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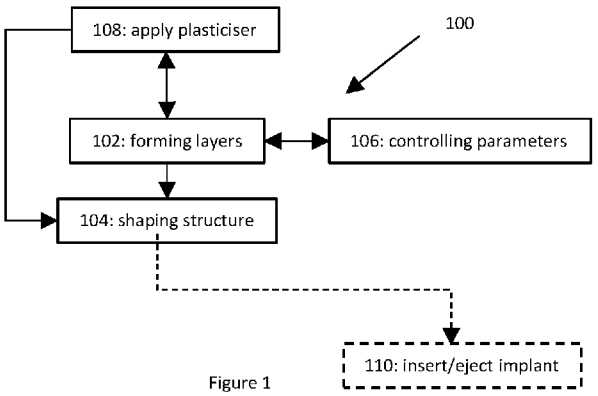



Figure 1

(57) Abstract: Disclosed is a implant for supporting a nasal passage. The implant includes a proximal end and a distal end extending from the proximal end, the distal end being expandable to support a nasal passage. In some embodiments, the distal end comprises a supporting 5 bridge to assist expansion of the distal end.

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# Nasal Implants And Methods For Production Of Nasal Implants

## Field of Invention

The present invention relates to an implant for supporting the nose, particularly the internal nasal valve of the nose. The present invention also relates to a method for forming such an implant.

## Background

In recent years, attention has been paid to correcting misshapen nasal septa. The nasal septum is the cartilage in the nose that separates the nostrils. Typically, it sits at the centre and divides the nostrils evenly. However, many people have an uneven nasal septum, which makes one nostril larger than the other. Severe unevenness is known as a deviated nasal septum. It can cause health complications such as a blocked nostril or difficulty breathing.

Deviated nasal septa can result from injury to the nose or a congenital defect. Such defects can result in people having different nasal orifice sizes, shape of the nose, and shape of the nasal passages or airways, depending on the size of the nose and the shape of cartilage. A deviated nasal septum can also worsen with age.

The internal nasal orifice and its pathway can be one of the narrowest passages which may affect the airway flow. A large percentage of inspiratory resistance is attributable to misshapen internal nasal orifice shape. Collapse of support in one or both internal nasal orifices is a common cause of nasal airway obstruction. This may lead to difficulty in respiration and snoring as well as other breathing related disorders such as sleep apnoea.

Internal nasal inflammation also commonly occurs. It may result in change of shape and can be a consequence of previous surgery, trauma, aging, or primary weakness of the upper or lower lateral cartilage. At times these conditions may be asymptomatic during active hours but cause sleep apnoea when at rest.

Severe deviation can be accompanied by facial pain or frequently have nosebleeds or sinus infections. It may also cause breathing difficulty which affects quality of life. Surgery is usually the main course to correct a deviated nasal septum. The bone and cartilage under the skin give the nose most of its size and shape. Other structures inside and behind the nose help you breathe.

Collapse and weakening of the nasal cartilage can also lead to external deformities and cosmetic changes to the nose. Loss of support and volume of the lower lateral cartilages, mid-nasal portion or the dorsum can lead to undesirable cosmetic changes. Relative tissue defects on the dorsum of the nose may lead to an irregular nasal profile.

It would be desirable to address or alleviate at least one of the above difficulties.

**Summary**

Disclosed herein is an implant for supporting a nasal passage, comprising:

a proximal end;

a distal end extending from the proximal end, the distal end being expandable to support a nasal passage.

The distal end may comprise a supporting bridge to assist expansion of the distal end.

The implant may have a collapsed condition for insertion into the nasal passage, and an expanded condition for supporting the nasal passage. The distal end may be Y-shaped, and

at least the distal end may comprise shape memory material for expanding under warmth, from the collapsed condition to the expanded condition.

An external surface or external surfaces of the distal end may comprise a plurality of layers, and at least one layer may comprise a pharmaceutical compound for delivery to tissue of the nasal passage.

The implant may be formed from one or more of acrylic (PMMA), acrylonitrile butadiene styrene (ABS), nylon polyamide (PA), polyethyelene (PE), PLA, Polycaprolactone, L-lactide/caprolactone copolymer, Nylon, Polytetrafluoroethylene (Teflon) and thermoplastic polyurethanes (TPU).

Disclosed herein is a method of producing an implant for supporting a nasal passage, comprising:

forming a structure comprising a plurality of layers, the plurality of layers having at least an internal layer and an external layer and at least one of the internal layer and external layer comprises a shape memory material, wherein the internal layer and external layer are formed from a respective polymer having respectively different intrinsic viscosity (IV);

shaping the structure such that the shape memory material will assume a predetermined shape when positioned in the nasal passage.

In other words, the layers are formed from different polymers and those polymers have different IVs. The internal layer and external layer may be formed from a respective polymer such that a ratio of the IVs is at least 1.05. Forming the structure may comprise forming a first one of the internal layer and the external layer to be thicker than a second one of the internal layer and external layer, the first layer having higher intrinsic viscosity than the second layer and being at least twice the thickness of the second layer. The external layer may have a lower viscosity than the internal layer, the lower viscosity being

less than 1.0.

As used herein, the term "shape memory" refers to a structure that has a first (usually expanded) shape, and a second (usually contracted, reduced or shrunken) shape – e.g. to facilitate delivery of the implant. The structure is typically formed in the first shape and is forced to attain the second shape, for example under pressure and heat treatment. The structure then returns to the first shape on fulfilment of some condition, such as warming of the structure. For example, an implant may be formed in a first shape, reduced in cross-section to a second shape to permit delivery or injection into the nasal airway, and then expanded back to the first shape on being heated/warmed by a heating element, device or the body. On returning to the first (i.e. predetermined) shape, the implant may have the desired shape – e.g. may conform to the desired shape of the nasal airway, particularly in the case of custom-made implants – or may then undergo further shaping from the predetermined shape to the desired shape. Notably, the second shape may be the same as the first shape, but with different dimensions (e.g. shrunk), or may have different form (e.g. a bent first shape may be straightened into a second shape to facilitate delivery).

Forming the structure may comprise forming the internal layer to be thicker than the external layer and to comprise the shape memory material.

Forming the structure may comprise forming the internal layer from at least a crystalline polymer having an intrinsic viscosity between 3.0 and 10.0.

The internal layer may be formed on a substrate. In an embodiment, the substrate may be a fluoropolymer. The internal layer may be formed from a plurality of layers of an aliphatic polyester polymer having different crystalline structure and is layered on a fluoropolymer.

The fluoropolymer may then be removed after temperature treatment. In such embodiments, the substrate is used in the forming step, the shaping step or both the

forming and shaping steps, but does not form part of the implant.

The method may further comprise controlling a drying time of one or both of the internal layer and external layer, to control crystal formation of said one or both of the internal layer and external layer.

Shaping the structure may comprise shaping the structure into a cylindrical shape with the internal layer disposed internally of the external layer. The structure has a length and shaping the structure may further comprise shaping the structure to have different diameters along the length.

Shaping the structure may comprise extruding one or both of the internal layer and external layer.

Forming the structure may comprise forming the internal layer and external layer by one or more of moulding, dip coating, spray coating and solution casting. Notably, the forming and shaping steps may occur in any order – e.g. shaping before forming or forming before shaping – or may be performed concurrently.

The method may further comprise controlling at least one parameter of:

temperature;

rate of distance over time of a solution of one of the internal layer and external layer relative to an already formed layer of another one of the internal layer and external layer;

structure surface adhesion properties;

rate of evaporation of solvent from a wetting zone;

environmental mixture; and

relative humidity.

The method may further comprise applying a plasticiser to set one or both of the internal

layer and external layer. Applying a plasticiser to set one or both of the internal layer and external layer may comprise applying the plasticiser after insertion of the implant into the nasal passage.

One or both of the internal layer and external layer may be formed form a bioabsorbable material.

Also disclosed in an implant for nasal passage support comprising a structure comprising a plurality of layers, the plurality of layers having at least an internal layer and an external layer, at least one of the internal layer and external layer comprising a shape memory material, the structure being shaped such that the shape memory material will assume a predetermined shape when positioned in the nasal passage.

The implant may be formed by a method as described above.

The structure may form a tubular shape having changing diameter along its length.

**Brief description of Figures**

Embodiments of the invention will be described, by way of non-limiting example only, with reference to the accompanying drawings in which:

Figure 1 illustrates a method for forming an implant in accordance with present teachings.

Figure 2 depicts a tube formed from multilayering and having different diameters.

Figure 3a is a perspective view of an implant of an alternative embodiment, Figure 3b is a plan drawing of the implant of Figure 3a, and Figure 3c is an end view of the implant shown in Figure 3b.

Figures 4 and 5 show alternative embodiments of an implant in accordance with the present teachings.

Figure 6 depicts a PTFE form for solution layering.

Figure 7 illustrates an exemplary polymer with lower intrinsic viscosity (caprolactone) having a thickness of 90 μm vs the overall polymer thickness of 120 μm having higher intrinsic viscosity. This results in a ratio of 3:4.

Figure 8 shows an alternative embodiment of a nasal implant for supporting a nasal passage of a subject.

**Detailed Description**

The present disclosure relates to a method of making an implant or implant device for internally supporting the nasal passage – e.g. nostril or nasal cavity including the nasal septum. Some embodiments may focus on supporting the nasal valve through its natural orifice. Some implants act as a dilator, and may achieve an outer aesthetic change to the shape of the nose. Such implants can take the form of a device with a distal end that can change shape in the nostril, and support the nostril from within. This enables the device to be largely, or entirely, hidden from view, while also being readily withdrawn from the nostril, if desired. Since the device is intended for insertion or ejection through the natural orifice, procedures involving the device are minimally invasive. The implants described herein may also be introduced via other means generally known to the person skilled in the art.

Treatment of the internal nasal valve includes ejecting an implant into the nasal passage to abut lateral tissue of the patient. Typically, the implant will perform a dilatory function,

opening the internal nasal valve of the patient. The injection (this term being used interchangeably within "ejection" and similar) of the present implant into the tissue surrounding internal nasal valve will induce an alteration or a change in the internal nasal valve angle.

In an embodiment, the present disclosure relates to a method of making shaped prosthesis substrates having different layers of crystalline structure or composition. Such a method 100, producing an implant for supporting a nasal passage, is shown in Figure 1. Broadly, the method 100 comprises:

102: forming a substrate comprising a plurality of layers.

104: shaping the substrate.

Step 102 involve forming multiple layers. There may be any number of layers, from two to more than two, depending on the application and the desired properties of the implant. The parameters are controlled at step 106, and may be adjusted during performance of step 102 while the layers are being formed, and potentially also during performance of step 104 if any post-fabrication treatment is applied to the layers – e.g. controlling the temperature to heat-treat an outer layer of the substrate or to ensure ideal, temporary attachment of a pharmaceutical compound to the external structure of the substrate in the event that the implant is to be drug-eluting. Presently, the implant produced by method 100 comprises at least an internal layer and an external layer. The external layer is, in practice, positioned between the internal layer and the skin of the nasal passage. Thus, the term "external" means outermost and thus abutting the skin of the nasal passage when the implant is in use. Conversely, the term "inner" means that the internal layer is positioned inwardly of the nasal passage relative to the external layer. Other layers may be disposed between the internal layer and external layer.

At least one of the internal layer and external layer comprises, or is formed from, a shape

memory material. This allows the implant, when in position in the nasal passage, to assume a predetermined shape. That predetermined shape may conform to a desired shape of an internal surface of the nasal passage – e.g. the outer diameter OD (see Figure 2) of the implant has the shape desired to be imparted to, or maintained in, the nasal passage.

Step 104 involves shaping the substrate so that the shape memory material assumes the predetermined shape when positioned in the nasal passage. The phrase "when positioned in the nasal passage" may mean immediately upon being positioned therein, or may mean after the implant has absorbed heat and the shape memory material has thereby been enabled to resile back towards the predetermined shape from some contracted shape – i.e. the shape memory material or corresponding layer (typically the internal layer/substrate) has an expanded condition when in use and contracted condition when in storage, and moves from the latter to the former when in the nasal passage.

One or more, and generally all, layers of the implant may be made from a polymer. In this regard, it has been found that intrinsic viscosity (IV) is important for maintaining a position of the implant in the nasal passage and for permitting mucus, air and other substances to pass along the nasal passage. The polymers may be biopolymers.

The choice of polymers, the IV ratio between layers, and the thickness ratio between layers is important for the shape memory property. In particular, step 102 may involve forming the substrate by forming the internal layer and external layer from a respective polymer having respectively different IV. Step 102 may instead involve sandwiching one or more layers of a first IV, between layers of a second IV – the second IV may be higher, or may be lower, than the first IV. In other words, the IV of the internal layer is different to the IV of the external layer. For example, the ratio between the IVs of the two layers may be 1.05 or more. Similarly, the internal layer may be made thicker than the external layer, and to comprise the shape memory material. Thus, the shape memory property imparted to the internal layer by the shape memory material will apply sufficient force during resiling back

to the predetermined shape, that it can force the external layer to assume the necessary shape – e.g. the external layer may stretch, deform or become otherwise re-shaped by movement of the internal layer to the expanded condition.

The method 100 may also involve controlling fabrication parameters (step 106), to control properties of the implant. For example, step 106 may involve controlling a drying time of one or both of the internal layer and external layer, thereby to control crystal formation in the respective internal layer and external layer. Step 106 may also, or alternatively, involve controlling fabrication parameters to impart desired porosity characteristic to a particular layer, or to avoid porosity. As such, the shaped prosthesis or implant can have porosity or no porosity at any layers to control the strength and degradation of the implant. Similarly, the step 106 may involve controlling the temperature close to the prosthesis during addition or formation of multiple layers. Control step 106 may be performed during step 102 and/or step 104, although Figure 1 only shows performance of step 106 during step 102.

The fabrication process as a whole may be controlled to create a prosthesis of any desired form/shape, although such prostheses will typically be cylindrical (with the internal layer radially inwardly of the external layer) to ensure an internal air passage is maintained. Since the desired shape will be intended to maintain a shape of the nasal passage, or to reshape the nasal passage, the implant may have different diameters along its length (L – see Figure 2).

As a result of the method 100, an implant (which can interchangeably be referred to as a prosthesis) with self-dilatable design can be created that, due to its shape memory, is able to maintain superior stiffness for internal nasal valve wall support, expand the cartilage to improve breathing and resist migration when expanded.

Figures 3a to 3c show such a device or nasal implant 300, for supporting the nose. The nasal

implant 300 shown in Figure 3a may have any suitable cross-section. To avoid sharp corners, which may be uncomfortable for a user, implant 300 is cylindrical in shape (cross-section) along the handle 302. Similarly, to ensure a comfortable fit in the nasal passage, the handle 302 has a diameter of 1.2 mm and an overall length of 27mm, although other diameters and lengths may be used as appropriate.

The proximal end or handle 302 has a varying cross-sectional area – e.g. changing diameter. The variations serve a number of purposes. The size of the variations may be used to control flexibility of the handle 302. The variations may also provide grip for a user to insert or remove the implant 300. In other cases, the surface of the handle may be textured to afford control or grip while being positioned in the nostril.

The distal end 304 of the implant 300 is shaped to anchor the implant 300 in the nasal passage and to support the nasal valve or elsewhere in the nasal passage or cavity. Presently, distal end 304 is Y-shaped though it may have another shape if desired, such as a cylindrical shape as shown in Figure 6. After insertion into the nasal passage, the distal end 304 expands to anchor the implant 300 in position in the nasal passage. To ensure sufficient outward pressure can be applied by the distal end 304 to internal walls of the nasal passage, a supporting bridge 306 is provided. The supporting bridge 306 provides additional lateral (i.e. outward) force to supplement that provided by the distal end 304. A centre of the supporting bridge 306 and that of the distal end 304 (i.e. where the distal end 304 connects to the proximal end 302) draw closer together as the implant 300 expands. Thus, the supporting bridge 306 and distal end 304 apply opposite forces relative to a longitudinal axis 310 of the implant 300.

Figures 3b and 3c show the implant 300 in plan view and end view, respectively.

Where the implant 300 is formed with some shape memory properties, it may have a collapsed configuration in which the distal end 304 is squeezed such that the arms of the

Y-shape are close or touching. While in the collapsed configuration the implant 300 may be chilled maintain its collapsed shape. Upon insertion into, or being warmed by, the nasal passage the distal end 304 may expand to an expanded condition. Expansion, and the shape attained by the implant 300 after expansion, is based on its shape memory functionality to support internal walls of the nasal passage. The proximal end 302 extend from the distal end 304 towards the nostril and potentially partially out of the nostril. This enables the implant 300 to be readily withdrawn, if desired.

Figure 4 shows an alternative embodiment in which implant 400 has a distal end 402 that, in plan view, has a similar appearance to implant 300. However, the arms 404 forming the Y-shape of the distal end 402 are broader. This increases the contact area between the implant 400 and the internal walls of the nasal passage. This may also enable the distal end 402 to apply greater outwardly directed force to the internal walls of the nasal passage. The broader surface of arms 404 also makes it easier to apply a compound or pharmaceutical agent to the outer surfaces of the arms 404 (i.e. surfaces facing or abutting the nasal passage).

The nasal implant 300/400 may have multiple layers. The layers may be configured to impart certain functionality on the implant, such as shape memory or shape control. Layers, particularly outer layers, may be loaded with therapeutic agents. The therapeutic agents can include anti-inflammatory agents, pain-killers and others.

The proximal end 406 and supporting bridge 408 serve the same function as proximal end 302 and supporting bridge 306 of implant 300.

In an embodiment, the implant device may increase an internal nasal valve angle and support the structural strength of the tissue surrounding a nasal valve in the nasal passageway. This prevents the tissue from collapsing during inspiration. The implant will affect the lateral structures of the nose which causes adjustment of the position of the

lateral aspect of the lateral nasal cartilage, affecting the external nasal valve.

In accordance with an embodiment, treatment methods include inserting an implant device adjacent to lower lateral cartilage, the nasal dorsum, the paramedian tissue of the nasal dorsum, or the collumella to change the external shape of the nose if required. The size is selected such that the implant can fit in the core of a hollow tube or introducer for delivery. It is introduced into the nasal tissue by inserting the tube into the desired location. The implant is then maintained in that position by application of gentle pressure on the implant by an advancement shaft as the hollow tube is withdrawn. Thus, the method 100 may also involve inserting/ejecting the implant into the desired position – step 110, shown in broken lines since it is not strictly a step of producing the implant *per se*.

The implant may have variable and various physical properties, depending on the particular application it needs to fulfil in the nasal passage – e.g. support, reshaping, drug delivery etc, whether it needs to be retrievable or resorbable/bioabsorbable. Implants may have a rigid or flexible shape, particular rigidity or flexibility provided in different layers, or configuration at different areas of the tubular shape. For example, an implant may be more rigid in some areas than others, to ensure structural support in the rigid areas while providing flexibility in less rigid areas to facilitate proper positioning or use of the implant. Moreover, different layers or areas can be coated – the coatings will typically be applied to the external layer, which may have a single coating along its length, different coatings at different portions of its length, or be formed from different material at different portions of its length where those materials are adapted to promote or inhibit tissue growth to differing degrees, or to deliver different pharmaceutical compounds.

An implant 500 adapted to promote or inhibit tissue growth, or to deliver pharmaceutical compounds the tissue of the nasal passage, is shown in Figure 5. When compared with implants 300 and 400, the distal end 502 has a larger area and is formed with a lattice or strut pattern. This increased area again increases the contact surface between the implant

500 and internal walls of the nasal passage, as well as increasing flexibility and patient comfort for the patient. Again, the proximal end 504 and supporting bridge 506 are the same purpose as those elements in implant 300. Similarly, implants 400 and 500 may have shape memory properties and be inserted and/or withdrawn in a similar manner to implant 300.

The lattice pattern can promote the growth of tissue into the distal end 502. To that end, at least the distal end 502 should desirably be formed from biocompatible or bioabsorbable material. On the whole, implants 300, 400 and 500, and other implants in accordance with the present disclosure, can be made of various compounds including thermoplastic and thermoplastic elastomer (TPE). Examples of thermoplastic materials suitable for present purposes include Acrylic (polymethyl-methacrylate – PMMA), ABS, PLA, Nylon, Polybenzimidazole, Polycarbonate, Polyether sulfone, Polyoxymethylene, Polyether ether ketone, Polyetherimide, Polyethylene, Polyphenylene oxide, Polyphenylene sulfide, Polypropylene, Polystyrene, Polyvinyl chloride, Polyvinylidene fluoride, and Polytetrafluoroethylene (Teflon), nylon polyamide (PA). Examples of TPE materials suitable for present purposes include TPEs that come from block copolymer groups, amongst others, such as CAWITON, THERMOLAST K, THERMOLAST M, Arnitel, Hytrel, Dryflex, Mediprene, Kraton, Pibiflex, Sofprene, and Laprene. Out of these styrenic block copolymers (TPE-s) are CAWITON, THERMOLAST K, THERMOLAST M, Sofprene, Dryflex and Laprene. Laripur, Desmopan or Elastollan are examples of thermoplastic polyurethanes (TPU). Sarlink, Santoprene, Termoton, Solprene, THERMOLAST V, Vegaprene, or Forprene are examples of TPV materials. Examples of thermoplastic olefin elastomers (TPO) compound are For-Tec E or Engage and Ninjaflex.

The insert may be shape mouldable such that the shape is changed and maintained just before or after implantation. The implant may later be modified as desired by the patient or as needed to obtain the results desired above its glass transition temperature ($T_g$).

Each layer of the implant may be made from any suitable material such as biodegradable and/or bioabsorbable polymers. This may include polymers which can be used for making the implant material via multi-layering processes such as one or more of polylactide (PLA), poly-L-lactide (PLLA), L-lactide/caprolactone copolymer, poly-D-lactide (PDLA), polycaprolactone-polylactic acid copolymer (PCL-PLA copolymer), polygluconate, polyanhydride, polyphosphoester, polyglycolide (PGA), poly(lactide-co-glycolide) (PLGA), polycaprolactone (PCL), PLA-co-PCL, poly(e-caprolactone), polyhydroxybutyrate, polydioxanone, polyanhydride, trimethylene carbonate, poly(β-hydroxybutyrate), poly(g-ethyl glutamate), poly(DTH iminocarbonate), poly(bisphenol A iminocarbonate), poly(ortho ester), polylactic acid-polyethylene oxide copolymers, polycyanoacrylate, and polyphosphazene, poly(amino acids), polydioxanone, cellulose, collagen and chitosan, and copolymers, terpolymers and combinations and mixtures thereof.

There are also a number of biodegradable polymers derived from natural sources such as modified polysaccharides (cellulose, chitin, chitosan, dextran) or modified proteins (fibrin, casein) that may be selected alone or in combination with other polymer(s) mentioned herein.

These examples of polymers that may be utilized for forming the implant substrate are not intended to be limiting or exhaustive but are intended to be illustrative of potential polymers that may be used.

Referring back to Figure 1, in some embodiments, the method 100 may comprise forming or attaching sutures at one or more locations on the substrate. The sutures may be at one or both ends of the substrate. The method 100 may involve pushing the suture(s) through the substrate prior to, or after, insertion in to the nasal passage. The method 100 may also involve adjusting the position of the implant in the hollow tube, using the sutures – this can provide a decrease in the diameter of the largest diameter portion of the implant that is adjacent to the lateral cartilage. This may be achieved by loading the implant in a launcher

tube where it is in situ reduced in diameter for up to a predetermined period of time (e.g. up to 20 minutes). The time limit is defined by an amount that facilitates the desired shrinking or constriction of the implant – e.g. to a size convenient to deposit into the nasal airways – and/or a period that is sufficiently short so as not to cause plastic deformation of the implant – i.e. so that it still expands back to the desired shape. Thus, the predetermined period of time prevents creep before the implant is ejected out from the launcher tube. The portion of the implant with a smaller diameter serves as a handle and allows the implant to be pulled into the launcher– the suture or sutures can similarly be used to drawn the implant into the introducer or to otherwise reposition the implant once it is within the introducer. The launcher tube or introducer is a device that will be apparent to the skilled person in view of present teachings and introducers used in other applications.

The attached sutures can then be used to guide the implantation of the implant, and/or to adjust a position of the implant in or on the tissue immediately after implantation. The sutures may then be trimmed as needed.

The above method 100 can be used to produce an implant to improve nasal patency. Nasal patency is critical to the airway, and nasal obstruction can contribute to snoring, sleep apnoea, and disrupted sleep. The patency of a good nasal airway is also critical for the growing number of people using continuous positive airway pressure (CPAP) for sleep apnoea.

Depending on the equipment setup used in the method 100, the mechanical properties of the implant can be manipulated, such as stiffness of the dilatable part of the implant – notably, the shape memory material may be disposed along a length of the implant, or along only one or more predetermined portions of the implant to achieve the desired predetermined shape. For example, manufacturing of polymeric prosthesis for implants such as a multi-step diameter tubular shaped form can involve manufacturing steps to create a substrate form via extrusion, 3D printing, injection moulding, hot moulding and/or

solution casting methods. The raw substrate form or single diameter cylindrical tube, which will generally be used to produce the internal layer or both the internal and external layers, may be created by extrusion, moulding or solution casting methods prior to forming to its final form – e.g. by heating and expanding/reshaping. Some substrates are able to achieve a relatively high level of geometric precision and the mechanical strength is normally determined by a combination of processes and base materials used.

In other embodiments, dip coating or solution casting may be used. Dip coating involves the deposition of a liquid film via the precise and controlled withdrawal of a substrate from a solution. This is typically done using an instrument known as a 'dip coater'. Most dip coaters have a motorized arm that moves vertically, and holding a rack with several mandrels. A substrate is mounted on each mandrel and a solution holder is located beneath the substrates. The motorized arm immerses the mandrels and their substrates in the solution at a controlled immersion speed and time. The substrate is withdrawn at a specified speed and a wet film is formed on the substrate.

The desirable characteristics of the substrate may be achieved by dip coating multiple layers. The molecular weight of polymers is typically one of the factors in determining the mechanical properties such as ductility of the substrate. The method 100 may involve controlling a rate of withdrawal of the substrate to control the thickness of each layer. When the selected starting material is in resin form, its IV is not the only criterion for determining the mechanical properties of the substrate formed from that resin. Instead, the entire process from the polymer resin mixing process to the formation of first layer (whether it is the internal layer or external layer) and its intermediate layering process is affected by the fabrication parameters. For example, the method 100 may involve controlling one or both of the pressure and temperature to control the porosity (or otherwise) of each layer. This will similarly influence the mechanical strength of the tube prior to the implant being constricted to fit inside a delivery device or tool. Relatedly, for some implant materials, it is desirable that the implant be constricted for less than 20

minutes to avoid creep – to avoid plastic deformation of the implant that might inhibit its ability to move to the expanded condition.

A supporting main column of the substrate (e.g. a thick internal layer) may be utilized for solution layering or dip coating the polymeric solution so that after multiple layering steps, and by controlling solvent evaporation, a polymeric shell with multiple layers is formed from the solution. The dip coater setup assembly can have at least two rail shafts so that the vertical moving direction slider moves the slider holding the solution layering substrates up and down at desired speed of mm/s driven by a motor. With two-rail shafts, the sliding force is better distributed. The vertical motion slider may hold a frame secured with several columns inserted in the lumen of the substrate via interference fit for solution layering. Placing the supporting main column of the structure in an enclosed chamber allows control of the drying time, chamber temperature and inert gas environment where the coating is exposed.

Each of the dipping processes contributes to the formation of substrate through layering and will contribute to its final mechanical strength. The dipping may only be partial (i.e. partial immersion of the substrate) for all or a number of the coating steps so that the entire tube has a predetermined, uniform form, or has a fusion of different polymers at different sections along the length of the predetermined form. Drug coating, growth factor ingredients or other compounds may also be added to promote cartilage growth and reduce inflammation of mucosa membrane. This addition may involve coating the finished substrate or mixing pharmaceutical or active compounds into the substrate during formation. The outermost layer – i.e. the layer that is deposited last – may have an IV that is sufficiently high to attach to the compound and ensure it is held in the implant, but is also sufficiently low to allow that compound to diffuse into surrounding tissue – e.g. at a desired rate – on contact with that tissue.

In other embodiments, the fabrication parameters require environmental control during

the prosthesis substrate fabrication to reduce porosity at low temperature – e.g. at 20 Degrees Celsius or lower. Moreover, different polymers, particularly when formed under controlled fabrication parameters, will have different crystallinity. The different crystallinity may be achieved through the layering method and controlling the evaporation of the solvent by maintaining the temperature below the boiling point. In some embodiments, the temperature is maintained above the boiling point of the solvent for drying of each layer, or may vary between temperatures above and below the boiling point.

For example, step 102 may involve forming the internal layer as a crystalline polymer having an intrinsic viscosity between 3.0 and 10.0. The ability to control the solution evaporation rate during the solution layering process and withdrawal is critical to produce coatings without porosity, that have desirable mechanical properties.

Where porosity in the layers is desirable, the method may involve controlling environmental conditions such as air or gas mixture, relative humidity and temperature. This will induce layering films with porosity that will affect the next layer's adhesion and its mechanical strength in a multi-layered prosthesis, before cutting or final formation of the prosthesis for its intended function.

It should be understood from present teachings that solution layering is not restricted to a vertical dip coating process. For example, a polymer dissolved in a solvent may be dispensed along the length of a rotating substrate – e.g. the external layer may be deposited in liquid form over the internal layer – as the substrate traverses longitudinally along its length, and rotates horizontally about its longitudinal axis, with respect to gravitational force or ground zero. Step 102 may involve controlling one or more of the speed of rotation, longitudinal or transverse speed, intrinsic viscosity of each polymer layer, solvent type. Controlling these parameters will determine the wall thickness of the implant and environmental temperature and pressure will determine the evaporation rate of the solvent and thus control formation of the solvent meniscus during the layering of each

multilayer. This will determine the overall mechanical properties of the implant such as ductility and expansion properties for dilation – i.e. expansion back to the expanded condition.

The desired substrate surface properties are important to enable the first base layer to adhere to the dipping tool or substrate on which the first base layer is to be coated. The first layering thickness – i.e. thickness of the first base layer or innermost layer of the implant – and IV of the first base layer should produce a crystalline polymer having IV above IV3.0 and below IV10.0. This enables the first base layer to adhere to the dipping tool or dipping substrate, for forming the layers according to step 102, while being sufficiently low to enable detachment of the layers, from the dipping tool or dipping substrate, once formed. In an embodiment, the first layer is formed from PLLA having an IV of 6.0. A thickness of 60 to 80 um may be obtained by moving the substrate into a PLLA solution. This may require at least one, preferably two cycles of moving the substrate into the PLLA solution and lifting the substrate up at a speed of 4mm/s to 5mm/s. This allows the solution to be layered upon the surface of the substrate with a pause time in an environment of low humidity of less than 50% RH while maintaining a temperature of at least 20 degrees Celsius for less than one hour for each layer. In this case, no porosity is created for intermediate layers.

In another embodiment, the first layering thickness can be PLC forming a layer with a dry thickness of 10 um followed by PLLA having an IV of 6.0 forming a 30um layer, as shown in Figure 7. Using PLC imparts flexibility and shape memory to the implant, while PLA provides structure.

In embodiments, it is preferable to use a higher IV polymer PLLA which will provide the strength, rigidity and toughness thus needed to facilitate the shape memory, and the stretchable PLC will provide the malleability.

The substrate material used for first layer adherence (i.e. the dipping substrate) should have surface properties that can be custom etched by chemical etching, radiation, machining, and/or polishing to have moderate ascending contact angle (de-ionized water) ranging from 50 to 140 degrees. These processing steps – e.g. etching – affect how the polymer solution for the first layer (i.e. the first layer or first base layer to be deposited onto the dipping substrate) interacts with the solid surface of the substrate material. In turn, this will affect the dimensional aspects of the subsequent layer.

Some examples of suitable substrate materials (dipping substrate) include fluoropolymers such as Polytetrafluoroethylene (PTFE), Polyvinylidene Fluoride (PVDF), Polyvinyl Fluoride (PVF) or Fluorinated Ethylene Propylene (FEP) etc. For example, a PTFE substrate typically has a water contact angle of 120 degrees, can be etched in sodium solution to reduce the water contact angle to less than 100 degrees. The water contact angle cannot be too low, or less than 70 degrees or hydrophillic, as it will enhance adhesion of the first polymer layer (first base layer) to the substrate. This will pose a challenge when breaking the bond to remove the polymer layers from PTFE substrate. This is also partly due to the rigidity of the PTFE substrates that have an average wall thickness of 0.22 mm ± 0.02. The wall thickness of the PTFE substrate can range from approximately 100 to 250 um.

Having too high a water contact angle is also undesirable. By having a less hydrophobic (i.e. water contact angle less than 140 degrees) PTFE surface, the first layer (e.g. a Poly-L-lactide (PLLA) solution drawn from the PLLA polymer solution) with intrinsic viscosity less than IV 10.0 will have better adhesion and form a more uniform layer of wet thickness on the substrate. The dry thickness will be formed by the control of solvent evaporation of the initial wet film formed. Notably, the dry thickness will be less than the wet thickness.

The solvent compatibility with the solute (polymer) used to dissolve the polymer resins with a typical inherent viscosity is important. Polymers do not dissolve instantaneously. Dissolution is controlled by either the disentanglement of the polymer chains or by the

diffusion of the chains through a boundary layer adjacent to the polymer–solvent interface. For example, PLLA resins are usually compatible with solvents such as chloroform or dichloromethane (DCM). There is a myriad bioresorbable polymers that can be used for solution layering or dip coating. Each is soluble in respective, potentially different, solvents. The ratio of the weight of polymer to solvent and time used to stir, for example, will affect the degree of dissolution of the resins, which in turn will affect the mechanical properties of the substrate formed layer by layer. In the present embodiment, the ratio of polymer to solvent is between 1 and 100 in ratio of w/v. In such cases, a polymer such as Poly-L-lactide (PLLA) or PDLA (Poly-DL-lactide) (IV2.0 to IV10.0) can be used to form the first base layer on a substrate for adhesion of a first multi-layer having known contact angle properties of 85 degrees. This base layer will usually have the highest modulus among all resorbable polymers used for the implant. However, this may be changed depending on how the layers of the implant should degrade and in what order. In an embodiment, the first layer formation, thickness and material may be as discussed above with reference to Figure 7.

In an embodiment, where the substrate involves a multilayering process, the first layer or first base layer may be formed from PLLA with IV6.0 mixed with dichloromethane at a ratio of 1/16 w/v, for a substrate length of 100mm and OD of 1.0mm. It is stirred for up to 60 hours at room temperature (between 20 Degrees Celsius to 30 Degrees Celsius) at around 2000rpm. Another solution of PLA-co-PCL (polylactic acid/polycaprolactone biodegradable block co-polymer – though other biodegradable polymers may be used) of IV3.8 is mixed with dichloromethane at a ratio of 1/30 w/v to form the next layer on top of the first layer. For example, this may be a GMP grade copolymer of L-lactide and ε-Caprolactone in a 70/30 molar ratio and with an inherent viscosity midpoint of 3.8 dl/g.

The solution is visually cleared and shown to have all resins fully dissolved.

In an embodiment, the same mixture solution may be stirred at 20 Degrees Celsius. There are undissolved pellets of PLLA observed after 18 hours. In this case, the environmental

temperature affects the dissolution of the PLLA in dichloromethane. If the solvent used is chloroform, it will take more than 24 hours. If the PLLA resins are not fully dissolved, the layer coating coated on the substrate will not be homogenous and free from undissolved resin pellets. The time and environment temperature of the PLLA solution mixture is critical to the degree of dissolution that will partially affect the mechanical properties, as the substrate is built layer by layer from fully dissolved polymer solution. Its IV also affects the time taken for full dissolution of PLLA. A lower inherent viscosity of PLLA at IV 4.0 will take a shorter time of 12 hours at between 20 Degrees Celsius to 25 Degrees Celsius to achieve a clear mixed solution for solution layering. The environment temperature that affects the solution temperature is critical in achieving a clear mixed solution after hours of stirring.

In an alternative embodiment, the method 100 may involve insulating a container – e.g. glassware – holding the polymer resins and the solvent during stirring using insulating materials. The heat transferred from the magnetic stirrer base could improve the solubility of the resins in the solvent in temperature range that is around 15 Degrees Celsius below the boiling point of the solvents.

In an embodiment, where a vertical tower layering machine (dip coater) is used, the withdrawal stage of the substrate from the polymer solution can be simply seen as the interaction of several sets of forces. These forces can be placed into one of two categories: draining forces and entraining forces. Draining forces work to draw the liquid away from the substrate and back towards the bath. Conversely, entraining forces are those that work to retain fluid onto the substrate. The balance between these sets of forces determines the thickness of the wet film coated onto the substrate.

The dynamic meniscus and the flow of solution in this region determines the wet film thickness. This is affected by three main parameters: the rate of distance over time of the solution relative to the substrate for vertical withdrawal; the substrate surface adhesion properties, that affect the meniscus of the solution; and the evaporation of the solvent

from the wetting zone. Therefore, understanding the physics that underpins the curvature of the dynamic meniscus and the thickness of the stagnation point are important. This is the example for first solution layering on the substrate– i.e. forming the first base layer being the 10μm PLA layer in Figure 7. In subsequent layers on top of the first layer, the evaporation control of the first layer will affect the wet thickness of the subsequent layers and of the final dry layer that forms a shell film to maintain the thickness of the implant.

Another important factor is the solution layering length of travel that accounts for the bonding of each layer with the first deposited layer, and the evaporation of solvents from the first layer. If the first layer on the substrate is still in its semi-wet state, or solvent is still evaporating from it, it will affect bonding between layers. This will, in turn, affect the mechanical strength of the layered substrate of the implant. This issue is exacerbated if the environment induces porosity due to condensation of water moisture when the solvent is evaporated on the surfaces of the layer exposed to the environment.

In an experiment, using a PTFE substrate with starting diameter of 0.82mm, a wall thickness between 60 to 80um may be achieved after 2 to 3 cycles of moving the substrate into the PLLA IV6.0 solution at a ratio of 1/16 w/v and lifting it up at a speed of 4mm/s to 5mm/s to allow the solution to be layered upon the surface of the substrate with a pause time in a low humidity environment of less than 50% relative humidity (RH) and maintaining a temperature of at least 20 Degrees Celsius for less than 1 hour for each layer. Under this process, no porosity was found in intermediate layers. A second biopolymer such as PLLA-co-PCL with intrinsic viscosity of 3.8 at a ratio of 1/30 w/v can be layered (15um each layer) with four cycles on top of the PLLA layers formed earlier by moving the substrate with PLLA layers into the PLLA-co-PCL solution and lifting it up at a speed of 4mm/s to 5mm/s to allow the solution to be layered upon the surface of the PLLA to provide some malleability for the nasal valve infrastructure support (i.e. the cartilage of the nasal septa and the tissue wall). The nasal septa cartilage may shift if the rigidity is too high.

After the solution layering process, a formed OD 1.06mm cylindrically shaped implant will be left mounted on the substrate and supporting column in a low temperature (i.e. less than 20 Degrees Celsius) and DCM filled environment. The implant may have any desired shape, such as oval cross-section, circular or other desired shape to properly support or form the shape of the internal nasal passageway. The chamber where the implant is stored will be flushed with N2 gas for evaporation of residue solvents up to at least 15 hours before transferring to a convection air circulating oven to be heated between up 80 hours at 85 Degrees Celsius to remove any residual solvents formed under outermost or external layer of the shape implant by solution layering. This results in the dry thickness of the layers having a reduced thickness compared to the wet thickness. The modulus of tube achieve is greater than 3000MPa and elongation at break of more than 40%. The PTFE substrate will be later removed upon drying the biopolymer.

In another experiment, a wall thickness between 30 to 50um may be achieved after 2 to 3 cycles of moving the substrate into the PLLA solution with IV 6.0 at a ratio of 1/20 w/v and lifting it up at a speed of 4mm/s to 5mm/s to allow the solution to be layered upon the surface of the substrate with a pause time in a low humidity environment of less than 50%RH and with temperature maintained at temp of at least 20 Degrees Celsius for less than 1 hour for each layer. In this case, no porosity was found for intermediate layers. A second biopolymer such as PLLA-co-PCL with intrinsic viscosity of 3.8 at a ratio of 1/30 w/v can be layered (15um each layer) with six (or predetermined number of) cycles on top of the PLLA layers formed earlier by moving the substrate with PLLA layers into the PLLA-co-PCL solution and lifting it up at a speed of 4mm/s to 5mm/s to allow the solution to be layered upon the surface of the PLA. After the solution layering process, a formed OD1.1mm [PLLA+ PLC] with multilayer and multi biopolymer cylindrically shaped form will be left mounted on its substrate and supporting column in a low temperature (i.e. less than 20 Degrees Celsius) environment and DCM filled environment.

The chamber where it is stored will be flushed with N2 gas for evaporation of residue

solvents for at least 15 hours before transferring to a convection air circulating oven to be heated for up to 80 hours at 75 Degrees Celsius to remove solvents formed or collected under the outermost layer of the shaped implant. This results in the dry thickness of the layers having a reduced thickness compared to the wet thickness. The modulus of tube achieved is greater than 3000MPa and elongation at break of more than 60%. For this configuration, the entire device will fully degrade in 36 months. For this, the PLA-co-PCL will degrade from the internal layers before the PLA layer that is pressing against the wall of the cartilage nasal septa. The implant is therefore designed to degrade from the internal layer, outwardly. This maintains support for the nasal passage, in the desired shape.

In some embodiments, the implant may be malleable, or the external layer may be malleable. This permits the shape of the implant to be adjusted before or after implantation. To fix the shape of the implant once the desired shape has been ascertained, whether before or after implantation into the nasal passage, one or more plasticizers such as Polyethylene Glycol (PEG) may be added when required for adjustment or fixation of shapes per Step 108 of Figure 1. For example, less than 5% of PEG may be added to the PLA layer during formation of the layers. While not required, it may be preferred to use an implant made of a material which with shape memory properties or polymers that can induce shape memory, fabricated through solution layering and heating at a temperature above glass transition temperature Tg – preferably body temperature in the nasal passage or a higher temperature. This property would permit the shape memory properties to be activated, or adjusted after implantation with the application of an external condition, such as temperature.

For example, solvent evaporation from the wet film has to be controlled in an enclosed inert gas environment, for example N2 gas mixed with solvent. The humidity and the temperature of the enclosed environment are set – e.g. at a humidity of less than or equal to 25% RH and a temperature between 4 to 20 Degrees Celsius– to allow the shape and thickness of each layer of dry film to set during the solution layering process. This will

influence the mechanical strength properties of the coating.

The formed tube (implant) for both polymers is further processed for its final form, as shown in Figure 2. The implant 200 comprises a substrate comprising an internal layer 202 and external layer 204, one or both layers comprising shape memory material as described above.

The formed tube 200 may be cut into lengths of 25mm or any length to suit the particular application. A heated rod of diameter 2mm with length of 24mm and end tapered to 0.9mm can be used to flare the distal end to a larger diameter – e.g. up to 2mm at between 160 Degrees Celsius and 210 Degrees Celsius. Slot designs are cut to produce a fin-like structure from the formed larger diameter portion, to enable expansionof the implant (i.e. enlarging the nasal airway and/or expanding the implant past its diameter as initially formed at step 104) for dilated support for the internal nasal valve. This ensures the implant can attain a size (e.g. diameter) necessary for supporting and contacting nasal cavity walls. A drug eluting coating on the surface layer(s) (i.e. layers/surfaces of the implant that contact the nasal cavity wall(s)), such as mometasone furoate, can elute anti-inflammatory drugs and/or reduce polyps. Preferably, the drugs would be applied after the thickness of the layer has been reduced from being baked in an air-circulating oven. This also reduces the likelihood that the drugs may be denatured by heat exposure. A surface to wall coating may be used having, for example, a IV <1.0 aliphatic polyester polymer such as PDLA to allow the drug to properly elute. Thus applying a compound to the outer layer of the implant may comprise applying a coating (e.g. by spraying) having an IV from which the compound can properly elute – the IV of the coating may be around 1.0. The slots may be formed or cut into the one or more portions of the implant – e.g. the larger or larger diameter portion, or area having outer diameter $OD_1$ in Figure 2 – i.e. part 202. Presently, three slots are shown though there may be any number as needed. The slots may be equidistantly spaced around a circumference of the implant as shown, or may be non-uniformly/unequally spaced. In general, there will be a sufficient number of slots to achieve

smooth contraction and expansion of the implant (e.g. part 202 thereof). Thus, the number of slots may depend on the size or diameter of the implant or the part of the implant in which the slots are formed.

Depending on the size of base substrate diameter used (i.e. dipping substrate), different wall thickness and different polymers can be layered on each other along the length of the device. For example, a two-diameter section PTFE tube (i.e. a tube having two sections of respectively different diameter) can be used as a substrate, 1mm for the smaller diameter and 2mm for the larger diameter section, total length is 28mm, as shown in Figure 6. For this, the finished tube does not need to go through a heat forming process to obtain the enlarged diameter of 2mm. The dipping substrate and the resulting implant may have one, two, three or any other number of different diameters.

Similarly, the first layer is formed from PLLA with IV6.0 mixed with dichloromethane at a ratio of 1/16 w/v. It is stirred up to 60 hours at room temperature (between 20degC to 30degC) for up 2000rpm. Another solution of PLA-co-PCL of IV3.8 is mixed with dichloromethane at a ratio of 1/30 w/v stirred at 2000 rpm at the same temperature for up to 48 hours. The solution is visually clear and shown to have all resins fully dissolved.

The total length of the substrate from the larger diameter D2 to D1 is 24mm. PLLA can be coated over the entire length and PLA-co-PCL can be coated only over 2/3 of the length from the 1mm diameter section (i.e. the smaller section). This will give 2 layers of PLA throughout the entire length which will have an average modulus of more than 3000 MPA and the PLA-co-PCL will only have 2 layers up to 2/3 of the length from the proximal edge of the 1mm diameter. This is another configuration and the degradation time is about 36 months. Therefore, step 102 may comprise forming each layer over the full length of the implant, forming one or more layers over less than the full length of the implant or, where the implant comprises multiple sections of respectively different diameter, forming one or more layers over one or more, but not all, sections. The solid tube with dual diameters may

be cut or form with any design to allow drug coatings to be coated and for elution to control mucosa inflammation. Growth factor such as I-GF1 can be incorporated to promote cartilage growth. More layers can be layered up to 200um thickness when required.

In another embodiment, the fully resorbable implants for insertion into the nose as shown in Figure 6 may be 2.4 cm long and 0.12 mm thick and have a dilatable area with diameter at 2mm manufactured from two polymer with layers from PLLA poly (L-lactide) and PLA-co-PCL) polymer.

The implant can be introduced using a tool with a hollow tube to eject the implant into the nose valve. The angle where the larger diameter can be folded into the hollow tube is important. It is desirable to reduce the size (e.g. diameter) of the larger diameter portion – 202 – prior to ejection into the nasal airway. This makes it easier to properly position the implant without causing damage to the nasal airway. This size reduction is achieved by pulling or delivering the implant into a hollow tube (e.g. tube 203) having internal diameter 205 that is less than the outer diameter $OD_1$. The internal diameter 205 may be between the $OD_1$ and $OD_2$, or may in some instances between equal to or less than $OD_2$. As the implant is pulled into the hollow tube 203, the area 202 of the implant with a larger diameter $OD_1$ than the diameter of the tube 203 is compressed. The extent of this compression depends on the ability of the implant 200 to collapse – this is assisted by cutting slots 207 (as reflected in end view of implant 200, in Figure 2) into portion 202 of the implant 200 with a larger diameter, which imparts a degree of flexibility on that portion 202.

Figure 8 shows an implant 800 in an expanded condition as it would sit in a nasal passage of a subject. The implant 800 comprises a proximal end 802 and distal end 804. A shaft 806 may be considered to constitute part of the proximal end 802, the proximal end 802 therefore forming a region, and the distal end 804 comprises the increasing diameter section 808 and/or lattice/patterned section 810. The proximal end 802 comprises a

protrusion of bulb 812 to afford gripping and control of the implant 800 in the nasal passage, to ensure proper positioning. The shaft 806 is formed with varying diameter to increase flexibility and position control of the stent 800. The distal end 804, presently comprising a distal region, comprises the increasing diameter section 808 that extends between the shaft 806 and lattice section 810. The increasing diameter section 808 ensure the implant 800 can avoid a significant step change in diameter between the shaft 806 and lattice section 810. A step change may result in force concentrations between the implant 800 and nasal passage, which may reduce patient (subject) comfort, and potential reduction in shape control of the implant 800 when the expanded condition as shown. The lattice section 810 can facilitate tissue ingrowth, or increase surface area for delivery of pharmaceutical compounds to tissue of the nasal passage.

The design of the delivery device (which may be a tube or other shape suitable for controlled insertion into the nasal passage – e.g. through a nostril – the tube containing the implant the deployment of which involves the implant being pushed from the tube – e.g. using an introducer) will be suitable to fit the type of device and sizes required to uplift the internal nasal valve and provide proper placement and anchoring (e.g. by sutures). The polymer layers are bioabsorbable. The implant can be inserted transcutaneously through the nose natural orifice over the medial portion of the nose.

The distal end larger diameter can be heat formed and flared to 2mm. The implant may be shaped to provide an upward force on a portion of the nasal passageway – e.g. medial portion of the upper lateral cartilage. The implant has structural strength from the PLLA layer, and by providing an upward force on the medial portion of the upper lateral cartilage, it will support the internal nasal valve, preventing its collapse. The PLA-co-PCL layers will provide it with the flexibility and malleable properties to fit the shape. The solid tube may be cut or formed with any design to allow drug coatings to be coated onto or into one or more layers of the substrate and for elution to control mucosa inflammation. Growth factor such as I-GF1 can be incorporated to promote cartilage growth. These implants may be

placed adjacent to the upper lateral cartilage, below the nasal surface. This will apply lateral force to the medial portion of the lateral nasal cartilage, dilating the internal nasal valves open.

The implants may be placed adjacent to the lateral edge of the lower lateral cartilages. The implants may extend to the bony process of the anterior maxillary bone. This will secure the lateral cartilage more securely to the maxillary bone, preventing lateral nasal collapse.

A post insertion examination, is performed to visually confirm that the desired structural and shape change to the nose has been achieved. It is uncommon for diagnostic imaging to be used at this stage as the implants are supposed to be in a non-surgical area for which a diagnostic tool is not required.

Implants are typically manoeuvred into place directed by diagnostic equipment. The method 100 may further include providing a detectable marker at a predetermined location on the implant, to facilitate detection of proper placement. For example, the implant may include a radio-opaque material such as a marker at one or both distal and proximal ends of the implant device or BaSO4 which can be mixed into the bioresorbable polymer layers. The radiopaque or MRI visible material may be in the form of one or more markers (e.g., bands of rare metal such as Platinum etc).

In accordance with a further embodiment, the ratio of IV of at least two polymers use for fabrication should be more than 1.05 – e.g. IV4.0/IV3.8 – which is important for shape memory with the higher IV polymer formed from a polymer such as PLLA or poly-L-lactide-co-glycolide acid (PLGA) with the lower IV polymer formed with layers having at least 2/3 of overall thickness.

For example, Figure 7 illustrates ¾ thickness of the lower IV polymer. In this embodiment, the lower intrinsic viscosity polymer is caprolactone with 3/4 of overall thickness of higher

IV polymer. The higher intrinsic viscosity polymer may be a 6.0 PLA sandwiched between layers of Poly-L-Lactide-co-caprolactone (PLC) with IV 3.8. In other words, the layers of lower IV – being internal and external layers labelled PLC – constitute 90um of the 120um overall thickness of the implant, with the higher IV polymer – labelled PLLA – constituting the remaining 30um of the overall thickness.

The mechanical strength of the formed tube will have sufficient toughness without inter layer porosity, as a result of the solution layering method. This demonstrates the implant is not limited to a particular shape of substrate, or the total number of layers. The implant may be cut to size and used as a stent. The mechanical strength is determined by the number of layers formed on top of the substrate or layers of the same material or different material, the solvent's compatibility with the solute, the time taken to dissolve the resin pallets in the solvent and the solution lift off rate from polymers dissolved in the solvent. These factors affect the evaporation rate, the thickness of the wet-coated film during the solution lift off from the meniscus of the solution and the resulting dry film properties. An external layer of low IV with IV less than 1.0 for drug loading – e.g. mometasone fluorate or dexamethasone – having a thickness of less than 50um will be used for controlled release for up to 28 days at 370ug of drugs for anti-inflammatory treatment.

Induced porosity due to environmental relative humidity and temperature will also affect the mechanical strength of the form achieved by solution layering. The evaporation of solvents during the drying phase cools both the substrate and the film. This cooling could lead to several problems during subsequent film formation, leaving crater-like marks in the fine structure of the film. On a macroscale, this can create a hazy coating where there should be a transparent one. At the wrong conditions, there will be formation of porosity on the surfaces of the layers. Determining the amount of porosity is complex but is controllable through control of the environmental settings – e.g. temperature and humidity. Not only does the porosity vary the density of the layer in comparison to the raw material itself - it also impacts the drying dynamics. As mentioned previously - at the drying

front, at the point of contact between the dry film and the wet film, the wet film will be drawn into the dry film via capillary action. The porosity of the film also strongly influences this, determining the rate at which solution will be drawn into the dry film, the distance into the dry film it will go, and the rate at which this absorbed material will dry.

The implant may be manufactured from a solid material, a composite of materials and may itself be a single material or may be a composite of one or more materials layered in multilayers to form the full thickness of the implant. The implant may be in the form of a hollow tube or layered-like structure or may have a woven or braided structure made of multi-layers. The implant may be woven or braided with several materials. In addition, the implant may be manufactured with biodegradable materials.

Materials, including biodegradable materials, may have shape memory properties, allowing for the implant to assume a predetermined shape after implantation. Use of inserts made of materials which have shape memory properties permit the implant to assume a pre-set shape after insertion. Alternatively, certain conditions may be applied, such as application of heat, pressure, vacuum forming that will allow the material to assume a desired fixed or modified shape after implantation with the use of different layers through heat treatment above its Tg to induce higher crystallinity to provide its shape memory and toughness. The necessary condition from assuming the memorised shape will depend on the intrinsic properties of the shape memory material chosen to produce the implant. The fixed shape of the implant may also be adjusted before or after insertion. The implant may be composed of biodegradable materials, with or without shape memory.

While exemplary embodiments have been presented in the foregoing detailed description of the invention, it should be appreciated that a vast number of variations exist. It should further be appreciated that the exemplary embodiments are only examples, and are not intended to limit the scope, applicability, operation, or configuration of the invention in any way. Rather, the foregoing detailed description will provide those skilled in the art with

a convenient road map for implementing an exemplary embodiment of the invention, it being understood that various changes may be made in the function and arrangement of steps and method of operation described in the exemplary embodiment without departing from the scope of the invention as set forth in the appended claims.

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**Claims**

1. An implant for supporting a nasal passage, comprising:

a proximal end;

a distal end extending from the proximal end, the distal end being expandable to support a nasal passage.

2. The implant of claim 1, wherein the distal end comprises a supporting bridge to assist expansion of the distal end.

3. The implant of claim 1, wherein the implant has a collapsed condition for insertion into the nasal passage, and an expanded condition for supporting the nasal passage.

4. The implant of claim 3, wherein the distal end is Y-shaped, and at least the distal end may comprise shape memory material for expanding under warmth, from the collapsed condition to the expanded condition.

5. The implant of claim 1, wherein an external surface or external surfaces of the distal end comprise a plurality of layers, and wherein at least one layer comprises a pharmaceutical compound for delivery to tissue of the nasal passage.

6. The implant of any one of 1 to 5, being formed from one or more of acrylic (PMMA), acrylonitrile butadiene styrene (ABS), nylon polyamide (PA), polyethyelene (PE), PLA, Polycaprolactone, L-lactide/caprolactone copolymer, Nylon, Polytetrafluoroethylene (Teflon) and thermoplastic polyurethanes (TPU).

7. The implant of any one of claims 1 to 6, wherein comprising a structure, the proximal end and distal end being ends of the structure, wherein the structure comprises a plurality of layers, the plurality of layers having at least an internal layer and an external layer, at least one of the internal layer and external layer comprising

a shape memory material, the structure being shaped such that the shape memory material will assume a predetermined shape when positioned in the nasal passage.

8. The implant of any one of claims 1 to 7, wherein the structure forms a tubular shape having changing diameter along its length.

9. A method of producing an implant for supporting a nasal passage, comprising:

forming a structure comprising a plurality of layers, the plurality of layers having at least an internal layer and an external layer and at least one of the internal layer and external layer comprises a shape memory material, wherein the internal layer and external layer are formed from a respective polymer having respectively different intrinsic viscosity (IV);

shaping the structure such that the shape memory material will assume a predetermined shape when positioned in the nasal passage.

10. The method of claim 9, wherein forming the structure comprises forming the internal layer to be thicker than the external layer and to comprise the shape memory material.

11. The method of claim 9, wherein forming the structure comprises forming the internal layer from at least a crystalline polymer having an intrinsic viscosity between 3.0 and 10.0.

12. The method of claim 9, comprising forming the internal layer and external layer from a respective polymer such that a ratio of the IVs is at least 1.05 and/or the external layer has a lower viscosity than the internal layer, with the lower viscosity being less than 1.0.

13. The method of claim 9, wherein forming the structure comprises forming a first one of the internal layer and the external layer to be thicker than a second one of the

internal layer and external layer, the first layer having higher intrinsic viscosity than the second layer and being at least twice the thickness of the second layer.

14. The method of claim 9, further comprising controlling a drying time of one or both of the internal layer and external layer, to control crystal formation of said one or both of the internal layer and external layer.

15. The method of claim 9, wherein shaping the structure comprising shaping the structure into a cylindrical shape with the internal layer disposed internally of the external layer.

16. The method of claim 9, further comprising controlling at least one parameter of:

temperature;

rate of distance over time of a solution of one of the internal layer and external layer relative to an already formed layer of another one of the internal layer and external layer;

structure surface adhesion properties;

rate of evaporation of solvent from a wetting zone;

environmental mixture; and

relative humidity.

17. The method of claim 9, further comprising applying a plasticiser to set one or both of the internal layer and external layer.

18. The method of claim 17, wherein applying a plasticiser to set one or both of the internal layer and external layer comprises applying the plasticiser after insertion of the implant into the nasal passage.

19. The method of claim 9, wherein one or both of the internal layer and external layer is formed form a bioabsorbable material.

20. The method of claim 9, further comprising forming one or more slots in a portion of the implant, to permit expansion of said portion.

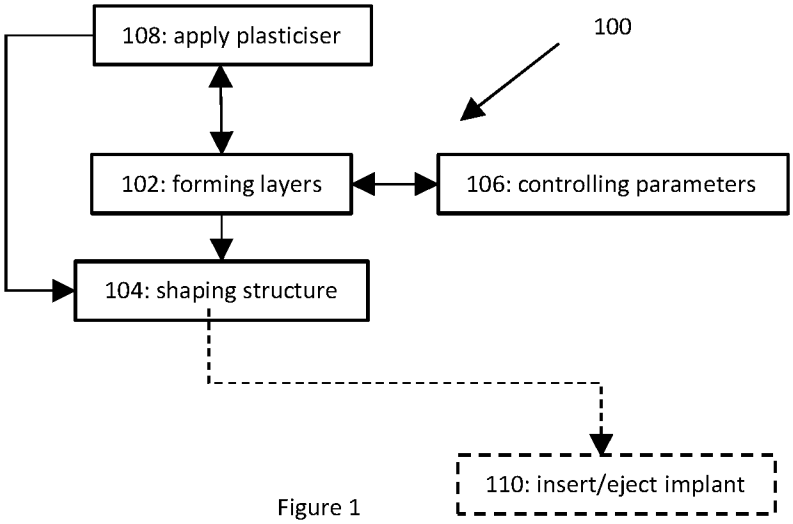



Figure 1

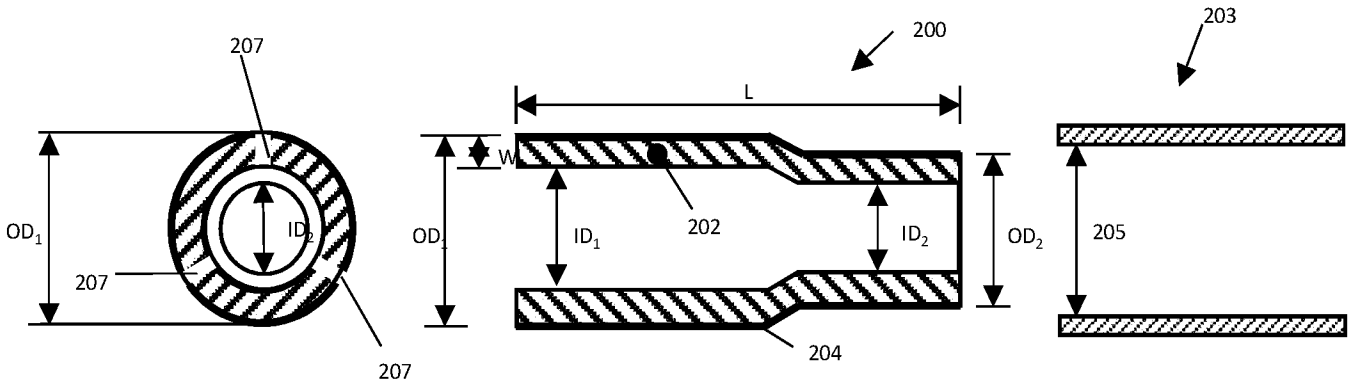



Figure 2

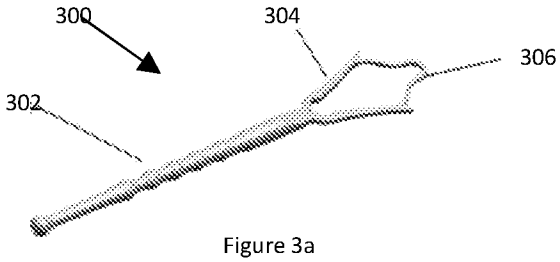



Figure 3a

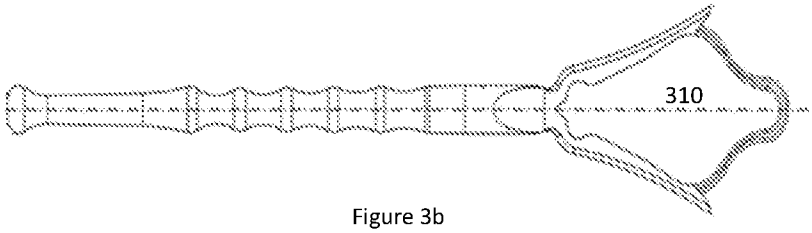



Figure 3b



Figure 3c

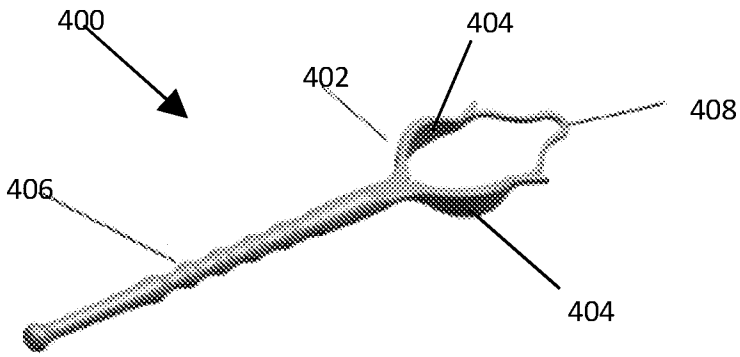



Figure 4

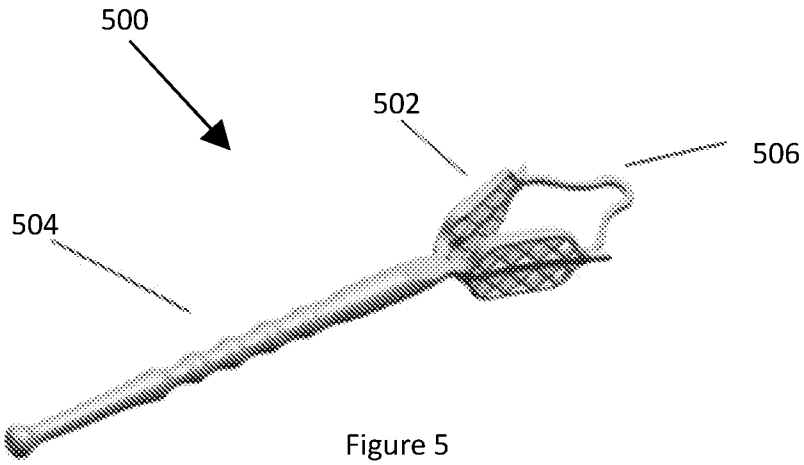



Figure 5

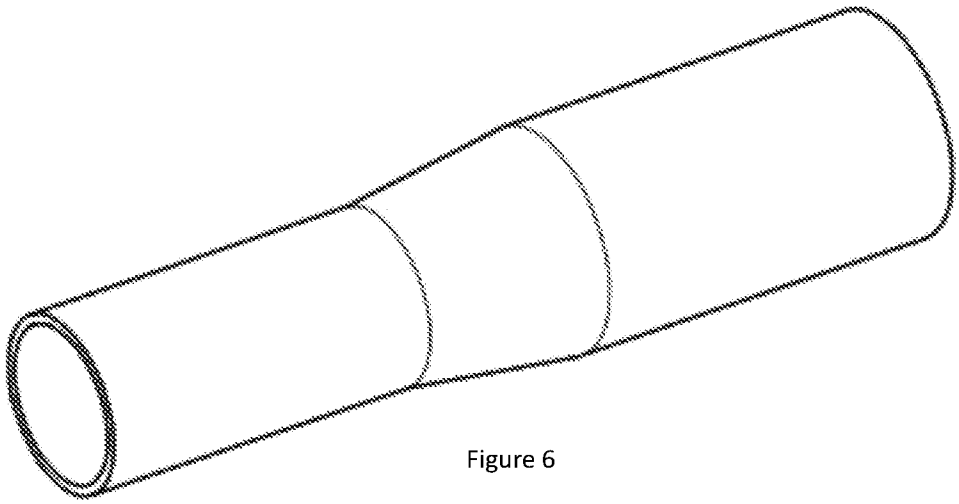


Figure 6

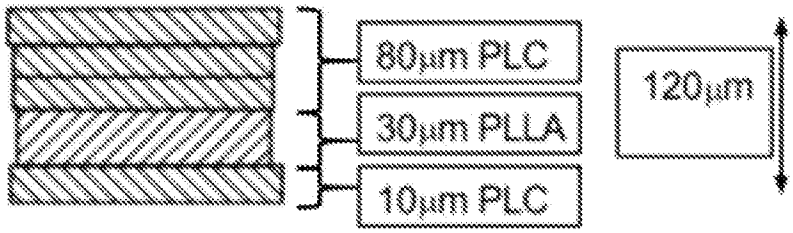



Figure 7

# INTERNATIONAL SEARCH REPORT

International application No.
**PCT/SG2022/050131**

## A. CLASSIFICATION OF SUBJECT MATTER

***A61F 5/08 (2006.01)***

According to International Patent Classification (IPC)

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61F

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

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

FAMPAT: nose, nasal, implant, septa, shape memory, polymer, acrylic, styrene, polyamide, polyethylene, polylactic acid, polycaprolactone, nylon, polytetrafluoroethylene, polyurethane, layer, expand and like terms

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2018/125868 A1 (SPIROX, INC.) 5 July 2018<br>Para. [00010]-[00013], [00078], [00091], [000138], [000160], [000162], [000170], [000193]-[000194], [000196]-[000197], [000199], [000202]-[000204]; figs. 3A-3B, 5A-62 | 1-8 |
| X | US 2017/0273626 A1 (MACDONALD L.S.) 28 September 2017<br>Para. [0033], [0101]-[0104], [0120]-[0121]; fig. 1 | 1-3, 5-8 |
| X | US 2015/0068537 A1 (BECK A.) 12 March 2015<br>Para. [0018], [0041], [0049]; fig. 2A | 1, 3, 5-8 |
| X | US 2018/0193181 A1 (PONA A.) 12 July 2018<br>Para. [0016], [0040]-[0041], [0043], [0046], [0050]; fig. 1-8 | 1, 3, 5-8 |
| X | US 6626172 B1 (KAROW E.M. ET AL.) 30 September 2003<br>Col. 4 lines 43-62; col. 5 lines 46-52; fig. 1-2, 6-8 | 1-7 |

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

*Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 10/06/2022 *(day/month/year)* | 27/06/2022 *(day/month/year)* |

| Name and mailing address of the ISA/SG | Authorized officer |
|---|---|
| **Intellectual Property Office of Singapore**<br>1 Paya Lebar Link, #11-03<br>PLQ 1, Paya Lebar Quarter<br>Singapore 408533<br>Email: pct@ipos.gov.sg | Angelina Lim (Dr)<br>IPOS Customer Service Tel. No.: (+65) 6339 8616 |

# INTERNATIONAL SEARCH REPORT

International application No.
**PCT/SG2022/050131**

**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 2011/0125091 A1 (ABBATE A.J.) 26 May 2011<br>Whole document | - |
| A | US 2012/0010636 A1 (BOEY Y.C.F. ET AL.) 12 January 2012<br>Whole document | - |

# INTERNATIONAL SEARCH REPORT

International application No.
**PCT/SG2022/050131**

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:

   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:

   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:

   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please refer to Supplemental Box (Continuation of Box No. III).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

   1-8

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
**PCT/SG2022/050131**

*Note: This Annex lists known patent family members relating to the patent documents cited in this International Search Report. This Authority is in no way liable for these particulars which are merely given for the purpose of information.*

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2018/125868 A1 | 05/07/2018 | US 2019/0343622 A1 | 14/11/2019 |
| | | CA 3048848 A1 | 05/07/2018 |
| | | CN 110225732 A | 10/09/2019 |
| | | EP 3562446 A1 | 06/11/2019 |
| | | AU 2017388207 A1 | 18/07/2019 |
| | | JP 2020504656 A | 13/02/2020 |
| US 2017/0273626 A1 | 28/09/2017 | WO 2017/165583 A1 | 28/09/2017 |
| US 2015/0068537 A1 | 12/03/2015 | WO 2011/013122 A2 | 03/02/2011 |
| | | CY 1117952 T1 | 17/05/2017 |
| | | PL 2459261 T3 | 30/12/2016 |
| | | US 2011/0048430 A1 | 03/03/2011 |
| | | ES 2587852 T3 | 27/10/2016 |
| | | EP 2459261 A2 | 06/06/2012 |
| US 2018/0193181 A1 | 12/07/2018 | NONE | |
| US 6626172 B1 | 30/09/2003 | AU 4895599 A | 16/11/1999 |
| | | WO 99/55404 A1 | 04/11/1999 |
| | | CA 2330301 A1 | 04/11/1999 |
| | | IS 5692 A | 27/10/2000 |
| | | EP 1075294 A1 | 14/02/2001 |
| | | JP 2002512860 A | 08/05/2002 |
| | | AT 277659 T | 15/10/2004 |
| | | ES 2229733 T3 | 16/04/2005 |
| US 2011/0125091 A1 | 26/05/2011 | EP 2429624 A1 | 21/03/2012 |
| | | CN 106039547 A | 26/10/2016 |
| | | HK 1201125 A1 | 28/08/2015 |
| | | CN 102573981 A | 11/07/2012 |
| | | CA 2761769 A1 | 18/11/2010 |
| | | EP 2754463 A2 | 16/07/2014 |
| | | EP 3103502 A1 | 14/12/2016 |
| | | CA 3001814 A1 | 18/11/2010 |
| | | WO 2010/132648 A1 | 18/11/2010 |
| | | US 2019/0314622 A1 | 17/10/2019 |
| | | AU 2010248992 A1 | 01/12/2011 |
| US 2012/0010636 A1 | 12/01/2012 | EP 2395941 A1 | 21/12/2011 |
| | | WO 2010/093333 A1 | 19/08/2010 |
| | | CN 102316823 A | 11/01/2012 |
| | | JP 2012517319 A | 02/08/2012 |
| | | US 2014/0044861 A1 | 13/02/2014 |
| | | JP 2015147098 A | 20/08/2015 |

# INTERNATIONAL SEARCH REPORT

International application No.
**PCT/SG2022/050131**

**Supplemental Box**
**(Continuation of Box No. III)**

This International Searching Authority found multiple inventions in this international application, as follows:

Group 1: Claims 1-8 relate to an implant suitable for supporting a nasal passage wherein the implant comprises proximal and distal ends, wherein the distal end is expandable.

Group 2: Claims 9-20 relate to a method of making an implant suitable for supporting a nasal passage comprising the steps of forming a structure comprising a plurality of layers, the plurality of layers having at least an internal layer and an external layer and at least one of the internal layer and external layer comprises a shape memory material, wherein the internal layer and external layer are formed from a respective polymer having respectively different intrinsic viscosity; and shaping the structure such that the shape memory material will assume a predetermined shape when positioned in the nasal passage.

Please refer to **Box No. IV** of Written Opinion of The International Searching Authority (Form PCT/ISA/237) for detailed explanation.