solutions and reagents

Exemplary solutions and reagents are given below.

AlphaScreencAMP Assay Kit from Perkin Elmer Life Sciences (cat. No: 6760625M); containing Anti-cAMP Acceptor beads (10 U/µl), Streptavidin Donor beads (10 U/µl) and Biotinylated-cAMP (133 U/µl).

AlphaScreen Buffer, pH=7.4: 50 mM TRIS-HCl (Sigma, cat.no: T3253); 5 mM

HEPES (Sigma, cat.no: H3375); 10 mM$MgCl_2$, 6H_2O (Merck, cat.no: 5833); 150 mMNaCl (Sigma, cat.no: S9625); 0.01% Tween (Merck, cat.no: 822184). The following was added to the AlphaScreen Buffer prior to use (final concentrations indicated): BSA (Sigma, cat. no. A7906): 0.1%; IBMX (Sigma, cat. no. I5879): 0.5 mM; ATP (Sigma, cat. no. A7699): 1 mM; GTP (Sigma, cat. no. G8877): 1 µM.

cAMP standard (dilution factor in assay = 5): cAMP Solution: 5 µL of a 5 mMcAMP-stock + 495 µL AlphaScreen Buffer.

Suitable dilution series in AlphaScreen Buffer are prepared of the cAMP standard as well as the GLP-1 agonist to be tested, e.g. the following eight concentrations of the GLP-1 agonist: 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} and 10^{-14}M, and a series from, e.g., 10^{-6} to $3x10^{-11}$ of cAMP.

Membrane/Acceptor beads

Use hGLP-1/ BHK 467-12A membranes; 6 µg/well corresponding to 0.6 mg/ml (the amount of membranes used pr. well may vary)

"No membranes": Acceptor Beads (15µg/ml final) in AlphaScreen buffer

"6 µg/well membranes": membranes + Acceptor Beads (15µg/ml final) in AlphaScreen buffer

Add 10 µl "No membranes" to the cAMP standard (per well in duplicates) and the positive and negative controls

Add 10 µl "6 µg/well membranes" to GLP-1 and GLP-1 agonists (per well in duplicates/triplicates)

Pos. Control: 10 µl "no membranes" + 10 µl AlphaScreen Buffer

Neg. Control: 10 µl "no membranes" + 10 µl cAMP Stock Solution (50µM)

As the beads are sensitive to direct light, any handling is in the dark (as dark as possible), or in green light. All dilutions are made on ice.

Procedure

1. Make the AlphaScreen Buffer.
2. Dissolve and dilute the GLP-1 agonists/cAMP standard in AlphaScreen Buffer.
3. Make the Donor Beads solution and incubate 30 min. at RT.
4. Add the cAMP/GLP-1 agonists to the plate: 10 µl per well.
5. Prepare membrane/Acceptor Beads solution and add this to the plates: 10 µl per well.
6. Add the Donor Beads: 30 µl per well.
7. Wrap the plate in aluminum foil and incubate on the shaker for 3 hours (very slowly) at RT.

8. Count on AlphaScreen – each plate pre incubates in the AlphaScreen for 3 minutes before counting.

The EC_{50} [pM] values may be calculated using the Graph-Pad Prism software (version 5).If desired, the fold variation in relation to GLP-1 may be calculated as EC_{50} (GLP-1)/ EC_{50} (analogue) – 3693.2.

Assay (II): Half-life in Minipigs

The purpose of this study is to determine the protraction in vivo of GLP-1 agonists after i.v. administration to minipigs, i.e. the prolongation of their time of action. This is done in a pharmacokinetic (PK) study, where the terminal half-life of the GLP-1 agonist in question is determined. By terminal half-life is generally meant the period of time it takes to halve a certain plasma concentration, measured after the initial distribution phase.

Male Göttingenminipigsare obtained from EllegaardGöttingenMinipigs (Dalmose, Denmark) approximately 7-14 months of age and weighing from approximately 16-35 kg are used in the studies. The minipigs are housed individually and fed restrictedly once or twice daily with SDS minipig diet (Special Diets Services, Essex, UK). After at least 2 weeks of acclimatisation two permanent central venous catheters are implanted in vena cava caudalis or cranialis in each animal. The animals are allowed 1 week recovery after the surgery, and are then used for repeated pharmacokinetic studies with a suitable wash-out period between dosings.

The animals are fasted for approximately 18 h before dosing and for at least 4 h after dosing, but have ad libitum access to water during the whole period.

The GLP-1 agonist is dissolved in 50 mM sodium phosphate, 145 mM sodium chloride, 0.05% tween 80, pH 7.4 to a concentration of usually from 20-60 nmol/ml. Intravenous injections (the volume corresponding to usually 1-2 nmol/kg, for example 0.033ml/kg) of the compounds are given through one catheter, and blood is sampled at predefined time points for up till 13 days post dosing (preferably through the other catheter). Blood samples (for example 0.8 ml) are collected in EDTA buffer (8mM) and then centrifuged at 4°C and 1942G for 10 minutes. Plasma is pippetted into Micronic tubes on dry ice, and kept at -20°C until analyzed for plasma concentration of the respective GLP-1 compound using ELISA or a similar antibody based assay or LC-MS. Individual plasma concentration-time profiles are analyzed by a non-compartmental model in WinNonlin v. 5.0 (Pharsight Inc., Mountain View, CA, USA), and the resulting terminal half-lives (harmonic mean) determined.

Assay (III): Effect on Blood Glucose and Body Weight

The purpose of the study is to verify the effect of GLP-1 agonists on blood glucose (BG) and body weight (BW) in a diabetic setting.GLP-1 agonists may be tested in a dose-response study in an obese, diabetic mouse model (db/db mice) as described in the following.

Fifty db/db mice (Taconic, Denmark), fed from birth with the diet NIH31 (NIH 31M Rodent Diet, commercially available from Taconic Farms, Inc., US, see www.taconic.com), are enrolled for the study at the age of 7-9 weeks The mice are given free access to standard chow (e.g. Altromin 1324, Brogaarden, Gentofte, Denmark) and tap water and kept at 24°C. After 1-2 weeks of acclimatisation, the basal blood glucose is assessed twice on two consecutive days (i.e. at 9 am). The 8 mice with the lowest blood glucose values may be excluded from the experiments. Based on the mean blood glucose values, the remaining 42 mice may be selected for further experimentation and allocated to 7 groups (n=6) with matching blood glucose levels. The mice may be used in experiments with duration of 5 days for up to 4 times. After the last experiment the mice are euthanised.

The seven groups may receive treatment as follows:

1: Vehicle, subcutaneous
2: GLP-1 agonist, 0.3 nmol/kg, subcutaneous
3: GLP-1 agonist, 1.0 nmol/kg, subcutaneous
4: GLP-1 agonist, 3.0 nmol/kg, subcutaneous
5: GLP-1 agonist, 10 nmol/kg, subcutaneous
6: GLP-1 agonist, 30 nmol/kg, subcutaneous
7: GLP-1 agonist, 100 nmol/kg, subcutaneous
Vehicle: 50mM sodium phosphate, 145 mM sodium chloride, 0.05% tween 80, pH 7.4.

The GLP-1 agonist is dissolved in the vehicle, e.g. to concentrations of 0.05, 0.17, 0.5, 1.7, 5.0 and 17.0 nmol/ml. Animals are dosed subcutaneous with a dose-volume of 6 ml/kg (i.e. 300 µl per 50 g mouse).

On the day of dosing, blood glucose is assessed at time -½h (8.30 am), where after the mice are weighed. The GLP-1 agonist is dosed at approximately 9 am (time 0). On the day of dosing, blood glucose is assessed e.g. at times 1, 2, 4 and 8 h (10 am, 11 am, 1 pm and 5 pm).

On the following days, the blood glucose is assessed e.g. at time 24, 48, 72, and 96h after dosing (i.e. at 9 am on day 2, 3, 4, 5). On each day, the mice are weighed following blood glucose sampling.

The mice are weighed individually on a digital weight.

Samples for the measurement of blood glucose are obtained from the tail tip capillary of conscious mice. Blood, 10 µl, is collected into heparinised capillaries and transferred to 500 µl glucose buffer (EKF system solution, Eppendorf, Germany). The glucose concentration is measured using the glucose oxidase method (glucose analyser Biosen 5040, EKF Diagnostic, GmbH, Barleben, Germany). The samples are kept at room temperature for up to 1 h until analysis. If analysis has to be postponed, samples are kept at 4°C for a maximum of 24 h.

ED_{50} is the dose giving rise to half-maximal effect in nmol /kg. This value is calculated on the basis of the ability of the GLP-1 agonists to lower body weight as well as the ability to lower blood glucose, as explained below.

ED_{50} for body weight is calculated as the dose giving rise to half-maximum effect on delta BW 24 hours following the subcutaneous administration of the GLP-1 agonist. For example, if the maximum decrease in body weight after 24 hours is 4.0 g, then ED_{50} bodyweight would be that dose in nmol/kg which gives rise to a decrease in body weight after 24 hours of 2.0 g. This dose (ED_{50} body weight) may be read from the dose-response curve.

ED_{50} for blood glucose is calculated as the dose giving rise to half-maximum effect on AUC delta BG 8 hours following the subcutaneous administration of the GLP-1 agonist.

The ED_{50} value may only be calculated if a proper sigmoidal dose-response relationship exists with a clear definition of the maximum response. Thus, if this would not be the case the GLP-1 agonist in question is re-tested in a different range of doses until the sigmoidal dose-response relationship is obtained.

Assay (IV): Effect on Food Intake

The purpose of this experiment is to investigate the effect of GLP-1 agonists on food intake in pigs. This is done in a pharmacodynamic (PD) study as described below, in which food intake is measured 1, 2, 3, and 4 days after administration of a single dose of the GLP-1 agonist, as compared to a vehicle-treated control group.

Female Landrace Yorkshire Duroc (LYD) pigs, approximately 3 months of age, weighing approximately 30-35 kg are used (n=3-4 per group). The animals are housed in a group for 1-2 weeks during acclimatisation to the animal facilities. During the experimental period the animals are placed in individual pens from Monday morning to Friday afternoon for measurement of individual food intake. The animals are fed ad libitum with pig fodder (Svinefoder, Antonio) at all times both during the acclimatisation and the experimental period. Food intake is monitored on line by logging the weight of fodder every 15 minutes. The system used is Mpigwin (Ellegaard Systems, Faaborg, Denmark).

The GLP-1 agonists are dissolved in a phosphate buffer (50 mM phosphate, 0.05% tween 80, pH 8) e.g. at concentrations of 12, 40, 120, 400 or 1200 nmol/ml corresponding to doses of 0.3, 1, 3, 10, or 30 nmol/kg. The phosphate buffer served as vehicle. Animals are dosed with a single subcutaneous dose of the GLP-1 agonist or vehicle (dose volume 0.025 ml/kg) on the morning of day 1, and food intake is measured for 4 days after dosing. On the last day of each study, 4 days after dosing, a blood sample for measurement of plasma exposure of the GLP-1 agonist is taken from the heart in anaesthetised animals. The animals are thereafter euthanised with an intra-cardial overdose of pentobarbitone. Plasma content of the GLP-1 agonist is analysed using ELISA or a similar antibody based assay.

Food intake is calculated as mean ± SEM 24 h food intake on the 4 days.

Statistical comparisons of the 24 hour food intake in the vehicle vs. GLP-1 agonist group on the 4 days are done using one-way or two-way-ANOVA repeated measures, followed by Bonferroni post-test.

Assay (V): Stability againstDegradation by Intestinal Enzymes

The purpose of this example is to test the stability against degradation by intestinal enzymes. GLP-1(7-37) may be used in the assay as a comparative compound.

The strongest proteolytic activities in the intestine are of pancreatic origin and include the serine endopeptidases trypsin, chymotrypsin, and elastase as well as several types of carboxypeptidases.

An assay with small intestine extract from rats was developed and used as described in the following.

Extracts from rat small intestine

Small intestines are prepared from rats and flushed with 8 ml of 150 mMNaCl, 20 mMHepes pH 7.4. The solutions are centrifuged for 15 min at 4,600 rpm in a HeraeusMultifuge 3 S-R centrifuge with a 75006445 rotor. The supernatants are removed and filtered through a 0.22 µm Millipore Millex GV PVDF membrane. Filtrates of several animals are pooled to average out individual differences.

The protein content of the obtained extracts is determined by Bradford Assay (see e.g. Analytical Biochemistry (1976), vol. 72, p. 248-254, and Analytical Biochemistry (1996), vol. 236 p. 302-308).

Degradation assay

2.5 nmol of the GLP-1 agonists to be tested are incubated with the intestinal extract in a volume of 250 µl at 37°C over a period of one hour. Intestinal samples are assayed in

presence of 20 mMHepes at pH 7.4. The concentration of the intestinal extract is titrated in pilot experiments so that the half-life (t½) of GLP-1(7-37) is in the range of 10-20 minutes. The small intestine extract is used at a concentration of 1.4 µg/ml. All components except for the intestinal extract are mixed and pre-warmed for ten minutes at 37°C. Immediately after addition of the intestinal extract a sample of 50 µl is taken and mixed with the same volume of 1% trifluoroacetic acid (TFA). Further samples are taken accordingly after 15, 30, and 60 minutes.

Sample analysis

UPLC analysis

10 µl of the samples are analysed by UPLC using a Waters Acquity system with a BEH C18 1.7 µm 2.1 x 50 mm column and a 30 to 65% gradient of 0.1% TFA and 0.07% TFA in acetonitrile over 5 minutes at a flow rate of 0.6 ml/min. After baseline subtraction the peak integrals of the intact compounds in the HPLC chromatogram recorded at a wavelength of 214 nm are determined.

MALDI-TOF analysis

1 µl of each sample is transferred to a Bruker/Eppendorf PAC HCCA 384 MALDI target. Analysis is performed with a BrukerAutoflex matrix-assisted laser desorption and ionisation - time of flight (MALDI-TOF) mass spectrometer using the pre-defined method “PAC_measure” with an extended detection range of 500 to 5000 Da and the pre-defined calibration method “PAC_calibrate”.

Data analysis

The peak integrals of the HPLC chromatograms are plotted against time. The half-life of the respective compound is calculated by fitting the data using SigmaPlot 9.0 software and an equation for a 2-parameter exponential decay. For each GLP-1 agonist tested, the relative half-life (relative $T_{½}$) is calculated as the half-life ($T_{½}$) of the compound in question, divided by the half-life ($T_{½}$) of GLP-1(7-37), determined in the same way.

While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

CLAIMS

1. A method for
a) reduction of HbA1c;
b) prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or
c) prevention or treatment of obesity, reducing body weight and/or food intake, or inducing satiety;
whereinsaid method comprises administration of a GLP-1 agonist to a subject in need thereof,
wherein said GLP-1 agonist
i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II);
ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and
iii) is administered once weekly or less often.

2. The method according to any one of the preceding claims, wherein said GLP-1 agonist has a half-life of at least 96 hours, at least 120 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

3. The method according to any one of the preceding claims, wherein the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100pM, optionally determined by Assay (I).

4. Themethod according to any one of the preceding claims, wherein said GLP-1 agonist is administered in an amount of
i) at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, per week; or
ii) in an amount equivalent to at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, semaglutide per week.

5. The method according to any one of any one of the preceding claims, wherein the GLP-1 agonist is a GLP-1 peptide.

6. The method according to any one of the preceding claims, wherein said GLP-1 peptide comprises no more than 15, such as no more than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

7. Themethod according to any one of the preceding claims, wherein said GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

8. The method according to any one of the preceding claims, wherein said GLP-1 agonist is administered by parenteral administration, such as subcutaneous (s.c.) injection.

9. The method according to any one of the preceding claims, wherein said GLP-1 agonist is administered simultaneously or sequentially with another therapeutic agent.

10. The method according to any one of the preceding claims, wherein the method comprises prevention, treatment, reduction or induction in one or more diseases or conditions selected from a) and b), a) and c), b) and c), or a), b) and c) as defined in claim 1.

11. A GLP-1 agonist for use in
a) thereduction of HbA1c;
b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or
c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety;
wherein said use comprises administration ofsaid GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week,
and wherein said GLP-1 agonist and/or administration optionally is as defined in any of claims 1-10.

12. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in
a) the reduction of HbA1c;
b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or
c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety;

wherein said GLP-1 agonist

i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); and

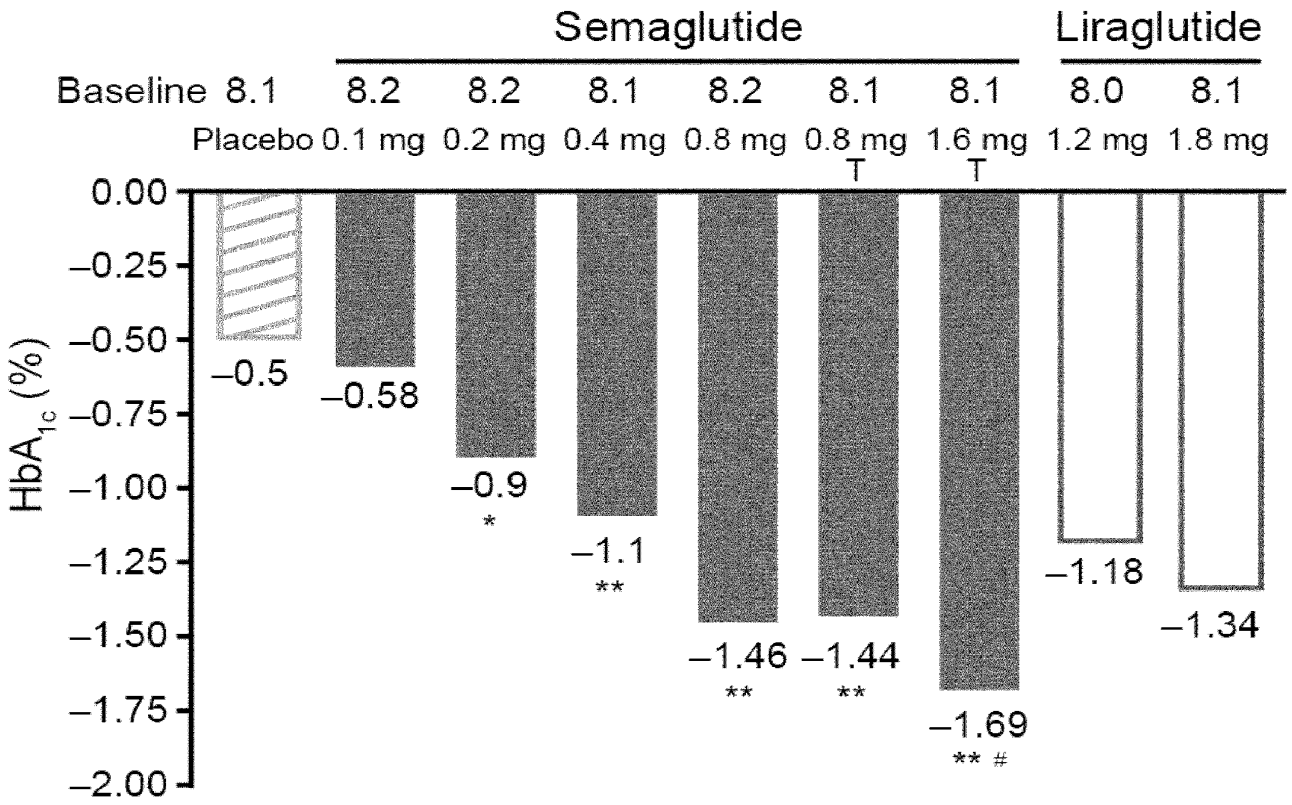
ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and

wherein said composition is administered once weekly or less often, and

wherein said GLP-1 agonist and/or administration optionally is as defined in any of claims 1-10.

ABSTRACT

The invention relates to use of long-acting GLP-1 peptides in certain dosage regimes for the treatment of type 2 diabetes, obesity, etc.



*$p<0.05$ vs. placebo
**$p<0.001$ vs. placebo
#Semaglutide 1.6 mg T superior to liraglutide 1.2 mg and 1.8 mg
Data are LS means.

Fig. 1

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Bescheinigung	Certificate	Attestation
Die angehefteten Unterlagen stimmen mit der als ursprünglich eingereicht geltenden Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.	The attached documents are exact copies of the text in which the European patent application described on the following page is deemed to have been filed.	Les documents joints à la présente attestation sont conformes au texte, considéré comme initialement déposé, de la demande de brevet européen qui est spécifiée à la page suivante.

Patentanmeldung Nr. **Patent application No.** **Demande de brevet n°**

12186781.6 / EP12186781

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP12186781.

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le President de l'Office européen des brevets
p.o.

U. Ingmann

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0254

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Anmelder / Applicant(s) / Demandeur(s):

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Bezeichnung der Erfindung / Title of the invention / Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, oder falls die Anmeldung in einer Nicht-Amtssprache des EPA eingereicht wurde, siehe Beschreibung bezüglich ursprünglicher Bezeichnung.
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USE OF LONG-ACTING GLP-1 PEPTIDES

In Anspruch genommene Priorität(en) / Priority(Priorities) claimed / Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

Am Anmeldetag benannte Vertragstaaten / Contracting States designated at date of filing / Etats contractants désignées lors du dépôt:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0255

USE OF LONG-ACTING GLP-1 PEPTIDES

The present invention relates to improved uses of GLP-1 peptides in therapy.

SUMMARY

In one embodiment the invention relates to a method for a) reduction of HbA1c; b) prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) prevention or treatment of obesity, reducing body weight and/or food intake, or inducing satiety; wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof, wherein said GLP-1 agonist i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and iii) is administered once weekly or less often.

In one embodiment the invention relates to a GLP-1 agonist for use in a) the reduction of HbA1c; b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety; wherein said use comprises administration of said GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week, and wherein said GLP-1 agonist and/or administration optionally is as defined herein.

In one embodiment the invention relates to a composition comprising a GLP-1 agonist for use in a) the reduction of HbA1c; b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety; wherein said GLP-1 agonist i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); and ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and wherein said composition is administered once weekly or less often, and wherein said GLP-1 agonist and/or administration optionally is as defined herein.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows change in HbA1c following subcutaneousadministration of placebo, semaglutide, or liraglutide to human subjects.*$p<0.05$ vs. placebo; **$p<0.001$ vs. placebo (based on adjusted means). Baseline values are for information only: data are model-adjusted for baseline HbA1c. Data are model-adjusted LS means, FAS LOCF. The estimates

are from an ANOVA model with treatment, country and previous treatment as fixed effects and baseline HbA1c as covariate.

Fig. 2 shows mean change in HbA1c from baseline versus time; data are mean (1.96SE), FAS LOCF. The treatments are placebo (A); semaglutide 0.1 mg (B, dashed line), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F, dashed line), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I).

Fig. 3 shows subjects reaching the AACE or ADA criteria for glycaemic control. The number of patients reaching the criteria per treatment is indicated in each bar. The treatments are placebo (A); semaglutide 0.1 mg (B), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I).*$p<0.05$ vs. placebo; **$p<0.001$ vs. placebo; ***$p<0.0001$ vs. placebo (based on adjusted means). Data are FAS LOCF. The estimates are from a logistic regression model treatment, country and previous treatment as fixed effects and baseline HbA1c as covariate. ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists.

Fig. 4 shows mean body weight change versus time; data are mean (1.96SE), FAS LOCF. The treatments are placebo (A); semaglutide 0.1 mg (B, dashed line), 0.2 mg (C), 0.4 mg (D), 0.8 mg (E), 0.8 mg T (F, dashed line), 1.6 mg T (G); liraglutide 1.2 mg (H), 1.8 mg (I).

Fig. 5 shows body weight change from baseline at week 12. **$p<0.001$ vs. placebo; ***$p<0.0001$ vs. placebo (based on adjusted means. †: Baseline values for information only: data are model-adjusted for baseline weight. Data are model-adjusted LS means, FAS LOCF. The estimates are from an ANOVA model with treatment, country and previous treatment as fixed effects and baseline weight as covariate.

SE: Standard error. FAS: Full analysis set. LOCF: Last observation carried forward.

DESCRIPTION

The present invention relates to an improved use of GLP-1 agonists in therapy. In one embodiment the invention relates to certain dosage regimes of GLP-1 agonists which provide improved effect in diseases or conditions, such as prevention and/or treatment of type 2 diabetes and obesity. In one embodiment the methods of the present invention provides surprisingly showed improved reduction of HbA1c and reduction of body weight. In one embodiment the GLP-1 agonist is administered in an amount which provides an improved a) reduction in HbA1c or b) reduction in body weight compared to administration of 1.8 mg liraglutide or less, such as 0.8 mg liraglutide or less, per day.

In one embodiment the invention relates to a method for reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or

non-insulin dependent diabetes, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.In one embodiment the method is for reduction of HbA1c.In one embodiment the method is for prevention or treatment of type 2 diabetes. In one embodiment the method is for prevention or treatment of hyperglycemia. In one embodiment the method is for prevention or treatment of impaired glucose tolerance. In one embodiment the method is for prevention or treatment of non-insulin dependent diabetes. In one embodiment the method of the invention comprises delaying or preventing diabetic disease progression.In one embodiment a HbA1c level below 7% is achieved. In one embodiment the level of HbA1c is determined according to the method defined by the Diabetes Control and Complications Trial (DCCT). In one embodiment the level of HbA1c is determined according to the method defined by the International Federation of Clinical Chemistry (IFCC).

In one embodiment the invention relates to a method for treating or preventing obesity, for reducing body weight and/or food intake, or for inducing satiety, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week. In one embodiment the method is for prevention or treatment of obesity. In one embodiment the method is for reducing body weight and/or food intake. In one embodiment the method is for inducing satiety.

In one embodiment the GLP-1 agonist has a half-life of at least 24 hours, such as at least 48 hours, at least 60 hours, or at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours, or optionally at least 120 hours, at least 132 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

In one embodiment the GLP-1 agonist is administered twice weekly or less often, once weekly or less often, or once weekly or less often.In one embodiment the GLP-1 agonist is administered once every secondly week or less often, once every third week or less often, or once a month or less often.

In one embodiment the GLP-1 agonist is administered in an amount per weekof at least 0.8 mg, at least 0.9 mg, or at least 1.0 mg. In one embodiment the GLP-1 agonist is administered in an amount per weekofat least 1.1 mg, at least 1.2 mg, or at least 1.3 mg. In one embodiment the GLP-1 agonist is administered in an amount per weekofat least 1.4 mg, at least 1.5 mg, or at least 1.6 mg.

In one embodiment the GLP-1 agonist is administered in an amount per weekequivalent to at least 0.8 mg, at least 0.9 mg, or at least 1.0 mg semaglutide. In one

embodiment the GLP-1 agonist is administered in an amount per weekequivalent to at least 1.1 mg, at least 1.2 mg, or at least 1.3 mg semaglutide. In one embodiment the GLP-1 agonist is administered in an amount per weekequivalent to at least 1.4 mg, at least 1.5 mg, or at least 1.6 mg semaglutide.

In one embodiment the GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

In one embodiment the GLP-1 agonist is administered by parenteral administration, such as subcutaneous injection.

In one embodiment the GLP-1 agonist is a GLP-1 peptide.In one embodiment the GLP-1 peptide comprises no more than 5, such as no more than 4 or no more than 3, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37). In one embodiment the GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code.

In one embodiment the GLP-1 peptide is a DPPIV protected GLP-1 peptide. In one embodiment the GLP-1 peptide is DPPIV stabilised.

In one embodiment the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100pM, optionally determined by Assay (I).

In one embodiment the invention relates to a GLP-1 agonist for use in the reduction of HbA1c or for use in the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to a GLP-1 agonist for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to acomposition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg

semaglutide per week. In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the invention relates to acomposition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.In one embodiment the GLP-1 agonist and/or administration is as defined herein.

In one embodiment the GLP-1 agonist is administered with another therapeutic agent.Administration with another therapeutic agent may be carried out as administration of the GLP-1 agonist and the other therapeutic agent within the same therapeutic window (e.g. withinin a period of two weeks, a period of one week, or in a 96, 72, or 48 hour period, etc.). The treatment with a GLP-1 agonist according to the present invention may be combined with one or more additional therapeutic agents, e.g. selected from antidiabetic agents, antiobesity agents, appetite regulating agents, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity; examples of these therapeutic agents are: sulphonylureas, thiazolidinediones, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists, and DPP-IV (dipeptidyl peptidase-IV) inhibitors.

In one embodiment, as used herein, an “amount equivalent to” when used in relation to GLP-1 agonists refers to amounts of a first GLP-1 agonist and a second GLP-1 agonist having GLP-1 receptor potency (i.e. EC_{50}) within ±30%, such as within ±20% or within ±10%, of each other optionally determined by Assay (I) described herein and having a half-life within ±30%, such as within ±20% or within ±10%, of each other optionally determined by Assay (II) described herein.

In one embodiment an "effective amount" of a GLP-1 agonist as used herein means an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease or state and its complications. An amount adequate to accomplish this is defined as "effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary.

In one embodiment the term "treatment" or "treating" as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. In one embodiment the term "treatment" or "treating" is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications; to delay the progression of the disease, disorder, or condition; to alleviate or relieve the symptoms and complications; and/or, to cure or eliminate the disease, disorder, or condition as well as to prevent the condition. In one embodiment prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications.

In one embodiment the term "hydrophilic spacer" as used herein means a spacer that separates a peptide and an albumin binding residue with a chemical moiety which comprises at least 5 non- hydrogen atoms where 30-50% of these are either N or O.

In one embodiment the term "analogue" as used herein referring to a polypeptide means a modified peptide wherein one or more amino acid residues of the peptide have been substituted by other amino acid residues and/or wherein one or more amino acid residues have been deleted from the peptide and or wherein one or more amino acid residues have been added to the peptide. Such addition or deletion of amino acid residues can take place at the N-terminal of the peptide and/or at the C-terminal of the peptide. A simple system is used to describe analogues: For example Arg^{34}GLP-1 (7-37) Lys designates a GLP-1 analogue wherein the naturally occurring lysine at position 34 has been substituted with arginine and a lysine residue has been added to the C-terminal (position 38).

In one embodiment the term "GLP-1 peptide" as used herein means GLP-1 (7-37), a GLP-1 analogue, a GLP-1 derivative or a derivative of a GLP-1 analogue.

In one embodiment the term "exendin-4 peptide" as used herein means exendin-4 (1-39), an exendin-4 analogue, an exendin-4 derivative or a derivative of an exendin-4 analogue.

In one embodiment the term “DPP-IV protected” as used herein referring to a polypeptide means a polypeptide which has been chemically modified in order to render said compound resistant to the plasma peptidase dipeptidyl aminopeptidase-4 (DPP-IV). The DPP-IV enzyme in plasma is known to be involved in the degradation of several peptide hormones, e.g. GLP-1, Exendin-4 etc. Thus a considerable effort is being made to develop GLP-1 agonists less susceptible to DPP-IV mediated hydrolysis in order to reduce the rate of degradation by DPP-IV.

The present invention also relates to a GLP-1 agonist of the invention, for use as a medicament. In particular embodiments, the GLP-1 agonist of the invention may be used for the following medical treatments:

(i) prevention and/or treatment of all forms of diabetes, such as hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, non-insulin dependent diabetes, MODY (maturity onset diabetes of the young), gestational diabetes, and/or for reduction of HbA1c;

(ii) delaying or preventing diabetic disease progression, such as progression in type 2 diabetes, delaying the progression of impaired glucose tolerance (IGT) to insulin requiring type 2 diabetes, and/or delaying the progression of non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes;

(iii) prevention and/or treatment of eating disorders, such as obesity, e.g. by decreasing food intake, reducing body weight, suppressing appetite, inducing satiety; treating or preventing binge eating disorder, bulimia nervosa, and/or obesity induced by administration of an antipsychotic or a steroid; reduction of gastric motility; and/or delaying gastric emptying.

In another particular embodiment, the indication is (i). In a further particular embodiment the indication is (ii). In a still further particular embodiment the indication is (iii). In one embodiment the indication is type 2 diabetes and/or obesity.

In one embodiment the method comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions defined herein. In one embodiment the indication is (i) and (iii).In one embodiment the indication is (ii) and (iii).In one embodiment the method comprises prevention, treatment, reduction and/or induction in one or more diseases or conditions selected from a) and b), a) and c), b) and c), or a), b) and c) as defined in claim 1.

In one embodiment the invention relates to administration of an effective amount of a GLP-1 agonist.

In one embodiment as used herein, specific values given in relation to numbers or intervals may be understood as the specific value or as about the specific value.

FUNCTIONAL PROPERTIES

In a first functional aspect, the GLP-1 agonists of the invention have a good potency. Also, or alternatively, in a second functional aspect, the GLP-1 agonists of the invention have a protracted pharmacokinetic profile. Also, or alternatively, in a third functional aspect, the GLP-1 agonists of the invention are stable against degradation by gastro intestinal enzymes.

Biological activity (potency)

According to the first functional aspect, the GLP-1 agonists of the invention are biologically active, or potent. In a particular embodiment, "potency" and/or "activity" refers to in vitro potency, i.e. performance in a functional GLP-1 receptor assay, more in particular to the capability of stimulating cAMP formation in a cell line expressing the cloned human GLP-1 receptor.

The stimulation of the formation of cAMP in a medium containing the human GLP-1 receptor may preferably be determined using a stable transfected cell-line such as BHK467-12A (tk-ts13), and/or using for the determination of cAMP a functional receptor assay, e.g. based on competition between endogenously formed cAMP and exogenously added biotin-labelled cAMP, in which assay cAMP is more preferably captured using a specific antibody, and/or wherein an even more preferred assay is the AlphaScreencAMP Assay, such as the one described in Assay (I).

In one embodiment the term half maximal effective concentration (EC_{50}) generally refers to the concentration which induces a response halfway between the baseline and maximum, by reference to the dose response curve. EC_{50} is used as a measure of the potency of a compound and represents the concentration where 50% of its maximal effect is observed.

The in vitro potency of the GLP-1 agonists of the invention may be determined as described above, and the EC_{50} of the GLP-1 agonist in question determined. The lower the EC_{50}, the better the potency.

In a particular embodiment, the medium has the following composition (final in-assay concentrations): 50 mM TRIS-HCl; 5 mM HEPES; 10 mM$MgCl_2$, $6H_2O$; 150 mMNaCl; 0.01% Tween; 0.1% BSA ; 0.5 mM IBMX; 1 mM ATP; 1 μM GTP; pH 7.4.

In a further particular embodiment, the GLP-1 agonist of the invention has an in vitro potency corresponding to an EC_{50} at or below 3000pM, such as below 2000pM, below 1000pM, or below 500pM, or such as below 200 pM or below 100 pM.

In another particular embodiment the GLP-1 agonist of the invention are potent in vivo, which may be determined as is known in the art in any suitable animal model, as well as in clinical trials.

The diabetic db/db mouse is one example of a suitable animal model, and the blood glucose lowering effect may be determined in such mice in vivo, e.g. as described in Assay (III), or as described in Example 43 of WO09/030738.

Also, or alternatively, the effect on food intake in vivo may be determined in pharmacodynamic studies in pigs, e.g. as described in Assay (IV).

Protraction - half life in vivo in minipigs

According to the second functional aspect, the GLP-1 agonists of the invention are protracted. In a particular embodiment protraction may be determined as half-life ($T_{½}$) in vivo in minipigs after i.v. administration. In additional embodiments, the half-life is at least 24 hours, such as at least 48 hours, at least 60 hours, at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours.

A suitable assay for determining half-life in vivo in minipigs after i.v. administration is disclosed in Assay (II).

Degradation by gastro intestinal enzymes

According to the third functional aspect, the GLP-1 agonists of the invention are stable, or stabilised, against degradation by one or more gastro intestinal enzymes.

Gastro intestinal enzymes include, without limitation, exo and endo peptidases, such as pepsin, trypsin, chymotrypsin, elastases, and carboxypeptidases. The stability may be tested against these gastro intestinal enzymes in the form of purified enzymes, or in the form of extracts from the gastrointestinal system.

In a particular embodiment, the GLP-1 agonist of the invention has an in vitro half-life ($T_{½}$), in an extract of rat small intestines, divided by the corresponding half-life ($T_{½}$) of GLP-1(7-37), of at least 1, such as above 1.0, at least 1.2, at least 2.0, or such as at least 3.0, or at least 4.0. In other words, a ratio(SI) may be defined for each GLP-1 agonist, viz. as the in vitro half-life ($T_{½}$) of the GLP-1 agonist in question, in an extract of rat small intestines, divided by the corresponding half-life ($T_{½}$) of GLP-1(7-37).

A suitable assay for determining in vitro half-life in an extract of rat small intestines is disclosed in Assay (V).

GLP-1 AGONISTS

In one embodiment the GLP-1 peptide comprises an Aib residue in position 8.

In one embodiment the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

In one embodiment the GLP-1 peptide is attached to a hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

In one embodiment the GLP-1 peptide is exendin-4, an exendin-4-analogue, or a derivative of exendin-4.

In one embodiment the GLP-1 agonist peptide comprises the amino acid sequence of the following formula:

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2.

In one embodiment the GLP-1 agonist comprises an albumin binding residue attached via a hydrophilic spacer to the C-terminal amino acid residue of said GLP-1 peptide.

In one embodiment the GLP-1 agonist comprises a second albumin binding residue is attached to an amino acid residue which is not the C-terminal amino acid residue.

In one embodiment the GLP-1 peptide is selected from the group consisting of semaglutide, albiglutide and dulaglitide.

In one embodiment the GLP-1 peptide has the following structure:
His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg.

In one embodiment the GLP-1 peptide has the following structure:
(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-
Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2–
genetically fused to human albumin.

In one embodiment the GLP-1 peptide is dulaglitide.

In one embodiment the GLP-1 agonists of the invention have GLP-1 activity. In one embodiment "a GLP-1 agonist" is understood to refer to any compound, including peptides and non-peptide compounds, which fully or partially activate the human GLP-1 receptor. In one embodiment the "GLP-1 agonist" is any peptide or non-peptide small molecule that binds to a GLP-1 receptor, preferably with an affinity constant (K_D) or a potency (EC_{50}) of below 1 μM, e. g. below 100 nM as measured by methods known in the art (see e. g., WO 98/08871).In one embodiment methods for identifying GLP-1 agonists are described in WO 93/19175 (Novo Nordisk A/S) and examples of suitable GLP-1 agonists which can be used according to the present invention includes those referred to in WO 2005/027978 (Novo Nordisk A/S), the teachings of which are both incorporated by reference herein.“GLP-1 activity” refers to the ability to bind to the GLP-1 receptor and initiate a signal transduction pathway resulting in insulinotropic action or other physiological effects as is known in the art. For example, the GLP-1 agonists of the invention can be tested for GLP-1 activity using the assay described in Assay (I) herein.

In yet another embodiment the GLP-1 agonist is a stable GLP-1 agonist. As used herein a "stable GLP-1 agonist" means a GLP-1agonist which exhibits an in vivo plasma elimination half-life of at least 24 hours in man, optionally determined by the method described below. Examples of stable GLP-1 agonists can be found in WO2006/097537.

In one embodiment the method for determination of plasma elimination half-life of a compound in man may be carried out as follows: The compound is dissolved in an isotonic buffer, pH 7.4, PBS or any other suitable buffer. The dose is injected peripherally, preferably in the abdominal or upper thigh. Blood samples for determination of active compound are taken at frequent intervals, and for a sufficient duration to cover the terminal elimination part (e. g., Pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24 (day 2), 36 (day 2), 48 (day 3), 60 (day 3), 72 (day 4) and 84 (day 4) hours post dose). Determination of the concentration of active compound is performed as described in Wilken*et al.*, Diabetologia 43 (51), 2000. Derived pharmacokinetic parameters are calculated from the concentration-time data for each individual subject by use of non-compartmental methods, using the commercially available software WinNonlin Version 2.1 (Pharsight, Cary, NC, USA). The terminal elimination rate constant is estimated by log-linear regression on the terminal log-linear part of the concentration-time curve, and used for calculating the elimination half-life.

In one embodiment the GLP-1 agonist is formulated so as to have a half-life in manof at least 48 hours. This may be obtained by sustained release formulations known in the art.

In one embodiment the GLP-1 agonist is a GLP-1 peptide. In one embodiment the GLP-1 peptide is selected from GLP-1 (7-35), GLP-1 (7-36), GLP-1 (7-36)-amide, GLP-1 (7-37), GLP-1 (7-38), GLP-1 (7-39), GLP-1 (7-40), GLP-1 (7-41) or an analogue or derivative thereof. In one embodiment the GLP-1 peptide comprises no more than 15, such as no more than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37). In one embodiment the GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code. In yet another embodiment, the GLP-1 agonist is exendin-4 or exendin-3, an exendin-4 or exendin-3 analogue, or a derivative of any of these.

In one embodiment the GLP-1 peptide is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglitide. In one embodiment the GLP-1 peptide is semaglutide. WO 06/097537 discloses semaglutide (Example 4), a mono-acylated GLP-1 agonist for once weekly administration. In one embodiment the GLP-1 peptide is exenatide. In one embodiment the GLP-1 peptide comprises the amino acid sequence of the formula: H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-

Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2.Exenatide is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. Exenatide displays biological properties similar to GLP-1. In some embodiments the composition is BYDUREON® (a long acting release formula of exenatide in PLGA particles). In one embodiment the "Bydureon® composition" refer to a powder comprising exenatide, poly (D,L-lactide-co-glycolide), and sucrose which immediately prior to injection is reconstituted in a solvent comprising carmellose sodium, sodium chloride, polysorbate 20, monobasic sodium phosphate (e.g. its monohydrate), dibasic sodium phosphate (e.g. itsheptahydrate), and water for injections. In one embodiment the GLP-1 peptide has the structure (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2–genetically fused to human albumin. Albiglutide is a recombinant human serum albumin (HSA)-GLP-1 hybrid protein, likely a GLP-1 dimer fused to HSA. The constituent GLP-1 peptide is analogue, in which Ala at position 8 has been substituted by Glu. In one embodiment the GLP-1 peptide is dulaglitide. Dulaglutide is a GLP-1-Fc construct (GLP-1 - linker - Fc from IgG4). In one embodiment the GLP-1 peptide has the structure His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg. Liraglutide is a mono-acylated GLP-1 agonist for once daily administration which is marketed as of 2009 by Novo Nordisk A/S, is disclosed in WO 98/08871 Example 37.

In one embodiment the present invention encompasses pharmaceutically acceptable salts of the GLP-1 agonists. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium, and alkylated ammonium salts. Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present GLP-1 agonists are able to form.

In one embodiment the route of administration of GLP-1 agonists may be any route which effectively transports the active compound to the appropriate or desired site of action, such as parenteral. In one embodiment medicaments or pharmaceutical compositions comprising a GLP-1 agonist, such as semaglutide, may be administered parenterally to a patient in need thereof. In one embodiment 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. A further option is a composition which may be a powder or a liquid for the administration of a GLP-1 agonist in the form of a nasal or pulmonal spray. As a still further option, the GLP-1 agonist can also be administered transdermally, e.g., from a patch,

optionally an iontophoretic patch, or transmucosally, e.g., bucally. The above-mentioned possible ways to administer GLP-1 agonists are not considered as limiting the scope of the invention.

In one embodimentthe GLP-1 agonist is co-administered together with a further therapeutically active agent used in the treatments defined herein.

In one embodiment the GLP-1 peptide comprises the amino acid sequence of the formula (I):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa_{16}-Ser-Xaa_{18}-$Xaa_{19}Xaa_{20}$GluXaa_{22}-Xaa_{23}-Ala-Xaa_{25}-Xaa_{26}-Xaa_{27}-Phe-Ile-Xaa_{30}-Trp-Leu-Xaa_{33}-Xaa_{34}-Xaa_{35}-Xaa_{36}-Xaa_{37}-Xaa_{38}-Xaa_{39}-Xaa_{40}-Xaa_{41}-Xaa_{42}-Xaa_{43}-Xaa_{44}-Xaa_{45}-Xaa_{46}

Formula (I)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3- pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{25} is Ala or Val;

Xaa_{26} is Lys, Glu or Arg;

Xaa_{27} is Glu or Leu;

Xaa_{30} is Ala, Glu or Arg;

Xaa_{33} is Val or Lys;

Xaa_{34} is Lys, Glu, Asn or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg, Gly or Lys;

Xaa_{37} is Gly, Ala, Glu, Pro, Lys, amide or is absent;

Xaa_{38} is Lys, Ser, amide or is absent;

Xaa_{39} is Ser, Lys, amide or is absent;

Xaa_{40} is Gly, amide or is absent;

Xaa_{41} is Ala, amide or is absent;

Xaa_{42} is Pro, amide or is absent;

Xaa_{43} is Pro, amide or is absent;

Xaa_{44} is Pro, amide or is absent;

Xaa_{45} is Ser, amide or is absent;

Xaa_{46} is amide or is absent;

provided that if Xaa_{38}, Xaa_{39}, Xaa_{40}, Xaa_{41}, Xaa_{42}, Xaa_{43}, Xaa_{44}, Xaa_{45} or Xaa_{46} is absent then each amino acid residue downstream is also absent.

In one embodiment the GLP-1 peptide comprises the amino acid sequence of formula (II):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Xaa_{18}-Tyr-Leu-Glu-Xaa22-Xaa_{23}-Ala-Ala-Xaa_{26}-Glu-Phe-Ile-Xaa_{3o}-Trp-Leu-Val-Xaa_{34}-Xaa_{35}-Xaa_{36}-$Xaa_{37}Xaa_{38}$

Formula (II)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine,-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{26} is Lys, Glu or Arg; Xaa30 is Ala, Glu or Arg;

Xaa_{34} is Lys, Glu or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg or Lys;

Xaa_{37} is Gly, Ala, Glu or Lys;

Xaa_{38} is Lys, amide or is absent.

In one embodiment the GLP-1 peptide is a DPPIV protected GLP-1 peptide.

In one embodiment the GLP-1 peptide is DPPIV stabilised.

In one embodiment the GLP-1 peptide comprises an Aib residue in position 8.

In one embodiment the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

In one embodiment the GLP-1 peptide comprises Arg^{34}GLP-1 (7-37) or [Aib8,Arg34]GLP-1-(7-37).

In one embodiment the GLP-1 agonist comprises an albumin binding residue which is covalently attached, optionally via a hydrophilic spacer.In one embodiment said albumin binding residue is covalently attached, optionally via a hydrophilic spacer, to the C-terminal amino acid residue of said GLP-1 peptide or an amino acid residue which is not the C-terminal amino acid residue. In one embodiment the GLP-1 peptide is attached to a hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

Human Glucagon-Like Peptide-1 is GLP-1(7-37) and has the sequence HAEGTFTSDVSSYLEGQAAKEFI AWLVKGRG (SEQ ID NO: 1). GLP-1(7-37)may also be designated "native" GLP-1. In the sequence listing, the first amino acid residue of SEQ ID NO: 1 (histidine) is assigned no. 1. However, in what follows - according to established practice in the art - this histidine residue is referred to as no. 7, and subsequent amino acid residues are numbered accordingly, ending with glycine no. 37. Therefore, generally, any reference herein to an amino acid residue number or a position number of the GLP-1(7-37) sequence is to the sequence starting with His at position 7 and ending with Gly at position 37.A non-limiting example of a suitable analogue nomenclatureis [Aib^{8},Arg^{34},Lys^{37}]GLP-1(7-37), which designates a GLP-1(7-37) analogue, in which the alanine at position 8 has been substituted with α-aminoisobutyric acid (Aib), the lysine at position 34 has been substituted with arginine, and the glycine at position 37 has been substituted with lysine.

In one embodiment the GLP-1 agonist exhibits at least 60%, 65%, 70%, 80% or 90% sequence identity to GLP-1(7-37) over the entire length of GLP-1(7-37). As an example of a method for determination of sequence identity between two analogues the two peptides [Aib8]GLP-1(7-37) and GLP-1(7-37) are aligned. The sequence identity of [Aib8]GLP-1(7-37) relative to GLP-1(7-37) is given by the number of aligned identical residues minus the number of different residues divided by the total number of residues in GLP-1(7-37).

Accordingly, in said example the sequence identity is (31-1)/31. In one embodiment non-peptide moieties of the GLP-1 agonist are not included when determining sequence identity.

In one embodiment the GLP-1 agonist is a derivative. In one embodiment the term "derivative" as used herein in the context of a GLP-1 agonist, peptide or analogue means a chemically modified GLP-1 agonist, peptide or analogue, in which one or more substituents have been covalently attached to the agonist, peptide or analogue. The substituent may also be referred to as a side chain.Typical modifications are amides, carbohydrates, alkyl groups, acyl groups, esters and the like. An example of a derivative of GLP-1(7-37) is $N^{\varepsilon 26}$-(γ-Glu(N^{α}-hexadecanoyl)) - [Arg^{34}, Lys^{25}]) GLP-1 (7- 37).

In a particular embodiment, the side chain is capable of forming non-covalent aggregates with albumin, thereby promoting the circulation of the GLP-1 agonist with the blood stream, and also having the effect of protracting the time of action of the GLP-1 agonist, due to the fact that the aggregate of the GLP-1 agonist and albumin is only slowly disintegrated to release the active pharmaceutical ingredient. Thus, the substituent, or side chain, as a whole may be referred to as an albumin binding moiety.

In particular embodiments, the side chain has at least 10 carbon atoms, or at least 15, 20, 25, 30, 35, or at least 40 carbon atoms. In further particular embodiments, the side chain may further include at least 5 hetero atoms, in particular O and N, for example at least 7, 9, 10, 12, 15, 17, or at least 20 hetero atoms, such as at least 1, 2, or 3 N-atoms, and/or at least 3, 6, 9, 12, or 15 O-atoms.

In another particular embodiment the albumin binding moiety comprises a portion which is particularly relevant for the albumin binding and thereby the protraction, which portion may accordingly be referred to as a protracting moiety. The protracting moiety may be at, or near, the opposite end of the albumin binding moiety, relative to its point of attachment to the peptide.

In a still further particular embodiment the albumin binding moiety comprises a portion inbetween the protracting moiety and the point of attachment to the peptide, which portion may be referred to as a linker, linker moiety, spacer, or the like. The linker may be optional, and hence in that case the albumin binding moiety may be identical to the protracting moiety.

In particular embodiments, the albumin binding moiety and/or the protracting moiety is lipophilic, and/or negatively charged at physiological pH (7.4).

The albumin binding moiety, the protracting moiety, or the linker may be covalently attached to a lysine residue of the GLP-1 peptide by acylation. Additional or alternative conjugation chemistry includes alkylation, ester formation, or amide formation, or coupling to

a cysteine residue, such as by maleimide or haloacetamide (such as bromo-/fluoro-/iodo-) coupling.

In one embodiment an active ester of the albumin binding moiety, e.g. comprising a protracting moiety and a linker, is covalently linked to an amino group of a lysine residue, e.g. the epsilon amino group thereof, under formation of an amide bond (this process being referred to as acylation).

Unless otherwise stated, when reference is made to an acylation of a lysine residue, it is understood to be to the epsilon-amino group thereof.

For the present purposes, the terms "albumin binding moiety", "protracting moiety", and "linker" may include the unreacted as well as the reacted forms of these molecules. Whether or not one or the other form is meant is clear from the context in which the term is used.

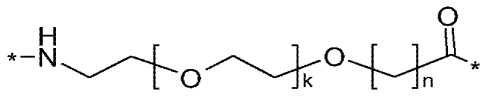
For the attachment to the GLP-1 agonist, the acid group of the fatty acid, or one of the acid groups of the fatty diacid, forms an amide bond with the epsilon amino group of a lysine residue in the GLP-1 peptide, e.g. via a linker.

In one embodiment the term "fatty acid" refers to aliphatic monocarboxylic acids having from 4 to 28 carbon atoms, it is optionally unbranched, and/or even numbered, and it may be saturated or unsaturated.

In one embodiment the term "fatty diacid" refers to fatty acids as defined above but with an additional carboxylic acid group in the omega position. Thus, fatty diacids are dicarboxylic acids.

Each of the twolinkersof the GLP-1 agonist of the invention may comprise the following first linker element:

Chem. 5:



,

wherein k is an integer in the range of 1-5, and n is an integer in the range of 1-5.

In a particular embodiment, when k=1 and n= 1, this linker element may be designated OEG, or a di-radical of 8-amino-3,6-dioxaoctanic acid, and/or it may be represented by the following formula:

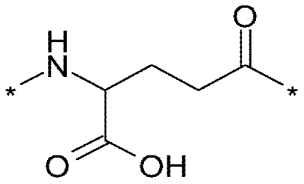
Chem. 5a:

-NH-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-CO-.

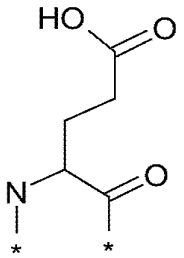
In another particular embodiment, each linker of the GLP-1 agonist of the invention may further comprise, independently, a second linker element, e.g. a Glu di-radical, such as

Chem. 6 and/or Chem. 7:

Chem. 6:



Chem. 7:



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wherein the Glu di-radical may be included p times, where p is an integer in the range of 1-3.

Chem. 6 may also be referred to as gamma-Glu, or briefly gGlu, due to the fact that it is the gamma carboxy group of the amino acid glutamic acid which is here used for connection to another linker element, or to the epsilon-amino group of lysine. As explained above, the other linker element may, for example, be another Glu residue, or an OEG molecule. The amino group of Glu in turn forms an amide bond with the carboxy group of the protracting moiety, or with the carboxy group of, e.g., an OEG molecule, if present, or with the gamma-carboxy group of, e.g., another Glu, if present.

Chem. 7 may also be referred to as alpha-Glu, or briefly aGlu, or simply Glu, due to the fact that it is the alpha carboxy group of the amino acid glutamic acid which is here used for connection to another linker element, or to the epsilon-amino group of lysine.

The above structures of Chem. 6 and Chem. 7 cover the L-form, as well as the D-form of Glu. In particular embodiments, Chem. 6 and/or Chem. 7 is/are, independently, a) in the L-form, or b) in the D-form.

In still further particular embodiments the linker has a) from 5 to 41 C-atoms; and/or b) from 4 to 28 hetero atoms.

The concentration in plasma of the GLP-1 agonists of the invention may be determined using any suitable method. For example, LC-MS (Liquid Chromatography Mass Spectroscopy) may be used, or immunoassays such as RIA (Radio Immuno Assay), ELISA (Enzyme-Linked Immuno Sorbent Assay), and LOCI (Luminescence Oxygen

ChannelingImmunoasssay). General protocols for suitable RIA and ELISA assays are found in, e.g., WO09/030738 on p. 116-118. A preferred assay is the LOCI (Luminescent Oxygen Channeling Immunoassay), generally as described for the determination of insulin by Poulsen and Jensen in Journal of Biomolecular Screening 2007, vol. 12, p. 240-247 - briefly blood samples may be collected at desired intervals, plasma separated, immediately frozen, and kept at -20°C until analyzed for plasma concentration of the respective GLP-1 agonist;the donor beads are coated with streptavidin, while acceptor beads are conjugated with a monoclonal antibody recognising a mid-/C-terminal epitope of the peptide;another monoclonal antibody, specific for the N-terminus, isbiotinylated;the three reactants are combined with the analyte and formed a two-sited immuno-complex;illumination of the complex releases singlet oxygen atoms from the donor beads, which are channeled into the acceptor beads and triggered chemiluminescence which may be measured in an Envision plate reader;the amount of light is proportional to the concentration of the compound.

In one embodiment the term “Aib” as used herein refers to α-aminoisobutyric acid.

PHARMACEUTICAL COMPOSITIONS

An administered dose may contain from 5 mg - 100 mg of the GLP-1 agonist, or from 5-50 mg, or from 5-20 mg, or from 5-10 mg of the GLP-1 agonist.

In one embodiment the composition is BYDUREON® (a long acting release formula of exenatide in PLGA particles).

Pharmaceutical compositions comprising a GLP-1 agonist of the invention or a pharmaceutically acceptable salt, amide, or ester thereof, and a pharmaceutically acceptable excipient may be prepared as is known in the art.

In one embodiment the term "excipient" broadly refers to any component other than the active therapeutic ingredient(s). The excipient may be an inert substance, an inactive substance, and/or a not medicinally active substance.The formulation of pharmaceutically active ingredients with various excipients is known in the art, see e.g. Remington: The Science and Practice of Pharmacy (e.g. 19th edition (1995), and any later editions).Non-limiting examples of excipients are: solvents, diluents, buffers, preservatives, tonicity regulating agents (e.gisotonic agents), chelating agents, stabilisers (e.g. oxidation inhibitors, aggregation inhibitors, surfactants, and/or protease inhibitors).

Examples of formulations include liquid formulations, i.e. aqueous formulations comprising water. A liquid formulation may be a solution, or a suspension. An aqueous formulation typically comprises at least 50% w/w water, or at least 60%, 70%, 80%, or even at least 90% w/w of water.

Alternatively, a pharmaceutical composition may be a solid formulation, e.g. a freeze-dried or spray-dried composition, which may be used as is, or whereto the physician or the patient adds solvents, and/or diluents prior to use.

The pH in an aqueous formulation may be anything between pH 3 and pH 10, for example from about 7.0 to about 9.5; or from about 3.0 to about 7.0.

Still further, a pharmaceutical composition may be formulated as is known in the art of oral formulations of insulinotropic compounds, e.g. using any one or more of the formulations described in WO 2008/145728.

A composition may be administered in several dosage forms, for example as a solution; a suspension; an emulsion; a microemulsion; multiple emulsions; a foam; a salve; a paste; a plaster; an ointment; a tablet; a coated tablet; a chewing gum; a rinse; a capsule such as hard or soft gelatine capsules; a suppositorium; a rectal capsule; drops; a gel; a spray; a powder; an aerosol; an inhalant; eye drops; an ophthalmic ointment; an ophthalmic rinse; a vaginal pessary; a vaginal ring; a vaginal ointment; an injection solution; an in situ transforming solution such as in situ gelling, setting, precipitating, and in situ crystallisation; an infusion solution; or as an implant.

A composition may further be compounded in a drug carrier or drug delivery system, e.g. in order to improve stability, bioavailability, and/or solubility. In a particular embodiment a composition may be attached to such system through covalent, hydrophobic, and/or electrostatic interactions. The purpose of such compounding may be, e.g., to decrease adverse effects, achieve chronotherapy, and/or increase patient compliance.

A composition may also be used in the formulation of controlled, sustained, protracting, retarded, and/or slow release drug delivery systems.

The composition may be administered by parenteral administration.Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal, or intravenous injection by means of a syringe, optionally a pen-like syringe, or by means of an infusion pump.

PRODUCTION PROCESSES

In one embodiment GLP-1 peptides can be produced by appropriate derivatisation of an appropriate peptide backbone which has been produced by recombinant DNA technology or by peptide synthesis (e.g., Merrifield-type solid phase synthesis) as known in the art of peptide synthesis and peptide chemistry.

In one embodiment the production of peptides like GLP-1(7-37) and GLP-1 analogues is well known in the art. The GLP-1 moiety of the GLP-1 peptide of the invention

(or fragments thereof) may for instance be produced by classical peptide synthesis, e.g., solid phase peptide synthesis using t-Boc or Fmoc chemistry or other well established techniques, see, e.g., Greene and Wuts, “Protective Groups in Organic Synthesis”, John Wiley & Sons, 1999, Florencio Zaragoza Dörwald, “Organic Synthesis on solid Phase”, Wiley-VCH Verlag GmbH, 2000, and “Fmoc Solid Phase Peptide Synthesis”, Edited by W.C. Chan and P.D. White, Oxford University Press, 2000.

In one embodiment GLP-1 agonists may be produced by recombinant methods, viz. by culturing a host cell containing a DNA sequence encoding the GLP-1 agonist and capable of expressing the peptide in a suitable nutrient medium under conditions permitting the expression of the peptide. Non-limiting examples of host cells suitable for expression of these peptides are: Escherichia coli,Saccharomyces cerevisiae, as well as mammalian BHK or CHO cell lines.

In one embodiment GLP-1 agonists of the invention which include non-natural amino acids and/or a covalently attached N-terminal mono- or dipeptide mimetic may e.g. be produced as described in the experimental part. Or see e.g., Hodgson et al: "The synthesis of peptides and proteins containing non-natural amino acids", Chemical Society Reviews, vol. 33, no. 7 (2004), p. 422-430; and WO 2009/083549 A1 entitled "Semi-recombinant preparation of GLP-1 analogues".

EMBODIMENTS

The following are non-limiting embodiments of the invention:

1. A method for reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, said method comprising administrationof a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.
2. A method for treating or preventing obesity, for reducing body weight and/or food intake, or for inducing satiety, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.
3. The method according to any one of the preceding embodiments, wherein said method comprises delaying or preventing diabetic disease progression.
4. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist has a half-life of at least 24 hours, such as at least 48 hours, at least 60 hours, or at least 72 hours, or such as at least 84 hours, at least 96 hours, or at least 108 hours, or

optionally at least 120 hours, at least 132 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

5. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered twice weekly or less often, once weekly or less often, such as less often than once weekly or once every secondly week or less often, or such as once every third week or less often or once a month or less often.

6. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount of at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, per week.

7. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount equivalent to at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, semaglutide per week.8. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount which provides an improved a) reduction in HbA1c orb) reduction in body weight compared to administration of 1.8 mg liraglutide or less, such as 0.8 mg liraglutide or less, per day.9. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

10. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered by parenteral administration, such as subcutaneous injection.

11. The method according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered simultaneously or sequentially with another therapeutic agent.

12. The method according to any one of any one of the preceding embodiments, wherein the GLP-1 agonist is a GLP-1 peptide.

13. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide comprises the amino acid sequence of the formula (I):

$$Xaa_7\text{-}Xaa_8\text{-Glu-Gly-Thr-Phe-Thr-Ser-Asp-}Xaa_{16}\text{-Ser-}Xaa_{18}\text{-}Xaa_{19}Xaa_{20}\text{Glu}Xaa_{22}\text{-}Xaa_{23}\text{-Ala-}Xaa_{25}\text{-}Xaa_{26}\text{-}Xaa_{27}\text{-Phe-Ile-}Xaa_{3}\text{o-Trp-Leu-}Xaa_{33}\text{-}Xaa_{34}\text{-}Xaa_{35}\text{-}Xaa_{36}\text{-}Xaa_{37}\text{-}Xaa_{38}\text{-}Xaa_{39}\text{-}Xaa_{4}\text{o-}Xaa_{41}\text{-}Xaa_{42}\text{-}Xaa_{43}\text{-}Xaa_{44}\text{-}Xaa_{45}\text{-}Xaa_{46}$$

Formula (I)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3- pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{25} is Ala or Val;

Xaa_{26} is Lys, Glu or Arg;

Xaa_{27} is Glu or Leu;

Xaa_{30} is Ala, Glu or Arg;

Xaa_{33} is Val or Lys;

Xaa_{34} is Lys, Glu, Asn or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg, Gly or Lys;

Xaa_{37} is Gly, Ala, Glu, Pro, Lys, amide or is absent;

Xaa_{38} is Lys, Ser, amide or is absent;

Xaa_{39} is Ser, Lys, amide or is absent;

Xaa_{40} is Gly, amide or is absent;

Xaa_{41} is Ala, amide or is absent;

Xaa_{42} is Pro, amide or is absent;

Xaa_{43} is Pro, amide or is absent;

Xaa_{44} is Pro, amide or is absent;

Xaa_{45} is Ser, amide or is absent;

Xaa_{46} is amide or is absent;

provided that if Xaa_{38}, Xaa_{39}, Xaa_{40}, Xaa_{41}, Xaa_{42}, Xaa_{43}, Xaa_{44}, Xaa_{45} or Xaa_{46} is absent then each amino acid residue downstream is also absent.

14. The method according to any one of the preceding embodiments, wherein said polypeptide is a GLP-1 peptide comprising the amino acid sequence of formula (II):

Xaa_7-Xaa_8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Xaa_{18}-Tyr-Leu-Glu-Xaa22-Xaa_{23}-Ala-Ala-Xaa_{26}-Glu-Phe-Ile-Xaa_{3o}-Trp-Leu-Val-Xaa_{34}-Xaa_{35}-Xaa_{36}-$Xaa_{37}Xaa_{38}$

Formula (II)

wherein

Xaa_7 is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine,-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine;

Xaa_8 is Ala, Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{22} is Gly, Glu or Aib;

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{26} is Lys, Glu or Arg; Xaa30 is Ala, Glu or Arg;

Xaa_{34} is Lys, Glu or Arg;

Xaa_{35} is Gly or Aib;

Xaa_{36} is Arg or Lys;

Xaa_{37} is Gly, Ala, Glu or Lys;

Xaa_{38} is Lys, amide or is absent.

15. The method according toany one of the preceding embodiments, wherein said GLP-1 peptide is selected from GLP-1 (7-35), GLP-1 (7-36), GLP-1 (7-36)-amide, GLP-1 (7-37), GLP-1 (7-38), GLP-1 (7-39), GLP-1 (7-40), GLP-1 (7-41) or an analogue or derivative thereof.

16. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 15, such as no more than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

17. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 5 amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

18. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises no more than 4 amino acid residues which are not encoded by the genetic code.

19. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide is a DPPIV protected GLP-1 peptide.

20. The method according to any one of the preceding embodiments, wherein GLP-1 peptide is DPPIV stabilised.

21. The method according to any one of the preceding embodiments, wherein said GLP-1 peptide comprises an Aib residue in position 8.

22. The method according to any one of the preceding embodiments, wherein the amino acid residue in position 7 of said GLP-1 peptide is selected from the group consisting of D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, N^{α}-acetyl-histidine, α-fluoromethyl-histidine, α-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine and 4- pyridylalanine.

23. The method according to any one of embodiments 7 to 16, wherein said GLP-1 peptide is attached to said hydrophilic spacer via the amino acid residue in position 23, 26, 34, 36 or 38 relative to the amino acid sequence of GLP-1 (7-37).

24. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide is exendin-4, an exendin-4-analogue, or a derivative of exendin-4.

25. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide comprises the amino acid sequence of the following formula:
H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2.

26. The method according to any one of the preceding embodiments wherein one albumin binding residue via said hydrophilic spacer is attached to the C-terminal amino acid residue of said GLP-1 peptide.

27. The method according to any one of the preceding embodiments, wherein a second albumin binding residue is attached to an amino acid residue which is not the C-terminal amino acid residue.

28. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide is selected from the group consisting of semaglutide, albiglutide and dulaglitide.

29. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide has the following structure:
His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg.

30. The method according to any one of the preceding embodiments, wherein the GLP-1 peptide has the following structure:
(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-
Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)2–
genetically fused to human albumin.

31. The method according to any one of the preceding embodiments wherein the GLP-1 peptide is dulaglitide.

32. The method according to any one of the preceding embodiments wherein the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100pM, optionally determined by Assay (I).

33. A GLP-1 agonist for use in the reduction of HbA1c or for use in the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

34. A GLP-1 agonist for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

35. A GLP-1 agonist for use according to embodiment 33 or 34, wherein the GLP-1 agonist and/or administration is as defined in any of embodiments 1-32 or 40.

36. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

37. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in the prevention or treatment of obesity, in the reduction of body weight and/or food intake, or in the induction satiety, wherein said GLP-1 agonist is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.

38. A composition for use according to any one of the preceding embodiments, wherein said GLP-1 agonist and/or administration is as defined in any one of embodiments 1-32 or 40.

39. A composition for use according to any one of the preceding embodiments, wherein said composition comprises the Bydureon® composition.

40. The method according to any one of the preceding claims, wherein the method comprises prevention, treatment, reduction or induction in one or more diseases or conditions defined in any one of the previous embodiments.

EXAMPLES

Abbreviations

The following abbreviations are used in the following, in alphabetical order:

ADA: American Diabetes Association

Example 1: The Glp-1 Peptide Semaglutide Provides Reduced HbA1c and Body Weight

Semaglutide is a unique acylated GLP-1 peptide with a half-life of 160 hours. The aim was to investigate HbA1c dose-response of once-weekly doses of semaglutide (five dose-levels) in subjects with type 2 diabetes. Safety, tolerability and pharmacodynamics of semaglutide versus placebo and open-label once-daily liraglutide were also investigated.

Materials and methods

Liraglutide may be prepared as described in Example 37 of WO98/08871. Semaglutide may be prepared as described in Example 4 of WO2006/097537. The composition of the GLP-1 agonists administered may be formulated as isotonic aqueous solutions with a phosphate buffer, such as a sodium dihydrogen phosphate buffer,having a pH in the range 7.0-9.0, such as pH 7.4 or pH8.15, for example further comprising the excipients propylene glycol and phenol. The composition of the GLP-1 agonists administered may be as described in WO2003/002136 or WO2005/049061. The placebo composition may be identical to the composition of the GLP-1 agonists, but not containing a GLP-1 agonist.

In a 12-week, randomised, double-blind, placebo-controlled trial, 411 human subjects (n=43–50 per group) with type 2 diabetes were exposed. Participants (male/female 65/35%; baseline HbA1c (mean±SD) 8.1±0.8%; baseline body weight 87.5±13.8 kg; duration of diabetes 2.6±3.1 years; metformin only/diet and exercise alone 80/20%) received subcutaneous injection of one of five semaglutide doses (0.1–1.6 mg) once weekly, open-label liraglutide (1.2 mg, 1.8 mg) once daily, or placebo once weekly. Two of the semaglutide doses were titrated (T) in weekly increments of 0.4 mg. The primary endpoint was change in HbA1c from baseline. Secondary efficacy endpoints included proportion of subjects reaching ADA HbA1c target (<7%) and change in body weight. Change and percentage to target were analysed by ANOVA and logistic regression, respectively. Comparisons between semaglutide and liraglutide were not corrected for multiplicity.Baseline characteristics of the subjects are shown in Table 1.

Table 1. Baseline characteristics of subjects

	Placebo	Semaglutide						Liraglutide	
		0.1 mg	0.2 mg	0.4 mg	0.8 mg	0.8 mg T	1.6 mg T	1.2 mg	1.8 mg
Exposed* subjects	46	47	43	48	42	43	47	45	50
D&E: metformin (%)	22:78	23:77	14:86	23:77	19:81	16:84	19:81	18:82	24:76
Female: male (%)	39:61	34:66	30:70	23:77	48:52	37:63	45:55	31:69	30:70
Age (years)	55.3 (10.6)	55.2 (10 .1)	54.7 (10.0)	53.8 (10.2)	55.0 (9.7)	55.9 (7.9)	56.4 (10.5)	54.8 (9.2)	54.3 (10.1)
Duration of diabetes (years)	2.4 (3.3)	3.6 (5.0)	2.3 (2.7)	2.0 (2.3)	3.0 (3.0)	2.6 (2.1)	1.8 (2.0)	3.3 (3.4)	2.5 (2.6)
HbA1c (%)	8.1 (0.8)	8.2 (0.9)	8.2 (0.9)	8.1 (0.9)	8.2 (0.9)	8.0 (0.8)	8.0 (0.7)	8.0 (0.8)	8.1 (0.7)
FPG (mmol/L)	8.9 (1.5)	9.8 (2.7)	9.5 (2.5)	9.3 (2.1)	9.5 (2.4)	9.6 (2.1)	9.0 (1.9)	9.0 (2.3)	9.3 (2.0)
Weight (kg)	90.5 (13.0)	89.5 (14.2)	86.3 (15.1)	87.0 (14.0)	85.9 (15.1)	85.7 (12.6)	84.5 (14.0)	90.5 (13.5)	87.2 (13.1)
BMI (kg/m^2)	31.7 (3.8)	31.5 (4.6)	30.4 (3.9)	29.7 (4.5)	30.7 (4.5)	31.2 (4.2)	30.9 (4.7)	31.0 (4.6)	30.9 (4.6)

Data are mean (SD) unless otherwise stated. *:Number of subjects exposed to actual treatment.D&E:Diet and exercise. FPG:Fasting plasma glucose. BMI: Body mass index.

Results

In the full analysis set, semaglutide (≥0.2 mg) dose-dependently reduced HbA1c from baseline (Fig. 1), and increased the likelihood of achieving HbA1c <7% ($p<0.05$ vs. placebo for doses ≥0.2 mg). The results with respect to change in HbA1c are shown in Fig. 1. The change in HbA1c in fig. 1 is from baseline at week 12. Fig. 2 shows the change in HbA1c over time with the different treatments. Treatment with semaglutide ≥0.8 mg numerically brought more patients to target than liraglutide 1.8 mg (0.8 mg T 69%, 0.8 mg 73%, 1.6 mg T 81% vs. liraglutide 1.8 mg 57%).The results (see e.g. Fig. 1) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T improved reduction of HbA1c

compared to treatment with liraglutide 1.2 mg or 1.8 mg; furthermore, treatment with semaglutide 1.6 mg T was statistically superior to treatment with liraglutide 1.2 mg or 1.8 mg with respect to reduction of HbA1c (based on unadjusted means). Fig. 3 shows the percentage and the number of subjects reaching the AACE or ADA criteria for glycaemic control with the different treatments. The results (see Fig. 3) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T improved the percentage and the number of subjects reaching the AACE or ADA criteria for glycaemic control compared to treatment with liraglutide 1.2 mg or 1.8 mg.

Body weight was dose-dependently reduced from baseline by up to 4.8 kg vs. placebo 1.2 kg ($p<0.01$ for doses ≥0.8 mg). Fig. 4 and 5 shows mean body weight change versus time and body weight change from baseline at week 12, respectively, with the different treatments. The results (see e.g. Fig. 5) shows that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg T increased reduction of body weight compared to treatment with liraglutide1.2 mg or 1.8 mg. Furthermore, the results (see e.g. Fig. 5) shows that treatment with semaglutide 0.8 mg T or 1.6 mg T was statistically superior to treatment with liraglutide 1.8 mg with respect to reduction of body weight; and that treatment with semaglutide 0.8 mg, 0.8 mg T, or 1.6 mg Twas statistically superior to liraglutide 1.2 mg with respect to reduction of body weight (based on unadjusted means).

There were no reports of pancreatitis or treatment-related changes in blood calcitonin. Proportion of subjects with nausea and vomiting increased with dose, but were generally mild or moderate and ameliorated by titration. Withdrawals due to gastrointestinal adverse events were 4.7%-27.7% for semaglutide and 2.2%-10% for liraglutide. Few subjects reported minor hypoglycaemia (semaglutide n=5, liraglutide n=3); no major hypoglycaemia. Injection site reactions were reported by 7 subjects: semaglutide n=2; liraglutide n=5. One subject (semaglutide 1.6 mg T) developed low titre non-neutralising anti-semaglutide antibodies (no cross-reaction to native GLP-1).

Conclusion

Over 12 weeks, semaglutide dose-dependently reduced HbA1c and body weight. The effect of semaglutide 0.4 mg on glycaemic control and body weight was comparable to that of liraglutide 1.2 mg, while semaglutide ≥0.8 mg appeared to bring more subjects to target and provided better weight loss than liraglutide 1.8 mg. No semaglutide safety concerns were identified. Dose escalation was not a major focus of this trial and it will be optimised in future clinical trials.

Pharmacological Methods

Assay (I): In Vitro Potency

The purpose of this example is to test the activity, or potency, of GLP-1 agonists in vitro. The potencies of GLP-1 agonists may be determined as described below, i.e. as the stimulation of the formation of cyclic AMP (cAMP) in a medium containing membranes expressing the human GLP-1 receptor.

Principle

Purified plasma membranes from a stable transfected cell line, BHK467-12A (tk-ts13), expressing the human GLP-1 receptor are stimulated with the GLP-1 agonist in question, and the potency of cAMP production is measured using the AlphaScreenTMcAMP Assay Kit from Perkin Elmer Life Sciences. The basic principle of The AlphaScreen Assay is a competition between endogenous cAMP and exogenously added biotin-cAMP. The capture of cAMP is achieved by using a specific antibody conjugated to acceptor beads.

Cell culture and preparation of membranes

A stable transfected cell line and a high expressing clone are selected for screening. The cells are grown at 5% CO_2 in DMEM, 5% FCS, 1% Pen/Strep (Penicillin/Streptomycin) and 0.5 mg/ml of the selection marker G418. Cells at approximate 80% confluence are washed 2X with PBS and harvested with Versene (aqueous solution of the tetrasodium salt of ethylenediaminetetraacetic acid), centrifuged 5 min at 1000 rpm and the supernatant removed. The additional steps are all made on ice. The cell pellet is homogenised by the Ultrathurax for 20-30 sec. in 10 ml of Buffer 1 (20 mM Na-HEPES, 10 mM EDTA, pH=7.4), centrifuged 15 min at 20,000 rpm and the pellet resuspended in 10 ml of Buffer 2 (20 mM Na-HEPES, 0.1 mM EDTA, pH=7.4). The suspension is homogenised for 20-30 sec and centrifuged 15 min at 20,000 rpm. Suspension in Buffer 2, homogenisation and centrifugation is repeated once and the membranes are resuspended in Buffer 2. The protein concentration is determined and the membranes stored at -80°C until use.

The assay is performed in ½-area 96-well plates, flat bottom (e.g. Costar cat. no:3693). The final volume per well is 50 µl.

Solutions and reagents

Exemplary solutions and reagents are given below.

AlphaScreencAMP Assay Kit from Perkin Elmer Life Sciences (cat. No: 6760625M); containing Anti-cAMP Acceptor beads (10 U/µl), Streptavidin Donor beads (10 U/µl) and Biotinylated-cAMP (133 U/µl).

AlphaScreen Buffer, pH=7.4: 50 mM TRIS-HCl (Sigma, cat.no: T3253); 5 mM

HEPES (Sigma, cat.no: H3375); 10 mM$MgCl_2$, 6H_2O (Merck, cat.no: 5833); 150 mMNaCl (Sigma, cat.no: S9625); 0.01% Tween (Merck, cat.no: 822184). The following was added to the AlphaScreen Buffer prior to use (final concentrations indicated): BSA (Sigma, cat. no. A7906): 0.1%; IBMX (Sigma, cat. no. I5879): 0.5 mM; ATP (Sigma, cat. no. A7699): 1 mM; GTP (Sigma, cat. no. G8877): 1 µM.

cAMP standard (dilution factor in assay = 5): cAMP Solution: 5 µL of a 5 mMcAMP-stock + 495 µL AlphaScreen Buffer.

Suitable dilution series in AlphaScreen Buffer are prepared of the cAMP standard as well as the GLP-1 agonist to be tested, e.g. the following eight concentrations of the GLP-1 agonist: 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} and 10^{-14}M, and a series from, e.g., 10^{-6} to $3x10^{-11}$ of cAMP.

Membrane/Acceptor beads

Use hGLP-1/ BHK 467-12A membranes; 6 µg/well corresponding to 0.6 mg/ml (the amount of membranes used pr. well may vary)

"No membranes": Acceptor Beads (15µg/ml final) in AlphaScreen buffer

"6 µg/well membranes": membranes + Acceptor Beads (15µg/ml final) in AlphaScreen buffer

Add 10 µl "No membranes" to the cAMP standard (per well in duplicates) and the positive and negative controls

Add 10 µl "6 µg/well membranes" to GLP-1 and GLP-1 agonists (per well in duplicates/triplicates)

Pos. Control: 10 µl "no membranes" + 10 µl AlphaScreen Buffer

Neg. Control: 10 µl "no membranes" + 10 µl cAMP Stock Solution (50µM)

As the beads are sensitive to direct light, any handling is in the dark (as dark as possible), or in green light. All dilutions are made on ice.

Procedure

1. Make the AlphaScreen Buffer.
2. Dissolve and dilute the GLP-1 agonists/cAMP standard in AlphaScreen Buffer.
3. Make the Donor Beads solution and incubate 30 min. at RT.
4. Add the cAMP/GLP-1 agonists to the plate: 10 µl per well.
5. Prepare membrane/Acceptor Beads solution and add this to the plates: 10 µl per well.
6. Add the Donor Beads: 30 µl per well.
7. Wrap the plate in aluminum foil and incubate on the shaker for 3 hours (very slowly) at RT.

8. Count on AlphaScreen – each plate pre incubates in the AlphaScreen for 3 minutes before counting.

The EC_{50} [pM] values may be calculated using the Graph-Pad Prism software (version 5). If desired, the fold variation in relation to GLP-1 may be calculated as EC_{50} (GLP-1)/ EC_{50} (analogue) – 3693.2.

Assay (II): Half-life in Minipigs

The purpose of this study is to determine the protraction in vivo of GLP-1 agonists after i.v. administration to minipigs, i.e. the prolongation of their time of action. This is done in a pharmacokinetic (PK) study, where the terminal half-life of the GLP-1 agonist in question is determined. By terminal half-life is generally meant the period of time it takes to halve a certain plasma concentration, measured after the initial distribution phase.

Male Göttingenminipigsare obtained from EllegaardGöttingenMinipigs (Dalmose, Denmark) approximately 7-14 months of age and weighing from approximately 16-35 kg are used in the studies. The minipigs are housed individually and fed restrictedly once or twice daily with SDS minipig diet (Special Diets Services, Essex, UK). After at least 2 weeks of acclimatisation two permanent central venous catheters are implanted in vena cava caudalis or cranialis in each animal. The animals are allowed 1 week recovery after the surgery, and are then used for repeated pharmacokinetic studies with a suitable wash-out period between dosings.

The animals are fasted for approximately 18 h before dosing and for at least 4 h after dosing, but have ad libitum access to water during the whole period.

The GLP-1 agonist is dissolved in 50 mM sodium phosphate, 145 mM sodium chloride, 0.05% tween 80, pH 7.4 to a concentration of usually from 20-60 nmol/ml. Intravenous injections (the volume corresponding to usually 1-2 nmol/kg, for example 0.033ml/kg) of the compounds are given through one catheter, and blood is sampled at predefined time points for up till 13 days post dosing (preferably through the other catheter). Blood samples (for example 0.8 ml) are collected in EDTA buffer (8mM) and then centrifuged at 4°C and 1942G for 10 minutes. Plasma is pippetted into Micronic tubes on dry ice, and kept at -20°C until analyzed for plasma concentration of the respective GLP-1 compound using ELISA or a similar antibody based assay or LC-MS. Individual plasma concentration-time profiles are analyzed by a non-compartmental model in WinNonlin v. 5.0 (Pharsight Inc., Mountain View, CA, USA), and the resulting terminal half-lives (harmonic mean) determined.

Assay (III): Effect on Blood Glucose and Body Weight

The purpose of the study is to verify the effect of GLP-1 agonists on blood glucose (BG) and body weight (BW) in a diabetic setting.GLP-1 agonists may be tested in a dose-response study in an obese, diabetic mouse model (db/db mice) as described in the following.

Fifty db/db mice (Taconic, Denmark), fed from birth with the diet NIH31 (NIH 31M Rodent Diet, commercially available from Taconic Farms, Inc., US, see www.taconic.com), are enrolled for the study at the age of 7-9 weeks The mice are given free access to standard chow (e.g. Altromin 1324, Brogaarden, Gentofte, Denmark) and tap water and kept at 24°C. After 1-2 weeks of acclimatisation, the basal blood glucose is assessed twice on two consecutive days (i.e. at 9 am). The 8 mice with the lowest blood glucose values may be excluded from the experiments. Based on the mean blood glucose values, the remaining 42 mice may be selected for further experimentation and allocated to 7 groups (n=6) with matching blood glucose levels. The mice may be used in experiments with duration of 5 days for up to 4 times. After the last experiment the mice are euthanised.

The seven groups may receive treatment as follows:

1: Vehicle, subcutaneous
2: GLP-1 agonist, 0.3 nmol/kg, subcutaneous
3: GLP-1 agonist, 1.0 nmol/kg, subcutaneous
4: GLP-1 agonist, 3.0 nmol/kg, subcutaneous
5: GLP-1 agonist, 10 nmol/kg, subcutaneous
6: GLP-1 agonist, 30 nmol/kg, subcutaneous
7: GLP-1 agonist, 100 nmol/kg, subcutaneous

Vehicle: 50mM sodium phosphate, 145 mM sodium chloride, 0.05% tween 80, pH 7.4.

The GLP-1 agonist is dissolved in the vehicle, e.g. to concentrations of 0.05, 0.17, 0.5, 1.7, 5.0 and 17.0 nmol/ml. Animals are dosed subcutaneous with a dose-volume of 6 ml/kg (i.e. 300 µl per 50 g mouse).

On the day of dosing, blood glucose is assessed at time -½h (8.30 am), where after the mice are weighed. The GLP-1 agonist is dosed at approximately 9 am (time 0). On the day of dosing, blood glucose is assessed e.g. at times 1, 2, 4 and 8 h (10 am, 11 am, 1 pm and 5 pm).

On the following days, the blood glucose is assessed e.g. at time 24, 48, 72, and 96h after dosing (i.e. at 9 am on day 2, 3, 4, 5). On each day, the mice are weighed following blood glucose sampling.

The mice are weighed individually on a digital weight.

Samples for the measurement of blood glucose are obtained from the tail tip capillary of conscious mice. Blood, 10 µl, is collected into heparinised capillaries and transferred to 500 µl glucose buffer (EKF system solution, Eppendorf, Germany). The glucose concentration is measured using the glucose oxidase method (glucose analyser Biosen 5040, EKF Diagnostic, GmbH, Barleben, Germany). The samples are kept at room temperature for up to 1 h until analysis. If analysis has to be postponed, samples are kept at 4°C for a maximum of 24 h.

ED_{50} is the dose giving rise to half-maximal effect in nmol /kg. This value is calculated on the basis of the ability of the GLP-1 agonists to lower body weight as well as the ability to lower blood glucose, as explained below.

ED_{50} for body weight is calculated as the dose giving rise to half-maximum effect on delta BW 24 hours following the subcutaneous administration of the GLP-1 agonist. For example, if the maximum decrease in body weight after 24 hours is 4.0 g, then ED_{50} bodyweight would be that dose in nmol/kg which gives rise to a decrease in body weight after 24 hours of 2.0 g. This dose (ED_{50} body weight) may be read from the dose-response curve.

ED_{50} for blood glucose is calculated as the dose giving rise to half-maximum effect on AUC delta BG 8 hours following the subcutaneous administration of the GLP-1 agonist.

The ED_{50} value may only be calculated if a proper sigmoidal dose-response relationship exists with a clear definition of the maximum response. Thus, if this would not be the case the GLP-1 agonist in question is re-tested in a different range of doses until the sigmoidal dose-response relationship is obtained.

Assay (IV): Effect on Food Intake

The purpose of this experiment is to investigate the effect of GLP-1 agonists on food intake in pigs. This is done in a pharmacodynamic (PD) study as described below, in which food intake is measured 1, 2, 3, and 4 days after administration of a single dose of the GLP-1 agonist, as compared to a vehicle-treated control group.

Female Landrace Yorkshire Duroc (LYD) pigs, approximately 3 months of age, weighing approximately 30-35 kg are used (n=3-4 per group). The animals are housed in a group for 1-2 weeks during acclimatisation to the animal facilities. During the experimental period the animals are placed in individual pens from Monday morning to Friday afternoon for measurement of individual food intake. The animals are fed ad libitum with pig fodder (Svinefoder, Antonio) at all times both during the acclimatisation and the experimental period. Food intake is monitored on line by logging the weight of fodder every 15 minutes. The system used is Mpigwin (Ellegaard Systems, Faaborg, Denmark).

The GLP-1 agonists are dissolved in a phosphate buffer (50 mM phosphate, 0.05% tween 80, pH 8) e.g. at concentrations of 12, 40, 120, 400 or 1200 nmol/ml corresponding to doses of 0.3, 1, 3, 10, or 30 nmol/kg. The phosphate buffer served as vehicle. Animals are dosed with a single subcutaneous dose of the GLP-1 agonist or vehicle (dose volume 0.025 ml/kg) on the morning of day 1, and food intake is measured for 4 days after dosing. On the last day of each study, 4 days after dosing, a blood sample for measurement of plasma exposure of the GLP-1 agonist is taken from the heart in anaesthetised animals. The animals are thereafter euthanised with an intra-cardial overdose of pentobarbitone. Plasma content of the GLP-1 agonist is analysed using ELISA or a similar antibody based assay.

Food intake is calculated as mean ± SEM 24 h food intake on the 4 days. Statistical comparisons of the 24 hour food intake in the vehicle vs. GLP-1 agonist group on the 4 days are done using one-way or two-way-ANOVA repeated measures, followed by Bonferroni post-test.

Assay (V): Stability againstDegradation by Intestinal Enzymes

The purpose of this example is to test the stability against degradation by intestinal enzymes. GLP-1(7-37) may be used in the assay as a comparative compound.The strongest proteolytic activities in the intestine are of pancreatic origin and include the serine endopeptidases trypsin, chymotrypsin, and elastase as well as several types of carboxypeptidases. An assay with small intestine extract from rats was developed and used as described in the following.

Extracts from rat small intestine

Small intestines are prepared from rats and flushed with 8 ml of 150 mMNaCl, 20 mMHepes pH 7.4. The solutions are centrifuged for 15 min at 4,600 rpm in a HeraeusMultifuge 3 S-R centrifuge with a 75006445 rotor. The supernatants are removed and filtered through a 0.22 µm Millipore Millex GV PVDF membrane. Filtrates of several animals are pooled to average out individual differences.

The protein content of the obtained extracts is determined by Bradford Assay (see e.g. Analytical Biochemistry (1976), vol. 72, p. 248-254, and Analytical Biochemistry (1996), vol. 236 p. 302-308).

Degradation assay

2.5 nmol of the GLP-1 agonists to be tested are incubated with the intestinal extract in a volume of 250 µl at 37°C over a period of one hour. Intestinal samples are assayed in presence of 20 mMHepes at pH 7.4. The concentration of the intestinal extract is titrated in pilot experiments so that the half-life (t½) of GLP-1(7-37) is in the range of 10-20 minutes.

The small intestine extract is used at a concentration of 1.4 µg/ml. All components except for the intestinal extract are mixed and pre-warmed for ten minutes at 37°C. Immediately after addition of the intestinal extract a sample of 50 µl is taken and mixed with the same volume of 1% trifluoroacetic acid (TFA). Further samples are taken accordingly after 15, 30, and 60 minutes.

Sample analysis

UPLC analysis: 10 µl of the samples are analysed by UPLC using a Waters Acquity system with a BEH C18 1.7 µm 2.1 x 50 mm column and a 30 to 65% gradient of 0.1% TFA and 0.07% TFA in acetonitrile over 5 minutes at a flow rate of 0.6 ml/min. After baseline subtraction the peak integrals of the intact compounds in the HPLC chromatogram recorded at a wavelength of 214 nm are determined.

MALDI-TOF analysis: 1 µl of each sample is transferred to a Bruker/Eppendorf PAC HCCA 384 MALDI target. Analysis is performed with a BrukerAutoflex matrix-assisted laser desorption and ionisation - time of flight (MALDI-TOF) mass spectrometer using the pre-defined method “PAC_measure” with an extended detection range of 500 to 5000 Da and the pre-defined calibration method “PAC_calibrate”.

Data analysis: The peak integrals of the HPLC chromatograms are plotted against time. The half-life of the respective compound is calculated by fitting the data using SigmaPlot 9.0 software and an equation for a 2-parameter exponential decay. For each GLP-1 agonist tested, the relative half-life (relative $T_{½}$) is calculated as the half-life ($T_{½}$) of the compound in question, divided by the half-life ($T_{½}$) of GLP-1(7-37), determined in the same way.

While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

CLAIMS

1. A method for
a) reduction of HbA1c;
b) prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or
c) prevention or treatment of obesity, reducing body weight and/or food intake, or inducing satiety;
wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof,
wherein said GLP-1 agonist
i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II);
ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and
iii) is administered once weekly or less often.

2. The method according to any one of the preceding claims, wherein said GLP-1 agonist has a half-life of at least 96 hours, at least 120 hours, or at least 144 hours, wherein said half-life optionally is determined by Assay (II).

3. The method according to any one of the preceding claims, wherein the GLP-1 agonist has an EC_{50} at or below 3000pM, such as at or below 500pM or at or below 100pM, optionally determined by Assay (I).

4. Themethod according to any one of the preceding claims, wherein said GLP-1 agonist is administered in an amount of
i) at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, per week; or
ii) in an amount equivalent to at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, semaglutide per week.

5. The method according to any one of any one of the preceding claims, wherein the GLP-1 agonist is a GLP-1 peptide.

6. The method according to any one of the preceding claims, wherein said GLP-1 peptide comprises no more than 15, such as no more than 10 or no more than 6, amino acid residues which have been substituted, inserted or deleted as compared to GLP-1 (7-37).

7. Themethod according to any one of the preceding claims, wherein said GLP-1 agonist is selected from the group consisting of semaglutide, exenatide, albiglutide, and dulaglutide.

8. The method according to any one of the preceding claims, wherein said GLP-1 agonist is administered by parenteral administration, such as subcutaneous (s.c.) injection.

9. The method according to any one of the preceding claims, wherein said GLP-1 agonist is administered simultaneously or sequentially with another therapeutic agent.

10. The method according to any one of the preceding claims, wherein the method comprises prevention, treatment, reduction or induction in one or more diseases or conditions selected from a) and b), a) and c), b) and c), or a), b) and c) as defined in claim 1.

11. A GLP-1 agonist for use in
a) the reduction of HbA1c;
b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or
c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety;
wherein said use comprises administration ofsaid GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week,
and wherein said GLP-1 agonist and/or administration optionally is as defined in any of claims 1-10.

12. A composition comprising a GLP-1 agonist and one or more pharmaceutically acceptable excipients for use in
a) the reduction of HbA1c;
b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or
c) the prevention or treatment of obesity, for reducing body weight and/or food intake, or for inducing satiety;

wherein said GLP-1 agonist

i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); and

ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and

wherein said composition is administered once weekly or less often, and

wherein said GLP-1 agonist and/or administration optionally is as defined in any of claims 1-10.

ABSTRACT

The invention relates to use of long-acting GLP-1 peptides in certain dosage regimes for the treatment of type 2 diabetes, obesity, etc.

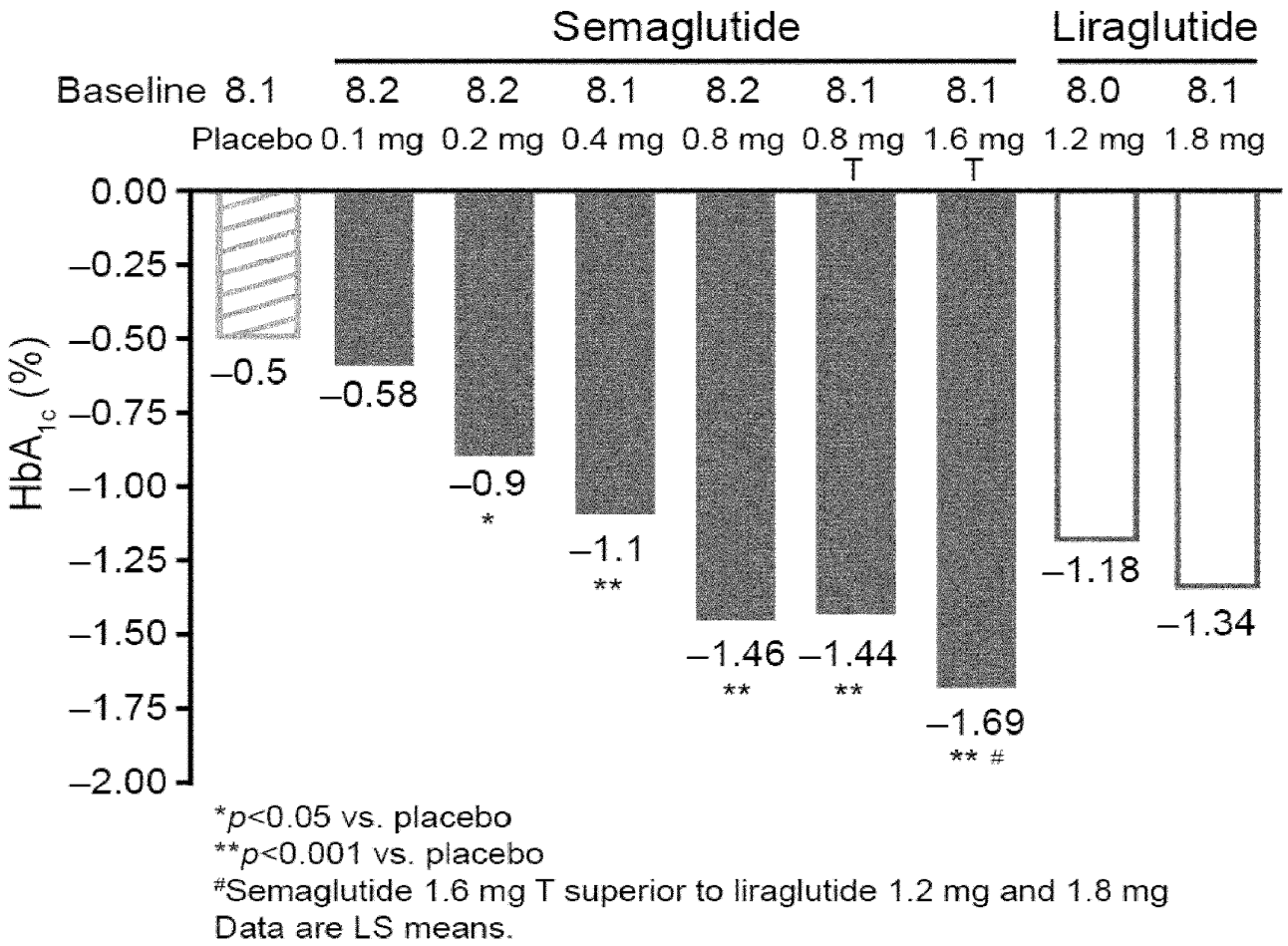

Semaglutide
Liraglutide
Baseline 8.1
8.2
8.2
8.1
8.2
8.1
8.1
8.0
8.1
Placebo
0.1 mg
0.2 mg
0.4 mg
0.8 mg
0.8 mg T
1.6 mg T
1.2 mg
1.8 mg
HbA1c (%)
0.00
–0.25
–0.50
–0.75
–1.00
–1.25
–1.50
–1.75
–2.00
–0.5
–0.58
–0.9 *
–1.1 **
–1.46 **
–1.44 **
–1.69 ** #
–1.18
–1.34
*p<0.05 vs. placebo
**p<0.001 vs. placebo
#Semaglutide 1.6 mg T superior to liraglutide 1.2 mg and 1.8 mg
Data are LS means.

Fig. 1

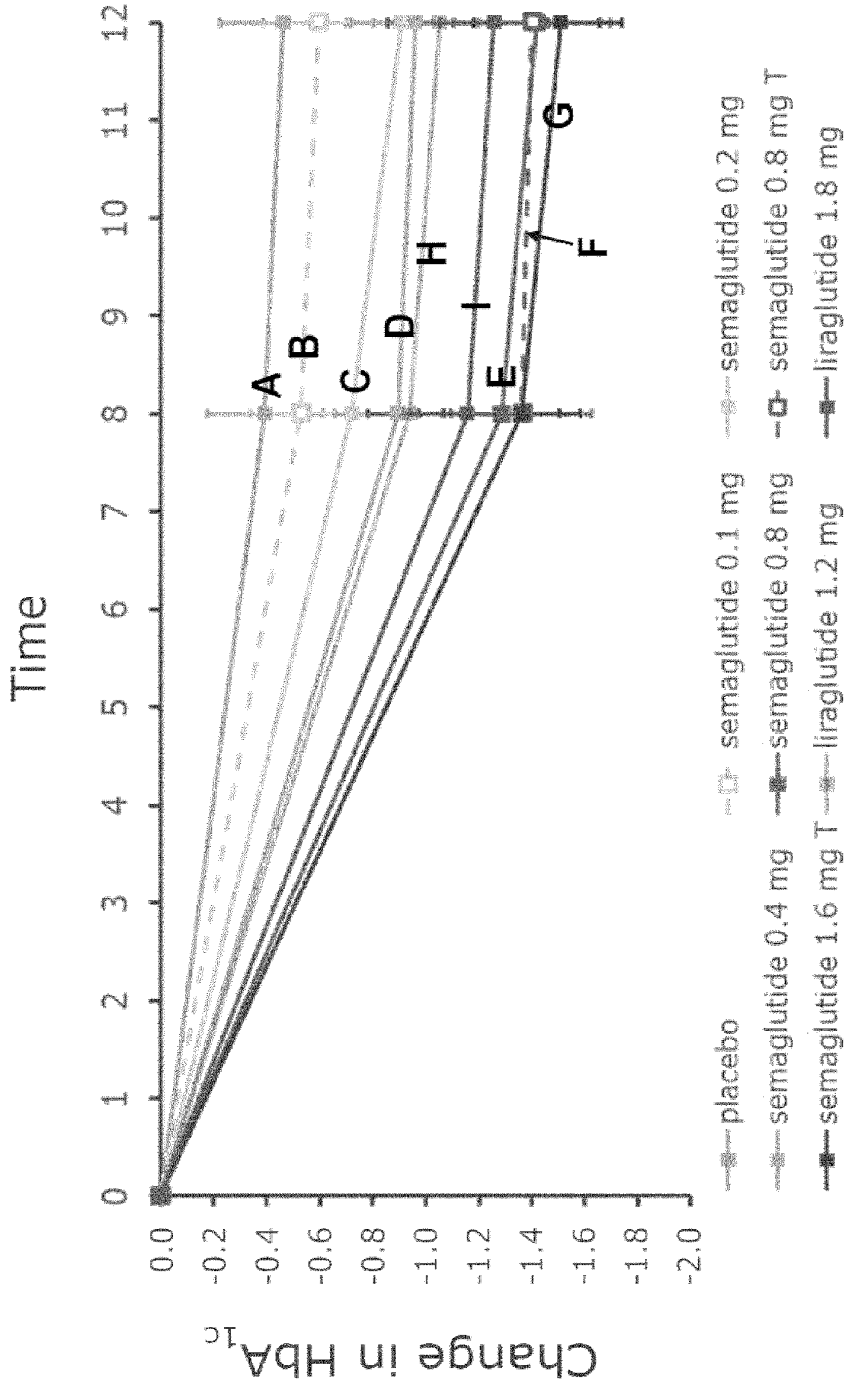


Fig. 2

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0297

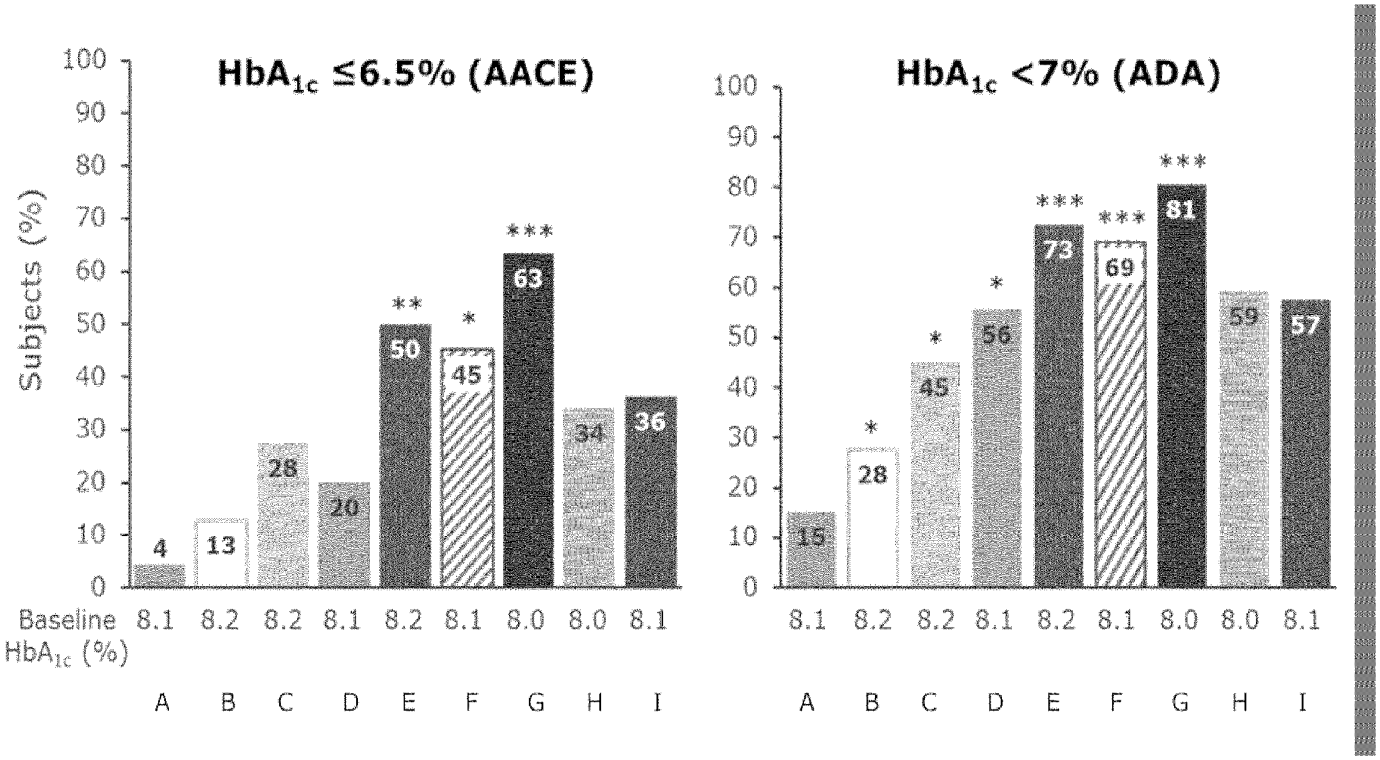
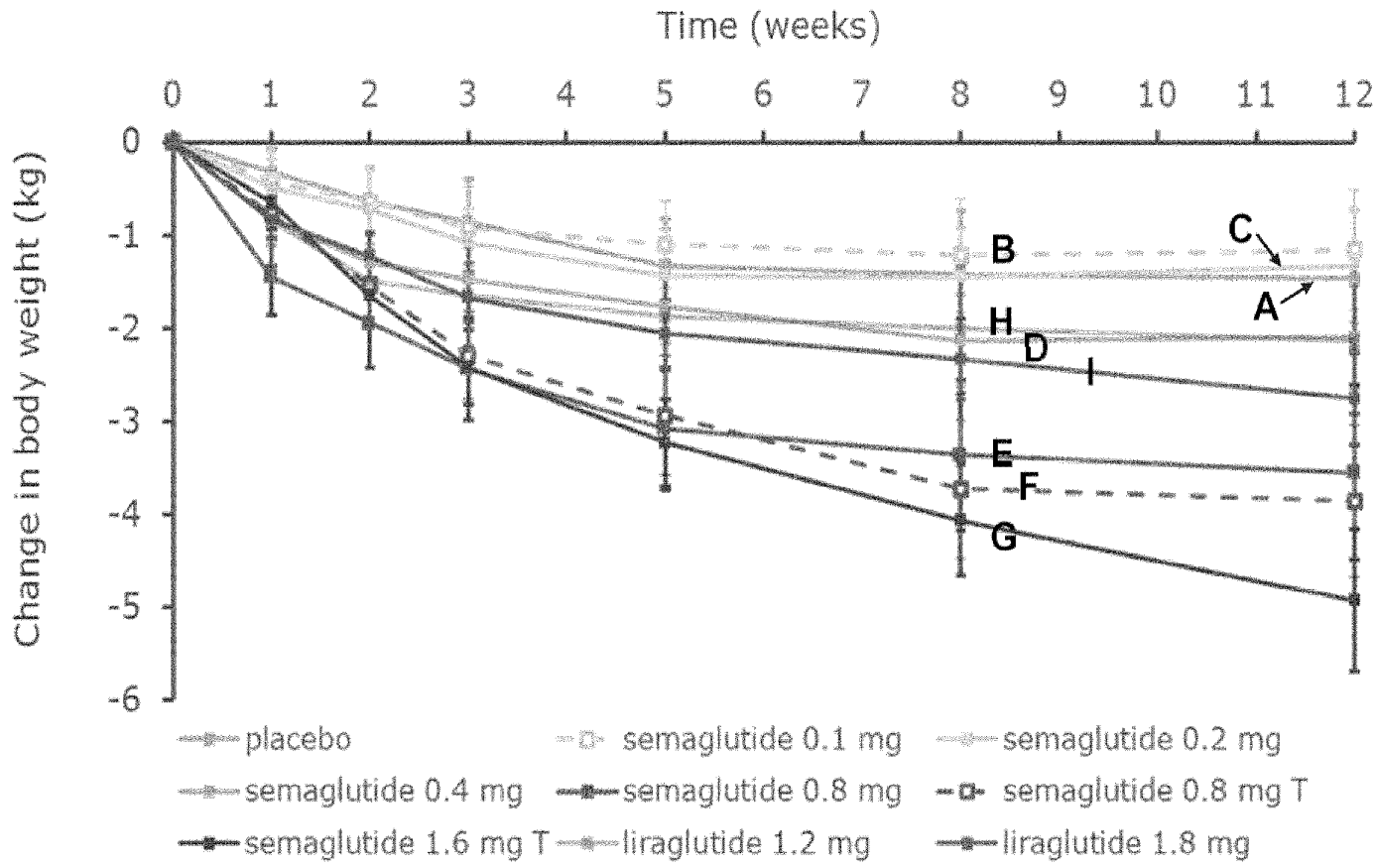

HbA1c ≤6.5% (AACE)
HbA1c <7% (ADA)
Subjects (%)
100
90
80
70
60
50
40
30
20
10
0
4
13
28
20
50
45
63
34
36
15
28
45
56
73
69
81
59
57
**
*
***
Baseline HbA1c (%)
8.1 8.2 8.2 8.1 8.2 8.1 8.0 8.0 8.1
A B C D E F G H I

Fig. 3


Time (weeks)
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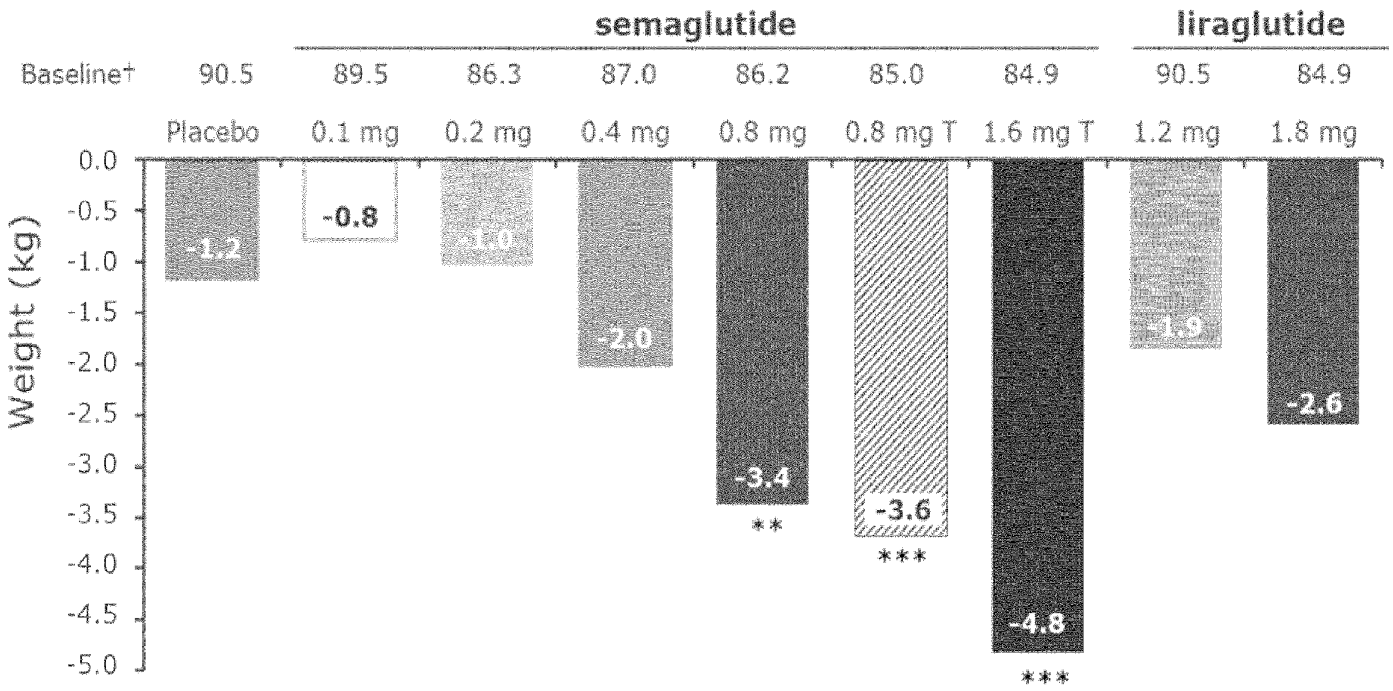
1
2
3
4
5
6
7
8
9
10
11
12
Change in body weight (kg)
0
-1
-2
-3
-4
-5
-6
A
B
C
D
E
F
G
H
placebo
semaglutide 0.1 mg
semaglutide 0.2 mg
semaglutide 0.4 mg
semaglutide 0.8 mg
semaglutide 0.8 mg T
semaglutide 1.6 mg T
liraglutide 1.2 mg
liraglutide 1.8 mg

Fig. 4


semaglutide
liraglutide
Baseline†
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89.5
86.3
87.0
86.2
85.0
84.9
90.5
84.9
Placebo
0.1 mg
0.2 mg
0.4 mg
0.8 mg
0.8 mg T
1.6 mg T
1.2 mg
1.8 mg
Weight (kg)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
-1.2
-0.8
-1.0
-2.0
-3.4
**
-3.6
***
-4.8
***
-1.9
-2.6

Fig. 5

SEQUENCE LISTING

<110> Novo Nordisk A/S

<120> USE OF LONG-ACTING GLP-1 PEPTIDES

<130> 8545.010-EP

<160> 6

<170> PatentIn version 3.5

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Ala Ala Xaa Glu Phe Ile Xaa Trp Leu Val Xaa Xaa Xaa Xaa Xaa
            20                  25                  30
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02	9712

23650 7590 07/23/2018
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NEW JERSEY 08536
UNITED STATES OF AMERICA

EXAMINER
HELLMAN, KRISTINA M

ART UNIT	PAPER NUMBER
1675	

NOTIFICATION DATE	DELIVERY MODE
07/23/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

KISW@novonordisk.com
lklw@novonordisk.com
nnipatent@novonordisk.com

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0307

Office Action Summary	Application No. 15/656,042	Applicant(s) Jensen et al.	
	Examiner KRISTINA M HELLMAN	Art Unit 1675	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 21 July 2017.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-10 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-10 is/are rejected.

8) ☑ Claim(s) 2-9 is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 13 December 2017 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☑ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☑ Certified copies of the priority documents have been received in Application No. 14/409493.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 7/21/2017; 10/2/2017.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0308

DETAILED ACTION

Claims 1-10 are pending and being examined on the merits in this action.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Claim Objections

Claims 2-9 are objected to because of the following informalities:

Claims 2, 4, and 6-9 recite "*said* GLP-1 agonist" whereas claims 3, and 5, "*the* GLP-1 agonist". Please amend the claims for claim consistency with either "the" or "said" GLP-1 agonist.

Claim 3 should be amended to recite "3000_pM".

Appropriate correction is required.

Examiner Comment

Claim 1 recites, "…comprises administration of…" at line 6 of the claim. However the term "administration" means "the process or activity of running a business, organization, etc." This appears to be in error. Applicant is advised to amend the claim to recite, "…comprises administering…"

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Independent claim 1 recites:

ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and

(iii) is administered once weekly or less often.

The term "such an amount equivalent to at least 0.7 mg semaglutide per week" in claim 1 is a relative term which renders the claim indefinite. The term "such an amount equivalent to at least 0.7 mg semaglutide per week" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, it is unclear as to what properties are rendered by "at least 0.7 mg semaglutide per week" for which the GLP-1 agonist should also exhibit. Thus, it is unclear as to what GLP-1 agonists do and don't fall within this claim term. Accordingly, the metes and bounds of this term are unclear.

The phrase "*an amount of at least 0.7 mg* per week" is deemed to be indefinite because there is no upper limit in the claims. Accordingly, the claim is interpreted as a

method of administering semaglutide once weekly in an amount of *at least 0.7 mg* which without an upper limit, further includes an amount that is broadly interpreted as up to an infinite amount (0.7 mg - infinite amount). Claim clarification is required.

Additionally, part (iii) recites "once weekly or less often" but part (ii) recites "at least 0.7 mg per week". The metes and bounds of the claim term “less often” as relating to part (ii) which recites a specific amount of a GLP-1 agonist “per week” are vague and indefinite.

Accordingly, the metes and bounds of claim 1 and dependent claims 2-10 are indefinite.

Claim 10 is deemed to be indefinite. Claim 10 recites:

10. The method according to claim 1, wherein the method comprises treatment, reduction or induction in one or more diseases or conditions selected from a) and b), a) and c), b) and c), or a), b) and c) as defined in claim 1.

The metes and bounds of the claim are indefinite. First, the selection of groups is confusing. Examiner recommends that the claim be amended to recite semi-colons ";" to properly distinguish between the groups.

Additionally, claim 10 recites "treatment, reduction or induction in one or more diseases or conditions ..." In reference to independent claim 1, part (a) of claim 1 recites "a) reduction of HbA1c”. It is unclear if reduction of HbA1c is a condition or disease. Please amend claim 10 for better clarification as relating back to independent claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10 are rejected under pre-AIA 35 U.S.C. 102b as being anticipated by Clinical Trial NCT00696657 ((3/25/2011) - accessed 9/24/15 at URL clinicaltrials.gov/archive/NCT00696657/2011_03_25; hereinafter referred to as "the '657 clinical trial"- cited in IDS filed 7/21/2017), as evidenced by Lau et al. (*J. Med. Chem. 58*:7370-7380 (2015)- cited in IDS filed 7/21/2017).

The '657 clinical trial compared semaglutide and liraglutide in treatment of type 2 diabetic patients. The semaglutide or liraglutide was used as on add-on therapy to type 2 diabetic patients already taking metformin. Efficacy of treatment was further assessed by a reduction in HbA1c levels. Patients in the Arm Labels E and F of the clinical trial were administered 0.8 mg once weekly by subcutaneous injection. As evidenced by Lau et al., the half-life of semaglutide is 165 hours and the EC_{50} value is 6.2 pM (p. 7370, last para.; Table 3). *See also* Fig. 2 for the amino acid sequence of semaglutide. Accordingly, the limitations of claims 1-10 are satisfied.

Claims 1-10 are rejected under pre-AIA 35 U.S.C. 102b as being anticipated by Madsbad et al. (*Diabet. Obes. Metab. 13*:394-407 (Jan. 2011)- cited in IDS filed 7/21/2017), as evidenced by the Eperzan assessment report, (*Euro. Med. Agency*, pp.

1-124 (2014)- accessed 9/24/2015 at URL:

ema.europa.eu/docs/en_GB/document_library/EPAR_-

_Public_assessment_report/human/002735/WC500165119.pdf- cited in IDS filed

7/21/2017).

Madsbad et al. is a review article discussing type 2 diabetes treatment by once-weekly administration of several GLP-1 agonists. The reference specifically discusses exenatide (Bydureon), taspoglutide, albiglutide, dulaglutide, and semaglutide.

The discussion of albiglutide is found on p. 401 of Madsbad et al. Albiglutide is a GLP-1 agonist consisting of two copies of a 30-amino acid sequence of GLP-1 coupled to serum human albumin. The plasma half-life is about 5 days (p. 401, para. 2). In a dose-response study, albiglutide was found to have a mean half-life of 6-8 days. *Id.* at para. 3. In a phase 2 study, type 2 diabetic patients on metformin were given albiglutide weekly by injection at concentrations of 4, 15, or 30 mg. *Id.* at para. 4. Patients in the trial had a reduction in Hb1Ac levels, reduction in fasting blood glucose, and treatment of type 2 diabetes. Madsbad et al. further teach a phase III clinical trial in which albiglutide is being administered as a monotherapy, a combination therapy of metformin and albiglutide, or a triple combo therapy of albiglutide/metformin/glitazone or albiglutide/metformin/sulfonyl urea (p. 401, para. 9). As evidenced by the Eperzan assessment report, Eperzan is also known as albiglutide. Albiglutide has a half-life of 5 days and an EC_{50} of 0.24 nM (or 240 pM) (p. 11, para. 3; p. 21, section 2.3.2 Pharmacology). *See also* Fig. 1 for the amino acid sequence of albiglutide.

Accordingly, the limitations of claims 1-10 are satisfied.

Claims 1-10 are rejected under pre-AIA 35 U.S.C. 102b as being anticipated by Madsbad et al. (*Diabet. Obes. Metab. 13*:394-407 (Jan. 2011)- cited in IDS filed 7/21/2017), as evidenced by the Trulicity assessment report (*Euro. Med. Agency*, pp. 1-172 (2014)- accessed 9/24/2015 at URL: ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002825/WC500179473.pdf-)- cited in IDS filed 7/21/2017).

Madsbad et al. is a review article discussing type 2 diabetes treatment by once-weekly administration of several GLP-1 agonists. The reference specifically discusses exenatide (Bydureon), taspoglutide, albiglutide, dulaglutide, and semaglutide.

The discussion of dulaglutide is found on pp. 401-402 of Madsbad et al. Dulaglutide is a fusion of GLP-1 to an IgG4 Fc fragment (p. 401, para. 10). In a clinical study, obese type 2 patients on two oral antidiabetic medications were further administered once-weekly injections of dulaglutide for 16 weeks. Patients were given the following dulaglutide dosages: 0.5 mg for 4 weeks, followed by 1.0 mg for 12 weeks; 1.0 mg for 4 weeks, followed by 2.0 mg for 12 weeks; or 1.0 mg for 16 weeks (p. 402, para. 1). Patients in the trial exhibited a reduction in Hb1Ac levels, reduction in fasting plasma glucose levels, weight loss, and treatment of type 2 diabetes. *Id.* As evidenced by the Trulicity assessment report, Trulicity is also known as dulaglutide. Dulaglutide has a half-life of 7 days and an EC_{50} of 12.5 pM (p. 22, section 2.3.1; p. 24, section 2.3.2). *See also* Fig. 1 for a schematic of dulaglutide.

Accordingly, the limitations of claims 1-10 are satisfied.

Claims 1-8 and 10 are rejected under pre-AIA 35 U.S.C. 102b as being anticipated by Kim et al. (*Diabetes Care 30*:1487-1493 (2007)- cited in IDS filed 7/21/2017), as evidenced by Bydureon NDA 022200/S-008 package information (Feb. 2014)-)- cited in IDS filed 7/21/2017).

Kim et al. is a journal article teaching the results of a clinical trial involving once-weekly dosing of a long-acting release formulation of exenatide (exenatide LAR manufactured by Amylin Pharmaceuticals; also known as Bydureon) (abstract). During the clinical trial, type 2 diabetic patients were administered either 0.8 mg or 2.0 mg exenatide LAR subcutaneously once a week (abstract, methods). Trial results indicated that patients had a reduction in HbA1c levels, reduction in body weight, effective treatment of type 2 diabetes, a reduction in hyperglycemia, and improved glycemic control (abstract, results, conclusions). Exenatide LAR has a half-life of two weeks (p. 1492, middle column, para. 2). Accordingly, the limitations of instant claims 1, 2, 4-8, and 10 are satisfied. Regarding claim 3, as evidenced by Bydureon NDA 022200/S-008 package information, Bydureon (exenatide LAR by Amylin) has a reported EC_{50} value of 52.8 pM, 56.8 pM, or 83.5 pM (p. 3 last bullet point to p. 4, first full para.). Although the reported EC_{50} value for Bydureon varies, each of the reported values is less than 3000 pM.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

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Claims 1-4, 7, and 8 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 9,764,003 (hereinafter "the '003 patent"). The instant application is a CON of the '003 patent.

Although the claims at issue are not identical, they are not patentably distinct from each other because for the following reasons.

Claim 1 of the '003 patent is drawn to a method for reducing body weight, comprising administering semaglutide once weekly in an amount of at least 0.7 mg and up to 1.6 mg to a subject in need thereof, wherein said semaglutide is administered without another therapeutic agent. Dependent claims recites dosing of 0.8 mg, parenteral administration, and that the subject is suffering from diabetes.

Accordingly, claims 1-6 of the '003 patent anticipate instant claims 1-4, 7, and 8. It is noted that instant claims 2 and 3 recite physical properties of semaglutide.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTINA M HELLMAN whose telephone number is (571)272-2836. The examiner can normally be reached on M-F 9:00 am-5:30 pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JAMES ALSTRUM-ACEVEDO can be reached on 571-272-5548. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/KRISTINA M HELLMAN/
Examiner, Art Unit 1675

/JULIE HA/
Primary Examiner, Art Unit 1675

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15656042
Filing Date	2017-07-21
First Named Inventor	Christine Bjoern Jensen
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	8545US02

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/K.M.H/	2	2413530	RU	C2	2011-03-10	Novo Nordiks As	corresponds to US8,748,376	☒

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(Not for submission under 37 CFR 1.99)

Application Number	15656042
Filing Date	2017-07-21
First Named Inventor	Christine Bjoern Jensen
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	8545US02

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Application Number	15656042
Filing Date	2017-07-21
First Named Inventor	Christine Bjoern Jensen
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	8545US02

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☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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Signature	/Leon Y. Lum/	Date (YYYY-MM-DD)	2017-09-29
Name/Print	Leon Y. Lum	Registration Number	62,124

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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Application Number	
Filing Date	2017-07-21
First Named Inventor	Christine Bjoern Jensen
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	8545US02

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/K.M.H/	1	8536122	A1	2013-09-17	Lau et al.	
/K.M.H/	2	8129343	A1	2012-03-06	Lau et al.	

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/K.M.H/	1	20110301080		2011-12-08	Bush et al.	
/K.M.H/	2	20100292133		2010-11-18	Spetzler et al.	
/K.M.H/	3	20100047762		2010-02-25	Button et al.	

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Application Number	
Filing Date	2017-07-21
First Named Inventor	Christine Bjoern Jensen
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	8545US02

/K.M.H/	1	12136790	WO	A1	2012-10-11	Glaxo Group Ltd		
	2	12130136	WO	A1	2012-10-04	Tianjin Inst Pharm Research		
	3	12016419	WO	A1	2012-02-09	Zhejiang Beta Pharma Inc		
	4	102229668	CN	A	2011-11-02	Zhejiang Beta Pharma Co.,ltd		X
	5	2010/092163	WO	A2	2010-08-19	Boehringer Ingelheim Int		☐
	6	2011138421	WO	A1	2011-11-10	Boehringer Ingelheim Int		☐
	7	2012177929	WO	A2	2012-12-27	Amylin Pharmaceuticals, Inc		☐
	8	2012107476	WO	A1	2012-08-16	Boehringer Ingelheim Int		☐
	9	2011/080103	WO	A1	2011-07-07	Novo Nordisk As		☐
	10	2006/097537	WO	A2	2006-09-21	Novo Nordisk As		☐
	11	2012080471	WO	A1	2012-06-21	Novo Nordisk As		☐

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	First Named Inventor	Christine Bjoern Jensen
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
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/K.M.H/	1	Madsbad S et al. An Overview of once-weekly glucagon-like peptide-1 receptor agonists available efficacy and safety data and perspectives for the future, 'Diabetes, Obesity and Metabolism" Year 2011, Vol 13, No 5, Pages 394-407	
	2	BUSE B. J. et al., Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study, Lancet, 2013, Vol. 381, pages 117-124	
	3	Kim et al. "Effects of Once-Weekly Dosing of a Long-Acting Release Formulation of Exentide on Glucose Control and Body Weight in Subjects with Type 2 Diabetes." Diabetes care (2007) Vol 30 pgs 1487-1493.	
	4	Bydureon NDA 022200/S-008 Package Information pages 1-179 (February 2014).	
	5	Clinical Trial NCT00696657 entitled "A Randomized Controlled Clinical Trial in Type 2 Diabetes Comparing Semaglutide to Placebo and Liraglutide." pages 1-5 March 2015. Accessed September 24, 2015 at clinicaltrials.gov/archive/NCT00696657/2011_03_25.	
	6	Lau et al. "Discovery of the Once-WEekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide." J. Med. Chem. (2015) Vol 58 pgs 7370-7380	
	7	Eperzan Assessment Report. Euro. Med. Agency. pages 1-124 (2014) accessed September 24, 2015 at URL ema.europa.ed/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002735/WC500165119.pdf	
	8	Trulicity Assessment Report. Euro. Med. Agency. pages 1-172 (2014) accessed September 24, 2015 at URL ema.europa.ed/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002825/WC500179473.pdf	
	9	Mizuta et al. "The Role for GLP-1 in Regulation of Body Weight." Progress in Medicine 2008 Vol 28 No 8 pgs 1909-1912	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2017-07-21
	First Named Inventor	Christine Bjoern Jensen
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	8545US02

	10	CDC, "National Health and Nutrition Examination Survey: Healthy Weight, Overweight and Obesity among U.S. adults" 03-0260 pp 1-2 (July 2003), accessed 5/10/2016 at URL cdc.gov/nchs/data/nhanes/databriefs/adultweight.pdf

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Examiner Signature	/KRISTINA M HELLMAN/	Date Considered	07/10/2018

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.M.H/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2017-07-21
First Named Inventor	Christine Bjoern Jensen
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	8545US02

CERTIFICATION STATEMENT

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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Leon Y. Lum/	Date (YYYY-MM-DD)	2017-07-20
Name/Print	Leon Y. Lum	Registration Number	62,124

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Petitioner Apotex Exhibit 1002-0326

Bibliographic Data

Application No: 15/656,042

Foreign Priority claimed: ◉ Yes ○ No

35 USC 119 (a-d) conditions met: ☑ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /KRISTINA M HELLMAN/ (Examiner's Signature) | Initials

Title: Use of Long-Acting GLP-1 Peptides

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
07/21/2017 **RULE**	514	1675	8545US02

APPLICANTS

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Mads Frederik Rasmussen Copenhagen OE, DENMARK

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Peter Kristensen Broenshoej, DENMARK

CONTINUING DATA

This application is a CON of 14409493 12/19/2014 PAT 9764003

14409493 is a 371 of PCT/EP2013/063004 06/21/2013

PCT/EP2013/063004 has PRO of 61708162 10/01/2012

PCT/EP2013/063004 has PRO of 61694837 08/30/2012

FOREIGN APPLICATIONS

EPO 12174535.0 07/01/2012

EPO 12186781.6 10/01/2012

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L1	64991	jensen.inv.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 18:55
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L7	0	"zdravkovic.inc"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 18:56
L8	25926	rasmussen.inv.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 18:56
L9	255	l8 and mads	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 18:56
L10	107	zdravkovic.inv.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 18:57
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L12	5893	kristensen.inv.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 18:57
L13	595	l12 and peter	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 18:57
L14	836	l4 or l9 or l11 or l13	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 18:57
L15	7164	novo nordisk.as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 18:57
L16	540	semaglutide	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 18:58
L17	3156	GLP-1 adj2 agonist	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 19:02
L18	135	l17 and l15	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 19:02
L19	2	l17 and l14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 19:02
L20	137	l19 or l18	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 19:02
L21	21	l20 and l16	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	OFF	2018/07/10 19:02

7/ 10/ 2018 7:03:00 PM

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 8545US02
Application Number 15/656,042	Filed July 21, 2017
For Use of Long-Acting GLP-1 Peptides	
Art Unit 1654	Examiner K. M. Hellman

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☐	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
x	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$ 1,400.00
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

x The Director has already been authorized to charge fees in this application to a Deposit Account.

x The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 14-1447 .

x Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

x attorney or agent of record. Registration number 62,124 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____ .

/Leon Y. Lum/	January 23, 2019
Signature	Date
Leon Y. Lum	(609) 987-5800
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

x * Total of 1 forms are submitted.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0330

Docket No.: 8545US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christine Bjoern Jensen et al.

Application No.: 15/656,042 | Confirmation No.: 9712

Filed: July 21, 2017 | Art Unit: 1654

For: Use of Long-Acting GLP-1 Peptides | Examiner: Kristina M. Hellman

AMENDMENT AND REPLY UNDER 37 CFR 1.111

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This communication is responsive to the Non-Final Office Action dated July 23, 2018. Please amend the claims as indicated below and consider the remarks herein. Applicant hereby petitions under 37 CFR 1.136(a) for a three-month extension to make this response timely.

Amendments to the Claims begin on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0331

AMENDMENT TO THE CLAIMS

The following list of claims replaces all previous versions of claims.

Listing of claims

1. (Currently Amended) A method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof

~~a) reduction of HbA1c;~~

~~b) treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or~~

~~c) treatment of obesity, reducing body weight and/or food intake, or inducing satiety;~~

~~wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof,~~

~~wherein said GLP-1 agonist~~

~~i) has a half-life of at least 72 hours;~~

~~ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and~~

~~iii) is administered once weekly or less often~~.

2. – 7. (Canceled)

8. (Currently Amended) The method according to claim 1, wherein the semaglutide ~~said GLP-1 agonist~~ is administered by parenteral administration.

9. – 10. (Canceled)

11. (New) The method according to claim 8, wherein the solution is administered by subcutaneous injection.

12. (New) The method according to claim 1, wherein the semaglutide is administered in the form of an isotonic aqueous solution comprising phosphate buffer at a pH in the range of 7.0 – 9.0.

13. (New) The method according to claim 12, wherein the solution further comprises propylene glycol and phenol.

14. (New) The method according to claim 12, wherein the pH is 7.4.

15. (New) The method according to claim 14, wherein the solution further comprises propylene glycol and phenol.

16. (New) The method according to claim 12, wherein the phosphate buffer is a sodium dihydrogen phosphate buffer.

17. (New) The method according to claim 1, wherein the semaglutide is administered by subcutaneous injection in the form of an isotonic aqueous solution comprising at a sodium dihydrogen phosphate buffer at a pH in the range of 7.0 – 9.0, and wherein the solution further comprises propylene glycol and phenol.

18. (New) The method according to claim 17, wherein the pH is 7.4.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0333

REMARKS

Status of the claims

Claims 1-10 were previously pending.

With this response, claim 1 is amended to recite semaglutide and focus on methods for treating type 2 diabetes. Corresponding changes are made to claim 8.

Claims 2-7 and 9-10 are canceled.

New claims 11-18 are added.

Support for the amendments can be found in the claims and specification as originally filed, such as at pages 4 and 27-28 (Example 1). Thus, the amendments do not introduce new matter and entry thereof is warranted. Upon such entry, claims 1, 8, and 11-18 will be pending and presented for consideration on the merits.

Claim objections and rejections

The Office Action objects to, and rejects, claims 1-10 for a variety of reasons. Without acquiescing to the merits of the objections and rejections, and purely to advance prosecution, the claims are amended as indicated above. Thus, Applicant respectfully requests that the objections and rejections be withdrawn.

Double Patenting

The Office Action rejects claims 1-4, 7, and 8 on the ground of nonstatutory double patenting in view of U.S. Patent No. 9,764,003. Without acquiescing to the merits of the rejection and purely to advance prosecution, the claims are amended as indicated above. Thus, Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

Applicant believes the application is in condition for allowance. Should the Examiner believe a telephone interview would be productive to move this application forward to allowance, she is respectfully requested to contact the undersigned.

Applicant believes that no additional fee other than the three-month extension fee is due with this response. However, if such additional fee is due, please charge Deposit Account No. 14-1447, under Order No. 8545US02, from which the undersigned is authorized to draw.

Dated: January 23, 2019

Respectfully submitted,

Electronic signature: /Leon Y. Lum/
Leon Y. Lum
Registration No.: 62,124
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536
(609) 987-5800
Attorney For Applicant

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0335

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 8545US02

In re Application of: Christine Bjoern Jensen et al.

Application No.: 15/656,042

Filed: July 21, 2017

For: Use of Long-Acting GLP-1 Peptides

The applicant, Novo Nordisk A/S, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 9764003 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 62,124

/Leon Y. Lum/ — Signature
February 28, 2019 — Date

Leon Y. Lum — Typed or printed name

Attorney for Applicant(s) — Title
(609) 987-5800 — Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0336

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
* 15/656,042 *	15/656,042	Jensen et al.	
	Examiner	**Art Unit**	
	HELLMAN, KRISTINA M	1654	

Document Code - DISQ	**Internal Document - DO NOT MAIL**

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: **28 February 2019**	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

/LAWANA R HIXON/

Technology Center: OPLC

Telephone: (571)272-6074

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0337

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

23650 7590 03/06/2019
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

EXAMINER
HELLMAN, KRISTINA M

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 03/06/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02	9712

TITLE OF INVENTION: Use of Long-Acting GLP-1 Peptides

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	06/06/2019

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0338

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23650 7590 03/06/2019
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02	9712

TITLE OF INVENTION: Use of Long-Acting GLP-1 Peptides

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	06/06/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
HELLMAN, KRISTINA M	1654	514-004900

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0339

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02	9712

23650 7590 03/06/2019
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

EXAMINER
HELLMAN, KRISTINA M

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 03/06/2019

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0340

Notice of Allowability	Application No. 15/656,042	Applicant(s) Jensen et al.	
	Examiner KRISTINA M HELLMAN	Art Unit 1654	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to reply filed 1/23/2019.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1,8 and 11-18 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. attached hereto.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/JULIE HA/ Primary Examiner, Art Unit 1654	/KRISTINA M HELLMAN/ Examiner, Art Unit 1654

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0341

NOTICE OF ALLOWANCE

Examiner acknowledges receipt of the reply filed 1/23/2019, in response to the non-final office action mailed 7/23/2019.

Claims 1, 8, and 11-18 are pending. Claims 2-7, 9 and 10 have been cancelled. Claims 11-18 are newly added.

Claims 1, 8, and 11-18 are being allowed on the merits in this office action.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Terminal Disclaimer

The terminal disclaimer filed on 2/28/2019 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 9,764,003 has been reviewed and was accepted 3/2/2019. The terminal disclaimer has been recorded. *See* PAIR.

Claim Objections- withdrawn

The objection to 2-9 is withdrawn in view of the amendment filed 1/23/2019.

Claim Rejections - 35 USC § 112- withdrawn

The rejection of claims 1-10 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, is withdrawn in view of the amendment filed 1/23/2019.

Claim Rejections - 35 USC § 102- withdrawn

The rejection of claims 1-10 under pre-AIA 35 U.S.C. 102b as being anticipated by Clinical Trial NCT00696657 ((3/25/2011) - accessed 9/24/15 at URL clinicaltrials.gov/archive/NCT00696657/2011_03_25; hereinafter referred to as "the '657 clinical trial"- cited in IDS filed 7/21/2017), as evidenced by Lau et al. (*J. Med. Chem. 58*:7370-7380 (2015)- cited in IDS filed 7/21/2017), is withdrawn in view of the amendment filed 1/23/2019.

The rejection of claims 1-10 under pre-AIA 35 U.S.C. 102b as being anticipated by Madsbad et al. (*Diabet. Obes. Metab. 13*:394-407 (Jan. 2011)- cited in IDS filed 7/21/2017), as evidenced by the Eperzan assessment report, (*Euro. Med. Agency*, pp. 1-124 (2014)- accessed 9/24/2015 at URL: ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002735/WC500165119.pdf- cited in IDS filed 7/21/2017), is withdrawn in view of the amendment filed 1/23/2019.

The rejection of claims 1-10 under pre-AIA 35 U.S.C. 102b as being anticipated by Madsbad et al. (*Diabet. Obes. Metab. 13*:394-407 (Jan. 2011)- cited in IDS filed 7/21/2017), as evidenced by the Trulicity assessment report (*Euro. Med. Agency*, pp. 1-172 (2014)- accessed 9/24/2015 at URL: ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002825/WC500179473.pdf-)- cited in IDS filed 7/21/2017), is withdrawn in view of the amendment filed 1/23/2019.

The rejection of claims 1-8 and 10 under pre-AIA 35 U.S.C. 102b as being anticipated by Kim et al. (*Diabetes Care 30*:1487-1493 (2007)- cited in IDS filed

7/21/2017), as evidenced by Bydureon NDA 022200/S-008 package information (Feb. 2014)-)- cited in IDS filed 7/21/2017), is withdrawn in view of the amendment filed 1/23/2019.

Double Patenting- withdrawn

The rejection of claims 1-4, 7, and 8 on the ground of nonstatutory double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 9,764,003 (hereinafter "the '003 patent"), is withdrawn in view of the terminal disclaimer filed 2/28/2019.

The terminal disclaimer filed on 2/28/2019 has been reviewed and was accepted 3/2/2019. The terminal disclaimer has been recorded. *See* PAIR.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: a method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof is free of the prior art.

The closest prior art to the instant claims is Clinical Trial NCT00696657 ((3/25/2011) hereinafter referred to as "the '657 clinical trial"- previously cited).

The '657 clinical trial compared semaglutide and liraglutide in treatment of type 2 diabetic patients. The semaglutide or liraglutide was used as on add-on therapy to type 2 diabetic patients already taking metformin. Efficacy of treatment was further assessed by a reduction in HbA1c levels. Patients in the Arm Labels D and E of the clinical trial

were administered 0.8 mg once weekly by subcutaneous injection. However, the reference does not teach or disclose a higher amount of 1 mg semaglutide.

Accordingly, the instant claims are free of the prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 1, 8, and 11-18 are allowed as set forth in the amendment filed 1/23/2019.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTINA M HELLMAN whose telephone number is (571)272-2836. The examiner can normally be reached on M-F 9:00 am-5:30 pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JAMES ALSTRUM-ACEVEDO can be reached on 571-272-5548. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KRISTINA M HELLMAN/
Examiner, Art Unit 1654

/JULIE HA/
Primary Examiner, Art Unit 1654

Examiner-Initiated Interview Summary	Application No. 15/656,042	Applicant(s) Jensen et al.	
	Examiner KRISTINA M HELLMAN	Art Unit 1654	AIA (FITF) Status No

All participants (applicant, applicant's representative, PTO personnel):

(1) KRISTINA M. HELLMAN. (3) _____.

(2) Leon Lum. (4) _____.

Date of Interview: 26 February 2019.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☑ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Examiner contacted Mr. Lum to discuss allowance of the instant application. Examiner stated that a terminal disclaimer (TD) would be needed to overcome the outstanding ODP rejection. Mr. Lum contacted Applicant for authorization of the TD. Mr. Lum informed Examiner that the TD would be forthcoming..

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/KRISTINA M HELLMAN/ Examiner, Art Unit 1654	/JULIE HA/ Primary Examiner, Art Unit 1654

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0347

Docket No.: 8545US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Christine Bjoern Jensen et al.

Application No.: 15/656,042 | Confirmation No.: 9712

Filed: July 21, 2017 | Art Unit: 1654

For: Use of Long-Acting GLP-1 Peptides | Examiner: K. M. Hellman

PETITION TO CORRECT INVENTORSHIP UNDER 37 CFR 1.48

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

On behalf of the Assignee hereof and the inventors, the undersigned hereby petitions in accordance with 37 C.F.R. 1.48 (a), to change the inventorship in the above-captioned application to delete **Mads Frederik Rasmussen, Milan Zdravkovic,** and **Peter Kristensen** as inventors.

Per 37 C.F.R. 1.48 (a), Applicant hereby provides a Substitute Application Data Sheet identifying the inventors associated with the above-captioned application as well as the processing fee set forth in §1.17(i).

Per 37 C.F.R. 1.48 (c), because this request to change the inventorship is filed after an Office Action on the merits has been given or mailed in the application, please charge the fee set forth in §1.17(d) to Deposit Account No. 14-1447.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0348

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 14-1447, under Order No. 8545US02 from which the undersigned is authorized to draw.

Dated: April 15, 2019

Respectfully submitted,

By /Leon Y. Lum/
Leon Y. Lum
Registration No.: 62,124
NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536
(609) 987-5800
Attorney For Applicant

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0349

Corrected Application Data Sheet

Inventor Information

Inventor Number::	1
Given Name::	Christine
Middle Name::	Bjoern
Family Name::	Jensen
City of Residence::	Charlottenlund
Country of Residence::	Denmark
Street of mailing address::	c/o Novo Nordisk A/S
	Novo Alle
City of mailing address::	Bagsvaerd
Country of mailing address::	Denmark
Postal or Zip Code of mailing address::	DK-2880

~~Inventor Number::~~	~~2~~
~~Given Name::~~	~~Mads~~
~~Middle Name::~~	~~Frederik~~
~~Family Name::~~	~~Rasmussen~~
~~City of Residence::~~	~~Copenhagen OE~~
~~Country of Residence::~~	~~Denmark~~
~~Street of mailing address::~~	~~c/o Novo Nordisk A/S~~
	~~Novo Alle~~
~~City of mailing address::~~	~~Bagsværd~~
~~Country of mailing address::~~	~~Denmark~~
~~Postal or Zip Code of mailing address::~~	~~DK-2880~~

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0350

~~Inventor Number::~~	~~3~~
~~Given Name::~~	~~Milan~~
~~Family Name::~~	~~Zdravkovic~~
~~City of Residence::~~	~~Holte~~
~~Country of Residence::~~	~~Denmark~~
~~Street of mailing address::~~	~~c/o Novo Nordisk A/S~~
	~~Novo Alle~~
~~City of mailing address::~~	~~Bagsværd~~
~~Country of mailing address::~~	~~Denmark~~
~~Postal or Zip Code of mailing address::~~	~~DK-2880~~

~~Inventor Number::~~	[[4]]
~~Given Name::~~	~~Peter~~
~~Family Name::~~	~~Kristensen~~
~~City of Residence::~~	~~Broenshoej~~
~~Country of Residence::~~	~~Denmark~~
~~Street of mailing address::~~	~~c/o Novo Nordisk A/S~~
	~~Novo Alle~~
~~City of mailing address::~~	~~Bagsværd~~
~~Country of mailing address::~~	~~Denmark~~
~~Postal or Zip Code of mailing address::~~	~~DK-2880~~

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0351

Correspondence Information

Correspondence Customer Number::	23650
E-Mail address::	nnipatent@novonordisk.com

Application Information

Application Number::	~~Not Yet Assigned~~ 15/656,042
Filing Date::	07/21/2017
Application Type::	Regular
Subject Matter::	Utility
Title::	Use of Long-Acting GLP-1 Peptides
Attorney Docket Number::	8545US02

Representative Information

Representative Customer Number::	23650

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Leon Y. Lum/	Date (YYYY-MM-DD)	2019-04-15
Name	Leon Y. Lum	Registration Number	62,124

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0352

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/656,042	07/21/2017	1654	1740	8545US02	10	1

CONFIRMATION NO. 9712

UPDATED FILING RECEIPT

OC000000107553024

23650
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

Date Mailed: 04/22/2019

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Christine Bjoern Jensen, Charlottenlund, DENMARK;

Applicant(s)

Novo Nordisk A/S, Bagsvaerd, DENMARK;

Power of Attorney: The patent practitioners associated with Customer Number 23650

Domestic Priority data as claimed by applicant

This application is a CON of 14/409,493 12/19/2014 PAT 9764003
which is a 371 of PCT/EP2013/063004 06/21/2013
which claims benefit of 61/708,162 10/01/2012
and claims benefit of 61/694,837 08/30/2012

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
EUROPEAN PATENT OFFICE (EPO) 12186781.6 10/01/2012 No Access Code Provided
EUROPEAN PATENT OFFICE (EPO) 12174535.0 07/01/2012 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0353

Request to Retrieve - This application either claims priority to one or more applications filed in an intellectual property Office that participates in the Priority Document Exchange (PDX) program or contains a proper **Request to Retrieve Electronic Priority Application(s)** (PTO/SB/38 or its equivalent). Consequently, the USPTO will attempt to electronically retrieve these priority documents.

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

Use of Long-Acting GLP-1 Peptides

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0354

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02

CONFIRMATION NO. 9712

23650
NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

37 CFR 1.48 ACKNOWLEDGEMENT LETTER

OC000000107553025

Date Mailed: 04/22/2019

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(a)

This is in response to the applicant's request under 37 CFR 1.48(a) submitted on 04/17/2019.

The request under 37 CFR 1.48(a) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/ngfissha/

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0355

PART B–FEE(S) TRANSMITTAL

Complete and send this form, together with the applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By fax, send to: (571) 273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

NOVO NORDISK INC
800 Scudders Mill Road
Plainsboro, New Jersey 08536

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)

(Signature)

(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
15/656,042	07/21/2017	Christine Bjoern Jensen	8545US02	9712

TITLE OF INVENTION: Use of Long-Acting GLP-1 Peptides

APPLN: TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1,000.00			$1,000.00	06/06/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
K. M. Hellman	1654	514-004.900

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363)

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. Leon Y. Lum
2.
3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Novo Nordisk A/S

(B) RESIDENCE: (CITY and STATE or COUNTRY): Bagsvaerd, Denmark

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees Submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 14-1447

5. Change of Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29. NOTE: Absent a valid Certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27. NOTE: If the application was previously under micro entity status, checking this box will be taken as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Leon Y. Lum/ Date March 14, 2019

Typed or printed name Leon Y. Lum Registration No. 62,124

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0356

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/656,042	07/02/2019	10335462	8545US02	9712

23650 7590 06/12/2019

NOVO NORDISK INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 Scudders Mill Road
Plainsboro, NJ 08536

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Christine Bjoern Jensen, Charlottenlund, DENMARK;
Novo Nordisk A/S, Bagsvaerd, DENMARK;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

Apotex v. Novo - IPR2024-00631
Petitioner Apotex Exhibit 1002-0357

AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
NOVO NORDISK INC. and NOVO NORDISK A/S	RIO BIOPHARMACEUTICALS INC. and EMS S/A

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,129,343 B2	3/6/2012	Novo Nordisk A/S
2 9,132,239 B2	9/15/2015	Novo Nordisk A/S
3 9,457,154 B2	10/4/2016	Novo Nordisk A/S
4 9,687,611 B2	6/27/2017	Novo Nordisk A/S
5 10,335,462 B2	7/2/2019	Novo Nordisk A/S

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED 3/4/2022	U.S. DISTRICT COURT for the District of Delaware
PLAINTIFF NOVO NORDISK INC. and NOVO NORDISK A/S		DEFENDANT AUROBINDO PHARMA USA, INC., AUROBINDO PHARMA LTD. and EUGIA PHARMA SPECIALTIES LTD.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,129,343 B2	3/6/2012	Novo Nordisk A/S
2 9,132,239 B2	9/15/2015	Novo Nordisk A/S
3 9,457,154 B2	10/4/2016	Novo Nordisk A/S
4 9,687,611 B2	6/27/2017	Novo Nordisk A/S
5 10,335,462 B2	7/2/2019	Novo Nordisk A/S

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

ADDENDUM TO AO 120 (ADDITIONAL PATENTS)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
NOVO NORDISK INC. and NOVO NORDISK A/S	AUROBINDO PHARMA USA, INC., AUROBINDO PHARMA LTD. and EUGIA PHARMA SPECIALTIES LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
6	8,920,383 B2	12/30/2014	Novo Nordisk A/S
7	9,775,953 B2	10/3/2017	Novo Nordisk A/S
8	10,220,155 B2	3/5/2019	Novo Nordisk A/S
9	11,097,063 B2	8/24/2021	Novo Nordisk A/S
10	RE46,363 E	4/11/2017	Novo Nordisk A/S
11	7,762,994 B2	7/27/2010	Novo Nordisk A/S
12	8,114,833 B2	2/14/2012	Novo Nordisk A/S
13	8,536,122 B2	9/17/2013	Novo Nordisk A/S
14	8,579,869 B2	11/12/2013	Novo Nordisk A/S
15	8,684,969 B2	4/1/2014	Novo Nordisk A/S
16	9,108,002 B2	8/18/2015	Novo Nordisk A/S
17	9,616,180 B2	4/11/2017	Novo Nordisk A/S
18	9,861,757 B2	1/9/2018	Novo Nordisk A/S
19	10,357,616 B2	7/23/2019	Novo Nordisk A/S
20	10,376,652 B2	8/13/2019	Novo Nordisk A/S

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading		
	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
NOVO NORDISK INC. and NOVO NORDISK A/S	SUN PHARMACEUTICAL INDUSTRIES LTD. and SUN PHARMACEUTICAL INDUSTRIES, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 9,132,239 B2	9/15/2015	Novo Nordisk A/S
2 10,335,462 B2	7/2/2019	Novo Nordisk A/S
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
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DECISION/JUDGEMENT

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Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
NOVO NORDISK INC. and NOVO NORDISK A/S	ZYDUS WORLDWIDE DMCC, ZYDUS PHARMACEUTICALS (USA) INC. and CADILA HEALTHCARE LTD.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 9,132,239 B2	9/15/2015	Novo Nordisk A/S
2 10,335,462 B2	7/2/2019	Novo Nordisk A/S
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
NOVO NORDISK INC. and NOVO NORDISK A/S	DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,129,343 B2	3/6/2012	Novo Nordisk A/S
2	9,132,239 B2	9/15/2015	Novo Nordisk A/S
3	9,457,154 B2	10/4/2016	Novo Nordisk A/S
4	9,687,611 B2	6/27/2017	Novo Nordisk A/S
5	10,335,462 B2	7/2/2019	Novo Nordisk A/S

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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ADDENDUM TO AO 120 (ADDITIONAL PATENTS)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
NOVO NORDISK INC. and NOVO NORDISK A/S	DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
6	8,920,383 B2	12/30/2014	Novo Nordisk A/S
7	9,775,953 B2	10/3/2017	Novo Nordisk A/S
8	10,220,155	3/5/2019	Novo Nordisk A/S
9	11,097,063	8/24/2021	Novo Nordisk A/S
10	RE46,363 E	4/11/2017	Novo Nordisk A/S

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading		
	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
NOVO NORDISK INC. and NOVO NORDISK A/S	ALVOGEN, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,129,343 B2	3/6/2012	Novo Nordisk A/S
2	9,132,239 B2	9/15/2015	Novo Nordisk A/S
3	9,457,154 B2	10/4/2016	Novo Nordisk A/S
4	9,687,611 B2	6/27/2017	Novo Nordisk A/S
5	10,335,462 B2	7/2/2019	Novo Nordisk A/S

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
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DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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ADDENDUM TO AO 120 (ADDITIONAL PATENTS)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
NOVO NORDISK INC. and NOVO NORDISK A/S	ALVOGEN, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
6	8,920,383 B2	12/30/2014	Novo Nordisk A/S
7	9,775,953 B2	10/3/2017	Novo Nordisk A/S
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9	11,097,063	8/24/2021	Novo Nordisk A/S
10	RE46,363 E	4/11/2017	Novo Nordisk A/S

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading

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AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

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☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
NOVO NORDISK INC. and NOVO NORDISK A/S	AUROBINDO PHARMA USA, INC., AUROBINDO PHARMA LTD. and EUGIA PHARMA SPECIALTIES LTD.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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2 9,132,239 B2	9/15/2015	Novo Nordisk A/S
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4 9,687,611 B2	6/27/2017	Novo Nordisk A/S
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
See D.I. 7, Notice of Voluntary Dismissal

CLERK	(BY) DEPUTY CLERK	DATE
John A. Cerino, Clerk	/s/ K. Davis	3/29/2022

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

ADDENDUM TO AO 120 (ADDITIONAL PATENTS)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
NOVO NORDISK INC. and NOVO NORDISK A/S	AUROBINDO PHARMA USA, INC., AUROBINDO PHARMA LTD. and EUGIA PHARMA SPECIALTIES LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
6	8,920,383 B2	12/30/2014	Novo Nordisk A/S
7	9,775,953 B2	10/3/2017	Novo Nordisk A/S
8	10,220,155 B2	3/5/2019	Novo Nordisk A/S
9	11,097,063 B2	8/24/2021	Novo Nordisk A/S
10	RE46,363 E	4/11/2017	Novo Nordisk A/S
11	7,762,994 B2	7/27/2010	Novo Nordisk A/S
12	8,114,833 B2	2/14/2012	Novo Nordisk A/S
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19	10,357,616 B2	7/23/2019	Novo Nordisk A/S
20	10,376,652 B2	8/13/2019	Novo Nordisk A/S

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

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	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
22-294 (CFC)	3/4/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
NOVO NORDISK INC. and NOVO NORDISK A/S	SUN PHARMACEUTICAL INDUSTRIES LTD. and SUN PHARMACEUTICAL INDUSTRIES, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,132,239 B2	9/15/2015	Novo Nordisk A/S
2	10,335,462 B2	7/2/2019	Novo Nordisk A/S
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY
7/21/2022	☑ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,129,343 B2	3/6/2012	Novo Nordisk A/S
2	8,920,383 B2	12/30/2014	Novo Nordisk A/S
3	9,457,154 B2	10/4/2016	Novo Nordisk A/S
4	9,775,953 B2	10/3/2017	Novo Nordisk A/S
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