PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	09 NOV 2018

Applicant's or agent's file reference	FOR FURTHER ACTION
070391722WO1	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 18/48785	30 August 2018 (30.08.2018)	31 August 2017 (31.08.2017)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61N 1/36 (2018.01)
CPC - A61N 1/36, A61N 1/3601, A61N 1/3611, A61N 1/36128, A61N 1/36167, A61N 1/36135, A61N 1/3601, A61N 1/02, A61N 1/04, A61N 1/05, A61N 1/08, A61N 1/205, A61N 1/3702

Applicant MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH

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/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	25 October 2018	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/48785

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ 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:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/48785

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. 6-8, 14-16

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. 6-8, 14-16 are so unclear that no meaningful opinion could be formed *(specify)*:

because they are dependent claims and are 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. 6-8, 14-16

☐ 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.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/48785

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

1. Statement

Novelty (N)	Claims	1-5, 9-13, 17-20	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-5, 9-13, 17-20	NO
Industrial applicability (IA)	Claims	1-5, 9-13, 17-20	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-5, 9-13 and 17-20 lack an inventive step under PCT Article 33(3) as being obvious over US 2010/0125310 A1 to Wilson et al. (hereinafter Wilson) in view of US 2001/0018547 A1 to Mechlenburg et al. (hereinafter Mechlenburg).

Regarding claim 1, Wilson discloses a system for controlling breathing, the system comprising:
a sensing electrode that senses electromyography (EMG) or electroneurogram (ENG) data from a throat muscle or nerve of a patient (claim 55: an electrode configured to be positioned in contact with the internal branch of the superior laryngeal nerve of the subject...an electroneurogram signal recorded by the electrode);
a stimulation electrode that provides stimulation to a diaphragm of the patient (claim 71: a stimulation electrode and wherein the control unit further includes a stimulation module operatively connected to the monitoring and detection module and to the stimulation electrode, the stimulation module generating through the stimulation electrode a stimulation signal which acts to stimulate breathing; claim 36: a target of the stimulation signal is selected from a group consisting of the phrenic nerve, the intercostal nerve, the diaphragm muscle, the intercostal respiratory muscle and any combination thereof); and
an implantable medical device communicably coupled to the sensing electrode and the stimulation electrode (claim 55: a control unit operatively connected to the (sensing) electrode; claim 71: a stimulation electrode and wherein the control unit further includes a stimulation module operatively connected to the monitoring and detection module and to the stimulation electrode, the stimulation module generating through the stimulation electrode a stimulation signal which acts to stimulate breathing), the implantable medical device comprising:
a memory that is capable of storing computer executable instructions (para [0114]: a memory storing computer executable instructions is inherent to enable a processor such as a microcontroller, DSP or the like, to enable the processors intended function); and
a processor that is configured to facilitate execution of the executable instructions stored in memory (para [0114]: the various units, modules and sub-modules and algorithms may be implemented using, for example one or more electronic circuit, microcontroller or DSP), wherein the instructions cause the processor to:
receive the EMG or ENG data from the sensing electrode (claim 1, 55: an electroneurogram signal recorded by the electrode);
detect respiratory activity based on the received EMG or ENG data (claim 1, 55: computing an index of respiratory activity from the electroneurogram signal; para [0046]: the electroneurogram (ENG) of the internal branch of the superior laryngeal nerve (iSLN) is correlated with pressure in the upper airway 110 (see FIG. 1). This relationship can be demonstrated by calculating an index of respiratory activity (IRA) that is indicative of the amplitude and timing of the ENG signal); and deliver an electrical signal to the diaphragm via the stimulation electrodes (claim 36).
Wilson does not disclose the respiratory activity is specifically an intent of the patient to take a breath and the delivery of an electrical signal to the diaphragm occurs when the intent of the patient to take a breath is detected. However, Mechlenburg discloses a device and method for stimulation of muscles for the diagnosis and relief of a breathing disorder (abstract) including determining an intent of the patient to take a breath and the delivery of an electrical signal to the diaphragm occurs when the intent of the patient to take a breath is detected (para [0047], [0050]: stimulator can be activated during a specific window in the patient's respiratory cycle, such as at the onset of inspiration or at a period offset therefrom...monitoring the patient's EMG activity and stimulating the patient based thereon...a pressure sensor and/or an an EMG sensor..may be fixed to the patient for monitoring inspiration or muscle effort, respectively. The data from the combination of sensors can be compared and analyzed together to detect more accurately the onset of an upper airway event).
It would have been obvious to one of of ordinary skill in the art to use the timing of Mechlenburg in the system of Wilson, so that the stimulation can be synchronized with the patient's respiration (see Mechlenburg, para [0014]).

Regarding claim 2, Wilson in view of Mechlenburg discloses the system of claim 1, but does not specifically disclose wherein the throat muscle is a posterior cricoarytenoid muscle (Wilson discloses sensing from the internal branch of the superior laryngeal nerve (claim 55), which as is known in the art, innerverates the cricothyroid muscles). However, it would have been obvious to one of ordinary skill in the art to have optimized the system, such that the sensing electrode senses electromyography (EMG) or electroneurogram (ENG) data from a posterior cricoarytenoid muscle of the throat, either directly or through the recurrent laryngeal branch of the vagus nerve, based on routine experimentation, to optimize placement of the electrode.

Regarding claim 3, Wilson in view of Mechlenburg discloses the system of any one of claims 1 and 2. Mechlenburg further suggests wherein an intent of the patient to take a breath is detected based on an initiation of a contraction of the neck muscle (para [0050]: monitoring..muscle effort).

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/48785

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V(2) -- citations and explanations

Regarding claim 4, Wilson in view of Mechlenburg discloses the system of claim 3. Mechlenburg further suggests wherein the electrical signal comprises an onset delay (para [0047]: stimulator can be activated during a specific window in the patient's respiratory cycle, such as at the onset of inspiration or at a period offset therefrom).

Regarding claim 5, Wilson in view of Mechlenburg discloses the system of claim 4, but does not disclose wherein the onset delay corresponds to a natural delay between the initiation of the contraction of the throat muscle and a contraction of the diaphragm during normal breathing. However, it would have been obvious to one of ordinary skill in the art to have optimized the system such that the onset delay, as suggested by Mechlenburg (para [0047]) corresponds to a natural delay between the initiation of the contraction of the throat muscle and a contraction of the diaphragm during normal breathing, based on routine experimentation, to reflect a more natural breathing activation pattern.

Regarding claim 9, Wilson discloses a method of controlling breathing, the method comprising:
receiving, from a sensing electrode, electromyography (EMG) or electroneurogram (ENG) data from a throat muscle or a throat nerve of a patient (claim 1, 55: an electrode configured to be positioned in contact with the internal branch of the superior laryngeal nerve of the subject...an electroneurogram signal recorded by the electrode);
detecting, via a processor, a respiratory activity from the EMG or ENG data (claim 1, 55: computing an index of respiratory activity from the electroneurogram signal; para [0046]: the electroneurogram (ENG) of the internal branch of the superior laryngeal nerve (iSLN) is correlated with pressure in the upper airway 110 (see FIG. 1). This relationship can be demonstrated by calculating an index of respiratory activity (IRA) that is indicative of the amplitude and timing of the ENG signal); and
delivering, via a stimulation electrode, an electrical signal to a diaphragm or a phrenic nerve of the patient when the respiratory activity is detected (claim 36).
Wilson does not disclose the respiratory activity is specifically an intent of the patient to take a breath and the delivery of an electrical signal to the diaphragm or phrenic nerve occurs when the intent of the patient to take a breath is detected. However, Mechlenburg discloses a device and method for stimulation of muscles for the diagnosis and relief of a breathing disorder (abstract) including determining an intent of the patient to take a breath and the delivery of an electrical signal to the diaphragm or phrenic nerve occurs when the intent of the patient to take a breath is detected (para [0047], [0050]: stimulator can be activated during a specific window in the patient's respiratory cycle, such as at the onset of inspiration or at a period offset therefrom...monitoring the patient's EMG activity and stimulating the patient based thereon...a pressure sensor and/or an an EMG sensor..may be fixed to the patient for monitoring inspiration or muscle effort, respectively. The data from the combination of sensors can be compared and analyzed together to detect more accurately the onset of an upper airway event). It would have been obvious to one of of ordinary skill in the art to use the timing of Mechlenburg in the system of Wilson, so that the stimulation can be synchronized with the patient's respiration (see Mechlenburg, para [0014]).

Regarding claim 10, Wilson in view of Mechlenburg discloses the method of claim 9, but does not specifically disclose wherein the throat muscle is a posterior cricoarytenoid muscle (Wilson discloses sensing from the internal branch of the superior laryngeal nerve (claim 55), which as is known in the art, innerverates the cricothyroid muscles). However, it would have been obvious to one of ordinary skill in the art to have optimized the system, such that the sensing electrode senses electromyography (EMG) or electroneurogram (ENG) data from a posterior cricoarytenoid muscle of the throat, either directly or through the recurrent laryngeal branch of the vagus nerve, based on routine experimentation, to optimize placement of the electrode.

Regarding claim 11, Wilson in view of Mechlenburg discloses the method of any one of claims 9 and 10. Mechlenburg further suggests wherein the intent of the patient to take a breath is detected based on an initiation of a contraction of the throat muscle (para [0050]: monitoring..muscle effort).

Regarding claim 12, Wilson in view of Mechlenburg discloses the method of claim 11. Mechlenburg further suggests wherein the electrical signal comprises an onset delay (para [0047]: stimulator can be activated during a specific window in the patient's respiratory cycle, such as at the onset of inspiration or at a period offset therefrom).

Regarding claim 13, Wilson in view of Mechlenburg discloses the method of claim 12, but does not disclose wherein the onset delay corresponds to a natural delay between the initiation of the contraction of the throat muscle and a contraction of the diaphragm during normal breathing. However, it would have been obvious to one of ordinary skill in the art to have optimized the system such that the onset delay, as suggested by Mechlenburg (para [0047]) corresponds to a natural delay between the initiation of the contraction of the throat muscle and a contraction of the diaphragm during normal breathing, based on routine experimentation, to reflect a more natural breathing activation pattern.

Regarding claim 17, Wilson discloses an implantable medical device (IMD) (claim 55, 56: the system is fully implantable) configured to be communicably coupled to a sensing electrode (claim 55: an electrode configured to be positioned in contact with the internal branch of the superior laryngeal nerve of the subject...an electroneurogram signal recorded by the electrode) and a stimulation electrode (claim 71: a stimulation electrode and wherein the control unit further includes a stimulation module operatively connected to the monitoring and detection module and to the stimulation electrode, the stimulation module generating through the stimulation electrode a stimulation signal which acts to stimulate breathing; claim 36: a target of the stimulation signal is selected from a group consisting of the phrenic nerve, the intercostal nerve, the diaphragm muscle, the intercostal respiratory muscle and any combination thereof), the implantable medical device comprising a memory that is capable of storing computer executable instructions (para [0114]: a memory storing computer executable instructions is inherent to enable a processor such as a microcontroller, DSP or the like, to enable the processors intended function); and a processor that is configured to facilitate execution of the executable instructions stored in memory (para [0114]: the various units, modules and sub-modules and algorithms may be implemented using, for example one or more electronic circuit, microcontroller or DSP), wherein the instructions cause the processor to:
receive electromyography (EMG) or electroneurogram (ENG) data from a throat muscle or nerve of a patient (claim 1, 55: an electroneurogram signal recorded by the electrode); (claim 17 continued)

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 18/48785

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V(2) -- citations and explanations

(claim 17 continued) detect a respiratory event from the EMG or ENG data (claim 1, 55: computing an index of respiratory activity from the electroneurogram signal; para [0046]: the electroneurogram (ENG) of the internal branch of the superior laryngeal nerve (iSLN) is correlated with pressure in the upper airway 110 (see FIG. 1). This relationship can be demonstrated by calculating an index of respiratory activity (IRA) that is indicative of the amplitude and timing of the ENG signal); and
deliver an electrical signal to a diaphragm of the patient when the event is detected (claim 36).
Wilson does not disclose the respiratory activity is specifically an intent of the patient to take a breath
and the delivery of an electrical signal to the diaphragm occurs when the breath is detected.
However, Mechlenburg discloses a device and method for stimulation of muscles for the diagnosis and relief of a breathing disorder (abstract) including determining an intent of the patient to take a breath and the delivery of an electrical signal to the diaphragm occurs when the breath is detected (para [0047], [0050]: stimulator can be activated during a specific window in the patient's respiratory cycle, such as at the onset of inspiration or at a period offset therefrom...monitoring the patient's EMG activity and stimulating the patient based thereon...a pressure sensor and/or an an EMG sensor..may be fixed to the patient for monitoring inspiration or muscle effort, respectively. The data from the combination of sensors can be compared and analyzed together to detect more accurately the onset of an upper airway event). It would have been obvious to one of of ordinary skill in the art to use the timing of Mechlenburg in the system of Wilson, so that the stimulation can be synchronized with the patient's respiration (see Mechlenburg, para [0014]).

Regarding claim 18, Wilson in view of Mechlenburg discloses the IMD of claim 17, but does not specifically disclose wherein the throat muscle is a posterior cricoarytenoid muscle (Wilson discloses sensing from the internal branch of the superior laryngeal nerve (claim 55), which as is known in the art, innerverates the cricothyroid muscles). However, it would have been obvious to one of ordinary skill in the art to have optimized the system, such that the sensing electrode senses electromyography (EMG) or electroneurogram (ENG) data from a posterior cricoarytenoid muscle of the throat, either directly or through the recurrent laryngeal branch of the vagus nerve, based on routine experimentation, to optimize placement of the electrode.

Regarding claim 19, Wilson in view of Mechlenburg discloses the IMD of any one of claims 17 and 18. Mechlenburg further suggests wherein an intent of the patient to take a breath is detected based on an initiation of a contraction of the neck muscle (para [0050]: monitoring..muscle effort).

Regarding claim 20, Wilson in view of Mechlenburg discloses the IMD of claim 19. Mechlenburg further suggests wherein the electrical signal comprises an onset delay (para [0047]: stimulator can be activated during a specific window in the patient's respiratory cycle, such as at the onset of inspiration or at a period offset therefrom), but does not disclose wherein the onset delay corresponds to a natural delay between the initiation of the contraction of the throat muscle and a contraction of the diaphragm during normal breathing. However, it would have been obvious to one of ordinary skill in the art to have optimized the system such that the onset delay, as suggested by Mechlenburg (para [0047]) corresponds to a natural delay between the initiation of the contraction of the throat muscle and a contraction of the diaphragm during normal breathing, based on routine experimentation, to reflect a more natural breathing activation pattern.

Claims 1-5, 9-13 and 17-20 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.