PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 10034-010WO1	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2016/020686	International filing date *(day/month/year)* 03 March 2016 (03.03.2016)	Priority date *(day/month/year)* 03 March 2015 (03.03.2015)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant GEORGIA TECH RESEARCH CORPORATION		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 05 September 2017 (05.09.2017)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Athina Nickitas-Etienne e-mail: pct.team4@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	19 MAY 2016
Applicant's or agent's file reference 10034-010WO1	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2016/020686	03 March 2016	03 March 2015

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61B 18/00; A61N 1/00; A61N 1/05; A61N 1/18; A61N 1/32; A61N 1/36 (2016.01)
CPC - A61N 1/3605; A61N 1/36053; A61N 1/36057; A61N 1/36171 (2016.01)

Applicant GEORGIA TECH RESEARCH CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	29 April 2016	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
   - [X] the international application in the language in which it was filed.
   - [ ] a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. [ ] This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).

3. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
   - a. [ ] forming part of the international application as filed:
     - [ ] in the form of an Annex C/ST.25 text file.
     - [ ] on paper or in the form of an image file.
   - b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
   - c. [ ] furnished subsequent to the international filing date for the purposes of international search only:
     - [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
     - [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5-19, 23-40

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 5-19, 23-40 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 5-19 and 23-40 are dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 5-19, 23-40

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	None	YES
	Claims	1-4, 20-22, 41, 42	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-4, 20-22, 41, 42	NO
Industrial applicability (IA)	Claims	1-4, 20-22, 41, 42	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-4, 20-22, 41, and 42 lack novelty under PCT Article 33(2) as being anticipated by Tweden et al. (hereinafter Tweden).

Regarding Claim 1, Tweden discloses a method for causing a perturbation of blood glucose level in a subject (Title, Abstract; para. [0035] "a method and system comprises modulating the amount and/or secretion of a polypeptide such as glucagon-like peptide-1 (GLP-1), or glucose-dependent insulinotropic peptide (GIP) by application of a neural conduction block, or by application of neural stimulation, or a combination of both as described herein in order to facilitate glucose regulation"; para. [0047] "systems and devices for treating a condition associated with impaired glucose regulation"), comprising:
selectively inhibiting neural activity (para. [0072] "some of the electrodes may be connected to a blocking electrical signal source" and para. [0109] "neural conduction block is applied to a target nerve at a site with said neural conduction block selected to down-regulate neural activity on the nerve"; see also FIG. 6 regarding blocking of neural activity) of at least one of a hepatic branch of the subject's vagus nerve or the subject's greater splanchnic nerve (para. [0051] "the electrodes 212, 212a may be individually placed on the celiac nerve, the vagal nerve, the splanchnic nerve, or some combination of these, respectively, of a patient" and para. [0096] "the electrical signal is applied to an electrode positioned on the vagus nerve. In some cases, the electrical signal is applied on the hepatic branch of the vagus nerve" and para. [0097] "signal is applied to splanchnic nerve or the celiac branch of the vagus nerve"; see also paras. [0109]-[0110] regarding blocking neural activity using electrodes placed on at least one of a hepatic branch of the vagus nerve or the splanchnic nerve) using electrical stimulation having a frequency greater than about 5 kHz (see para. [0050]-[0051] regarding electrodes 212, 212a used to provide electrical stimulation using pulse generator 104; para. [0095] "When the signal is selected to downregulate activity on the nerve, the electrical signal is applied at a frequency of about 200 Hz to 5000 Hz"; see also para. [0137] regarding frequency preferences), wherein the selective inhibition of neural activity causes the subject's blood glucose level to increase or decrease as compared to a baseline level (FIG. 6 illustrates increase/decrease in vagal activity when compared to baseline level due to up-regulation and down-regulation; para. [0094] "increasing or modifying the amount of GLP1, GIP, or both comprising: applying an intermittent electrical signal to a target nerve, with said electrical signal selected to up regulate or down-regulate neural activity on the nerve and to restore neural activity on the nerve upon discontinuance of said signal, wherein the electrical signal is selected to modify the amount of GLP1, GIP, or both... In some embodiments, the electrical signal is selected to modify GLP1. In some embodiments, the electrical signal is selected to increase GLP1, especially when blood glucose is elevated"; and para. [0098] "the method further comprises detecting the level of GLP1 or GIP to determine whether to apply an electrical signal treatment. If the levels of GLP1 and/or GIP are increased to normal or baseline levels expected in a control sample from a subject without diabetes, treatment to increase GLP1 and/or GIP may cease until the levels fall below the expected levels required to maintain adequate glucose control").

Regarding Claim 2, Tweden discloses the method of claim 1, further comprising selectively exciting neural activity (para. [0120] "electrodes applied to a target nerve are energized with an up regulating signal") of at least one of the hepatic branch of the subject's vagus nerve or the subject's greater splanchnic nerve using electrical stimulation (para. [0051] "the electrodes 212, 212a may be individually placed on the celiac nerve, the vagal nerve, the splanchnic nerve, or some combination of these, respectively, of a patient" and para. [0122] "an up-regulating signal may be applied to a celiac nerve or splanchnic nerve. In other embodiments, an up-regulating or downregulating signal may be applied to a hepatic branch of the vagus nerve"), wherein the selective excitation and inhibition of neural activity causes the subject's blood glucose level to increase or decrease as compared to the baseline level (FIG. 6 illustrates increase/decrease in vagal activity when compared to baseline level due to up-regulation and down-regulation; para. [0094] "increasing or modifying the amount of GLP1, GIP, or both comprising: applying an intermittent electrical signal to a target nerve, with said electrical signal selected to up regulate or down-regulate neural activity on the nerve and to restore neural activity on the nerve upon discontinuance of said signal, wherein the electrical signal is selected to modify the amount of GLP1, GIP, or both... In some embodiments, the electrical signal is selected to modify GLP1. In some embodiments, the electrical signal is selected to increase GLP1, especially when blood glucose is elevated"; and para. [0098] "the method further comprises detecting the level of GLP1 or GIP to determine whether to apply an electrical signal treatment. If the levels of GLP1 and/or GIP are increased to normal or baseline levels expected in a control sample from a subject without diabetes, treatment to increase GLP1 and/or GIP may cease until the levels fall below the expected levels required to maintain adequate glucose control").

Regarding Claim 3, Tweden discloses the method of claim 2, wherein neural activity of the hepatic branch of the subject's vagus nerve is selectively excited using electrical stimulation (para. [0051] "the electrodes 212, 212a may be individually placed on the celiac nerve, the vagal nerve, the splanchnic nerve, or some combination of these, respectively, of a patient" and para. [0122] "an up-regulating or downregulating signal may be applied to a hepatic branch of the vagus nerve" and para. [0120] "electrodes applied to a target nerve are energized with an up regulating signal").

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding Claim 4, Tweden discloses the method of any of claims 1-3, wherein neural activity of the subject's greater splanchnic nerve is selectively inhibited (para. [0051] "the electrodes 212, 212a may be individually placed on the celiac nerve, the vagal nerve, the splanchnic nerve, or some combination of these, respectively, of a patient"; and paras. [0109]-[0110] "a neural conduction block is applied to a target nerve at a site with said neural conduction block selected to down-regulate neural activity on the nerve... the nerve is a nerve that innervates one or more alimentary organs, including but not limited to the vagus nerve, celiac nerves, hepatic branch of the vagus nerve, and splanchnic nerve. The signal applied may upregulate and/or down regulate neural activity on one or more of the nerves") using electrical stimulation having a frequency greater than about 5 kHz (see para. [0050]-[0051] regarding electrodes 212, 212a used to provide electrical stimulation using pulse generator 104; para. [0095] "When the signal is selected to downregulate activity on the nerve, the electrical signal is applied at a frequency of about 200 Hz to 5000 Hz"; see also para. [0137] regarding frequency preferences).

Regarding Claim 20, Tweden discloses a method for causing a perturbation of blood glucose level in a subject (Title, Abstract; para. [0035] "a method and system comprises modulating the amount and/or secretion of a polypeptide such as glucagon-like peptide-1 (GLP-1), or glucose-dependent insulinotropic peptide (GIP) by application of a neural conduction block, or by application of neural stimulation, or a combination of both as described herein in order to facilitate glucose regulation"; para. [0047] "systems and devices for treating a condition associated with impaired glucose regulation"), comprising:
providing a first electrode (electrodes 212, 212a; FIGS. 3-4) at a portion of a hepatic branch of the subject's vagus nerve (para. [0051] "the electrodes 212, 212a may be individually placed on the celiac nerve, the vagal nerve, the splanchnic nerve, or some combination of these, respectively, of a patient");
providing a second electrode (electrodes 212, 212a; FIGS. 3-4) at a portion of the subject's greater splanchnic nerve (para. [0051] "the electrodes 212, 212a may be individually placed on the celiac nerve, the vagal nerve, the splanchnic nerve, or some combination of these, respectively, of a patient");
providing a stimulus generator (pulse generator 104; FIGS. 3-4) operably coupled with the first electrode and the second electrode (FIGS. 3-4; paras. [0050]-[0051] "lead assemblies 106, 106a are electrically connected to the circuitry of the pulse generator 104 by conductors 114, 114a... lead assemblies 106, 106a include distal electrodes 212, 212a, which are placed on one or more nerves"); and
using the stimulus generator, providing a first stimulus signal to the first electrode (para. [0063] "pulse generator 104 generates upregulating signals and/or downregulating signals to the leads 106, 106a"), the first stimulus signal being configured to energize the first electrode and excite neural activity of the hepatic branch of the subject's vagus nerve (para. [0120] "electrodes applied to a target nerve are energized with an up regulating signal... application of an up signal again up-regulates neural activity"; and para. [0122] "an up-regulating or downregulating signal may be applied to a hepatic branch of the vagus nerve"), and
providing a second stimulus signal to the second electrode (para. [0063] "pulse generator 104 generates upregulating signals and/or downregulating signals to the leads 106, 106a"), the second stimulus signal being configured to energize the second electrode and inhibit neural activity of the subject's greater splanchnic nerve (paras. [0109]-[0110] "a neural conduction block is applied to a target nerve at a site with said neural conduction block selected to down-regulate neural activity on the nerve... the nerve is a nerve that innervates one or more alimentary organs, including but not limited to the vagus nerve, celiac nerves, hepatic branch of the vagus nerve, and splanchnic nerve. The signal applied may upregulate and/or down regulate neural activity on one or more of the nerves").

Regarding Claim 21, Tweden discloses the method of claim 20, wherein the subject's blood glucose level increases as compared to a baseline level in response to providing the first stimulus or providing the second stimulus signal (FIG. 6 illustrates increase/decrease in vagal activity when compared to baseline level due to up-regulation and down-regulation; para. [0094] "increasing or modifying the amount of GLP1, GIP, or both comprising: applying an intermittent electrical signal to a target nerve, with said electrical signal selected to up regulate or down-regulate neural activity on the nerve and to restore neural activity on the nerve upon discontinuance of said signal, wherein the electrical signal is selected to modify the amount of GLP1, GIP, or both... In some embodiments, the electrical signal is selected to modify GLP1. In some embodiments, the electrical signal is selected to increase GLP1, especially when blood glucose is elevated"; para. [0098] "the method further comprises detecting the level of GLP1 or GIP to determine whether to apply an electrical signal treatment. If the levels of GLP1 and/or GIP are increased to normal or baseline levels expected in a control sample from a subject without diabetes, treatment to increase GLP1 and/or GIP may cease until the levels fall below the expected levels required to maintain adequate glucose control"; and para. [0121] "an upregulating signal may be applied in combination with a down regulating signal in order to improve glucose regulation, decrease the amount of calories ingested or the amount of glucose absorbed from food, increase/modify the amount and/or secretion of GIP and /or GLP1, and/or decrease the amount of ghrelin secreted. The neural regulation signals can influence the amount of glucose produced by the liver, the amount of glucose absorbed from food, and the amount of GIP, GLP-1 and/or ghrelin secreted. The neural regulation provides for a decrease in the amount of insulin required by the subject").

Regarding Claim 22, Tweden discloses the method of any of claims 20 or 21, wherein the subject's blood glucose level decreases as compared to a baseline level in response to providing the first stimulus signal or providing the second stimulus signal (FIG. 6 illustrates increase/decrease in vagal activity when compared to baseline level due to up-regulation and down-regulation; para. [0094] "increasing or modifying the amount of GLP1, GIP, or both comprising: applying an intermittent electrical signal to a target nerve, with said electrical signal selected to up regulate or down-regulate neural activity on the nerve and to restore neural activity on the nerve upon discontinuance of said signal, wherein the electrical signal is selected to modify the amount of GLP1, GIP, or both... In some embodiments, the electrical signal is selected to modify GLP1. In some embodiments, the electrical signal is selected to increase GLP1, especially when blood glucose is elevated"; para. [0098] "the method further comprises detecting the level of GLP1 or GIP to determine whether to apply an electrical signal treatment. If the levels of GLP1 and/or GIP are increased to normal or baseline levels expected in a control sample from a subject without diabetes, treatment to increase GLP1 and/or GIP may cease until the levels fall below the expected levels required to maintain adequate glucose control"; and para. [0121] "an upregulating signal may be applied in combination with a down regulating signal in order to improve glucose regulation, decrease the amount of calories ingested or the amount of glucose absorbed from food, increase/modify the amount and/or secretion of GIP and /or GLP1, and/or decrease the amount of ghrelin secreted. The neural regulation signals can influence the amount of glucose produced by the liver, the amount of glucose absorbed from food, and the amount of GIP, GLP-1 and/or ghrelin secreted. The neural regulation provides for a decrease in the amount of insulin required by the subject")

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding Claim 41, Tweden discloses a device for causing a perturbation of blood glucose level in a subject (Title, Abstract; para. [0035] "a method and system comprises modulating the amount and/or secretion of a polypeptide such as glucagon-like peptide-1 (GLP-1), or glucose-dependent insulinotropic peptide (GIP) by application of a neural conduction block, or by application of neural stimulation, or a combination of both as described herein in order to facilitate glucose regulation"; para. [0047] "systems and devices for treating a condition associated with impaired glucose regulation"), comprising:
a first electrode (electrodes 212, 212a; FIGS. 3-4) configured to attach to a portion of a hepatic branch of the subject's vagus nerve (para. [0051] "the electrodes 212, 212a may be individually placed on the celiac nerve, the vagal nerve, the splanchnic nerve, or some combination of these, respectively, of a patient");
a second electrode (electrodes 212, 212a; FIGS. 3-4) configured to attach to a portion of the subject's greater splanchnic nerve (para. [0051] "the electrodes 212, 212a may be individually placed on the celiac nerve, the vagal nerve, the splanchnic nerve, or some combination of these, respectively, of a patient");
a stimulus generator (pulse generator 104; FIGS. 3-4) operably coupled with the first electrode and the second electrode (FIGS. 3-4; paras. [0050]-[0051] "lead assemblies 106, 106a are electrically connected to the circuitry of the pulse generator 104 by conductors 114, 114a... lead assemblies 106, 106a include distal electrodes 212, 212a, which are placed on one or more nerves"), the stimulus generator being configured to provide stimulus signals to at least one of the first electrode and the second electrode (para. [0063] "pulse generator 104 generates upregulating signals and/or downregulating signals to the leads 106, 106a"); and
a control unit operably coupled with the stimulus generator (para. [0077] "neuroregulator (pulse generator) generates electrical signals in the form of electrical pulses according to a programmed regimen"), the control unit comprising a processor and memory operably coupled to the processor (para. [0078] "pulse generator utilizes a conventional microprocessor and other standard electrical and electronic components, and communicates with an external programmer and/or monitor by asynchronous serial communication for controlling or indicating states of the device"; and para. [0060] "neuroregulator 104 also may include memory in which treatment instructions and/or patient data can be stored"; see also paras. [0083]-[0084] regarding programming and memory), wherein the control unit is configured to control the stimulus generator (para. [0060] "neuroregulator 104 can store one or more therapy programs in the programmable therapy delivery module indicating what therapy should be delivered to the patient") to:
provide a first stimulus signal configured to selectively excite neural activity of at least one of the hepatic branch of the subject's vagus nerve or the subject's greater splanchnic nerve (para. [0120] "electrodes applied to a target nerve are energized with an up regulating signal... application of an up signal again up-regulates neural activity"; and para. [0122] "an up-regulating signal may be applied to a celiac nerve or splanchnic nerve. In other embodiments, an up-regulating or downregulating signal may be applied to a hepatic branch of the vagus nerve"); and
provide a second stimulus signal having a frequency greater than about 5 kHz (para. [0095] "When the signal is selected to downregulate activity on the nerve, the electrical signal is applied at a frequency of about 200 Hz to 5000 Hz"; see also para. [0137] regarding frequency preferences) and configured to selectively inhibit neural activity of at least one of the hepatic branch of the subject's vagus nerve or the subject's greater splanchnic nerve (paras. [0109]-[0110] "a neural conduction block is applied to a target nerve at a site with said neural conduction block selected to down-regulate neural activity on the nerve... the nerve is a nerve that innervates one or more alimentary organs, including but not limited to the vagus nerve, celiac nerves, hepatic branch of the vagus nerve, and splanchnic nerve. The signal applied may upregulate and/or down regulate neural activity on one or more of the nerves"),
wherein the selective excitation and inhibition of neural activity causes the subject's blood glucose level to increase or decrease as compared to a baseline level (FIG. 6 illustrates increase/decrease in vagal activity when compared to baseline level due to up-regulation and down-regulation; para. [0094] "increasing or modifying the amount of GLP1, GIP, or both comprising: applying an intermittent electrical signal to a target nerve, with said electrical signal selected to up regulate or down-regulate neural activity on the nerve and to restore neural activity on the nerve upon discontinuance of said signal, wherein the electrical signal is selected to modify the amount of GLP1, GIP, or both... In some embodiments, the electrical signal is selected to modify GLP1. In some embodiments, the electrical signal is selected to increase GLP1, especially when blood glucose is elevated"; para. [0098] "the method further comprises detecting the level of GLP1 or GIP to determine whether to apply an electrical signal treatment. If the levels of GLP1 and/or GIP are increased to normal or baseline levels expected in a control sample from a subject without diabetes, treatment to increase GLP1 and/or GIP may cease until the levels fall below the expected levels required to maintain adequate glucose control"; and para. [0121] "an upregulating signal may be applied in combination with a down regulating signal in order to improve glucose regulation, decrease the amount of calories ingested or the amount of glucose absorbed from food, increase/modify the amount and/or secretion of GIP and /or GLP1, and/or decrease the amount of ghrelin secreted. The neural regulation signals can influence the amount of glucose produced by the liver, the amount of glucose absorbed from food, and the amount of GIP, GLP-1 and/or ghrelin secreted. The neural regulation provides for a decrease in the amount of insulin required by the subject").

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Regarding Claim 42, Tweden discloses a device for causing a perturbation of blood glucose level in a subject (Title, Abstract; para. [0035] "a method and system comprises modulating the amount and/or secretion of a polypeptide such as glucagon-like peptide-1 (GLP-1), or glucose-dependent insulinotropic peptide (GIP) by application of a neural conduction block, or by application of neural stimulation, or a combination of both as described herein in order to facilitate glucose regulation"; para. [0047] "systems and devices for treating a condition associated with impaired glucose regulation"), comprising:
a first electrode (electrodes 212, 212a; FIGS. 3-4) configured to attach to a portion of a hepatic branch of the subject's vagus nerve (para. [0051] "the electrodes 212, 212a may be individually placed on the celiac nerve, the vagal nerve, the splanchnic nerve, or some combination of these, respectively, of a patient");
a second electrode (electrodes 212, 212a; FIGS. 3-4) configured to attach to a portion of the subject's greater splanchnic nerve (para. [0051] "the electrodes 212, 212a may be individually placed on the celiac nerve, the vagal nerve, the splanchnic nerve, or some combination of these, respectively, of a patient");
a stimulus generator (pulse generator 104; FIGS. 3-4) operably coupled with the first electrode and the second electrode (FIGS. 3-4; paras. [0050]-[0051] "lead assemblies 106, 106a are electrically connected to the circuitry of the pulse generator 104 by conductors 114, 114a... lead assemblies 106, 106a include distal electrodes 212, 212a, which are placed on one or more nerves"), the stimulus generator being configured to provide stimulus signals to the first electrode and the second electrode (para. [0063] "pulse generator 104 generates upregulating signals and/or downregulating signals to the leads 106, 106a"); and
a control unit operably coupled with the stimulus generator (para. [0077] "neuroregulator (pulse generator) generates electrical signals in the form of electrical pulses according to a programmed regimen"), the control unit comprising a processor and memory operably coupled to the processor (para. [0078] "pulse generator utilizes a conventional microprocessor and other standard electrical and electronic components, and communicates with an external programmer and/or monitor by asynchronous serial communication for controlling or indicating states of the device"; and para. [0060] "neuroregulator 104 also may include memory in which treatment instructions and/or patient data can be stored"; see also paras. [0083]-[0084] regarding programming and memory), wherein the control unit is configured to control the stimulus generator (para. [0060] "neuroregulator 104 can store one or more therapy programs in the programmable therapy delivery module indicating what therapy should be delivered to the patient") to:
provide a first stimulus signal to the first electrode, the first stimulus signal being configured to excite neural activity of the hepatic branch of the subject's vagus nerve (para. [0120] "electrodes applied to a target nerve are energized with an up regulating signal... application of an up signal again up-regulates neural activity"; and para. [0122] "an up-regulating or downregulating signal may be applied to a hepatic branch of the vagus nerve"); and
provide a second stimulus signal to the second electrode, the second stimulus signal being configured to inhibit neural activity of the subject's greater splanchnic nerve (paras. [0109]-[0110] "a neural conduction block is applied to a target nerve at a site with said neural conduction block selected to down-regulate neural activity on the nerve... the nerve is a nerve that innervates one or more alimentary organs, including but not limited to the vagus nerve, celiac nerves, hepatic branch of the vagus nerve, and splanchnic nerve. The signal applied may upregulate and/or down regulate neural activity on one or more of the nerves").

Claims 1-4, 20-22, 41, and 42 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.