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ABSTRACT

NASAL DEVICES

A nasal delivery device for and a method of delivering substance to a nasal cavity of a subject, the delivery device comprising: a nozzle through which substance is in use delivered to the nasal cavity; and a delivery unit for delivering substance through the nozzle.

2008202441 02 Jun 2008

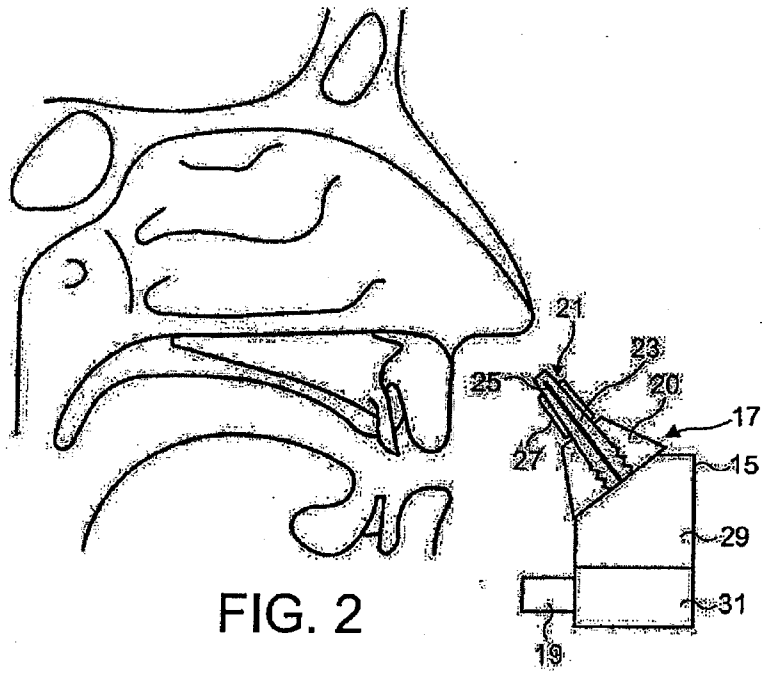

FIG. 2

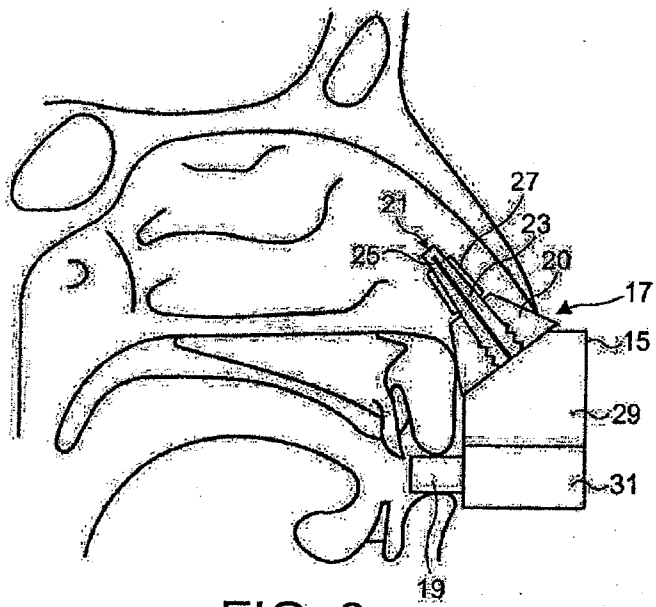

FIG. 3

2008202441 02 Jun 2008

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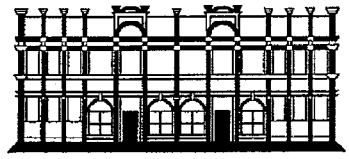

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COMPLETE SPECIFICATION
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Invention Title:

Nasal devices

The following statement is a full description of this invention including the best method of performing it known to us:-

2008202441 02 Jun 2008

NASAL DEVICES

The present invention relates to a nasal delivery device for and a method of delivering a substance, in particular one of a liquid, as a suspension or solution, or a powder containing a medicament, especially systemic or topical pharmaceuticals, or a vaccine to the nasal airway of a subject.

Referring to Figure 1, the nasal airway 1 comprises the two nasal cavities separated by the nasal septum, which airway 1 includes numerous ostia, such as the paranasal sinus ostia 3 and the tubal ostia 5, and olfactory cells, and is lined by the nasal mucosa. The nasal airway 1 can communicate with the nasopharynx 7, the oral cavity 9 and the lower airway 11, with the nasal airway 1 being in selective communication with the anterior region of the nasopharynx 7 and the oral cavity 9 by opening and closing of the oropharyngeal velum 13. The velum 13, which is often referred to as the soft palate, is illustrated in solid line in the closed position, as achieved by providing a certain positive pressure in the oral cavity 9, such as achieved on exhalation through the oral cavity 9, and in dashed line in the open position.

There are many nasal conditions which require treatment. One such condition is nasal inflammation, specifically rhinitis, which can be allergic or non-allergic and is often associated with infection and prevents normal nasal function. By way of example, allergic and non-allergic inflammation of the nasal airway can typically effect between 10 and 20 % of the population, with nasal congestion of the erectile tissues of the nasal concha, lacrimation, secretion of watery mucus, sneezing and itching being the most common symptoms. As will be understood, nasal congestion impedes nasal breathing and promotes oral breathing, leading to snoring and sleep disturbance. Other nasal conditions include nasal polyps which arise from the paranasal sinuses, hypertrophic adenoids, secretory otitis media, sinus disease and reduced olfaction.

In the treatment of certain nasal conditions, the topical administration of medicaments is preferable, particularly where the nasal mucosa is the prime pathological pathway, such as in treating or relieving nasal congestion. Medicaments that are commonly topically

delivered include decongestants, anti-histamines, cromoglycates, steroids and antibiotics. At present, among the known anti-inflammatory pharmaceuticals, topical steroids have been shown to have an effect on nasal congestion. Topical decongestants have also been suggested for use in relieving nasal congestion. The treatment of hypertrophic adenoids and chronic secretory otitis media using topical decongestants, steroids and anti-microbial agents, although somewhat controversial, has also been proposed. Further, the topical administration of pharmaceuticals has been used to treat or at least relieve symptoms of inflammation in the anterior region of the nasopharynx, the paranasal sinuses and the auditory tubes.

Medicaments can also be systemically delivered through the nasal pathway, the nasal pathway offering a good administration route for the systemic delivery of pharmaceuticals, such as hormones, for example, oxytocin and calcitionin, and analgetics, such as anti-migraine compositions, as the high blood flow and large surface area of the nasal mucosa advantageously provides for rapid systemic uptake.

Nasal delivery is also expected to be advantageous for the administration of medicaments requiring a rapid onset of action, for example, analgetics, anti-emetics, insulin, anti-epileptics, sedatives and hypnotica, and also other pharmaceuticals, for example, cardio-vascular drugs. It is envisaged that nasal administration will provide for a fast onset of action, at a rate similar to that of injection and at a rate much faster than that of oral administration. Indeed, for the treatment of many acute conditions, nasal administration is advantageous over oral administration, since gastric stasis can further slow the onset of action following oral administration.

It is also expected that nasal delivery could provide an effective delivery route for the administration of proteins and peptides as produced by modern biotechnological techniques. For such substances, the metabolism in the intestines and the first-pass-effect in the liver represent significant obstacles for reliable and cost-efficient delivery.

Furthermore, it is expected that nasal delivery using the nasal delivery technique of the present invention will prove effective in the treatment of many common neurological

diseases, such as Alzheimer's, Parkinson's, psychiatric diseases and intracerebral infections, where not possible using existing techniques. The nasal delivery technique of the present invention allows for delivery to the olfactory region, which region is located in the superior region of the nasal cavities and represents the only region where it is possible to circumvent the blood-to-brain barrier (BBB) and enable communication with the cerebrospinal fluid (CSF) and the brain.

Also, it is expected that the nasal delivery technique of the present invention will allow for the effective delivery of vaccines.

Aside from the delivery of medicaments, the irrigation of the nasal mucosa with liquids, in particular saline solutions, is commonly practised to remove particles and secretions, as well as to improve the mucociliary activity of the nasal mucosa. These solutions can be used in combination with active pharmaceuticals.

For any kind of drug delivery, accurate and reliable dosing is essential, but it is of particular importance in relation to the administration of potent drugs which have a narrow therapeutic window, drugs with potentially serious adverse effects and drugs for the treatment of serious and life-threatening conditions. For some conditions, it is essential to individualize the dosage to the particular situation, for example, in the case of diabetes mellitus. For diabetes, and, indeed, for many other conditions, the dosage of the pharmaceutical is preferably based on actual real-time measurements. Currently, blood samples are most frequently used, but the analysis of molecules in the exhalation breath of subjects has been proposed as an alternative to blood analysis for several conditions. Breath analysis is currently used for the diagnosis of conditions such as helicobacter pylori infections which cause gastric ulcers.

WO-A-00/51672 discloses a delivery device for delivering a substance, in particular a medicament, in a bi-directional flow through the nasal cavities, that is, an air flow which passes into one nostril, around the posterior margin of the nasal septum and in the opposite direction out of the other nostril. This bi-directional air flow advantageously

2008202441 02 Jun 2008

acts to stimulate the sensory nerves in the nasal mucosa, thereby conditioning the subject for the delivery and providing a more comfortable delivery situation.

It is an aim of the present invention to provide improved nasal delivery devices and nasal delivery methods for providing for the improved delivery of a substance to a nasal cavity of subject.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

In one aspect the present invention provides a nasal delivery device for delivering substance to a nasal airway of a subject, comprising: a nosepiece for fitting to a nostril of a subject, the nosepiece including a nozzle through which substance is in use delivered to the nasal airway, and at least one inflatable cuff member which is configured to be inflated subsequent to exhalation by the subject; a delivery unit for delivering substance through the nozzle of the nosepiece; and a mouthpiece unit through which the subject in use exhales to cause closure of the oropharyngeal velum of the subject.

In another aspect the present invention provides a nasal delivery device for delivering substance to a nasal airway of a subject, comprising: a nosepiece including a nozzle through which substance is in use delivered to the nasal airway, and at least one inflatable cuff member which is configured such as, when inflated, to provide a fluid-tight seal between the nosepiece and an inner wall of a nasal cavity of the subject; a delivery unit for delivering substance through the nozzle of the nosepiece; and a

mouthpiece unit through which the subject in use exhales to cause closure of the oropharyngeal velum of the subject.

In a further aspect the present invention provides a nasal delivery device for delivering substance to a nasal airway of a subject, comprising: a nosepiece for fitting to a nostril of a subject, the nosepiece including a nozzle through which substance is in use delivered to the nasal airway, and at least one cuff member which is configured such as, when fitted in a nasal cavity of the subject, to engage an inner wall of the nasal cavity of the subject and direct at least a distal end of the nozzle towards a site in the nasal airway of the subject; a delivery unit for delivering substance through the nozzle of the nosepiece; and a mouthpiece unit through which the subject in use exhales to cause closure of the oropharyngeal velum of the subject.

In yet another aspect the present invention provides a nasal delivery device for delivering substance to a nasal airway of a subject, comprising: a nosepiece for fitting to a nostril of a subject, the nosepiece including a nozzle through which substance is in use delivered to the nasal airway, and at least one cuff member, at least one of the at least one cuff member including at least one lobe which, when the at least one of the at least one cuff member is fitted in a nasal cavity of the subject, extends into a region of the nasal cavity of the subject such as to at least partially obstruct the same and prevent flow thereinto; a delivery unit for delivering substance through the nozzle of the nosepiece; and a mouthpiece unit through which the subject in use exhales to cause closure of the oropharyngeal velum of the subject.

In a yet further aspect the present invention provides a method of delivering substance to a nasal airway of a subject, comprising the steps of: fitting a nosepiece to a nasal cavity of a subject, the nosepiece including a nozzle through which substance is delivered to the nasal airway, and at least one inflatable cuff member; the subject exhaling through a mouthpiece unit to cause closure of the oropharyngeal velum of the subject; inflating the at least one cuff member subsequent to exhalation by the subject; and delivering substance through the nozzle of the nosepiece.

In yet another further aspect the present invention provides a method of delivering substance to a nasal airway of a subject, comprising the steps of: fitting a nosepiece to a nasal cavity of a subject, the nosepiece including a nozzle through which substance is delivered to the nasal airway, and at least one inflatable cuff member; the subject exhaling through a mouthpiece unit to cause closure of the oropharyngeal velum of the subject; inflating the at least one cuff member to provide a fluid-tight seal between the nosepiece and an inner wall of the nasal cavity of the subject; and delivering substance through the nozzle of the nosepiece.

In a still further aspect the present invention provides a method of delivering substance to a nasal airway of a subject, comprising the steps of: fitting a nosepiece to a nasal cavity of a subject, the nosepiece including a nozzle through which substance is delivered to the nasal airway, and at least one cuff member which engages an inner wall of the nasal cavity of the subject and directs at least a distal end of the nozzle towards a site in the nasal airway of the subject; the subject exhaling through a mouthpiece unit to cause closure of the oropharyngeal velum of the subject; and delivering substance through the nozzle of the nosepiece.

In still yet another further aspect the present invention provides a method of delivering substance to a nasal airway of a subject, comprising the steps of: fitting a nosepiece to a nasal cavity of a subject, the nosepiece including a nozzle through which substance is delivered to the nasal airway, and at least one cuff member, at least one of the at least one cuff member including at least one lobe which extends into a region of the nasal cavity of the subject such as to at least partially obstruct the same and prevent flow thereinto; the subject exhaling through a mouthpiece unit to cause closure of the oropharyngeal velum of the subject; and delivering substance through the nozzle of the nosepiece.

Preferred embodiments of the present invention will now be described hereinbelow by way of example only with reference to the accompanying drawings, in which:

Figure 1 schematically illustrates the anatomy of the upper respiratory tract of a human subject;

Figure 2 schematically illustrates a nasal delivery device in accordance with a first embodiment of the present invention;

Figure 3 schematically illustrates the delivery device of Figure 2 inserted in a nasal cavity of a subject for operation;

Figure 4 schematically illustrates the delivery device of Figure 2 during actuation;

Figure 5 schematically illustrates the delivery device of Figure 2 following actuation;

Figure 6 schematically illustrates a nasal delivery device in accordance with a second embodiment of the present invention;

Figure 7 schematically illustrates the delivery device of Figure 6 inserted in a nasal cavity of a subject for operation;

Figure 8 schematically illustrates the delivery device of Figure 6 during actuation;

Figure 9 schematically illustrates the delivery device of Figure 6 following actuation;

Figure 10 schematically illustrates a nasal delivery device in accordance with a third embodiment of the present invention;

Figure 11 schematically illustrates the delivery device of Figure 10 inserted in a nasal cavity of a subject for operation;

Figure 12 schematically illustrates the delivery device of Figure 10 during actuation;

Figure 13 schematically illustrates the delivery device of Figure 2 following actuation;

Figure 14 schematically illustrates a nasal delivery device in accordance with a fourth embodiment of the present invention;

Figure 15 schematically illustrates the delivery device of Figure 14 inserted in a nasal cavity of a subject for operation;

Figure 16 schematically illustrates the delivery device of Figure 14 during actuation;

Figure 17 schematically illustrates a nasal delivery device in accordance with a fifth embodiment of the present invention;

Figure 18 schematically illustrates the delivery device of Figure 17 inserted in a nasal cavity of a subject for operation;

Figure 19 schematically illustrates the delivery device of Figure 17 during actuation;

Figure 20 schematically illustrates a nasal delivery device in accordance with a sixth embodiment of the present invention;

Figure 21 schematically illustrates the delivery device of Figure 20 inserted in a nasal cavity of a subject for operation;

Figure 22 schematically illustrates the delivery device of Figure 20 during actuation;

Figure 23 schematically illustrates a nasal delivery device in accordance with a seventh embodiment of the present invention;

Figure 24 schematically illustrates the delivery device of Figure 23 inserted in a nasal cavity of a subject for operation;

Figure 25 schematically illustrates the delivery device of Figure 23 during actuation;

Figure 26 schematically illustrates the delivery device of Figure 23 following actuation;

Figure 27 schematically illustrates a nasal delivery device in accordance with an eighth embodiment of the present invention;

Figure 28 schematically illustrates the delivery device of Figure 27 inserted in a nasal cavity of a subject for operation;

Figure 29 schematically illustrates the delivery device of Figure 27 during actuation;

Figure 30 schematically illustrates the delivery device of Figure 27 following actuation;

Figure 31 schematically illustrates a nasal delivery device in accordance with a ninth embodiment of the present invention;

Figure 32 schematically illustrates the delivery device of Figure 31 inserted in a nasal cavity of a subject for operation;

Figure 33 schematically illustrates the delivery device of Figure 31 during actuation; and

Figure 34 schematically illustrates the delivery device of Figure 31 following actuation.

Figures 2 to 5 illustrate an exhalation breath-actuated nasal delivery device in accordance with a first embodiment of the present invention.

The delivery device comprises a housing 15, a nosepiece 17 for fitting in a nasal cavity of a subject, and a mouthpiece 19 through which the subject exhales to actuate the delivery device.

The nosepiece 17 comprises a guide member 20, in this embodiment a frusto-conical element, for guiding the nosepiece 17 into a nasal cavity of the subject, and an outlet

unit 21 for delivering substance into the nasal airway of the subject. In this embodiment the nosepiece 17 is a replaceable unit.

In this embodiment the outlet unit 21 comprises a delivery channel 23 which is in fluid communication with the mouthpiece 19 such that an air flow is delivered into and through the nasal airway of the subject on exhalation by the subject through the mouthpiece 19, and a nozzle 25 for delivering substance to the nasal airway of the subject. In this embodiment the nozzle 25 is disposed in the delivery channel 23 co-axially with the same. In this embodiment the nozzle 25 is configured to provide an aerosol spray. In an alternative embodiment, for the delivery of a liquid, the nozzle 25 could be configured to deliver a liquid jet as a column of liquid.

In this embodiment the outlet unit 21 is movably coupled to the housing 15, here as provided by a flexible coupling, such as to allow for the positioning of the outlet unit 21 in the nasal cavity of the subject, as will be described in more detail hereinbelow.

In an alternative embodiment the outlet unit 21 could be fixed to the housing 15, and the mouthpiece 19 instead movably coupled to the housing 15, here as provided by a flexible coupling, such as to allow for the positioning of the outlet unit 21 in the nasal cavity of the subject.

In this embodiment at least the tip of the delivery channel 23 comprises a tubular section of a flexible, preferably resilient, material. In a preferred embodiment the material is a semi-soft plastics material, such as silicone rubber.

In this embodiment at least the tip of the delivery channel 23 has a tapering section which narrows to the distal end thereof. The delivery channel 23, in having a narrowing taper, acts, on insertion, to expand the narrow nasal valve of the nasal cavity of the subject. In a preferred embodiment the delivery channel 23 has an elliptical section, preferably an oval section.

In a preferred embodiment the distal end of the outlet unit 21 is configured to extend at least about 2 cm, preferably at least about 3 cm, and more preferably from about 2 cm to about 3 cm, into the nasal cavity of the subject.

The nosepiece 17 further comprises at least one expandable cuff member 27 for expansion in the nasal cavity of the subject. In this embodiment the at least one cuff member 27 comprises an inflatable member.

In this embodiment the at least one cuff member 27 is in fluid communication with the delivery channel 23, whereby the air flow generated by the subject on exhalation through the mouthpiece 19 acts to inflate the at least one cuff member 27. In an alternative embodiment the delivery device could include a separate pump unit for inflating the at least one cuff member 27 subsequent to fitting of the nosepiece 17, and in a preferred embodiment subsequent to, preferably in response to, exhalation through the mouthpiece 19.

In this embodiment the at least one cuff member 27 is an inflatable member which is inflated on exhalation by the subject. In an alternative embodiment the at least one cuff member 27 could be inflated on the nosepiece 17 being located in the correct position.

In this embodiment the at least one cuff member 27 comprises a flexible balloon element which is inflated by the generation of a pressure in the delivery channel 23, with the at least one cuff member 27 deflating on the release of pressure from the delivery channel 23. In the alternative embodiment, where the at least one cuff member 27 is inflated by a separate pump unit, the at least one cuff member 27 could equally be deflated by the evacuation of gas therefrom using the same pump unit.

In one embodiment the at least one cuff member 27 could comprise a resilient balloon element which is inflated by the generation of a pressure in the delivery channel 23, with the at least one cuff member 27 returning to the original, deflated configuration on the release of pressure from the delivery channel 23.

In another embodiment the at least one cuff member 27 could comprise an inflatable sponge element, in one embodiment a foam element having an encapsulating sealing layer, which can be compressed, in this embodiment by evacuation, to adopt a compact configuration to allow for insertion into a nasal cavity of the subject and inflated, in this embodiment by breaking the vacuum, to allow for the introduction of a gas into the porous structure of the sponge element. In one embodiment such a cuff member 27 could be in selective fluid communication with the atmosphere. In another embodiment such a cuff member 27 could be in selective fluid communication with the delivery channel 23, whereby the pressure developed in the delivery channel 23 would assist in the inflation of the cuff member 27. In the alternative embodiment which includes a separate pump unit, the pump unit could be employed to assist in inflating such a cuff member 27 and in deflating the cuff member 27 by the evacuation of gas therefrom. In one embodiment the inflation could be triggered on exhalation by the subject. In another embodiment the inflation could be triggered on the nosepiece 17 being located in the correct position in the nasal cavity of the subject.

The at least one cuff member 27 is disposed to an outer surface of the outlet unit 21 such as, on expansion, to engage the inner wall of the nasal cavity of the subject. The at least one cuff member 27, in being expandable, provides for the expansion of the narrow nasal valve of the nasal cavity of the subject, the sealing of the nosepiece 17 in the nasal cavity of the subject, and the positioning, in particular the direction, of the outlet unit 21 in the nasal cavity of the subject.

In this embodiment the at least one cuff member 27 comprises a single annular cuff member 27 which is located about the outlet unit 21 such as to provide a seal between the delivery channel 23 and the inner wall of the nasal cavity of the subject when inflated.

In an alternative embodiment the at least one cuff member 27 could comprise a plurality of cuff members 27 which together provide a seal between the delivery channel 23 and the inner wall of the nasal cavity of the subject when inflated.

The delivery device further comprises a substance supply unit 29 for delivering metered doses of a substance, in this embodiment an aerosol canister for delivering metered volumes of a propellant, preferably a hydrofluoroalkane (HFA) propellant or the like, containing medicament, either as a suspension or solution, which is fluidly connected to the nozzle 25 to deliver substance from the nosepiece 17, in this embodiment as an aerosol spray.

In this embodiment the substance supply unit 29 is a multi-dose unit for delivering a plurality of metered doses of substance. In another embodiment the substance supply unit 29 could be a single-dose unit for delivering a single metered dose of substance.

The substance supply unit 29 is pre-primeable, in this embodiment by loading a resilient element, and includes a breath-actuated release mechanism 31 which, when triggered, releases the resilient element and actuates the substance supply unit 29 to deliver a metered dose of a substance through the nozzle 25.

In this embodiment the trigger mechanism 31 is configured to cause actuation of the substance supply unit 29 on generation of a predetermined flow rate through the delivery channel 23.

In another embodiment the trigger mechanism 31 could be configured to cause actuation of the substance supply unit 29 on generation of a predetermined pressure within the delivery channel 23.

In a further embodiment the trigger mechanism 31 could be configured to cause actuation of the substance supply unit 29 on generation of either one of a predetermined flow rate through the delivery channel 23 or a predetermined pressure within the delivery channel 23.

In an alternative embodiment the substance supply unit 29 could comprise a mechanical delivery pump, in particular a liquid delivery pump or a powder delivery pump, which delivers metered doses of a substance on actuation thereof.

In another alternative embodiment the substance supply unit 29 could comprise a dry powder delivery unit which delivers metered doses of a substance, as a dry powder, on actuation thereof.

In yet another alternative embodiment the substance supply unit 29 could comprise a nebulizer which delivers metered doses of a substance, as an aerosol spray, on actuation thereof.

Operation of the delivery device will now be described hereinbelow with reference to Figures 3 to 5 of the accompanying drawings.

Referring to Figure 3, the nosepiece 17 is first inserted into one of the nasal cavities of a subject until the guide member 20 abuts the nares of the nostril, at which point the distal end of the outlet unit 21 extends about 2 cm into the nasal cavity of the subject, and the mouthpiece 19 is gripped in the lips of the subject.

The subject then begins to exhale through the mouthpiece 19, which exhalation acts to close the oropharyngeal velum of the subject and drive an air flow through the delivery channel 23 of the outlet unit 21, with the air flow passing into the one nasal cavity, around the posterior margin of the nasal septum and out of the other nasal cavity, thereby achieving a bi-directional air flow through the nasal airway of the subject. Exhalation through the mouthpiece 19 acts to develop a pressure in the delivery channel 23, which pressure acts to inflate the at least one cuff member 27. As illustrated in Figure 4, the expansion of the at least one cuff member 27 acts to expand the nasal valve in the nasal cavity, seal the delivery channel 23 to the inner wall of the nasal cavity, and position the outlet unit 21 in relation to the nasal cavity of the subject. As will be noted from Figure 4, the outlet unit 21 is forced to adopt the required position by the at least one cuff member 27, in this embodiment as accommodated by flexing of the outlet unit 21.

In this embodiment, when the flow rate developed through the delivery channel 23 reaches a predetermined value, the release mechanism 31 is triggered to actuate the substance supply unit 29 to deliver a metered dose of a substance to the nozzle 25 and into the nasal cavity of the subject. In the alternative embodiment the release mechanism 31 could be triggered on the generation of a predetermined pressure in the delivery channel 23.

Following exhalation, the pressure in the delivery channel 23 decreases and the at least one cuff member 27 deflates, as illustrated in Figure 5, at which point the mouthpiece 19 is released and the nosepiece 17 withdrawn from the nasal cavity of the subject.

In one embodiment, where the delivery device is a single-dose device, the device can be discarded.

In another embodiment, where the delivery device is a multi-dose device, the device is ready for further use following priming of the substance supply unit 29. In a preferred embodiment, where the nosepiece 17 is replaceable, the nosepiece 17 can be replaced with a new nosepiece 17.

Figures 6 to 9 illustrate an exhalation breath-actuated nasal delivery device in accordance with a second embodiment of the present invention.

The delivery device of this embodiment is very similar to the delivery device of the above-described first embodiment, and thus, in order to avoid unnecessary duplication of description, only the differences will be described in detail, with like reference signs designating like parts

The delivery device of this embodiment differs from that of the above-described first embodiment in further comprising an oral exhalation breath-actuatable gas supply unit 33 for delivering a gas flow through the delivery channel 23 of the outlet unit 21 in response to exhalation by a subject, and in that the mouthpiece 19 is in fluid communication with the gas supply unit 33 and not the delivery channel 23 of the outlet

unit 21, whereby a gas flow is delivered to the delivery channel 23 of the outlet unit 21, and hence the nasal airway of the subject, in response to exhalation through the mouthpiece 19.

Operation of the delivery device is the same as for the above-described first embodiment, with a gas flow being delivered to the delivery channel 23 of the outlet unit 21 in response to exhalation through the mouthpiece 19.

Figures 10 to 13 illustrate an exhalation breath-actuated nasal delivery device in accordance with a third embodiment of the present invention.

The delivery device of this embodiment is very similar to the delivery device of the above-described first embodiment, and thus, in order to avoid unnecessary duplication of description, only the differences will be described in detail, with like reference signs designating like parts.

The delivery device of this embodiment differs from that of the above-described first embodiment only in that the nosepiece 17 comprises a plurality of, in this embodiment two, inflatable cuff members 27a, 27b. This arrangement of cuff members 27a, 27b enables the distalmost cuff member 27b to have a reduced size, and thereby facilitates insertion of the outlet unit 21 through the narrow nasal valve in the nasal cavity of the subject.

Operation of the delivery device is the same as for the above-described first embodiment.

Figures 14 to 16 illustrate an exhalation breath-actuated nasal delivery device in accordance with a fourth embodiment of the present invention.

The delivery device comprises a housing 35, a nosepiece 37 for fitting in a nasal cavity of a subject, and a mouthpiece 39 through which the subject exhales to actuate the delivery device.

The nosepiece 37 comprises a guide member 40, in this embodiment a frusto-conical element, for guiding the nosepiece 37 into the nasal cavity of the subject, and an outlet unit 41 for delivering substance into the nasal airway of the subject. In this embodiment the nosepiece 37 is a replaceable unit.

In this embodiment the outlet unit 41 comprises a delivery channel 43 which is in fluid communication with the mouthpiece 39 such that an air flow is delivered into and through the nasal airway of the subject on exhalation by the subject through the mouthpiece 39, and a nozzle 45 for delivering substance into the nasal cavity of the subject. In this embodiment the nozzle 45 is disposed in the delivery channel 43 co-axially with the same. In this embodiment the nozzle 45 is configured to provide an aerosol spray. In an alternative embodiment, for the delivery of a liquid, the nozzle 45 could be configured to deliver a liquid jet as a column of liquid.

In this embodiment at least the tip of the delivery channel 43 comprises a tubular section of a flexible, preferably resilient, material. In a preferred embodiment the material is a semi-soft plastics material, such as silicone rubber.

In this embodiment at least the tip of the delivery channel 43 has a tapering section which narrows to the distal end thereof. The delivery channel 43, in having a narrowing taper, acts, on insertion, to expand the narrow nasal valve of the nasal cavity of the subject. In a preferred embodiment the delivery channel 43 has an elliptical section, preferably an oval section.

In a preferred embodiment the outlet unit 41 is configured to extend at least about 2 cm, preferably at least about 3 cm, and more preferably from about 2 cm to about 3 cm, into the nasal cavity of the subject.

The nosepiece 37 further comprises at least one cuff member 47 for fitting in the nasal cavity of the subject. In this embodiment the at least one cuff member 47 is a resilient member which is deformable to allow for insertion into the nasal cavity of the subject

and, on insertion, expansion to adopt the required position in the nasal cavity, in which position the outlet unit 41 is correctly positioned. When so positioned, the at least one cuff member 47 provides for the expansion of the narrow nasal valve in the nasal cavity, the sealing of the outlet unit 41 in the nasal cavity, and the positioning, in particular the direction, of the outlet unit 41 in the nasal cavity of the subject. In this embodiment the at least one cuff member 47 comprises a sponge member, here a foam member. In an alternative embodiment the at least one cuff member 47 could comprise a gel-filled member, such as a silicone-filled member.

In this embodiment the at least one cuff member 47 is configured such that, when inserted in the nasal cavity, the outlet unit 41 is directed at a lower region of the nasal cavity of the subject. In preferred embodiments the at least one cuff member 47 can be configured to direct the outlet unit 41 at any region of the inferior meatus and the inferior region of the middle meatus, whereby substance can be targeted in particular at the inferior nasal concha, and the adenoids and tubal ostia in the superior region of the epipharynx.

Regions in the nasal airway adjacent the inferior meatus and the inferior region of the middle meatus represent the regions in the nasal airway which provide the path of least flow resistance therethrough. With existing nasal spray systems, the delivery is such that the delivered substance flows along the floor of the nasal cavity, with the result that the substance does not reach the adenoids or the tubal ostia.

In this embodiment the at least one cuff member 47 includes at least one lobe 54, here a single lobe 54, which is configured such as to extend into, and thereby obstruct, an upper region of the nasal cavity of the subject, the at least one lobe 54 acting to force the delivered flow to follow a flow path defined by the inferior meatus and the inferior region of the middle meatus. The achievement of such a flow path, allied with an optimization of the particle size distribution, provides that a much larger fraction of substance can be delivered to sites in the inferior meatus and the inferior region of the middle meatus.

2008202441 02 Jun 2008

In this embodiment the at least one cuff member 47 comprises a single annular cuff member 47 which is disposed about the outlet unit 41.

In an alternative embodiment the at least one cuff member 47 could comprise a plurality of cuff members 47 which are disposed about the outlet unit 41.

The delivery device further comprises a substance supply unit 49 for delivering metered doses of a substance, in this embodiment an aerosol canister for delivering metered volumes of a propellant, preferably a hydrofluoroalkane (HFA) propellant or the like, containing medicament, either as a suspension or solution, which is fluidly connected to the nozzle 45 to deliver substance from the nosepiece 37, in this embodiment as an aerosol spray.

In this embodiment the substance supply unit 49 is a multi-dose unit for delivering a plurality of metered doses of substance. In another embodiment the substance supply unit 49 could be a single-dose unit for delivering a single metered dose of substance.

The substance supply unit 49 is pre-primeable, in this embodiment by loading a resilient element, and includes a breath-actuated release mechanism 51 which, when triggered, releases the resilient element and actuates the substance supply unit 49 to deliver a metered dose of a substance through the nozzle 45.

In this embodiment the trigger mechanism 51 is configured to cause actuation of the substance supply unit 49 on generation of a predetermined flow rate through the delivery channel 43.

In another embodiment the trigger mechanism 51 could be configured to cause actuation of the substance supply unit 49 on generation of a predetermined pressure within the delivery channel 43.

In a further embodiment the trigger mechanism 51 could be configured to cause actuation of the substance supply unit 49 on generation of either one of a predetermined

flow rate through the delivery channel 43 or a predetermined pressure within the delivery channel 43.

In an alternative embodiment the substance supply unit 49 could comprise a mechanical delivery pump, in particular a liquid delivery pump or a powder delivery pump, which delivers metered doses of a substance on actuation thereof.

In another alternative embodiment the substance supply unit 49 could comprise a dry powder delivery unit which delivers metered doses of a substance, as a dry powder, on actuation thereof.

In yet another alternative embodiment the substance supply unit 49 could comprise a nebulizer which delivers metered doses of a substance, as an aerosol spray, on actuation thereof.

Operation of the delivery device will now be described hereinbelow with reference to Figures 15 and 16 of the accompanying drawings.

Referring to Figure 15, the nosepiece 37 is first inserted into a nasal cavity of a subject until the guide member 40 abuts the nares of the nostril, at which point the distal end of the outlet unit 41 extends about 2 cm into the nasal cavity of the subject, and the mouthpiece 39 is gripped in the lips of the subject.

The subject then begins to exhale through the mouthpiece 39, which exhalation acts to close the oropharyngeal velum of the subject and drive an air flow through the delivery channel 43 of the outlet unit 41, with the air flow passing into the one nasal cavity, around the posterior margin of the nasal septum and out of the other nasal cavity, thereby achieving a bi-directional air flow through the nasal airway of the subject.

In this embodiment, when the flow rate developed through the delivery channel 43 reaches a predetermined value, the release mechanism 51 is triggered to actuate the substance supply unit 49 to deliver a metered dose of a substance to the nozzle 45 and

into the nasal cavity of the subject. In the alternative embodiment the release mechanism 51 could be triggered on the generation of a predetermined pressure in the delivery channel 43.

Following exhalation, the mouthpiece 39 is released and the nosepiece 37 withdrawn from the nasal cavity of the subject.

In one embodiment, where the delivery device is a single-dose device, the device can be discarded.

In another embodiment, where the delivery device is a multi-dose device, the device is ready for further use following priming of the substance supply unit 49. In a preferred embodiment, where the nosepiece 37 is replaceable, the nosepiece 37 can be replaced with a new nosepiece 37.

Figures 17 to 19 illustrate an exhalation breath-actuated nasal delivery device in accordance with a fifth embodiment of the present invention.

The delivery device of this embodiment is very similar to the delivery device of the above-described fourth embodiment, and thus, in order to avoid unnecessary duplication of description, only the differences will be described in detail, with like reference signs designating like parts.

The delivery device of this embodiment differs from that of the above-described fourth embodiment only in the configuration of the outlet unit 41 and the at least one cuff member 47.

In this embodiment the at least one cuff member 47 is configured such that, when inserted in the nasal cavity of the subject, the outlet unit 41 is directed at a middle region of the nasal cavity of the subject. In a preferred embodiment the at least one cuff member 47 can be configured to direct the outlet unit 41 at any region of the middle meatus and the inferior region of the superior meatus, whereby substance can be

targeted in particular at the middle nasal concha, the sinus infundibulum and the sinus ostia.

The middle meatus is the region of the nasal cavity located under and lateral to the middle nasal concha, with the sinus infundibulum and the sinus ostia representing the sites of the main pathologies in many very common diseases, such as chronic sinusitis, which affects about 10 to 15 % of the population and has no FDA approved treatment, and nasal polyposis. The only known treatment of these conditions is the application of drops during a rigorous and complex procedure involving severe neck extension and the so-called "Mecca" position. As will be appreciated, however, owing to the complicated and often painful procedure, compliance is very poor. Existing nasal spray systems are ineffective in delivering substance to this region of the nasal cavity.

In this embodiment the at least one cuff member 47 includes upper and lower lobes 54a, 54b which are configured such as to extend into, and thereby obstruct, respective ones of the upper and lower regions of the nasal cavity of the subject, the lobes 54a, 54b acting to force a delivered flow to follow a flow path defined by the middle meatus and the inferior region of the superior meatus. The achievement of such a flow path, allied with an optimization of the particle size distribution, provides that a much larger fraction of substance can be delivered to sites in the middle meatus and the inferior region of the middle meatus.

Operation of the delivery device is the same as for the above-described fourth embodiment.

Figures 20 to 22 illustrate an exhalation breath-actuated nasal delivery device in accordance with a sixth embodiment of the present invention.

The delivery device of this embodiment is very similar to the delivery device of the above-described fourth embodiment, and thus, in order to avoid unnecessary duplication of description, only the differences will be described in detail, with like reference signs designating like parts.

The delivery device of this embodiment differs from that of the above-described fourth embodiment only in the configuration of the outlet unit 41 and the at least one cuff member 47.

In this embodiment the at least one cuff member 47 is configured such that, when inserted in the nasal cavity of the subject, the outlet unit 41 is directed at a superior region of the nasal cavity of the subject. In a preferred embodiment the at least one cuff member 47 can be configured to direct the outlet unit 41 at any region of the superior meatus, and in particular provide for the targeting of the superior nasal concha and the olfactory region.

The olfactory region is located in the superior region of the nasal cavity and typically has a surface area of from about 4 to 6 cm^2. The olfactory region represents the only region where it is possible to circumvent the blood-to-brain barrier (BBB) and enable communication with the cerebrospinal fluid (CSF) and the brain. Such delivery is necessary to enable effective treatment of neurological diseases, such as Alzheimer's and Parkinson's disease, psychiatric diseases and intracerebral infections.

The olfactory region is reached through narrow slit-like passages and the delivery of substance to this region is not possible using existing nasal delivery systems.

In existing nasal spray systems, substantially all of the particles are far too large to pass through the passages in communication with the olfactory region. Indeed, such spray systems are specifically designed to deliver particles having an average diameter of greater than 10 μm in order to comply with the FDA requirements which require that the maximum fraction of particles having a diameter of less than 10 μm be 5 % of the total fraction. The reason for this requirement is that, where the velum is not closed, as would be the case where a subject inhales through the nose as prescribed for delivery, particles having a diameter of less than 10 μm could escape from the nasal cavity and be inhaled into the lungs.

In addition, in existing nasal spray systems, the flow characteristics of particles delivered into the nasal cavity are not suited to enable delivery through the passages communicating with the olfactory region.

Furthermore, the sniffing action by a subject during delivery causes the particles to be drawn into the inferior and middle regions of the nasal cavity, where the flow resistance is the lowest, with only a minimal fraction, if any, of the particles being delivered to the olfactory region.

In this embodiment, by ensuring closure of the velum in delivery and optimizing both the particle size distribution so as to include a larger fraction of smaller particles, typically having a particle size of less than 10 μm, and the aerodynamic delivery conditions, the delivery device provides for the effective delivery of substance to the olfactory region. Such a delivery regime has not previously been known, and has been recognised by the present applicant as providing an improved delivery device and delivery method.

In this embodiment the at least one lobe 54 of the at least one cuff member 47 is configured such as to extend into, and thereby obstruct, a lower region of the nasal cavity of the subject, the at least one lobe 54 acting to force a delivered flow to follow a flow path defined by the superior meatus and in particular the olfactory region. The achievement of such a flow path, allied with an optimization of the particle size distribution, provides that a much larger fraction of substance can be delivered to sites in the superior meatus and in particular the olfactory region.

Operation of the delivery device is the same as for the above-described fourth embodiment.

Figures 23 to 26 illustrate an exhalation breath-actuated nasal delivery device in accordance with a seventh embodiment of the present invention.

The delivery device comprises a housing 55, a nosepiece 57 for fitting in a nasal cavity of a subject, and a mouthpiece 59 through which the subject exhales to actuate the delivery device.

The nosepiece 57 comprises a guide member 60, in this embodiment a frusto-conical element, for guiding the nosepiece 57 into a nasal cavity of the subject, and an outlet unit 61 for delivering substance into the nasal airway of the subject. In this embodiment the nosepiece 57 is a replaceable unit.

In this embodiment the outlet unit 61 comprises a delivery channel 63 which is in fluid communication with the mouthpiece 59 such that an air flow is delivered into and through the nasal airway of the subject on exhalation by the subject through the mouthpiece 59, and a nozzle 65 for delivering substance to the nasal airway of the subject. In this embodiment the nozzle 65 is disposed in the delivery channel 63 co-axially with the same. In this embodiment the nozzle 65 is configured to provide an aerosol spray. In an alternative embodiment, for the delivery of a liquid, the nozzle 65 could be configured to deliver a liquid jet as a column of liquid.

In this embodiment the outlet unit 61 is movably coupled to the housing 55, here as provided by a flexible coupling, such as to allow for the positioning of the outlet unit 61 in the nasal cavity of the subject, as will be described in more detail hereinbelow.

In an alternative embodiment the outlet unit 61 could be fixed to the housing 55, and the mouthpiece 59 instead movably coupled to the housing 55, here as provided by a flexible coupling, such as to allow for the positioning of the outlet unit 61 in the nasal cavity of the subject.

In this embodiment at least the tip of the delivery channel 63 comprises a tubular section of a flexible, preferably resilient, material. In a preferred embodiment the material is a semi-soft plastics material, such as silicone rubber.

In this embodiment at least the tip of the delivery channel 63 has a tapering section which narrows to the distal end thereof. The delivery channel 63, in having a narrowing taper, acts, on insertion, to expand the narrow nasal valve of the nasal cavity of the subject. In a preferred embodiment the delivery channel 63 has an elliptical section, preferably an oval section.

In a preferred embodiment the distal end of the outlet unit 61 is configured to extend at least about 2 cm, preferably at least about 3 cm, and more preferably from about 2 cm to about 3 cm, into the nasal cavity of the subject.

The nosepiece 57 further comprises at least one expandable cuff member 67 for expansion in the nasal cavity of the subject. In this embodiment the at least one cuff member 67 comprises an inflatable member.

In this embodiment the at least one cuff member 67 is in fluid communication with the delivery channel 63, whereby the air flow generated by the subject on exhalation through the mouthpiece 59 acts to inflate the at least one cuff member 67. In an alternative embodiment the delivery device could include a separate pump unit for inflating the at least one cuff member 67 subsequent to fitting of the nosepiece 57, and in a preferred embodiment subsequent to, preferably in response to, exhalation through the mouthpiece 59.

In this embodiment the at least one cuff member 67 is an inflatable member which is inflated on exhalation by the subject. In an alternative embodiment the at least one cuff member 67 could be inflated on the nosepiece 57 being located in the correct position.

In this embodiment the at least one cuff member 67 comprises a flexible balloon element which is inflated by the generation of a pressure in the delivery channel 63, with the at least one cuff member 67 deflating on the release of pressure from the delivery channel 63. In the alternative embodiment, where the at least one cuff member 67 is inflated by a separate pump unit, the at least one cuff member 67 could equally be deflated by the evacuation of gas therefrom using the same pump unit.

In one embodiment the at least one cuff member 67 could comprise a resilient balloon element which is inflated by the generation of a pressure in the delivery channel 63, with the at least one cuff member 67 returning to the original, deflated configuration on the release of pressure from the delivery channel 63.

In another embodiment the at least one cuff member 67 could comprise an inflatable sponge element, in one embodiment a foam element having an encapsulating sealing layer, which can be compressed, in this embodiment by evacuation, to adopt a compact configuration to allow for insertion into a nasal cavity of the subject and inflated, in this embodiment by breaking the vacuum, to allow for the introduction of a gas into the porous structure of the sponge element. In one embodiment such a cuff member 67 could be in selective fluid communication with the atmosphere. In another embodiment such a cuff member 67 could be in selective fluid communication with the delivery channel 63, whereby the pressure developed in the delivery channel 63 would assist in the inflation of the cuff member 67. In the alternative embodiment which includes a separate pump unit, the pump unit could be employed to assist in inflating such a cuff member 67 and in deflating the cuff member 67 by the evacuation of gas therefrom. In one embodiment the inflation could be triggered on exhalation by the subject. In another embodiment the inflation could be triggered on the nosepiece 57 being located in the correct position in the nasal cavity of the subject.

The at least one cuff member 67 is disposed to an outer surface of the outlet unit 61 such as, on expansion, to engage the inner wall of the nasal cavity of the subject. The at least one cuff member 67, in being expandable, provides for the expansion of the narrow nasal valve of the nasal cavity of the subject, the sealing of the nosepiece 57 in the nasal cavity of the subject, and the positioning, in particular the direction, of the outlet unit 61 in the nasal cavity of the subject.

In this embodiment the at least one cuff member 67 comprises a single annular cuff member 67 which is located about the outlet unit 61 such as to provide a seal between

the delivery channel 63 and the inner wall of the nasal cavity of the subject when inflated.

In an alternative embodiment the at least one cuff member 67 could comprise a plurality of cuff members 67 which together provide a seal between the delivery channel 63 and the inner wall of the nasal cavity of the subject when inflated.

In this embodiment the at least one cuff member 67 is configured such that, when inserted in the nasal cavity, the outlet unit 61 is directed at a lower region of the nasal cavity of the subject. In preferred embodiments the at least one cuff member 67 can be configured to direct the outlet unit 61 at any region of the inferior meatus and the inferior region of the middle meatus, whereby substance can be targeted in particular at the inferior nasal concha, and the adenoids and tubal ostia in the superior region of the epipharynx.

Regions in the nasal airway adjacent the inferior meatus and the inferior region of the middle meatus represent the regions in the nasal airway which provide the path of least flow resistance therethrough. With existing nasal spray systems, the delivery is such that the delivered substance flows along the floor of the nasal cavity, with the result that the substance does not reach the adenoids or the tubal ostia.

In this embodiment the at least one cuff member 67 includes at least one lobe 74, here a single lobe 74, which is configured such as to extend into, and thereby obstruct, an upper region of the nasal cavity of the subject, the at least one lobe 74 acting to force the delivered flow to follow a flow path defined by the inferior meatus and the inferior region of the middle meatus. The achievement of such a flow path, allied with an optimization of the particle size distribution, provides that a much larger fraction of substance can be delivered to sites in the inferior meatus and the inferior region of the middle meatus.

In this embodiment the at least one cuff member 67 comprises a single annular cuff member 67 which is disposed about the outlet unit 61.

In an alternative embodiment the at least one cuff member 67 could comprise a plurality of cuff members 67 which are disposed about the outlet unit 61.

The delivery device further comprises a substance supply unit 69 for delivering metered doses of a substance, in this embodiment an aerosol canister for delivering metered volumes of a propellant, preferably a hydrofluoroalkane (HFA) propellant or the like, containing medicament, either as a suspension or solution, which is fluidly connected to the nozzle 65 to deliver substance from the nosepiece 57, in this embodiment as an aerosol spray.

In this embodiment the substance supply unit 69 is a multi-dose unit for delivering a plurality of metered doses of substance. In another embodiment the substance supply unit 69 could be a single-dose unit for delivering a single metered dose of substance.

The substance supply unit 69 is pre-primeable, in this embodiment by loading a resilient element, and includes a breath-actuated release mechanism 71 which, when triggered, releases the resilient element and actuates the substance supply unit 69 to deliver a metered dose of a substance through the nozzle 65.

In this embodiment the trigger mechanism 71 is configured to cause actuation of the substance supply unit 69 on generation of a predetermined flow rate through the delivery channel 63.

In another embodiment the trigger mechanism 71 could be configured to cause actuation of the substance supply unit 69 on generation of a predetermined pressure within the delivery channel 63.

In a further embodiment the trigger mechanism 71 could be configured to cause actuation of the substance supply unit 69 on generation of either one of a predetermined flow rate through the delivery channel 63 or a predetermined pressure within the delivery channel 63.

In an alternative embodiment the substance supply unit 69 could comprise a mechanical delivery pump, in particular a liquid delivery pump or a powder delivery pump, which delivers metered doses of a substance on actuation thereof.

In another alternative embodiment the substance supply unit 69 could comprise a dry powder delivery unit which delivers metered doses of a substance, as a dry powder, on actuation thereof.

In yet another alternative embodiment the substance supply unit 69 could comprise a nebulizer which delivers metered doses of a substance, as an aerosol spray, on actuation thereof.

Operation of the delivery device will now be described hereinbelow with reference to Figures 24 to 26 of the accompanying drawings.

Referring to Figure 24, the nosepiece 57 is first inserted into one of the nasal cavities of a subject until the guide member 60 abuts the nares of the nostril, at which point the distal end of the outlet unit 61 extends about 2 cm into the nasal cavity of the subject, and the mouthpiece 59 is gripped in the lips of the subject.

The subject then begins to exhale through the mouthpiece 59, which exhalation acts to close the oropharyngeal velum of the subject and drive an air flow through the delivery channel 63 of the outlet unit 61, with the air flow passing into the one nasal cavity, around the posterior margin of the nasal septum and out of the other nasal cavity, thereby achieving a bi-directional air flow through the nasal airway of the subject. Exhalation through the mouthpiece 59 acts to develop a pressure in the delivery channel 63, which pressure acts to inflate the at least one cuff member 67. As illustrated in Figure 25, the expansion of the at least one cuff member 67 acts to expand the nasal valve in the nasal cavity, seal the delivery channel 63 to the inner wall of the nasal cavity, and position the outlet unit 61 in relation to the nasal cavity of the subject. As will be noted from Figure 25, the outlet unit 61 is forced to adopt the required position

by the at least one cuff member 67, in this embodiment as accommodated by flexing of the outlet unit 61.

In this embodiment, when the flow rate developed through the delivery channel 63 reaches a predetermined value, the release mechanism 71 is triggered to actuate the substance supply unit 69 to deliver a metered dose of a substance to the nozzle 65 and into the nasal cavity of the subject. In the alternative embodiment the release mechanism 71 could be triggered on the generation of a predetermined pressure in the delivery channel 63.

Following exhalation, the pressure in the delivery channel 63 decreases and the at least one cuff member 67 deflates, as illustrated in Figure 26, at which point the mouthpiece 59 is released and the nosepiece 57 withdrawn from the nasal cavity of the subject.

In one embodiment, where the delivery device is a single-dose device, the device can be discarded.

In another embodiment, where the delivery device is a multi-dose device, the device is ready for further use following priming of the substance supply unit 69. In a preferred embodiment, where the nosepiece 57 is replaceable, the nosepiece 57 can be replaced with a new nosepiece 57.

Figures 27 to 30 illustrate an exhalation breath-actuated nasal delivery device in accordance with an eighth embodiment of the present invention.

The delivery device of this embodiment is very similar to the delivery device of the above-described seventh embodiment, and thus, in order to avoid unnecessary duplication of description, only the differences will be described in detail, with like reference signs designating like parts.

The delivery device of this embodiment differs from that of the above-described seventh embodiment only in the configuration of the outlet unit 61 and the at least one cuff member 67.

In this embodiment the at least one cuff member 67 is configured such that, when inserted in the nasal cavity of the subject, the outlet unit 61 is directed at a middle region of the nasal cavity of the subject. In a preferred embodiment the at least one cuff member 67 can be configured to direct the outlet unit 61 at any region of the middle meatus and the inferior region of the superior meatus, whereby substance can be targeted in particular at the middle nasal concha, the sinus infundibulum and the sinus ostia.

The middle meatus is the region of the nasal cavity located under and lateral to the middle nasal concha, with the sinus infundibulum and the sinus ostia representing the sites of the main pathologies in many very common diseases, such as chronic sinusitis, which affects about 10 to 15 % of the population and has no FDA approved treatment, and nasal polyposis. The only known treatment of these conditions is the application of drops during a rigorous and complex procedure involving severe neck extension and the so-called "Mecca" position. As will be appreciated, however, owing to the complicated and often painful procedure, compliance is very poor. Existing nasal spray systems are ineffective in delivering substance to this region of the nasal cavity.

In this embodiment the at least one cuff member 67 includes upper and lower lobes 74a, 74b which are configured such as to extend into, and thereby obstruct, respective ones of the upper and lower regions of the nasal cavity of the subject, the lobes 74a, 74b acting to force a delivered flow to follow a flow path defined by the middle meatus and the inferior region of the superior meatus. The achievement of such a flow path, allied with an optimization of the particle size distribution, provides that a much larger fraction of substance can be delivered to sites in the middle meatus and the inferior region of the middle meatus.

Operation of the delivery device is the same as for the above-described seventh embodiment.

Figures 31 to 34 illustrate an exhalation breath-actuated nasal delivery device in accordance with a ninth embodiment of the present invention.

The delivery device of this embodiment is very similar to the delivery device of the above-described seventh embodiment, and thus, in order to avoid unnecessary duplication of description, only the differences will be described in detail, with like reference signs designating like parts.

The delivery device of this embodiment differs from that of the above-described seventh embodiment only in the configuration of the outlet unit 61 and the at least one cuff member 67.

In this embodiment the at least one cuff member 67 is configured such that, when inserted in the nasal cavity of the subject, the outlet unit 61 is directed at a superior region of the nasal cavity of the subject. In a preferred embodiment the at least one cuff member 67 can be configured to direct the outlet unit 61 at any region of the superior meatus, and in particular provide for the targeting of the superior nasal concha and the olfactory region.

The olfactory region is located in the superior region of the nasal cavity and typically has a surface area of from about 4 to 6 cm^2. The olfactory region represents the only region where it is possible to circumvent the blood-to-brain barrier (BBB) and enable communication with the cerebrospinal fluid (CSF) and the brain. Such delivery is necessary to enable effective treatment of neurological diseases, such as Alzheimer's and Parkinson's disease, psychiatric diseases and intracerebral infections.

The olfactory region is reached through narrow slit-like passages and the delivery of substance to this region is not possible using existing nasal delivery systems.

In existing nasal spray systems, substantially all of the particles are far too large to pass through the passages in communication with the olfactory region. Indeed, such spray systems are specifically designed to deliver particles having an average diameter of greater than 10 μm in order to comply with the FDA requirements which require that the maximum fraction of particles having an average diameter of less than 10 μm be 5 % of the total fraction. The reason for this requirement is that, where the velum is not closed, as would be the case where a subject inhales through the nose as prescribed for delivery, particles having an average diameter of less than 10 μm could escape from the nasal cavity and be inhaled into the lungs.

In addition, in existing nasal spray systems, the flow rate of particles delivered into the nasal cavity is too great to enable delivery through the passages communicating with the olfactory region.

Furthermore, inhalation by a subject during delivery causes the particles to be drawn into the inferior and middle regions of the nasal cavity, where the flow resistance is the lowest, with only a minimal fraction, if any, of the particles being delivered to the olfactory region.

In this embodiment, by ensuring closure of the velum in delivery and optimizing both the particle size distribution so as to include a larger fraction of smaller particles, typically having a particle size of less than 10 μm, and the aerodynamic delivery conditions, the delivery device provides for the effective delivery of substance to the olfactory region. Such a delivery regime has not previously been known, and has been recognised by the present applicant as providing an improved delivery device and delivery method.

In this embodiment the at least one lobe 74 of the at least one cuff member 67 is configured such as to extend into, and thereby obstruct, a lower region of the nasal cavity of the subject, the at least one lobe 74 acting to force a delivered flow to follow a flow path defined by the superior meatus and in particular the olfactory region. The achievement of such a flow path, allied with an optimization of the particle size

distribution, provides that a much larger fraction of substance can be delivered to sites in the superior meatus and in particular the olfactory region.

Operation of the delivery device is the same as for the above-described seventh embodiment.

Finally, it will be understood that the present invention has been described in its preferred embodiments and can be modified in many different ways without departing from the scope of the invention as defined by the appended claims.

In particular, it should be understood that features of any of the embodiments could be incorporated in any other of the embodiments. For example, the second and third embodiments could incorporate features of the first embodiment, in particular the at least one expandable cuff member 23 as in the first embodiment.

Also, in embodiments where an entraining gas flow is not required through the nasal airways of subjects, ones of the embodiments could be modified to include no such gas flow. For example, the first-described embodiment could be modified such that the outlet unit 21 includes only the nozzle 23 and no delivery channel 23.

In the described embodiments the mouthpieces are configured to be gripped in the lips of a subject. In alternative embodiments the mouthpieces could be configured to be gripped by the teeth of a subject and sealed by the lips of the subject. In preferred embodiments the mouthpieces could be specifically configured to have one or both of a shape or geometry which allows the delivery devices to be gripped repeatedly in the same position, thereby providing for the respective nosepieces to be reliably inserted in the same position in the nasal cavity.

In preferred embodiments the delivery devices are configured to deliver substance through one nostril of a subject at such a pressure as to flow around the posterior margin of the nasal septum and out of the other nostril of the subject, thereby achieving bi-directional delivery through the nasal cavities as disclosed in WO-A-00/51672. In

alternative embodiments the delivery device could be configured to deliver substance at a reduced pressure which is not sufficient to achieve bi-directional delivery through the nasal cavities. Such embodiments are still advantageous as compared to known delivery devices in providing for velum closure and being capable of achieving targeted delivery, particularly when certain regions of the nasal cavity are obstructed by cuff members.

Also, in another modification, the delivery devices could include two nosepieces, in one embodiment configured for the simultaneous delivery to each of the nasal cavities. Such embodiments would advantageously provide for three-point fixation of the delivery devices via the nosepieces and the mouthpieces.

CLAIMS

1. A nasal delivery device for delivering substance to a nasal airway of a subject, comprising:

a nosepiece for fitting to a nostril of a subject, the nosepiece including a nozzle through which substance is in use delivered to the nasal airway, and at least one inflatable cuff member which is configured to be inflated subsequent to exhalation by the subject;

a delivery unit for delivering substance through the nozzle of the nosepiece; and

a mouthpiece unit through which the subject in use exhales to cause closure of the oropharyngeal velum of the subject.

2. The delivery device of claim 1, wherein the at least one cuff member is configured to be inflated in response to exhalation by the subject.

3. The delivery device of claim 1 or 2, further comprising:

a flow channel fluidly connecting the nosepiece and the mouthpiece unit, whereby exhaled air from an exhalation breath is delivered through the nosepiece.

4. The delivery device of claim 1 or 2, further comprising:

a flow channel fluidly connected to the nosepiece through which a gas flow, separate to an exhaled air flow from an exhalation breath of the subject, is in use delivered to the nosepiece; and

a gas supply unit for supplying a gas flow to the flow channel.

5. The delivery device of any one of claims 1 to 4, wherein the delivery unit includes a dosing unit for supplying at least one substance.

6. The delivery device of claim 5, wherein the dosing unit comprises one of a nebulizer for supplying an aerosol, an aerosol canister for supplying an aerosol, a delivery pump unit for supplying one of an aerosol or a jet, a liquid pump unit

for supplying a liquid aerosol, a powder pump unit for supplying a powder aerosol or a powder delivery unit for delivering a powder aerosol.

7. The delivery device of any one of claims 1 to 6, further comprising:
an actuation mechanism for actuating the delivery unit in response to exhalation by the subject.

8. The delivery device of any one of claims 1 to 7, wherein the at least one cuff member is configured such as, when inflated, to direct at least a distal end of the nozzle towards a site in the nasal airway of the subject.

9. The delivery device of claim 8, wherein the site includes at least one of at least a part of the inferior meatus, at least a part of the middle meatus, an inferior part of the middle meatus, at least a part of the superior meatus, at least a part of the inferior nasal concha, at least a part of the middle nasal concha, at least a part of the superior nasal concha, at least a part of the olfactory region, at least sinus ostia, at least sinus infundibulum, at least a part of the epipharynx, at least adenoids and at least tubal ostia.

10. The delivery device of any one of claims 1 to 9, wherein the at least one cuff member is configured to be inflated by air from an exhalation breath of the subject.

11. The delivery device of any one of claims 1 to 9, wherein the at least one cuff member is configured to be inflated by a gas source separate to an exhalation breath of the subject.

12. The delivery device of any one of claims 1 to 11, wherein the nosepiece includes a single inflatable cuff member.

13. The delivery device of claim 12, wherein the at least one cuff member is a substantially annular member disposed about the delivery channel.

14. The delivery device of any one of claims 1 to 11, wherein the nosepiece includes a plurality of inflatable cuff members.

15. A nasal delivery device for delivering substance to a nasal airway of a subject, comprising:
a nosepiece including a nozzle through which substance is in use delivered to the nasal airway, and at least one inflatable cuff member which is configured such as, when inflated, to provide a fluid-tight seal between the nosepiece and an inner wall of a nasal cavity of the subject;
a delivery unit for delivering substance through the nozzle of the nosepiece; and
a mouthpiece unit through which the subject in use exhales to cause closure of the oropharyngeal velum of the subject.

16. The delivery device of claim 15, wherein the at least one cuff member is configured to be inflated in response to exhalation by the subject.

17. The delivery device of claim 15 or 16, further comprising:
a flow channel fluidly connecting the nosepiece and the mouthpiece unit, whereby exhaled air from an exhalation breath is delivered through the nosepiece.

18. The delivery device of claim 15 or 16, further comprising:
a flow channel fluidly connected to the nosepiece through which a gas flow, separate to an exhaled air flow from an exhalation breath of the subject, is in use delivered to the nosepiece; and
a gas supply unit for supplying a gas flow to the flow channel.

19. The delivery device of any one of claims 15 to 18, wherein the delivery unit includes a dosing unit for supplying at least one substance.

20. The delivery device of claim 19, wherein the dosing unit comprises one of a nebulizer for supplying an aerosol, an aerosol canister for supplying an aerosol, a delivery pump unit for supplying one of an aerosol or a jet, a liquid pump unit for supplying a liquid aerosol, a powder pump unit for supplying a powder aerosol or a powder delivery unit for supplying a powder aerosol.

21. The delivery device of any one of claims 15 to 20, further comprising:
an actuation mechanism for actuating the delivery unit in response to exhalation by the subject.

22. The delivery device of any one of claims 15 to 21, wherein the at least one cuff member is configured such as, when inflated, to direct at least a distal end of the nozzle towards a site in the nasal airway of the subject.

23. The delivery device of claim 22, wherein the site includes at least one of at least a part of the inferior meatus, at least a part of the middle meatus, an inferior part of the middle meatus, at least a part of the superior meatus, at least a part of the inferior nasal concha, at least a part of the middle nasal concha, at least a part of the superior nasal concha, at least a part of the olfactory region, at least sinus ostia, at least sinus infundibulum, at least a part of the epipharynx, at least adenoids and at least tubal ostia.

24. A nasal delivery device for delivering substance to a nasal airway of a subject, comprising:
a nosepiece for fitting to a nostril of a subject, the nosepiece including a nozzle through which substance is in use delivered to the nasal airway, and at least one cuff member which is configured such as, when fitted in a nasal cavity of the subject, to engage an inner wall of the nasal cavity of the subject and direct at least a distal end of the nozzle towards a site in the nasal airway of the subject;
a delivery unit for delivering substance through the nozzle of the nosepiece; and
a mouthpiece unit through which the subject in use exhales to cause closure of the oropharyngeal velum of the subject.

25. The delivery device of claim 24, wherein the at least one cuff member is one or both of shaped and sized such as to direct at least a distal end of the nozzle to a site in the nasal airway of the subject.

26. The delivery device of claim 24 or 25, further comprising:
a flow channel fluidly connecting the nosepiece and the mouthpiece unit, whereby exhaled air from an exhalation breath is delivered through the nosepiece.

27. The delivery device of claim 24 or 25, further comprising:
a flow channel fluidly connected to the nosepiece through which a gas flow, separate to an exhaled air flow from an exhalation breath of the subject, is in use delivered to the nosepiece; and
a gas supply unit for supplying a gas flow to the flow channel.

28. The delivery device of any one of claims 24 to 27, wherein the delivery unit includes a dosing unit for supplying at least one substance.

29. The delivery device of claim 28, wherein the dosing unit comprises a nebulizer for supplying an aerosol.

30. The delivery device of claim 28, wherein the dosing unit comprises an aerosol canister for supplying an aerosol.

31. The delivery device of claim 28, wherein the dosing unit comprises a delivery pump unit for supplying one of an aerosol or a jet.

32. The delivery device of claim 31, wherein the delivery pump unit comprises a liquid pump unit for supplying a liquid aerosol.

33. The delivery device of claim 31, wherein the delivery pump unit comprises a powder pump unit for supplying a powder aerosol.

34. The delivery device of claim 28, wherein the dosing unit comprises a powder delivery unit for supplying a powder aerosol.

35. The delivery device of any one of claims 24 to 34, wherein the substance is delivered as a powder aerosol.

36. The delivery device of any one of claims 24 to 34, wherein the substance is delivered as a liquid aerosol.

37. The delivery device of any one of claims 24 to 34, wherein the substance is delivered as a liquid jet.

38. The delivery device of any one of claims 24 to 37, wherein a major fraction of the particle size distribution is in one of the ranges of from about 1 μm to about 80 μm, from about 1 μm to about 50 μm, from about 1 μm to about 30 μm, from about 10 μm to about 30 μm, from about 10 μm to about 20 μm and from about 15 μm to about 30 μm.

39. The delivery device of any one of claims 24 to 38, wherein the site includes at least one of at least a part of the inferior meatus, at least a part of the middle meatus, an inferior part of the middle meatus, at least a part of the superior meatus, at least a part of the inferior nasal concha, at least a part of the middle nasal concha, at least a part of the superior nasal concha, at least a part of the olfactory region, at least sinus ostia, at least sinus infundibulum, at least a part of the epipharynx, at least adenoids and at least tubal ostia.

40. The delivery device of any one of claims 24 to 39, wherein at least one of the at least one cuff member includes at least one lobe which, when the at least one of the at least one cuff member is fitted in the nasal cavity of the subject, extends

into a region of the nasal cavity of the subject such as to at least partially obstruct the same and prevent flow thereinto.

41. The delivery device of claim 40, wherein the nasal cavity region is one of a lower region of the nasal cavity of the subject, a middle region of the nasal cavity of the subject or an upper region of the nasal cavity of the subject.

42. The delivery device of any one of claims 24 to 39, wherein at least one of the at least one cuff member includes a plurality of lobes which, when the at least one of the at least one cuff member is fitted in the nasal cavity of the subject, extend into regions of the nasal cavity of the subject such as to at least partially obstruct the same and prevent flow thereinto.

43. The delivery device of claim 42, wherein the nasal cavity regions are ones of lower and middle regions of the nasal cavity of the subject, lower and upper regions of the nasal cavity of the subject or middle and upper regions of the nasal cavity of the subject.

44. The delivery device of any one of claims 24 to 43, wherein the nosepiece includes a single cuff member.

45. The delivery device of claim 44, wherein the cuff member is a substantially annular member disposed about the nozzle.

46. The delivery device of any one of claims 24 to 43, wherein the nosepiece includes a plurality of cuff members.

47. The delivery device of claim 46, wherein the nosepiece includes a plurality of cuff members disposed about the periphery thereof.

48. The delivery device of claim 47, wherein the cuff members are disposed at one position along a length of the nozzle.

49. The delivery device of claim 47, wherein the nosepiece includes first and second cuff members in spaced positions along the length of the nozzle.

50. The delivery device of claim 49, wherein one of the cuff members is disposed at a distal end of the nozzle.

51. The delivery device of any one of claims 24 to 50, wherein the at least one cuff member is an expandable cuff member which is expanded when fitted in the nasal cavity of the subject.

52. The delivery device of claim 51, wherein the at least one expandable cuff member is configured to be expanded in response to exhalation by the subject.

53. The delivery device of claim 51 or 52, wherein the at least one cuff member is an inflatable member.

54. The delivery device of claim 53, wherein the at least one cuff member is configured to be inflated by air from an exhalation breath of the subject.

55. The delivery device of claim 53, wherein the at least one cuff member is configured to be inflated by a gas source separate to an exhalation breath of the subject.

56. The delivery device of claim 53, wherein the inflatable member comprises a compressed element which, when vented to atmosphere, is inflated.

57. The delivery device of any one of claims 24 to 56, further comprising:
an actuation mechanism for actuating the delivery unit in response to exhalation by the subject.

58. A nasal delivery device for delivering substance to a nasal airway of a subject, comprising:

a nosepiece for fitting to a nostril of a subject, the nosepiece including a nozzle through which substance is in use delivered to the nasal airway, and at least one cuff member, at least one of the at least one cuff member including at least one lobe which, when the at least one of the at least one cuff member is fitted in a nasal cavity of the subject, extends into a region of the nasal cavity of the subject such as to at least partially obstruct the same and prevent flow thereinto;

a delivery unit for delivering substance through the nozzle of the nosepiece; and

a mouthpiece unit through which the subject in use exhales to cause closure of the oropharyngeal velum of the subject.

59. The delivery device of claim 58, wherein the nasal cavity region is a lower region of the nasal cavity of the subject.

60. The delivery device of claim 58, wherein the nasal cavity region is a middle region of the nasal cavity of the subject.

61. The delivery device of claim 58, wherein the nasal cavity region is an upper region of the nasal cavity of the subject.

62. The delivery device of claim 58, wherein at least one of the at least one cuff member includes a plurality of lobes which, when the at least one of the at least one cuff member is fitted in the nasal cavity of the subject, extend into regions of the nasal cavity of the subject such as to at least partially obstruct the same and prevent flow thereinto.

63. The delivery device of claim 62, wherein the nasal cavity regions are lower and middle regions of the nasal cavity of the subject.

64. The delivery device of claim 62, wherein the nasal cavity regions are lower and upper regions of the nasal cavity of the subject.

65. The delivery device of claim 62, wherein the nasal cavity regions are middle and upper regions of the nasal cavity of the subject.

66. The delivery device of any one of claims 58 to 65, wherein the at least one cuff member is configured such as, when fitted in the nasal cavity of the subject, to engage an inner wall of the nasal cavity of the subject and direct at least a distal end of the nozzle towards a site in the nasal airway of the subject.

67. The delivery device of claim 66, wherein the site includes at least one of at least a part of the inferior meatus, at least a part of the middle meatus, an inferior part of the middle meatus, at least a part of the superior meatus, at least a part of the inferior nasal concha, at least a part of the middle nasal concha, at least a part of the superior nasal concha, at least a part of the olfactory region, at least sinus ostia, at least sinus infundibulum, at least a part of the epipharynx, at least adenoids and at least tubal ostia.

68. The delivery device of any one of claims 58 to 67, further comprising:
a flow channel fluidly connecting the nosepiece and the mouthpiece unit, whereby exhaled air from an exhalation breath is delivered through the nosepiece.

69. The delivery device of any one of claims 58 to 67, further comprising:
a flow channel fluidly connected to the nosepiece through which a gas flow, separate to an exhaled air flow from an exhalation breath of the subject, is in use delivered to the nosepiece; and
a gas supply unit for supplying a gas flow to the flow channel.

70. The delivery device of any one of claims 58 to 69, wherein the delivery unit includes a dosing unit for supplying at least one substance.

71. The delivery device of claim 70, wherein the dosing unit comprises one of a nebulizer for supplying an aerosol, an aerosol canister for supplying an aerosol, a delivery pump unit for supplying one of an aerosol or a jet, a liquid pump unit for supplying a liquid aerosol, a powder pump unit for supplying a powder aerosol or a powder delivery unit for supplying a powder aerosol.

72. The delivery device of any one of claims 58 to 71, wherein the at least one cuff member is an expandable cuff member which is expanded when fitted in the nasal cavity of the subject.

73. The delivery device of claim 72, wherein the at least one cuff member is an inflatable member.

74. The delivery device of claim 73, wherein the at least one cuff member is configured to be inflated by air from an exhalation breath of the subject.

75. The delivery device of claim 73, wherein the at least one cuff member is configured to be inflated by a gas source separate to an exhalation breath of the subject.

76. The delivery device of claim 73, wherein the inflatable member comprises a compressed element which, when vented to atmosphere, is inflated.

77. The delivery device of any one of claims 58 to 76, further comprising:
an actuation mechanism for actuating the delivery unit in response to exhalation by the subject.

78. A method of delivering substance to a nasal airway of a subject, comprising the steps of:
fitting a nosepiece to a nasal cavity of a subject, the nosepiece including a nozzle through which substance is delivered to the nasal airway, and at least one inflatable cuff member;

2008202441 02 Jun 2008

the subject exhaling through a mouthpiece unit to cause closure of the oropharyngeal velum of the subject;

inflating the at least one cuff member subsequent to exhalation by the subject; and

delivering substance through the nozzle of the nosepiece.

79. The method of claim 78, wherein the at least one cuff member is inflated in response to exhalation by the subject.

80. The method of claim 78 or 79, further comprising the step of:

providing a flow channel fluidly connecting the nosepiece and the mouthpiece unit, whereby exhaled air from an exhalation breath is delivered through the nosepiece.

81. The method of claim 78 or 79, further comprising the steps of:

providing a flow channel fluidly connected to the nosepiece through which a gas flow, separate to an exhaled air flow from an exhalation breath of the subject, is delivered to the nosepiece; and

supplying a gas flow to the flow channel.

82. The method of any one of claims 78 to 81, further comprising the step of:

delivering the substance in response to exhalation by the subject.

83. The method of any one of claims 78 to 82, wherein the at least one cuff member, when inflated, directs at least a distal end of the nozzle towards a site in the nasal airway of the subject.

84. The method of claim 83, wherein the site includes at least one of at least a part of the inferior meatus, at least a part of the middle meatus, an inferior part of the middle meatus, at least a part of the superior meatus, at least a part of the inferior nasal concha, at least a part of the middle nasal concha, at least a part of the superior nasal concha, at least a part of the olfactory region, at least sinus ostia,

at least sinus infundibulum, at least a part of the epipharynx, at least adenoids and at least tubal ostia.

85. A method of delivering substance to a nasal airway of a subject, comprising the steps of:

fitting a nosepiece to a nasal cavity of a subject, the nosepiece including a nozzle through which substance is delivered to the nasal airway, and at least one inflatable cuff member;

the subject exhaling through a mouthpiece unit to cause closure of the oropharyngeal velum of the subject;

inflating the at least one cuff member to provide a fluid-tight seal between the nosepiece and an inner wall of the nasal cavity of the subject; and

delivering substance through the nozzle of the nosepiece.

86. The method of claim 85, wherein the at least one cuff member is inflated in response to exhalation by the subject.

87. The method of claim 85 or 86, further comprising the step of:

providing a flow channel fluidly connecting the nosepiece and the mouthpiece unit, whereby exhaled air from an exhalation breath is delivered through the nosepiece.

88. The method of claim 85 or 86, further comprising the steps of:

providing a flow channel fluidly connected to the nosepiece through which a gas flow, separate to an exhaled air flow from an exhalation breath of the subject, is delivered to the nosepiece; and

supplying a gas flow to the flow channel.

89. The method of any one of claims 85 to 88, further comprising the step of:

delivering the substance in response to exhalation by the subject.

2008202441 02 Jun 2008

90. The method of any one of claims 85 to 89, wherein the at least one cuff member, when inflated, directs at least a distal end of the nozzle towards a site in the nasal airway of the subject.

91. The method of claim 90, wherein the site includes at least one of at least a part of the inferior meatus, at least a part of the middle meatus, an inferior part of the middle meatus, at least a part of the superior meatus, at least a part of the inferior nasal concha, at least a part of the middle nasal concha, at least a part of the superior nasal concha, at least a part of the olfactory region, at least sinus ostia, at least sinus infundibulum, at least a part of the epipharynx, at least adenoids and at least tubal ostia.

92. A method of delivering substance to a nasal airway of a subject, comprising the steps of:

fitting a nosepiece to a nasal cavity of a subject, the nosepiece including a nozzle through which substance is delivered to the nasal airway, and at least one cuff member which engages an inner wall of the nasal cavity of the subject and directs at least a distal end of the nozzle towards a site in the nasal airway of the subject;

the subject exhaling through a mouthpiece unit to cause closure of the oropharyngeal velum of the subject; and

delivering substance through the nozzle of the nosepiece.

93. The method of claim 92, wherein the at least one cuff member is one or both of shaped and sized such as to direct at least a distal end of the nozzle to a site in the nasal airway of the subject.

94. The method of claim 92 or 93, further comprising the step of:

providing a flow channel fluidly connecting the nosepiece and the mouthpiece unit, whereby exhaled air from an exhalation breath is delivered through the nosepiece.

95. The method of claim 92 or 93, further comprising the steps of:
providing a flow channel fluidly connected to the nosepiece through which a gas flow, separate to an exhaled air flow from an exhalation breath of the subject, is delivered to the nosepiece; and
supplying a gas flow to the flow channel.

96. The method of any one of claims 92 to 95, wherein the substance is delivered as a powder aerosol.

97. The method of any one of claims 92 to 95, wherein the substance is delivered as one of a liquid aerosol or a liquid jet.

98. The method of any one of claims 92 to 97, wherein a major fraction of the particle size distribution is in the range of from about 1 μm to about 80 μm.

99. The method of claim 98, wherein a major fraction of the particle size distribution is in the range of from about 1 μm to about 50 μm.

100. The method of claim 99, wherein a major fraction of the particle size distribution is in the range of from about 1 μm to about 30 μm.

101. The method of claim 100, wherein a major fraction of the particle size distribution is in the range of from about 10 μm to about 30 μm.

102. The method of claim 101, wherein a major fraction of the particle size distribution is in the range of from about 10 μm to about 20 μm.

103. The method of claim 101, wherein a major fraction of the particle size distribution is in the range of from about 15 μm to about 30 μm.

104. The method of any one of claims 92 to 103, wherein the site includes at least a part of the inferior meatus.

105. The method of any one of claims 92 to 104, wherein the site includes at least a part of the middle meatus.

106. The method of claim 105, wherein the site includes an inferior part of the middle meatus.

107. The method of any one of claims 92 to 106, wherein the site includes at least a part of the superior meatus.

108. The method of any one of claims 92 to 107, wherein the site includes at least a part of the inferior nasal concha.

109. The method of any one of claims 92 to 108, wherein the site includes at least a part of the middle nasal concha.

110. The method of any one of claims 92 to 109, wherein the site includes at least a part of the superior nasal concha.

111. The method of any one of claims 92 to 110, wherein the site includes at least a part of the olfactory region.

112. The method of any one of claims 92 to 111, wherein the site includes at least sinus ostia.

113. The method of any one of claims 92 to 112, wherein the site includes at least sinus infundibulum.

114. The method of any one of claims 92 to 113, wherein the site includes at least a part of the epipharynx.

115. The method of any one of claims 92 to 114, wherein the site includes at least adenoids.

116. The method of any one of claims 92 to 115, wherein the site includes at least tubal ostia.

117. The method of any one of claims 92 to 116, wherein at least one of the at least one cuff member includes at least one lobe which extends into a region of the nasal cavity of the subject such as to at least partially obstruct the same and prevent flow thereinto.

118. The method of claim 117, wherein the nasal cavity region is a lower region of the nasal cavity of the subject.

119. The method of claim 117, wherein the nasal cavity region is a middle region of the nasal cavity of the subject.

120. The method of claim 117, wherein the nasal cavity region is an upper region of the nasal cavity of the subject.

121. The method of any one of claims 92 to 116, wherein at least one of the at least one cuff member includes a plurality of lobes which extend into regions of the nasal cavity of the subject such as to at least partially obstruct the same and prevent flow thereinto.

122. The method of claim 121, wherein the nasal cavity regions are lower and middle regions of the nasal cavity of the subject.

123. The method of claim 121, wherein the nasal cavity regions are lower and upper regions of the nasal cavity of the subject.

124. The method of claim 121, wherein the nasal cavity regions are middle and upper regions of the nasal cavity of the subject.

125. The method of any one of claims 92 to 124, further comprising the step of: delivering the substance in response to exhalation by the subject.

126. A method of delivering substance to a nasal airway of a subject, comprising the steps of:
fitting a nosepiece to a nasal cavity of a subject, the nosepiece including a nozzle through which substance is delivered to the nasal airway, and at least one cuff member, at least one of the at least one cuff member including at least one lobe which extends into a region of the nasal cavity of the subject such as to at least partially obstruct the same and prevent flow thereinto;
the subject exhaling through a mouthpiece unit to cause closure of the oropharyngeal velum of the subject; and
delivering substance through the nozzle of the nosepiece.

127. The method of claim 126, wherein the nasal cavity region is a lower region of the nasal cavity of the subject.

128. The method of claim 126, wherein the nasal cavity region is a middle region of the nasal cavity of the subject.

129. The method of claim 126, wherein the nasal cavity region is an upper region of the nasal cavity of the subject.

130. The method of claim 126, wherein at least one of the at least one cuff member includes a plurality of lobes which extend into regions of the nasal cavity of the subject such as to at least partially obstruct the same and prevent flow thereinto.

131. The method of claim 130, wherein the nasal cavity regions are lower and middle regions of the nasal cavity of the subject.

132. The method of claim 130, wherein the nasal cavity regions are lower and upper regions of the nasal cavity of the subject.

133. The method of claim 130, wherein the nasal cavity regions are middle and upper regions of the nasal cavity of the subject.

134. The method of any one of claims 126 to 133, wherein the at least one cuff member engages an inner wall of the nasal cavity of the subject and directs at least a distal end of the nozzle towards a site in the nasal airway of the subject.

135. The method of claim 134, wherein the site includes at least one of at least a part of the inferior meatus, at least a part of the middle meatus, an inferior part of the middle meatus, at least a part of the superior meatus, at least a part of the inferior nasal concha, at least a part of the middle nasal concha, at least a part of the superior nasal concha, at least a part of the olfactory region, at least sinus ostia, at least sinus infundibulum, at least a part of the epipharynx, at least adenoids and at least tubal ostia.

136. The method of any one of claims 126 to 135, further comprising the step of:
providing a flow channel fluidly connecting the nosepiece and the mouthpiece unit, whereby exhaled air from an exhalation breath is delivered through the nosepiece.

137. The method of any one of claims 126 to 135, further comprising the steps of:
providing a flow channel fluidly connected to the nosepiece through which a gas flow, separate to an exhaled air flow from an exhalation breath of the subject, is delivered to the nosepiece; and
supplying a gas flow to the flow channel.

138. The method of any one of claims 126 to 137, wherein the substance is delivered as a powder aerosol.

139. The method of any one of claims 126 to 137, wherein the substance is delivered as one of a liquid aerosol or a liquid jet.

140. The method of any one of claims 126 to 139, wherein a major fraction of the particle size distribution is in one of the ranges of from about 1 μm to about 80 μm, from about 1 μm to about 50 μm, from about 1 μm to about 30 μm, from about 10 μm to about 30 μm, from about 10 μm to about 20 μm and from about 15 μm to about 30 μm.

141. The method of any one of claims 126 to 140, further comprising the step of: delivering the substance in response to exhalation by the subject.

142. A nasal delivery device for delivering a substance to a nasal cavity of a subject substantially as hereinbefore described with reference to any one of Figures 2 to 5, Figures 6 to 9, Figures 10 to 13, Figures 14 to 16, Figures 17 to 19, Figures 20 to 22, Figures 23 to 26, Figures 27 to 30 or Figures 31 to 34 of the accompanying drawings.

143. A method of delivering a substance to a nasal cavity of a subject substantially as hereinbefore described with reference to any one of Figures 2 to 5, Figures 6 to 9, Figures 10 to 13, Figures 14 to 16, Figures 17 to 19, Figures 20 to 22, Figures 23 to 26, Figures 27 to 30 or Figures 31 to 34 of the accompanying drawings.

2008202441 02 Jun 2008

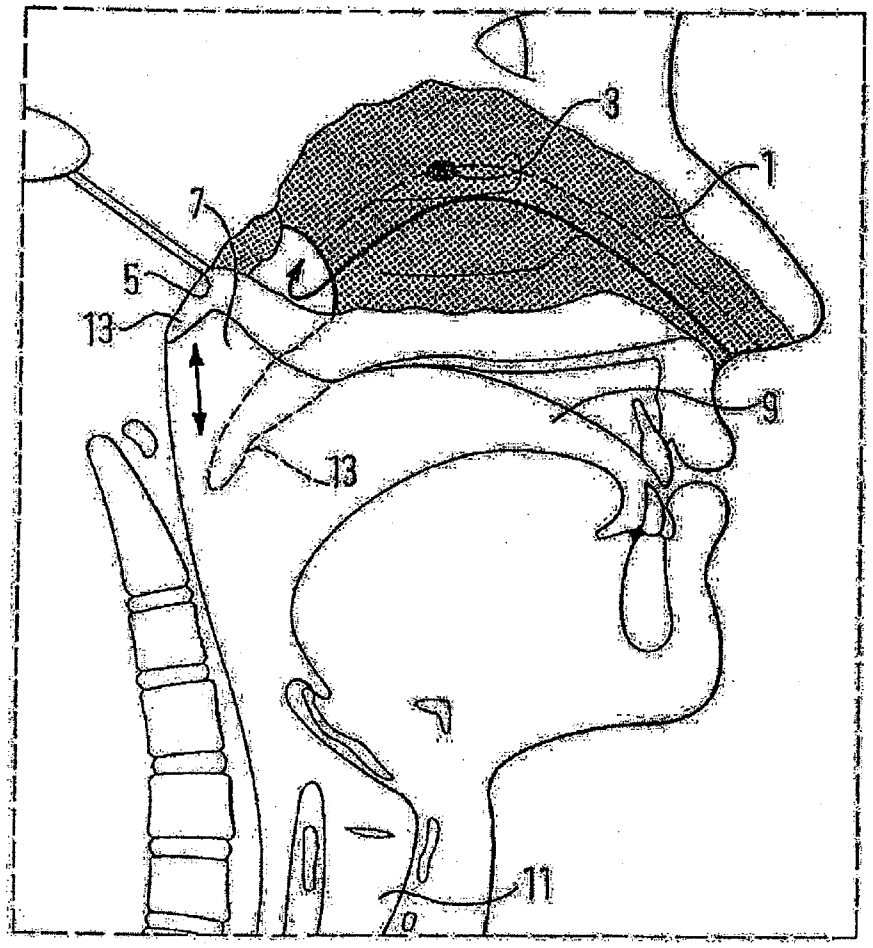

FIG. 1

2008202441 02 Jun 2008

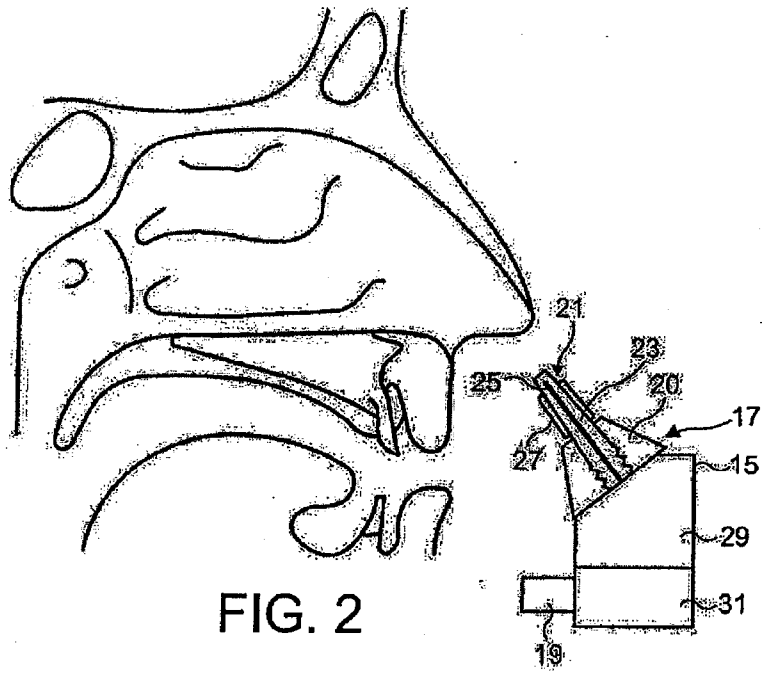

FIG. 2

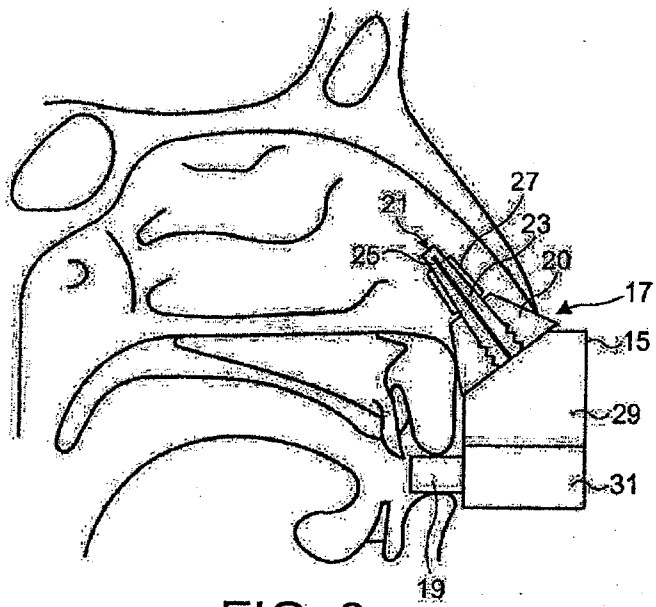

FIG. 3

2008202441 02 Jun 2008

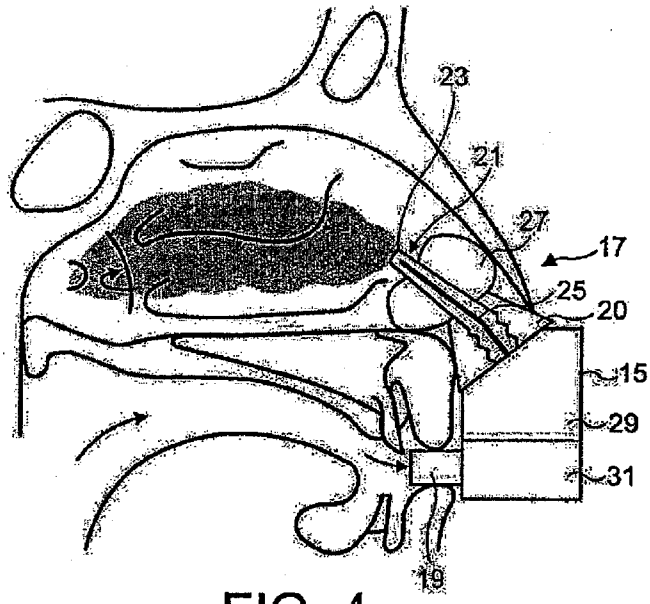

FIG. 4

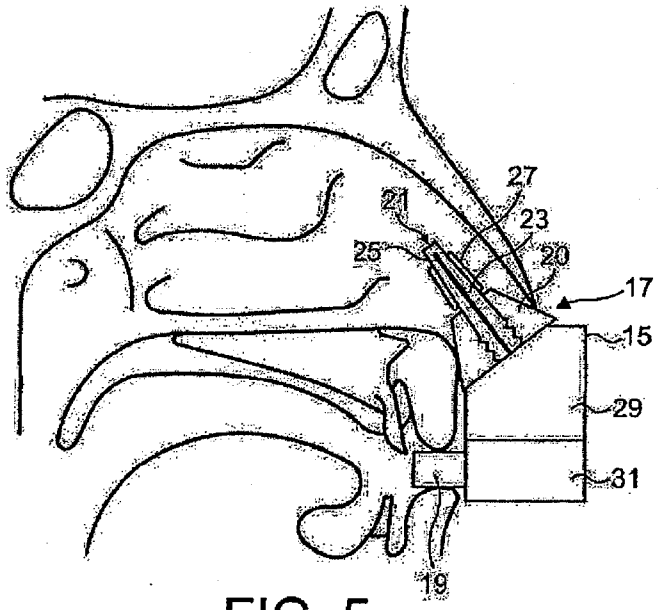

FIG. 5

2008202441 02 Jun 2008

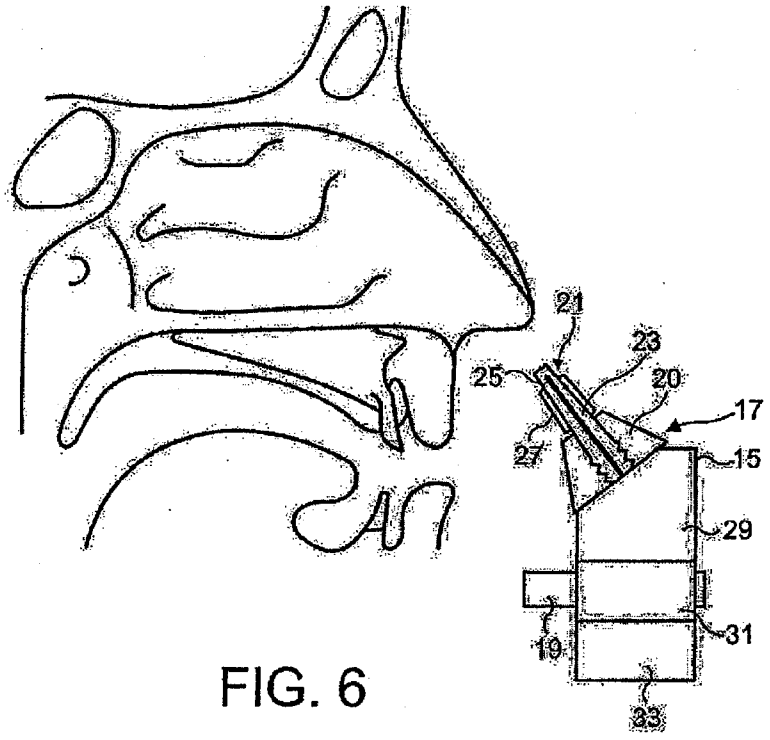

FIG. 6

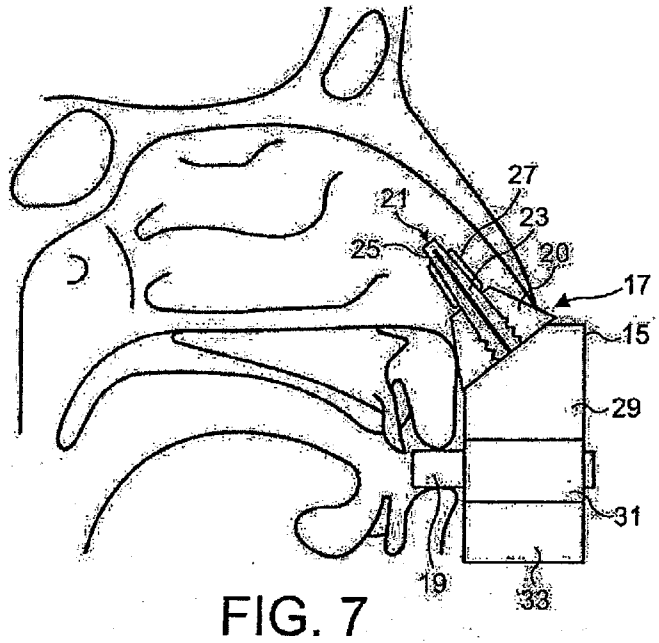

FIG. 7

2008202441 02 Jun 2008

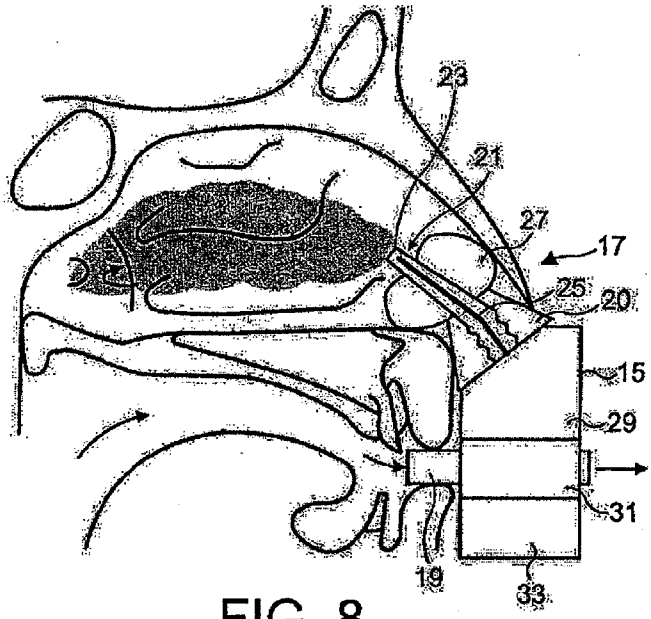

FIG. 8

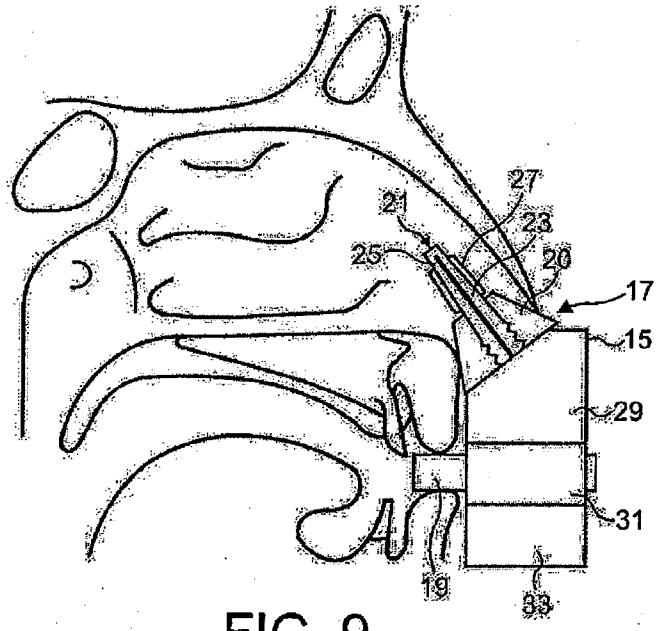

FIG. 9

2008202441 02 Jun 2008

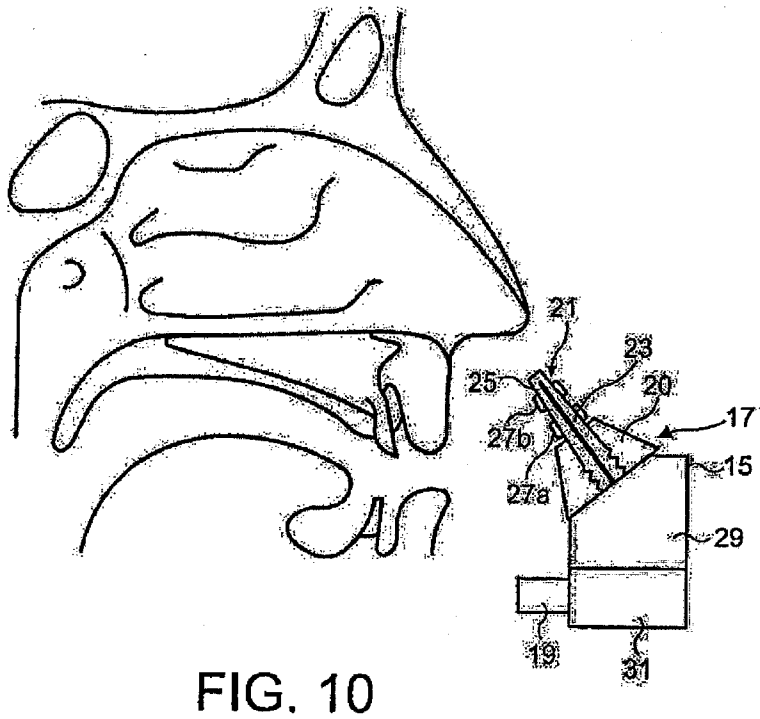

FIG. 10

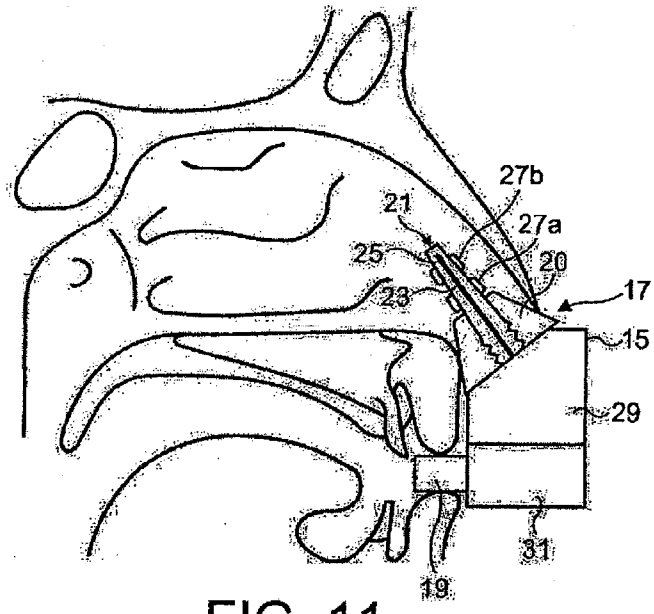

FIG. 11

2008202441 02 Jun 2008

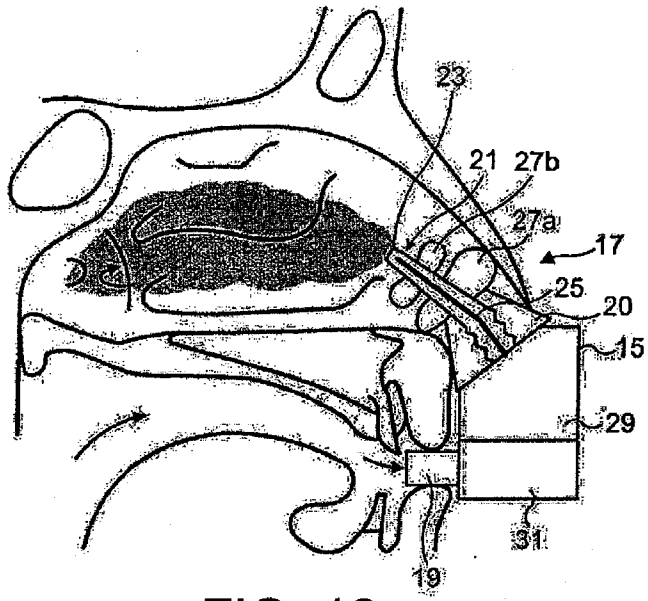

FIG. 12

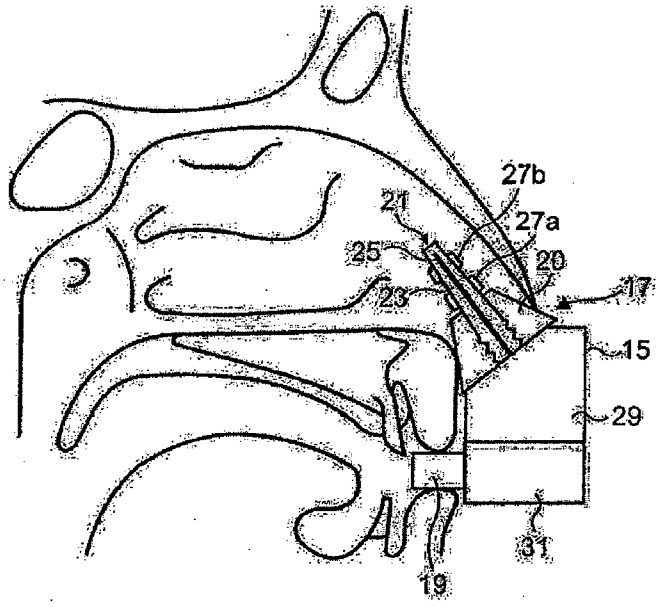

FIG. 13

2008202441 02 Jun 2008

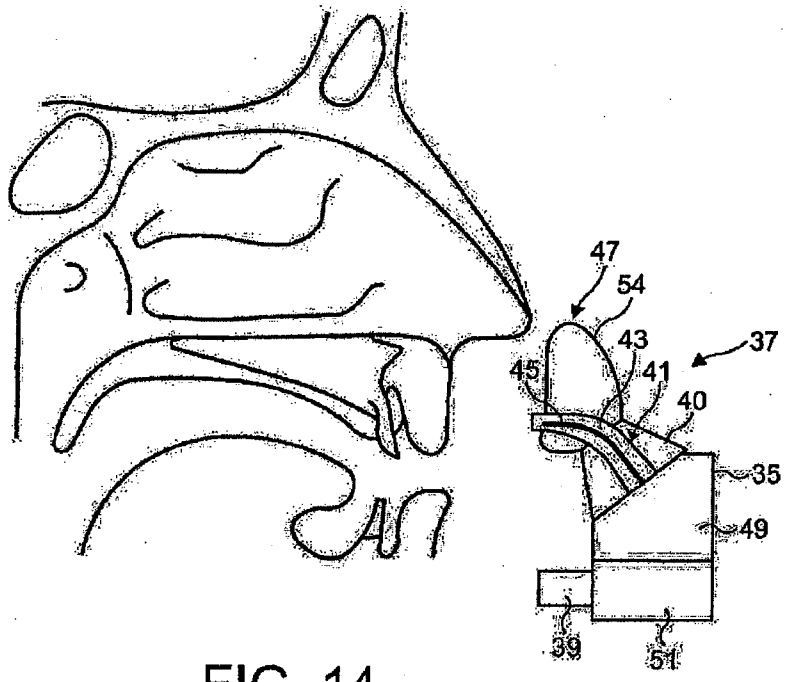

FIG. 14

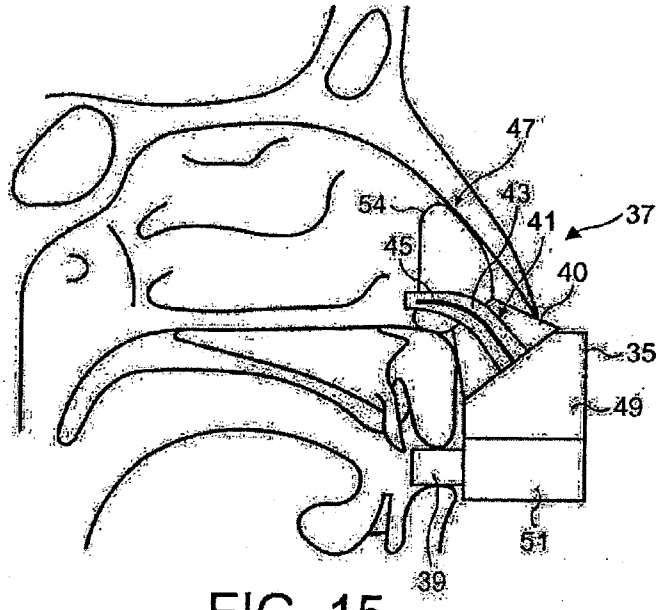

FIG. 15

2008202441 02 Jun 2008

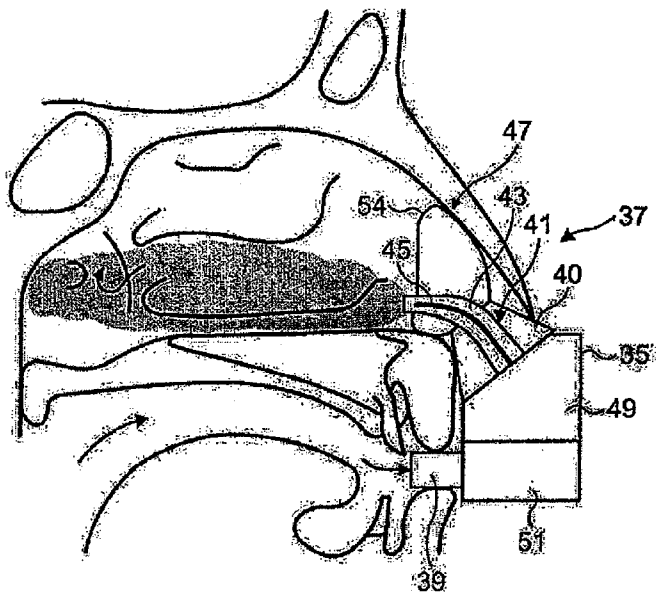

FIG. 16

2008202441 02 Jun 2008

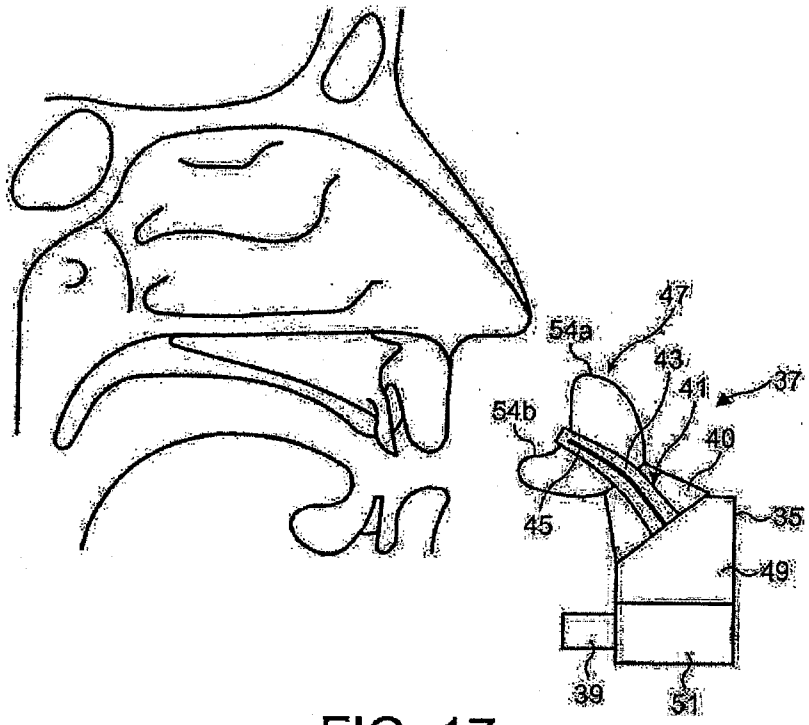

FIG. 17

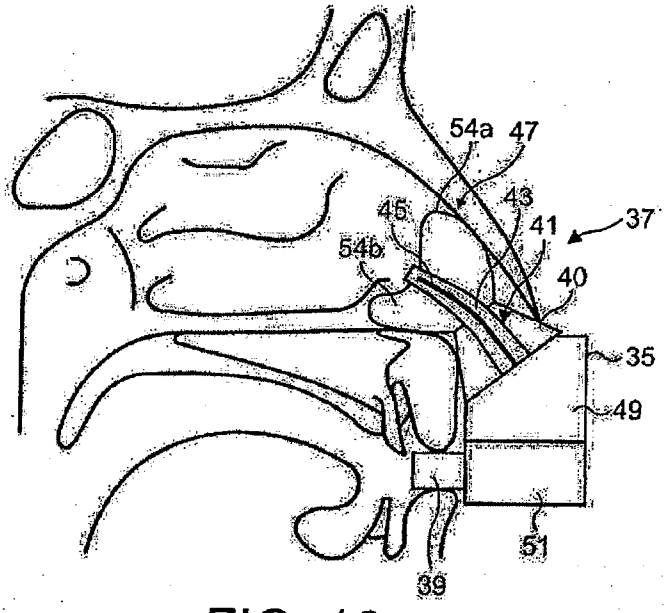

FIG. 18

2008202441 02 Jun 2008

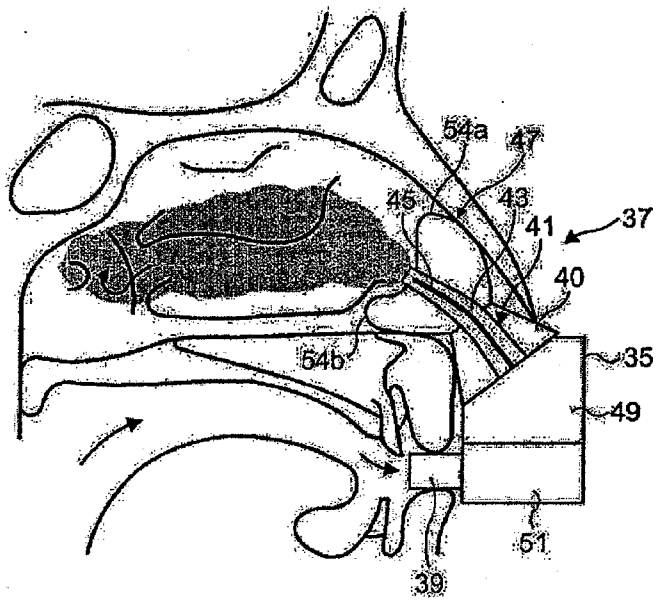

FIG. 19

2008202441 02 Jun 2008

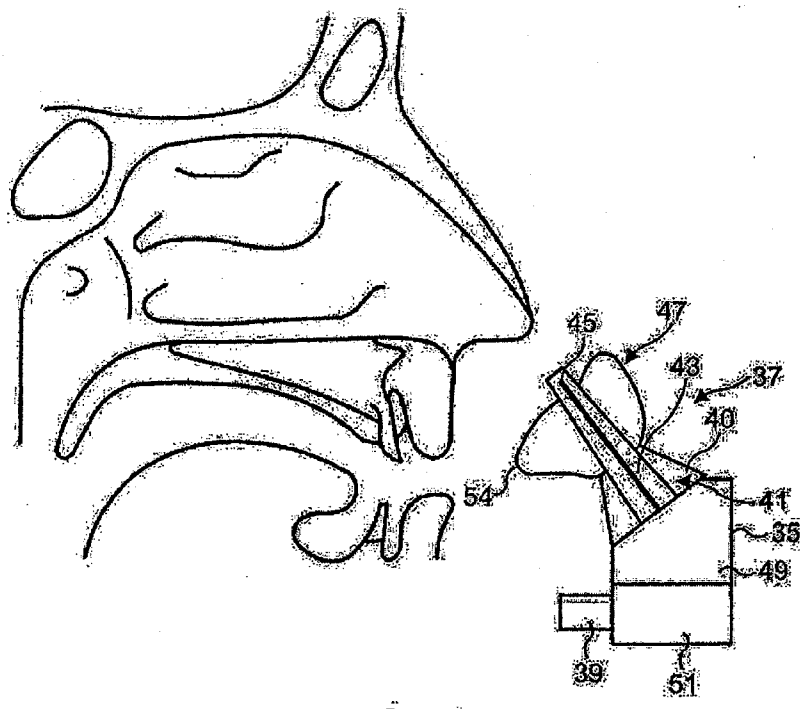

FIG. 20

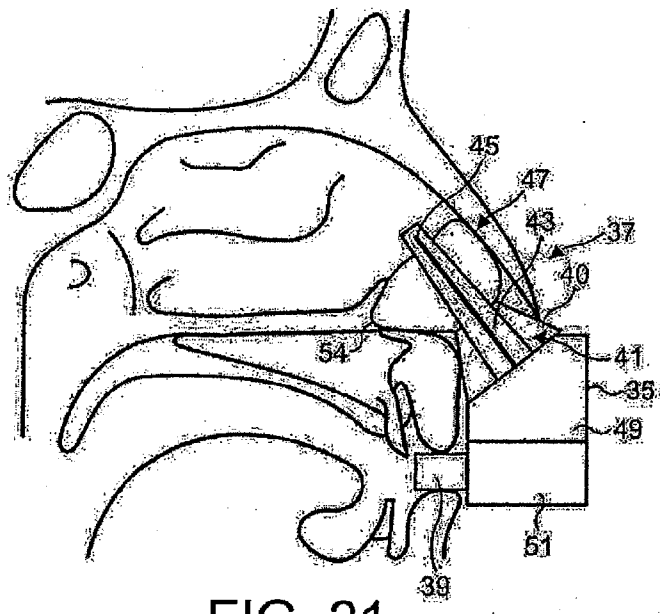

FIG. 21

2008202441 02 Jun 2008

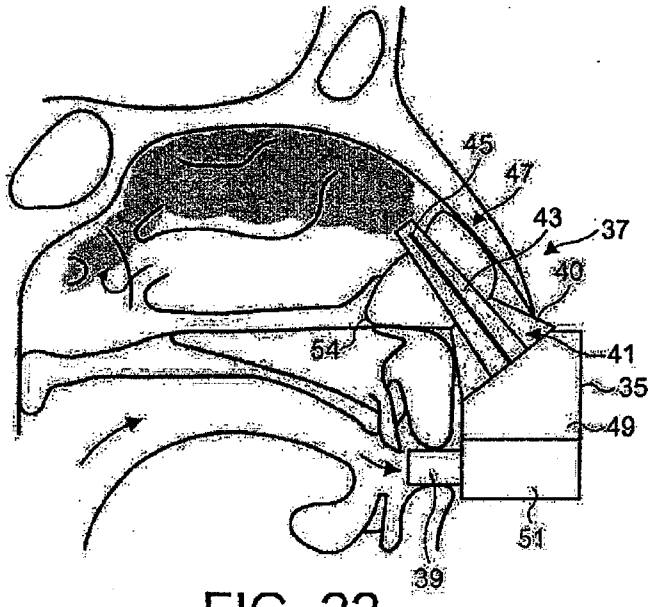

FIG. 22

2008202441 02 Jun 2008

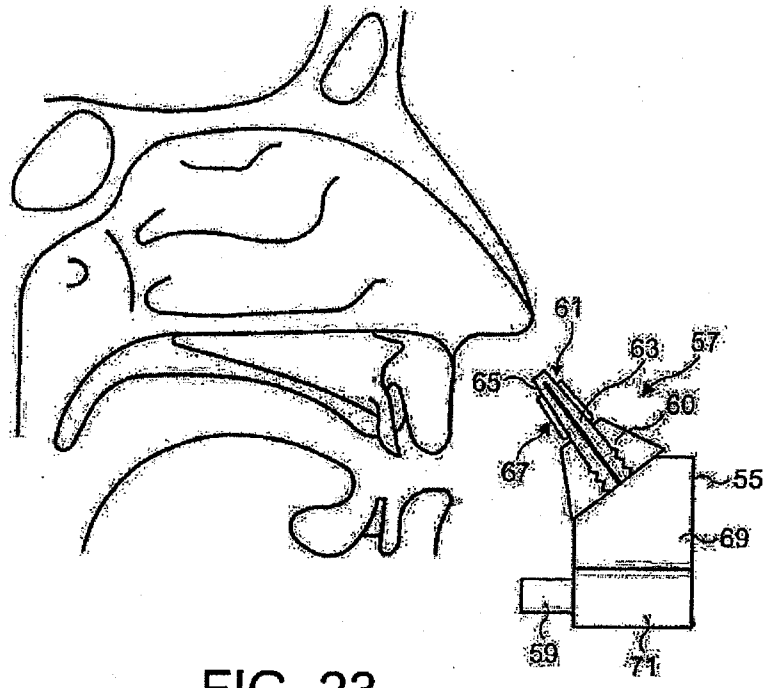

FIG. 23

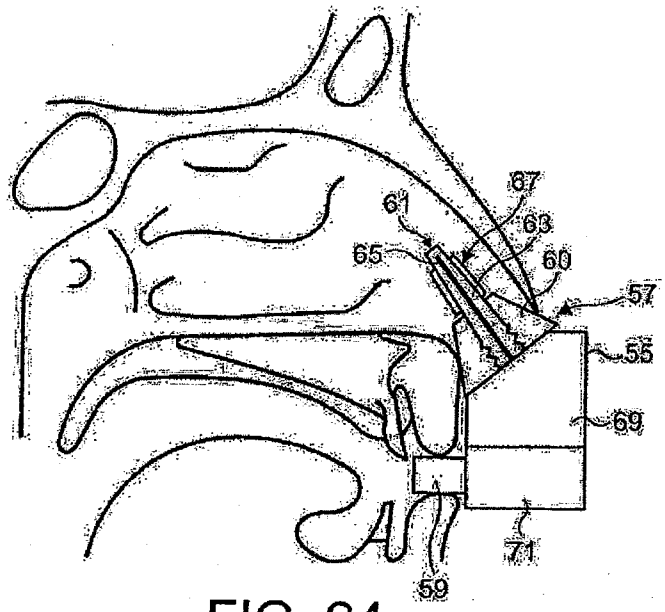

FIG. 24

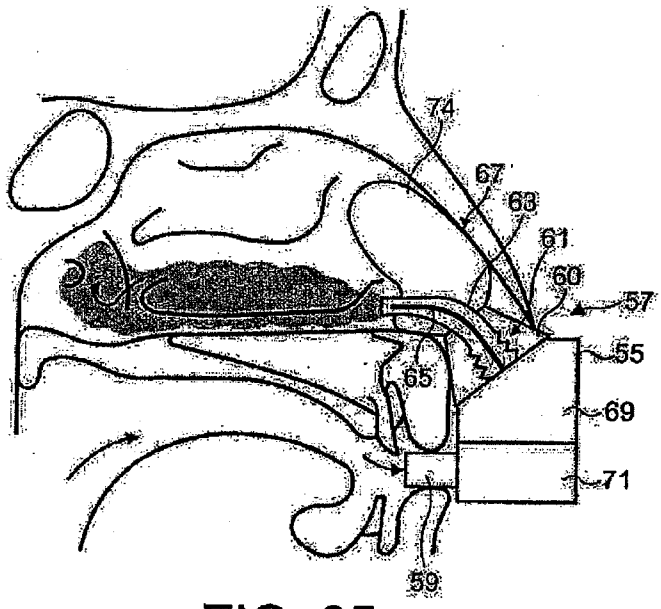

FIG. 25

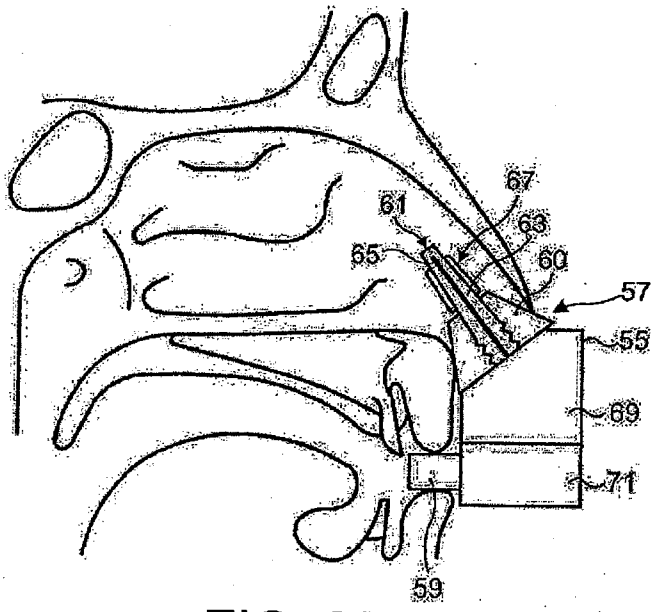

FIG. 26

2008202441 02 Jun 2008

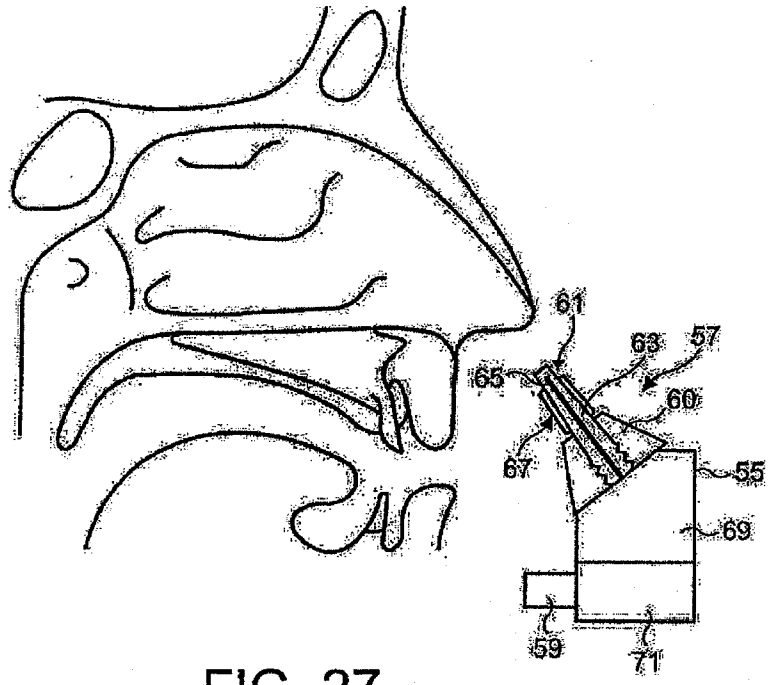

FIG. 27

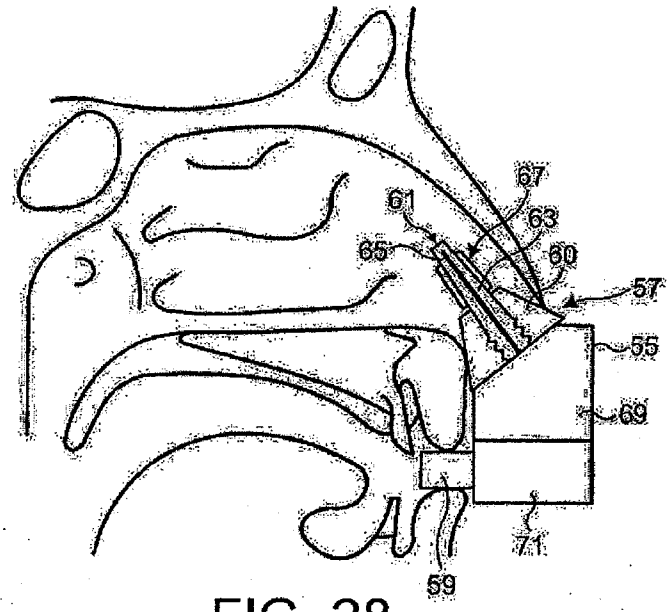

FIG. 28

2008202441 02 Jun 2008

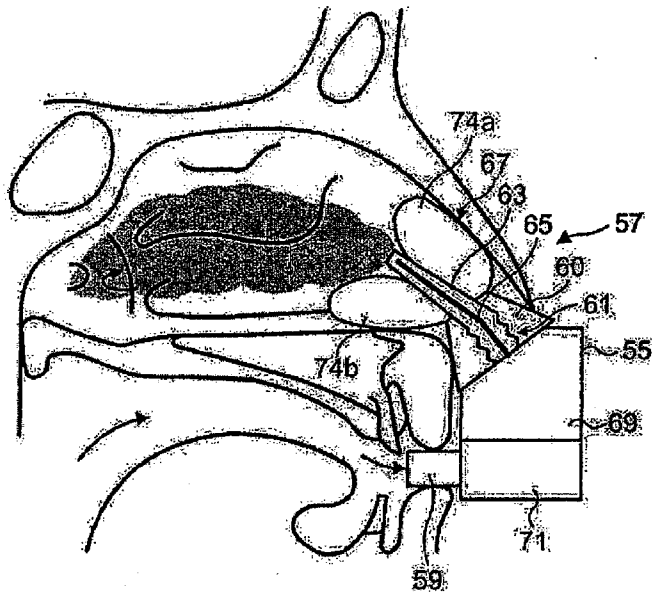

FIG. 29

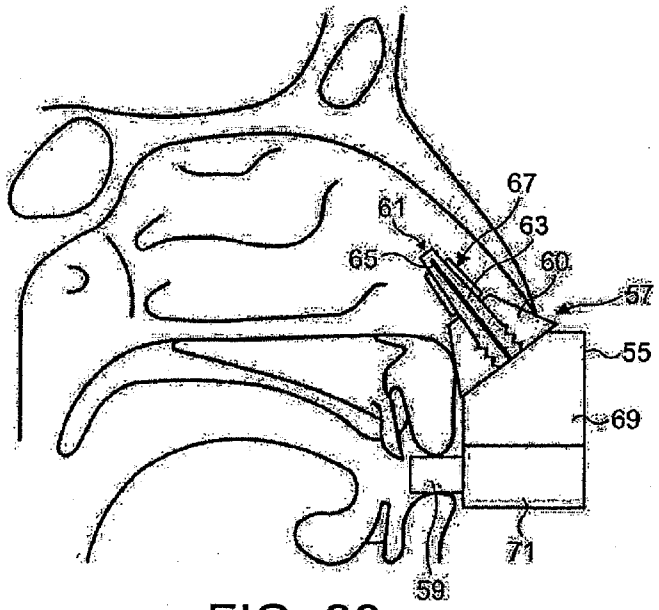

FIG. 30

2008202441 02 Jun 2008

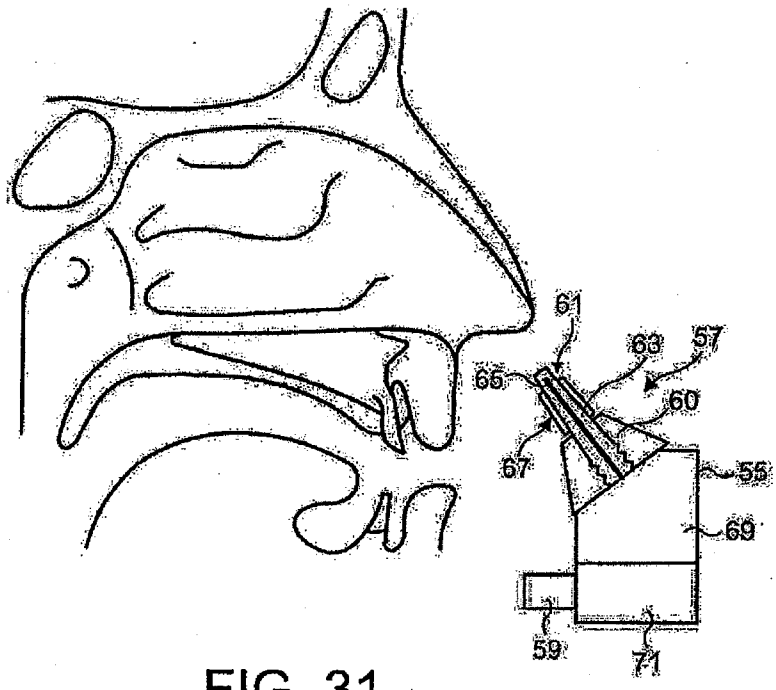

FIG. 31

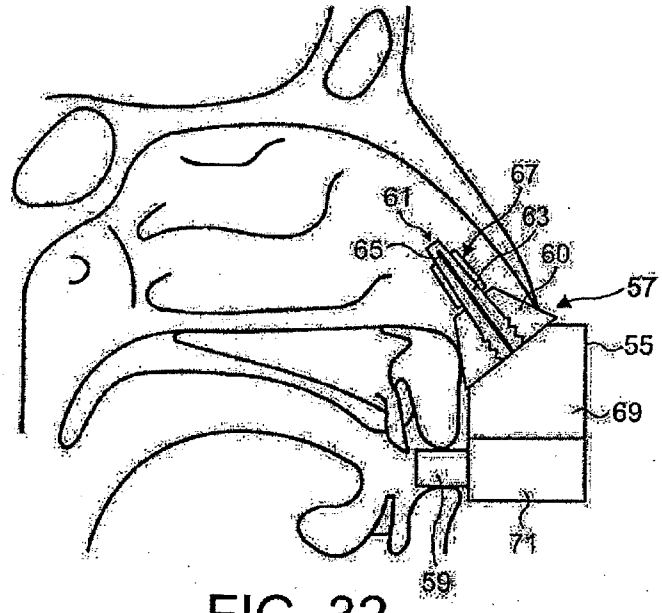

FIG. 32

2008202441 02 Jun 2008

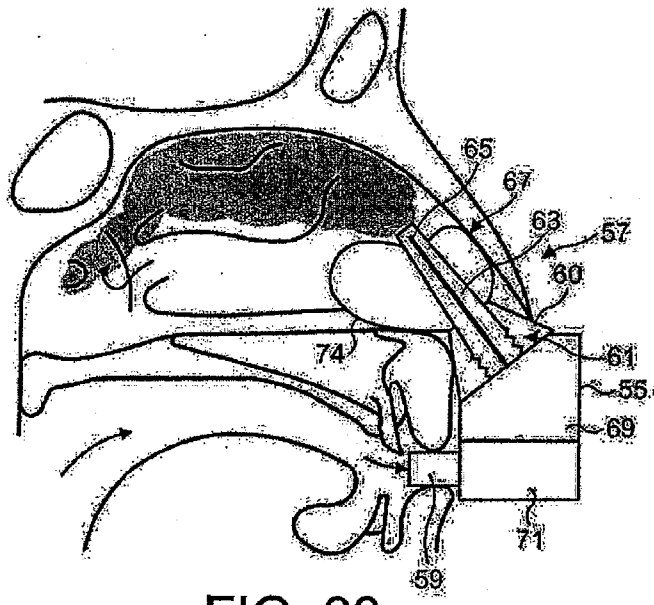

FIG. 33

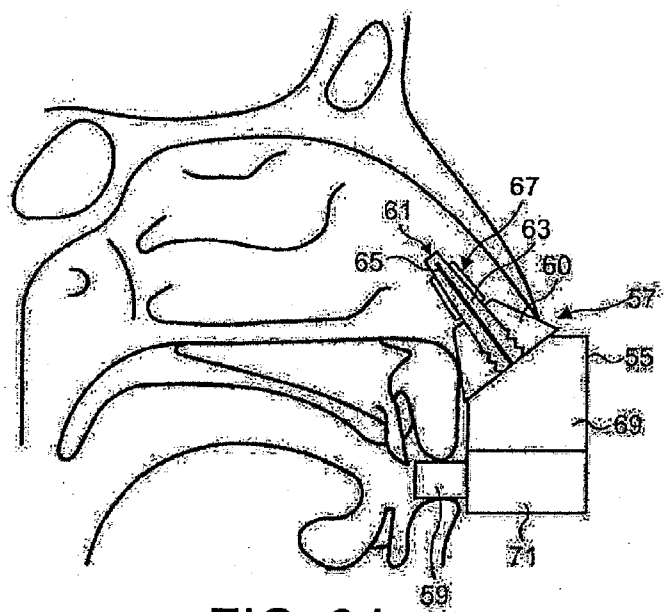

FIG. 34

2008202441 02 Jun 2008

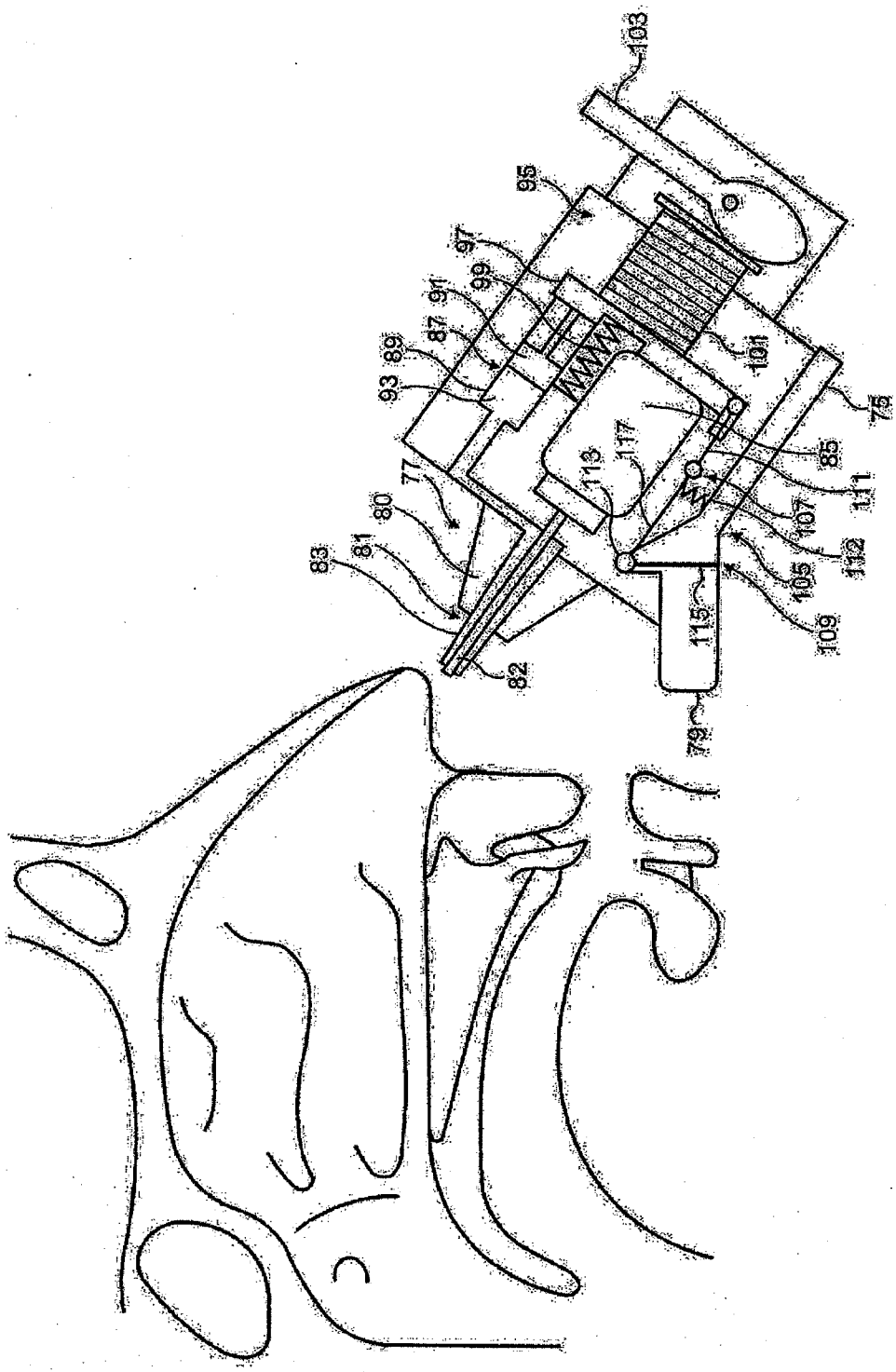

FIG. 35

2008202441 02 Jun 2008

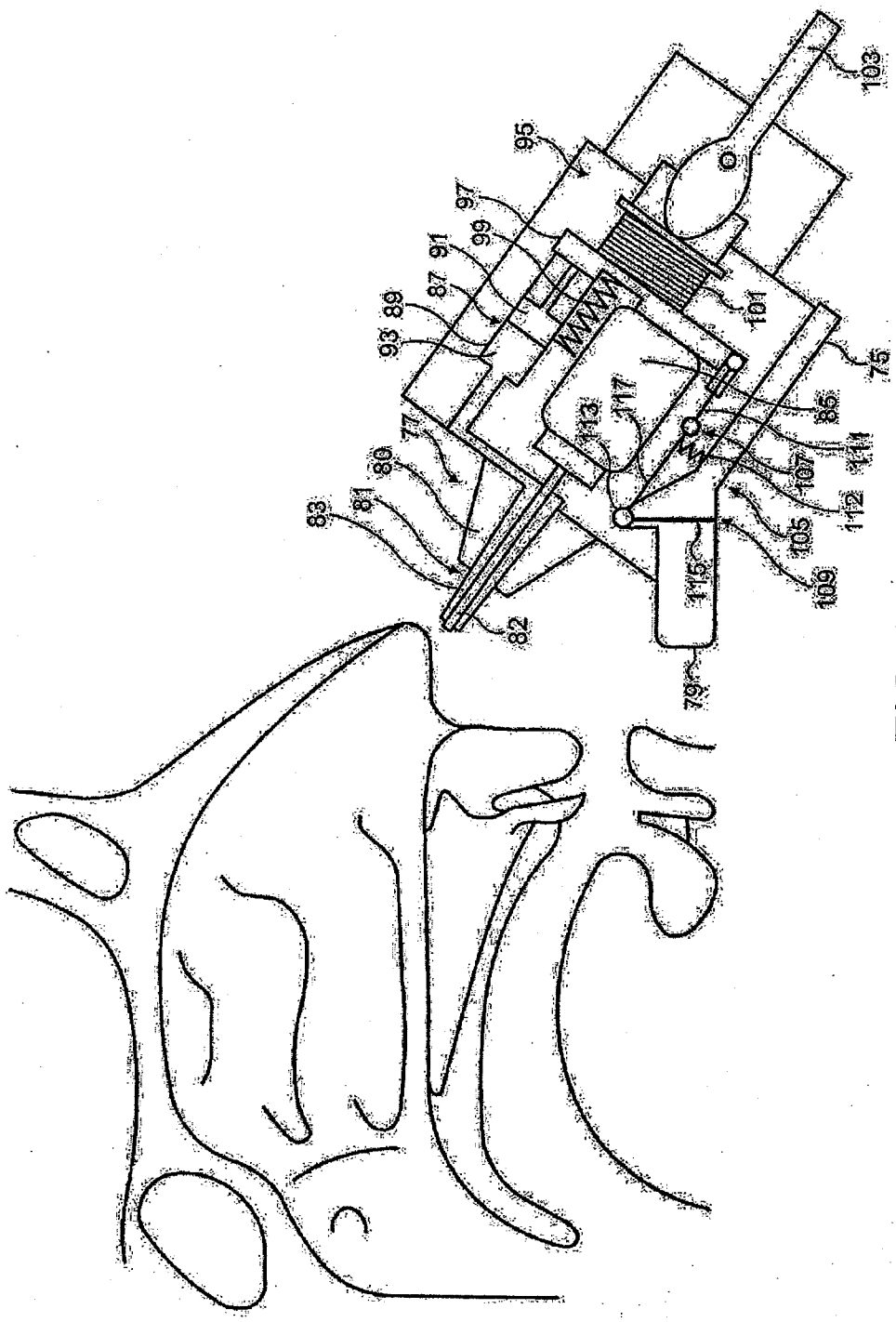

FIG. 36

2008202441 02 Jun 2008

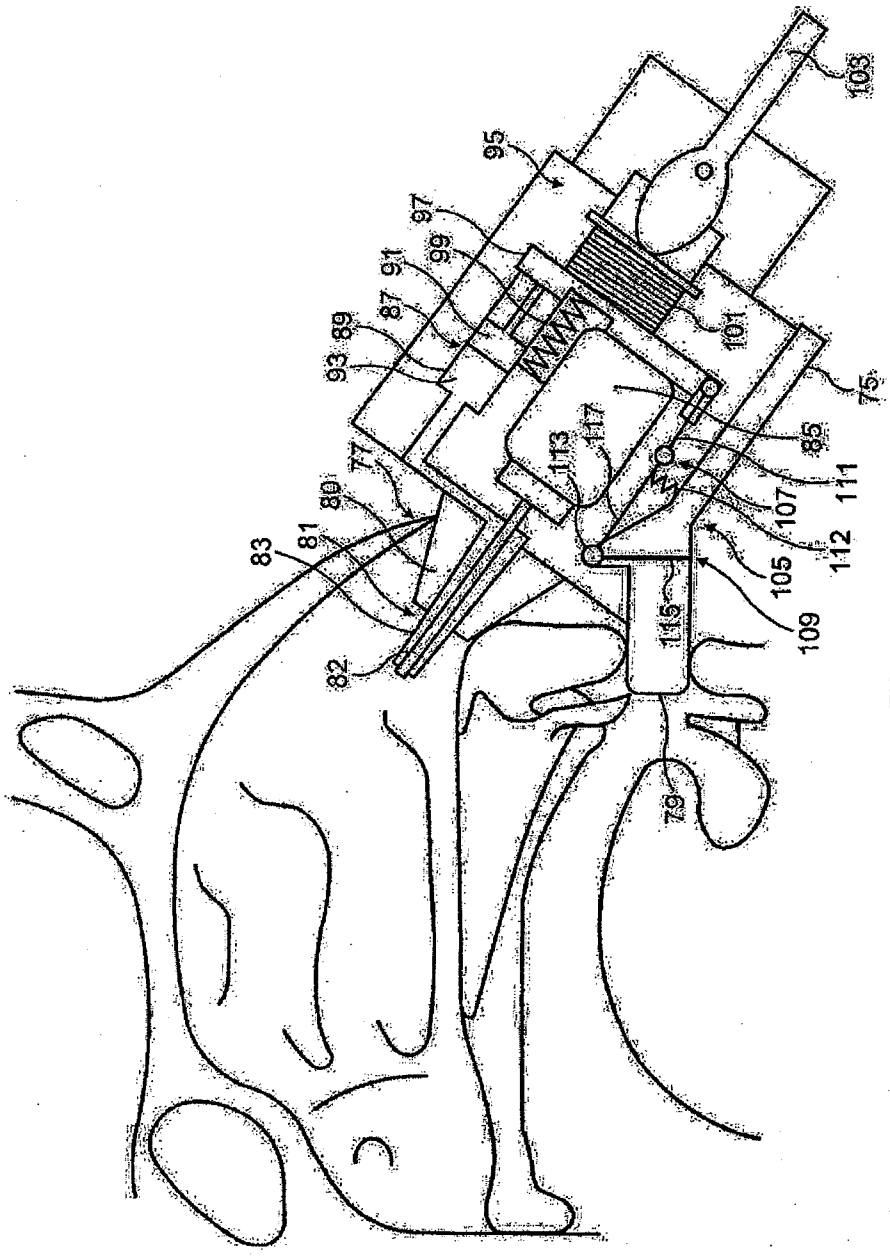

FIG. 37

2008202441 02 Jun 2008

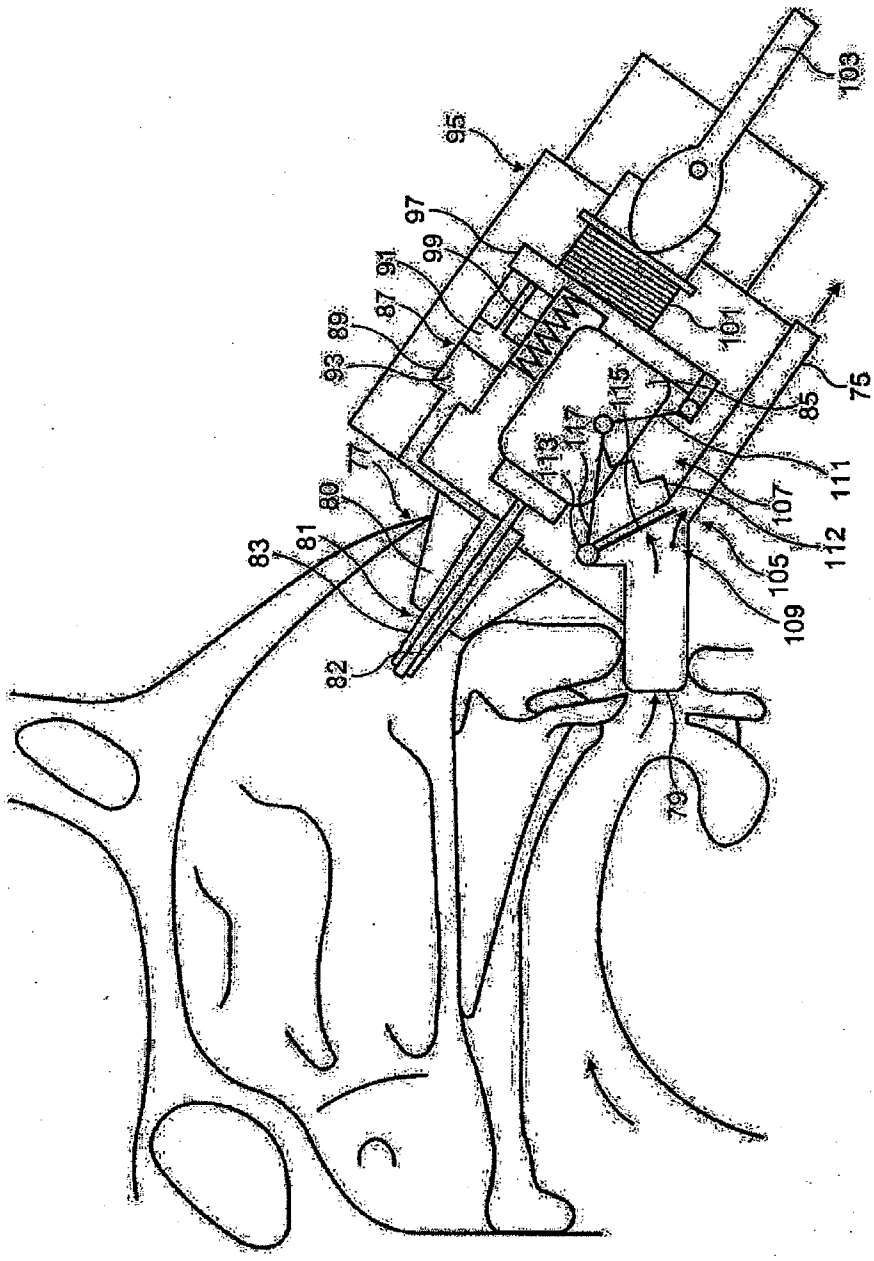

FIG. 38

2008202441 02 Jun 2008

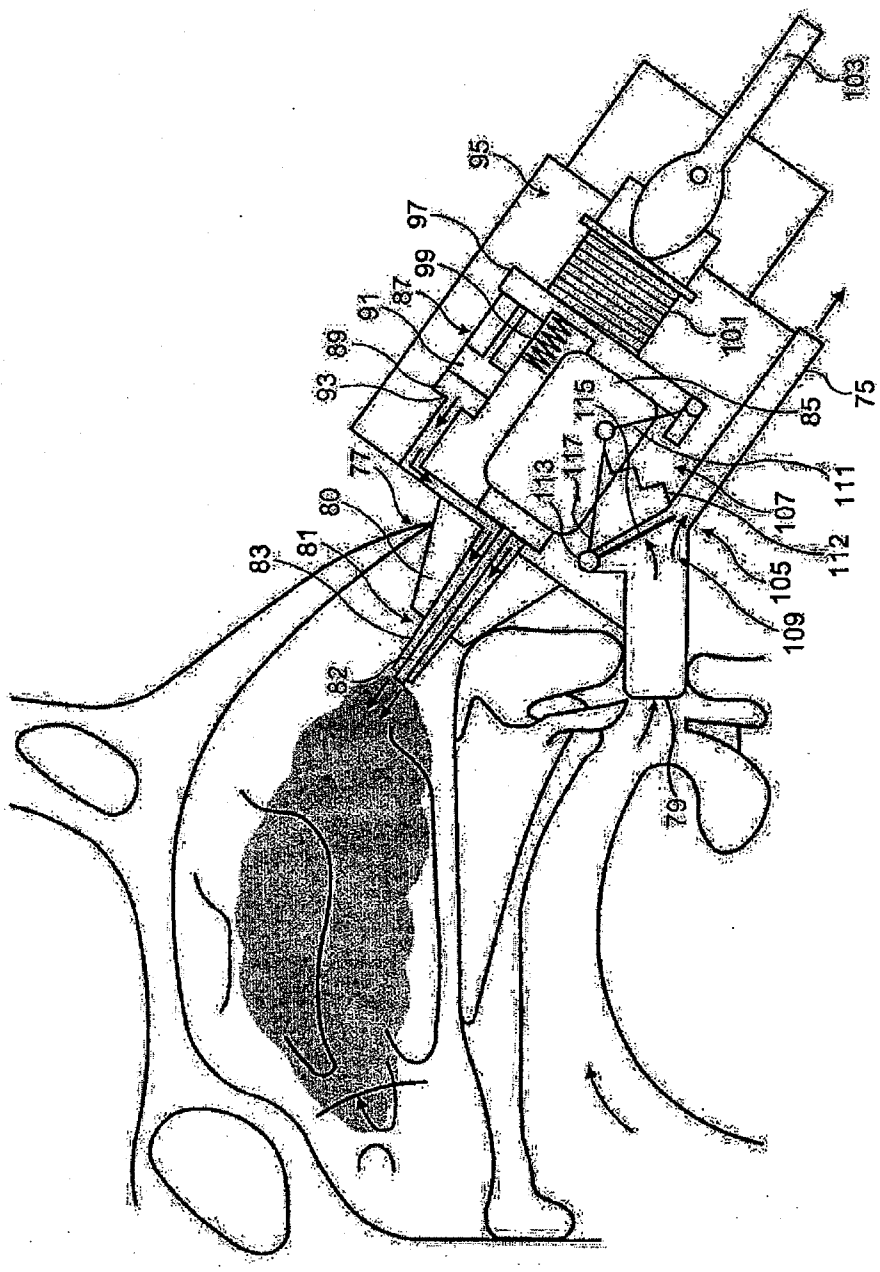

FIG. 39

2008202441 02 Jun 2008

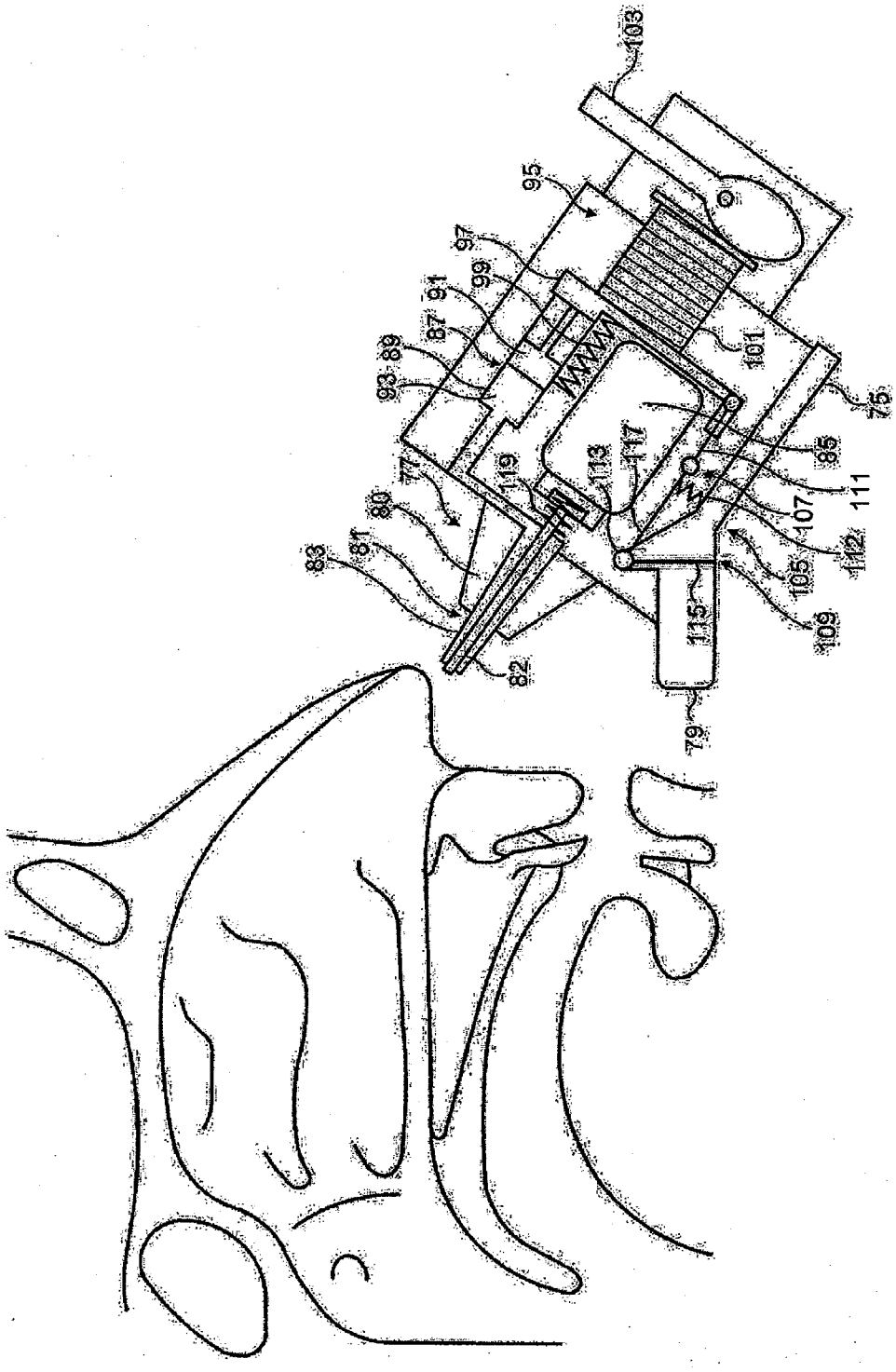

FIG. 40

2008202441 02 Jun 2008

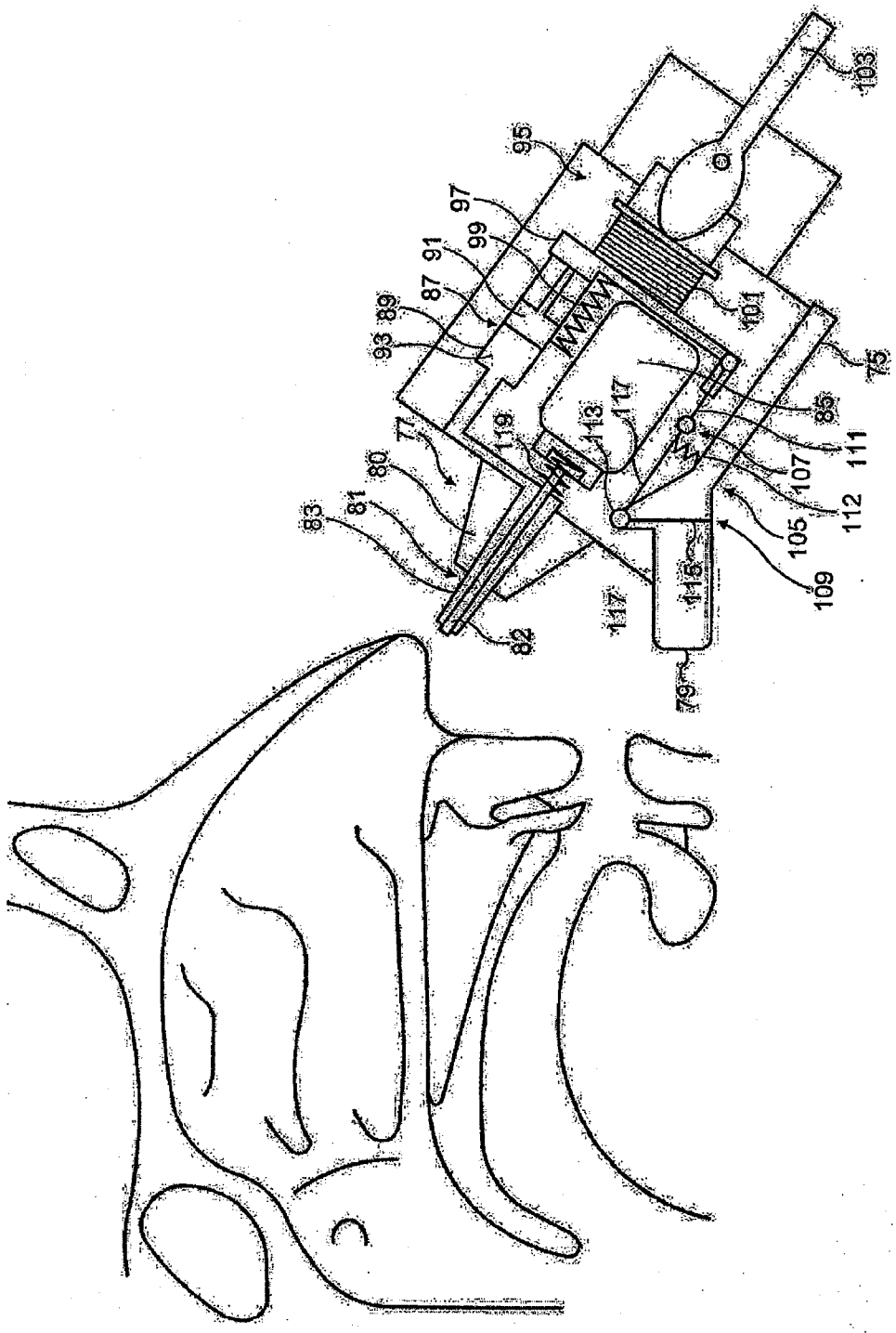

FIG. 41

2008202441 02 Jun 2008

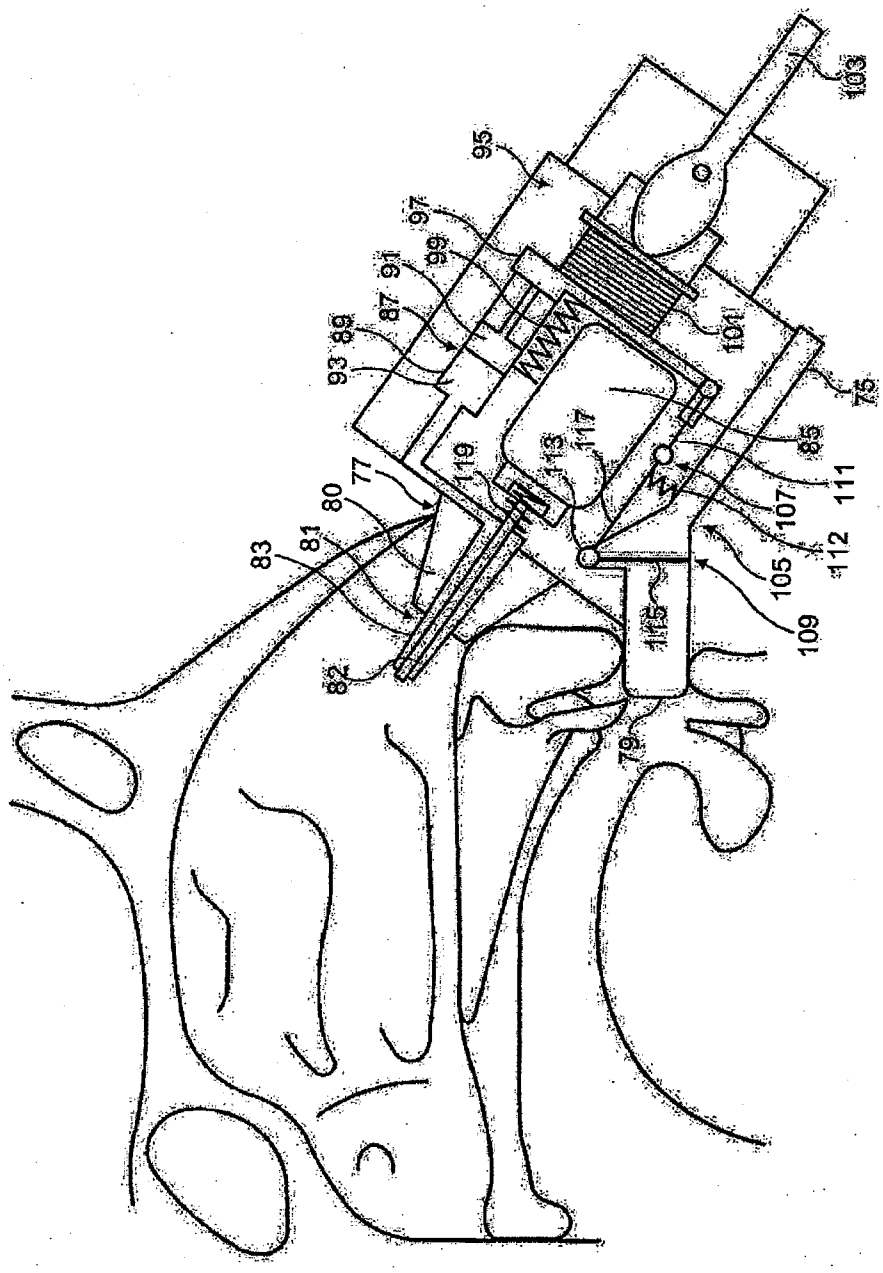

FIG. 42

2008202441 02 Jun 2008

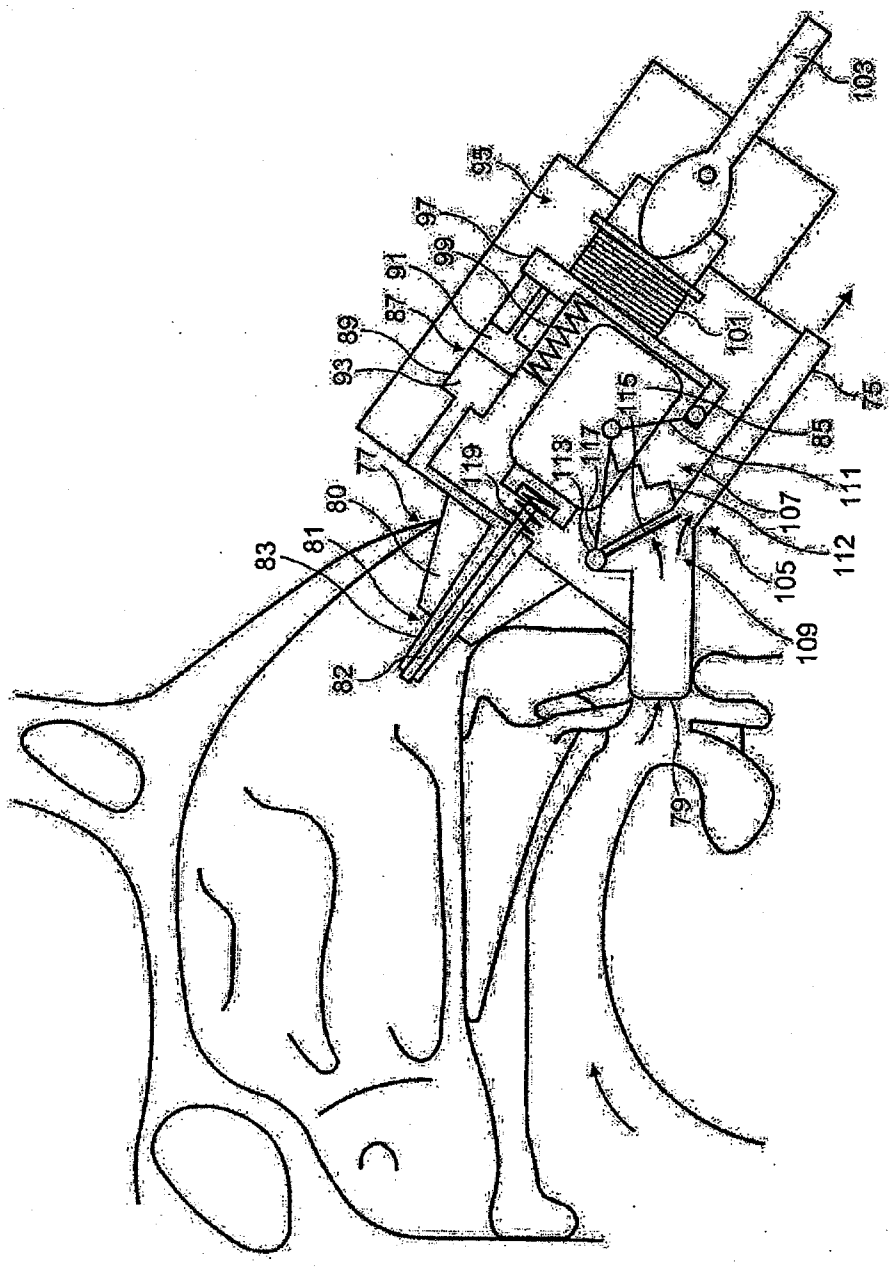

FIG. 43

2008202441 02 Jun 2008

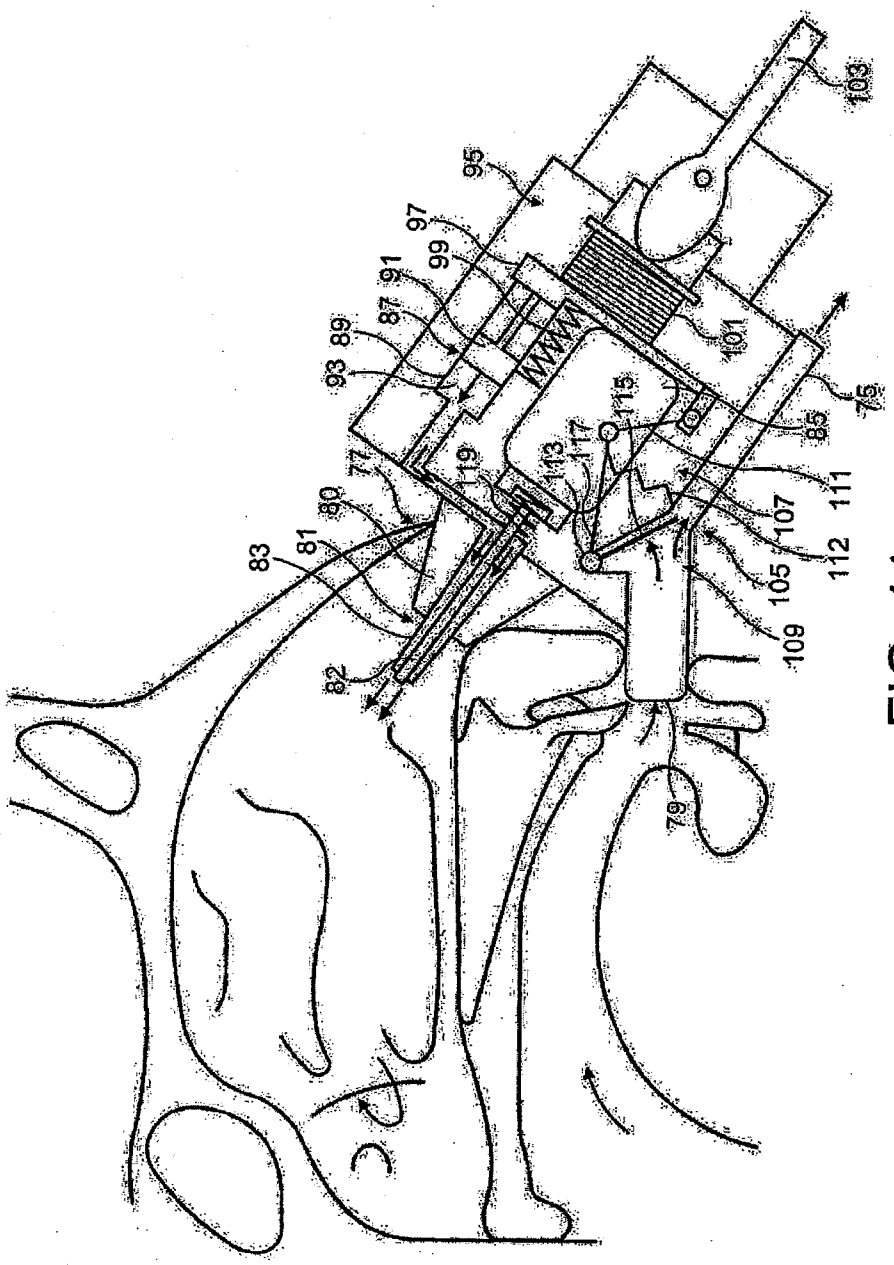

FIG. 44

2008202441 02 Jun 2008

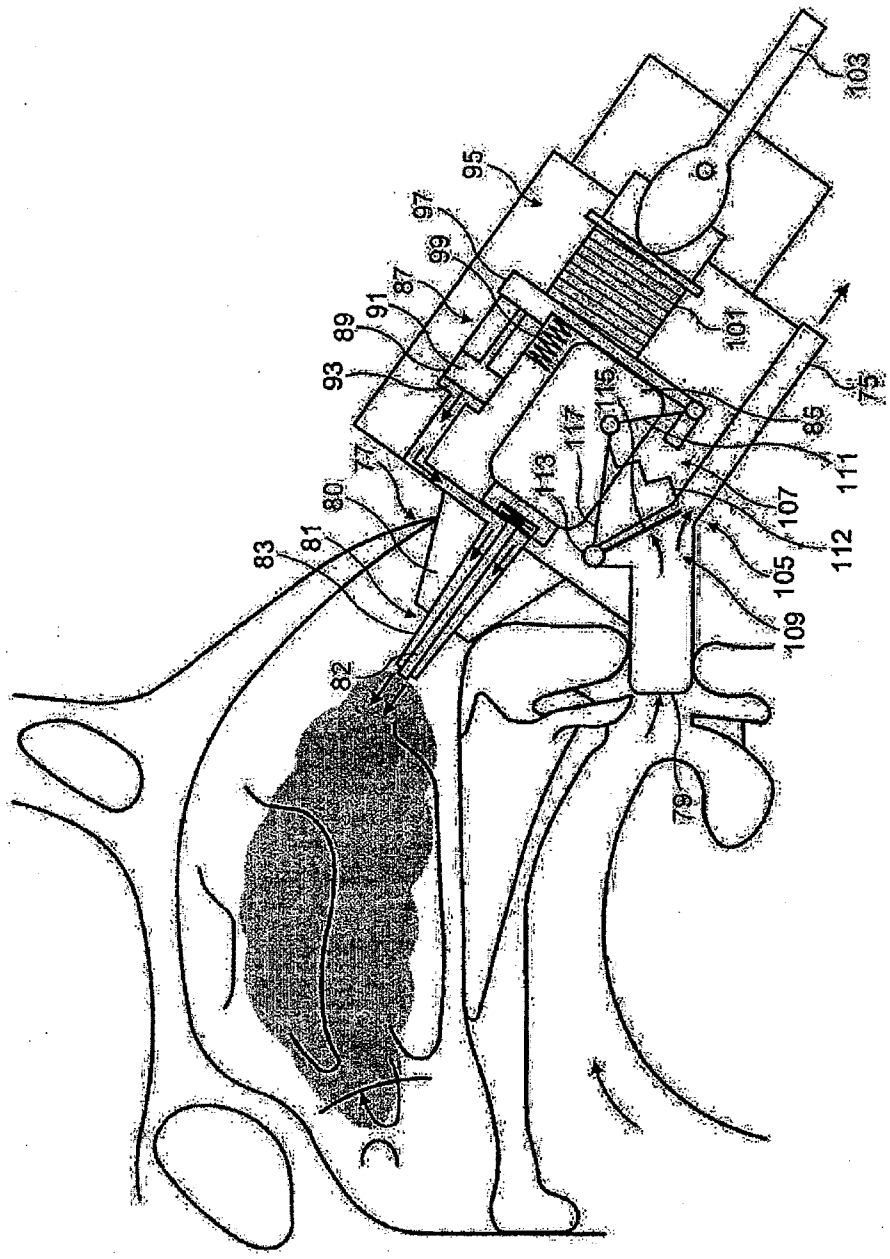

FIG. 45

2008202441 02 Jun 2008

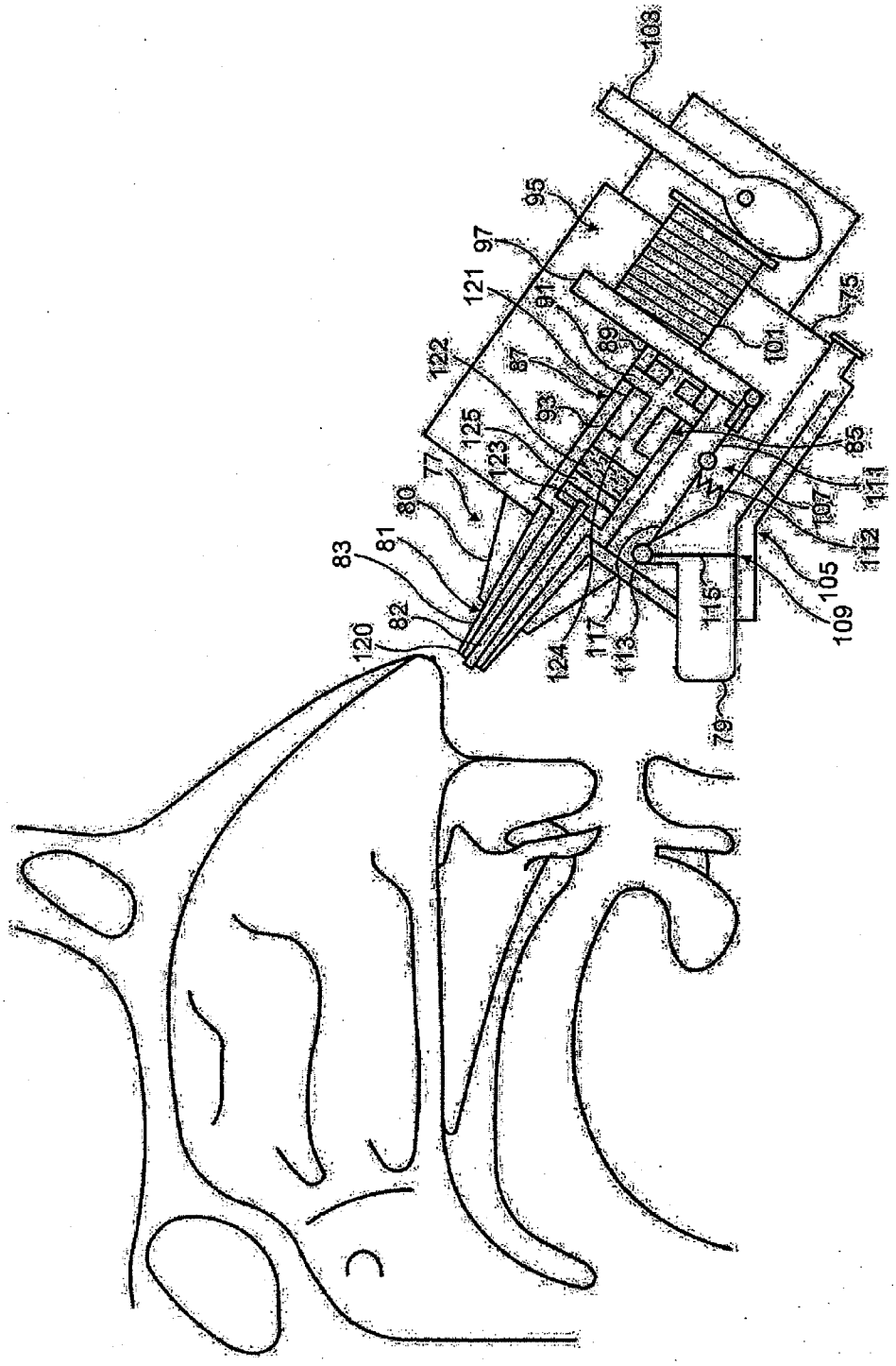

FIG. 46

2008202441 02 Jun 2008

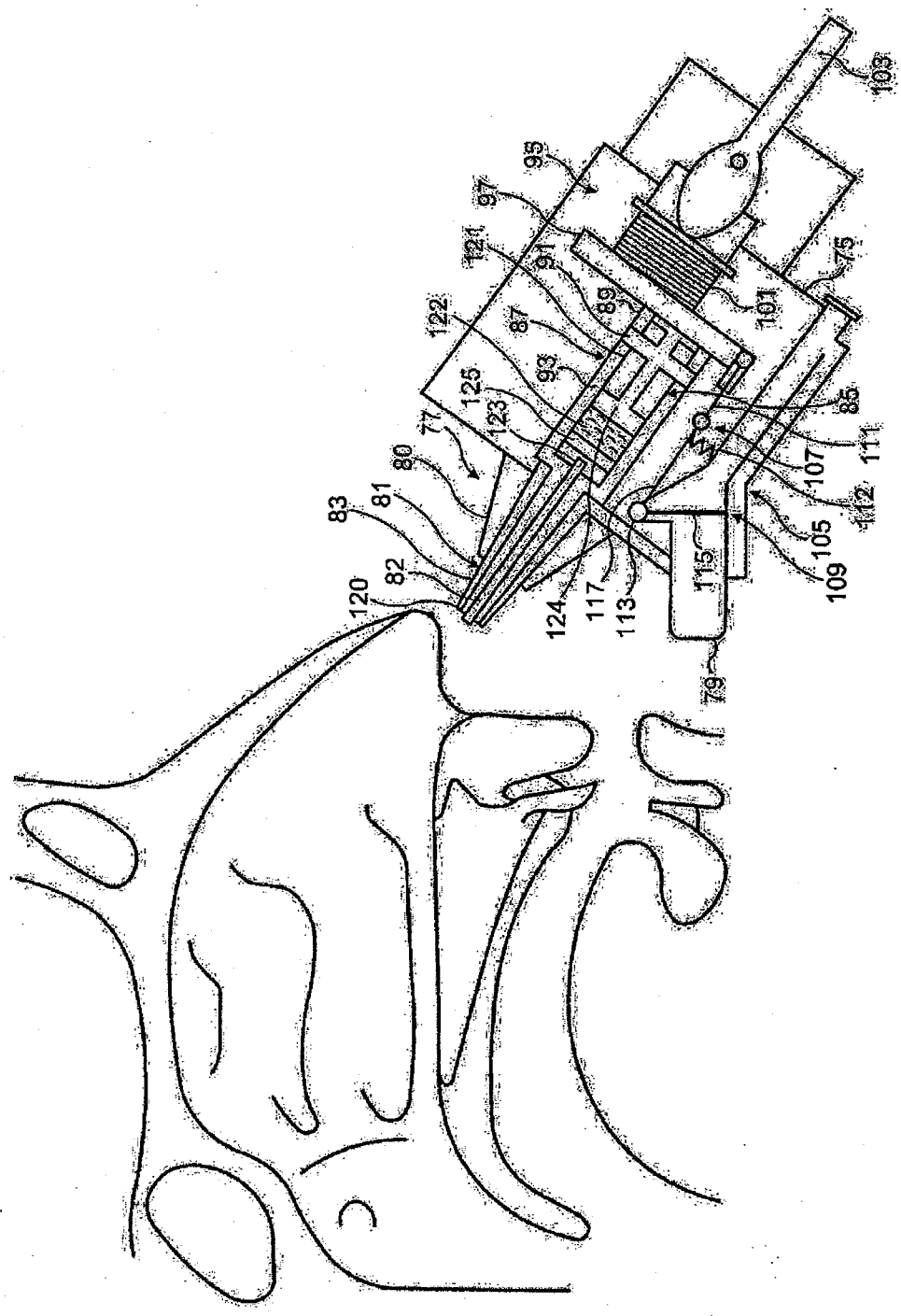

FIG. 47

2008202441 02 Jun 2008

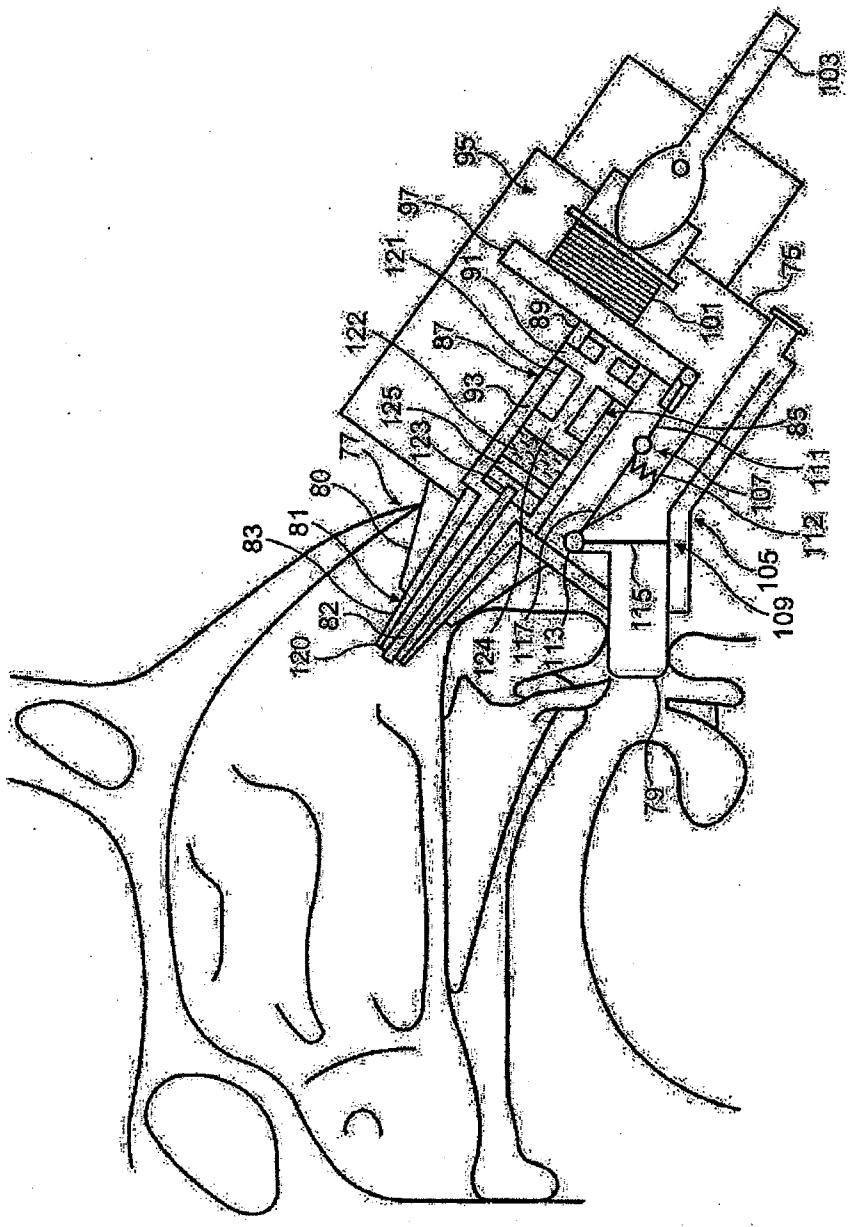

FIG. 48

2008202441 02 Jun 2008

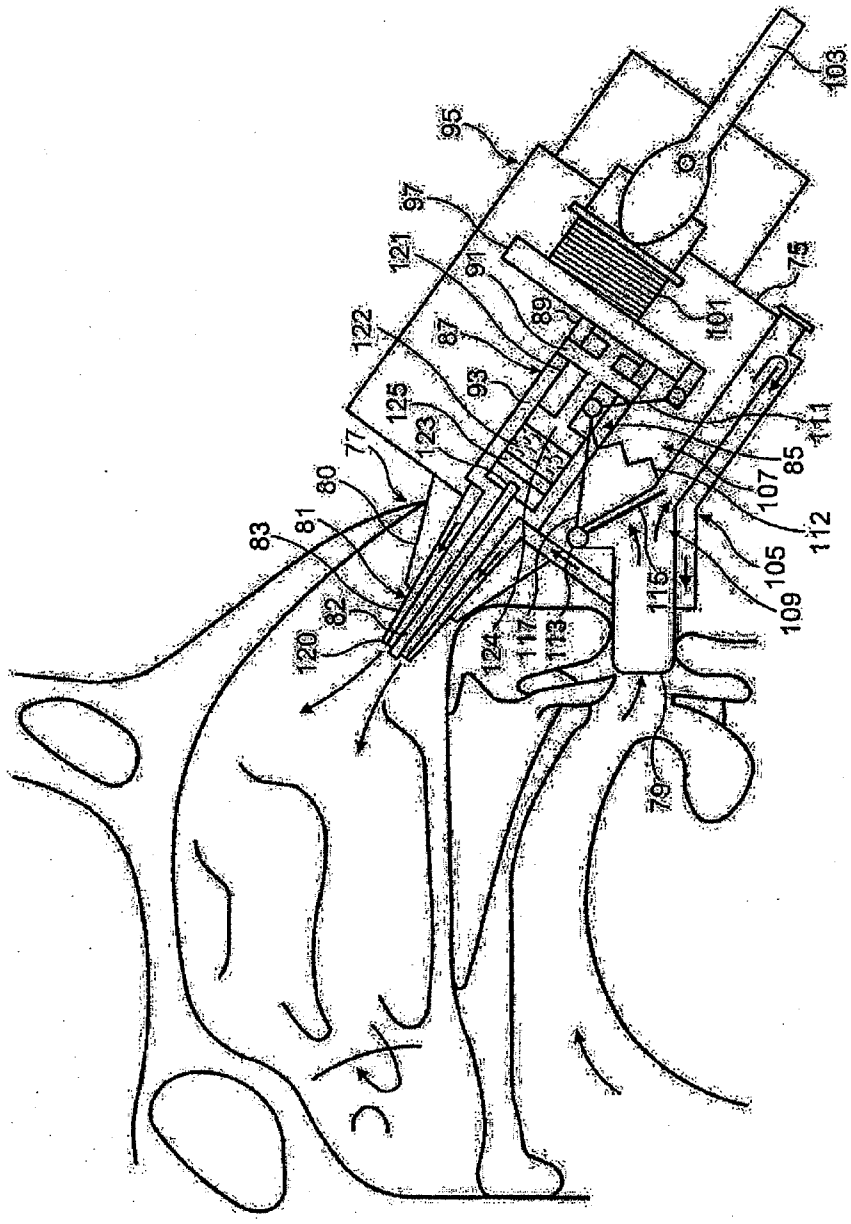

FIG. 49

2008202441 02 Jun 2008

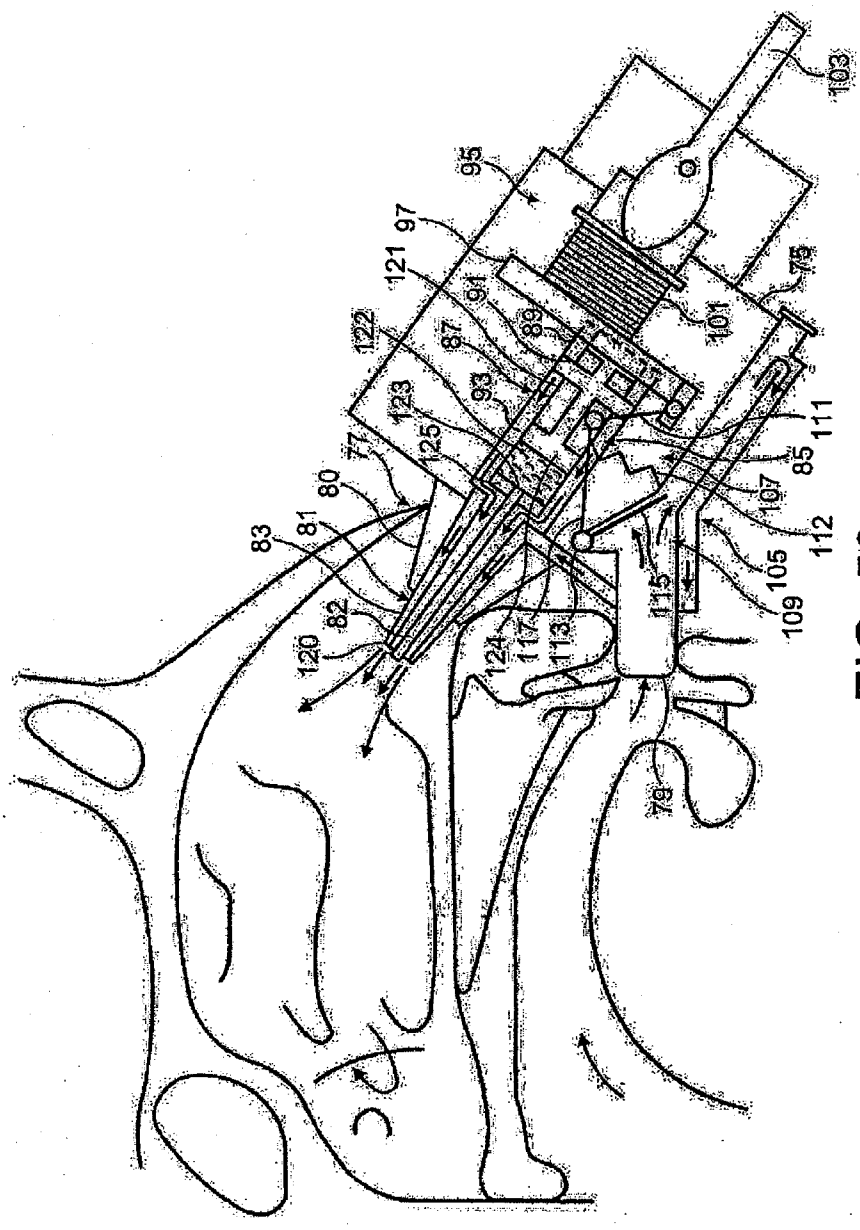

FIG. 50

2008202441 02 Jun 2008

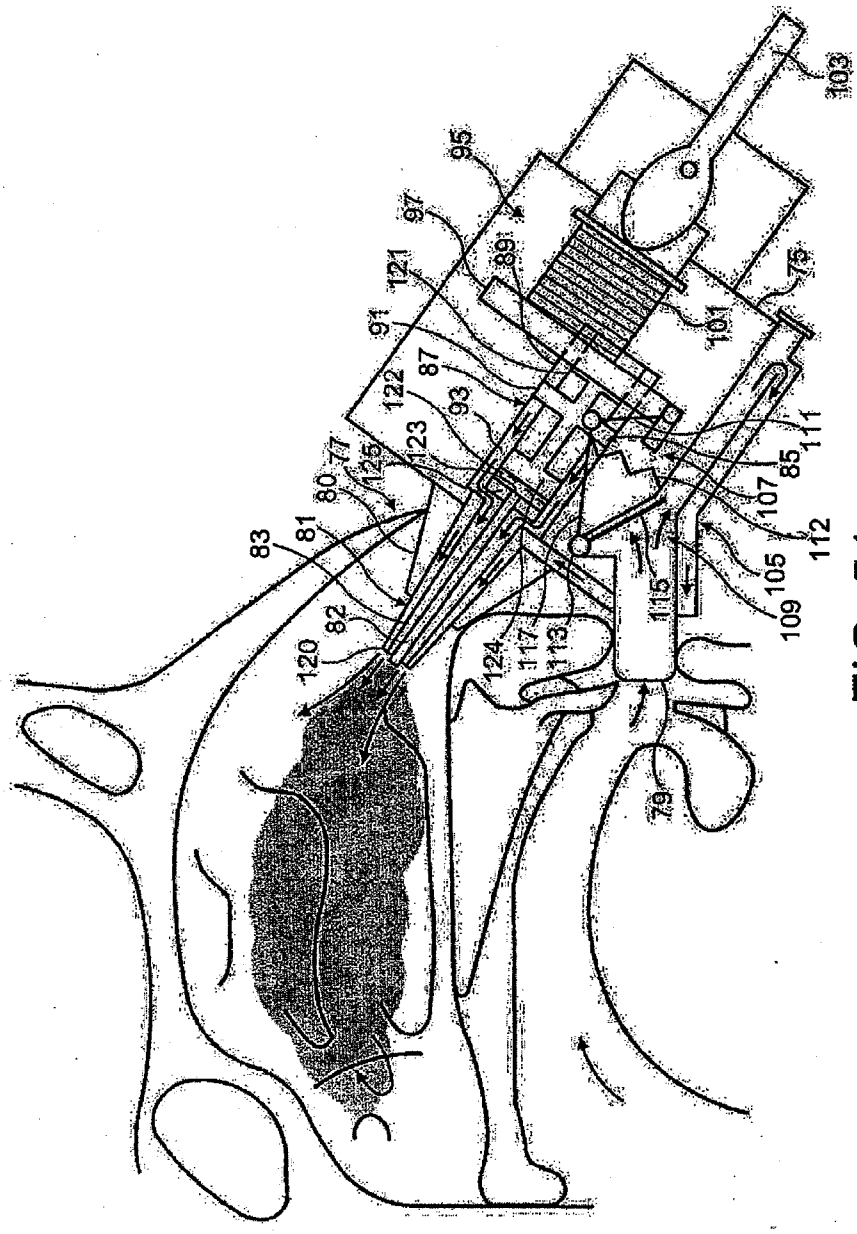

FIG. 51