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Original Article

Hylonome

A novel tongue implant for tongue advancement for obstructive sleep apnea: feasibility, safety and histology in a canine model

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Abstract

Obstructive sleep apnea (OSA) is a sleep related breathing disorder caused by partial or complete collapse of the upper airway during sleep. The disease is linked with important cardiovascular and cerebrovascular morbidity and mortality. Tongue base collapse is a major cause of upper airway occlusion in OSA and present surgical procedures to prevent this are invasive and inefficient. A novel implantable system to stabilize the tongue was evaluated in a canine model for feasibility, safety and histology. Successful implantation of the Advance System was performed in 21 canines and follow-up evaluations were performed at 30, 60, 90, 120 and 150 days. No technical or clinical adverse events were seen during the procedure. Minor clinical adverse events at some of the follow-up evaluations were treated successfully. Histologic evaluation of the implant was performed at different time points during follow-up and showed good biocompatibility, stability and osteointegration. The outcome of this study resulted in an implant for adjustable tongue advancement in humans with OSA.

Keywords: Tongue, Sleep Apnea

Introduction

Obstructive Sleep Apnea (OSA) is an underappreciated problem in our society resulting in social consequences and health concerns. A mounting body of evidence links the disorder to hypertension, stroke, cardiovascular morbidity and mortality[1], motor vehicle accidents[2] as well as a loss of productivity in the work-force. Treatments have been centered on behavioral modifications, medical treatments, dental and oral appliances, CPAP and surgical procedures to modify the predisposing anatomic abnormalities. There are multiple sites of obstruction identified[3] and successful treatment often requires a step-wise approach. The tongue base is the target of some current treatments for OSA[4]. In some OSA patients, the tongue base has been shown to collapse and contact the rear and side walls of the pharynx and/or the soft palate leading to airway obstruction. Various treatments including radiofrequency (RF) ablation and tongue advancement strategies[5] are used currently to increase the volume of the airway posterior to the tongue to prevent the tongue from obstructing the airway. OSA has been studied in many different species of animals such as lambs[6], goats[7], pigs[8] and rabbits[9]. A perfect model has not been found because naturally occurring sleep apnea has only been demonstrated in the English Bulldog[10]. However, important information about the mechanism and potential adverse effects of the disorder has been learned through these animal studies.

The present study in canines reports on aspects of safety, feasibility and histology of a newly designed anchoring device implanted in the tongue and attached to the mandible. The device provides an advancement of the tongue base, resulting in increased airway volume and reduced tendency of the tongue to collapse during sleep, thereby reducing the occurrence of apneic events in the targeted population. No functional outcome measures were included in this study. The outcome of this study resulted in an implant for adjustable tongue advancement in humans with obstructive sleep apnea[11].

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Figure 1. Tissue anchor.

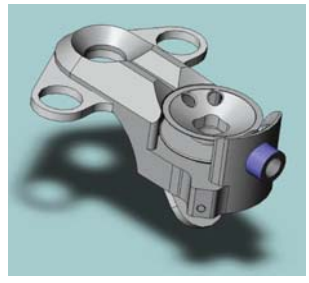

Figure 2. Bone anchor.

Material and method

The present study was performed between August 2005 and February 2006 in a licenced animal laboratory (California, USA). All principles of laboratory animal care (National Institues of Health: publication No. 86-23, revised 1985) were followed.

Test article

The Advance System consists of three components: an anchor system (bone- and tissue anchor), the delivery system, and an implant removal system.

Anchor system: the anchor system comprises a tissue anchor (Figure 1) constructed from titanium alloy (Ti6Al4V) and Nitinol alloy (NiTi), a tether line constructed from Dyneema (DSM, The Netherlands), and a bone anchor (Figure 2) constructed from stainless steel alloy (316LV), and Nitinol alloy (NiTi). The bone anchor is attached to the mandible with titanium alloy (Ti6A14V) bone screws.

Delivery system: the delivery system comprises an access trocar and cannula set used to tunnel into the genioglossal muscle to the intended location for the placement of the tissue anchor. A delivery handle is provided that will contain the tissue anchor in a delivery tube, advance the tissue anchor to the tip of the access cannula and deploy the tissue anchor into the tissue adjacent the tip of the access cannula. Also included in the delivery system is a snare for threading the tether line into the bone anchor, and an adjustor tool to titrate the degree of tongue advancement. The delivery system is constructed from various stainless steel alloys and delrin polymer.

Implant removal system: the implant removal system consists of a tether line snare, and a tunneling trocar and cannula set. This system allows the user to remove the tissue anchor if desired. The tissue anchor may be removed either acutely at the time of the procedure, or after a period of healing has occurred.

The part numbers and lot numbers provide traceability to the test system. The Advance system components will be sterilized via autoclave. Sterilization process indicators are placed on the product packaging.

There is no control test article.

The following accessory devices may be used during this study: bone drill with 1.2 mm drill bit (MicroAire 6000 or similar), cross slot screw driver for 1.5-2.0 mm screws and standard surgical instrument set (scalpel, hemostats, scissors, retractors).

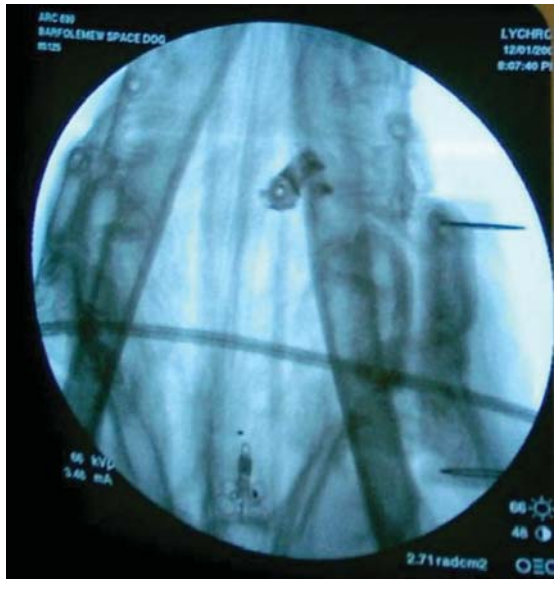

Figure 3. Fluoroscopy image of the implanted tissue anchor and bone anchor.

Test system

Twenty-one adult Hound crossbred canines a minimum of 6 months old are used in this study. The gender of the test system is not expected to influence the study results and either gender are used as provided by the animal source. At the onset of the study, the animals were experimentally naive. Adult animals selected for use in this study are as uniform in age and weight as possible. Their body weights range from 15-30 kg (ideally from 25-30 kg), and their exact age was commensurate with weight, but was a minimum of 6 months old. Animals were identified with a tattooed number.

Implantation

On the day of treatment the animals were anesthetized, weighed and instrumented to undergo the Advance procedure. Prior to the procedure, animals received 5mg/kg enrofloxacine IM once.

Subgroup	Description	Comments
A	Early Development Group	2 samples at 122 and 150 days post-implant. Early anchor designs & delivery/retrieval tools
B	Development Group	3 samples at 84 days. Close to final design & procedure
C	Pre-clinical Group – single fixation screw	2 samples at 30 days of the final implant design placed with one fixation screw and 3 samples at 30 days with a second screw placed at revision procedure
D	Pre-clinical Group – multiple fixation screw	11 samples: 2 at 30 days, 5 at 90 days and 4 at 180 days post-implant representing the final design, materials and implantation procedure.

Table 1. Devices design subgroups.

The implantation procedure involved the placement of a bone anchor in the mandible and a tissue anchor in the anterior tongue of canines. The treatment involved making an approximately 1-2 cm incision on the ventral aspect of the snout approximately 3 cm from the end of the snout. The Advance System was used to place the tissue anchor in the genioglossal muscle near the boundary between the genioglossal muscle and the intrinsic muscles of the tongue. An adjustable bone anchor was placed onto the mandible near the incision site, and the tether line attached to the bone anchor (Figure 3). Tension was placed on the tether line and bone anchor by spooling the tether line onto the bone anchor using the adjustor tool. Following the titration of the tether line tension, the wound was closed in layers, the canine recovered and monitored. After the procedure, buprenorfine 0.01-0.05 mg/kg IM was administered once. Enrofloxacine 5 mg/kg IM or PO SID was continued for a minimum of 7 days post procedure.

Retrieval procedure

At 1-2 weeks post-implantation, the animals were sedated, anesthetized, prepared, weighed and draped for aseptic procedures. Tools were not sterilized in those animals which were to be euthanized at the completion of the retrieval procedure. All animals were positioned for the study in a supine position. The anterior neck and chin was shaved and prepared. After the animal was prepared, the start time of the procedure was documented.

A small incision was made approximately coincident with the previous incision and proximate the estimated location of the bone anchor as determined by digital palpation. The titration needle was inserted through the incision and into the bone anchor. The spool was rotated clockwise and counterclockwise to verify the functionality of the adjustment mechanism and the security of the tissue anchor attachment to the bone anchor.

After verifying the functionality and security of the adjustment mechanism, blunt dissection was used to expose the bone anchor. The tether line was separated from the bone anchor by severing the knot on top of the bone anchor spool and pulling the tether line out of the bone anchor through the guide bushing. The tether lines were threaded into the retrieval system and gripped with the winding tool or a needle driver per the evaluator's preference. Blunt dissection was used to expose additional tether line as necessary to allow the user to get an adequate hold on the tether line by wrapping it several times around the winding tool or needle driver. The retrieval tool was then advanced along the tether line until the proximal hub of the tissue anchor was reached with the dilator tip,verified with fluoroscopy and palpation. The cannula was then further advanced over the tissue anchor while maintaining tension on the tether line until the tissue anchor was fully retracted into the retrieval tool.

Twenty-one canines were used in this study. The study population was divided in 4 subgroups. Implantation of the Advance System was performed in different groups for different purposes. The subgroups are presented in Table 1.

Outcome measures

Evaluation of the implant and the implanted animals were conducted at the time of implantation, at 30 days, 60 days, 90 days, 120 days and 150 days. At each evaluation some animals were sacrificed for histological analysis of the implant and surrounding tissues.

Implant procedure: feasibility was evaluated by measuring the procedure time, length of incision, implantation depth and location, amount of advancement and presence of technical or clinical adverse events.

Retrieval procedure: feasibility of attaching the tether winder to suture, feasibility and safety of accessing the tissue anchor with dilator, recapturing the tissue anchor into the recapture tube and controlling the integrity of the recaptured tissue anchor.

Each animal was clinically evaluated for the presence of infection, seroma formation, hematoma, implant extrusion or exposure, vocalisation and eating pattern at each of the follow-up examinations.

Samples of mandibular bone (bone anchor) and lingual soft tissue (tissue anchor) were harvested from 21 dogs with four distinctive subgroups at specified time points (Table 1). At each time point, the assigned animals were sacrificed and the bone, soft tissues, and associated anchors were removed. The bone anchors and fixation screws were evaluated for stability on the mandible. Finally the specimens were fixed in 10% formaldehyde for histological preparation and evaluation.

The specimens were exposed to soft x-ray to obtain contact radiographs for proper identification of the location and orientation of the anchors in mandible and in lingual tissues. The specimens were trimmed using an EXAKT™ saw to obtain

Characteristic		Grading	Score
I.	Severity on infiltration of lymphocytes	Severe	4
		Moderate to severe	3
		Moderate	2
		Mild	1
		None	0
	Presence of polymorphonuclear cells	Marked	4
		Moderate to marked	3
		Moderate	2
		Mild	1
		None	0
	Presence of macrophages	Marked	4
		Moderate to marked	3
		Moderate	2
		Mild	1
		None	0
	Presence of giant cells	Marked	4
		Moderate to marked	3
		Moderate	2
		Mild	1
		None	0
	Extent of fibrous encapsulation	Severe	4
		Moderate to marked	3
		Moderate	2
		Mild	1
		None	0
	Maximum score of section I		**20**
II.	Bone growth at implant site	Marked	4
		Moderate to marked	3
		Moderate	2
		Little	1
		None	0
	Sub total of section II		**4**
III.	Bone lysis around implant site	Marked	4
		Moderate to marked	3
		Moderate	2
		Little	1
		None	0
	Sub total of section III		**4**

Table 2. Histopathological scoring criteria.

the desired tissue slices, approximately 5 mm thick. The mandibular bone with the bone anchor was prepared in a coronal plane of the jaw through the middle of the anchor (approximately 1 cm x 1 cm x 1.2 cm). A mid sagittal plane was used to prepare the lingual anchor (approximately 1 cm x 1.5 cm), possibly including some portion of the tether line.

The slices were dehydrated and cleared using an automatic processor. Slices were infiltrated and embedded in methylmethacrylate (MMA) medium and sectioned to obtain one 200±50 um thick slide using the EXAKT™ saw. The slides were ground to about 50 um thick and then stained with toluidine blue.

Histopathological assessment of the stained slides was performed to determine the general tissue responses and bone integration. Scoring criteria for the histopathology is summarized in Table 2. Severity of infiltration of lymphocytes and presence of polymorphonuclear cells are evaluated as a measure of local inflammation. The inflammation was first scanned at lower magnification to find clusters of cells and then confirmed at higher magnifications on sections. The sections were viewed again at the lower magnification for an overall estimation by summation of the confirmed areas of cell infiltration at the higher magnifications to obtain a score for each parameter.

Presence of macrophages and giant cells is evaluated as a measure of the activation of local defence against foreign bodies.

Histological analysis was performed on all specimens.

Bone Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**	**Bone Growth**	**Bone Lysis**
533335	1	1	1	1	2	1	0
527939	1	1	1	1	1	1	0
Tissue Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**		
533335	1	0	2	2	1		
527939	4	0	2	0	1		

Table 3. Histopathology scores on bone and tissue anchors – Group A.

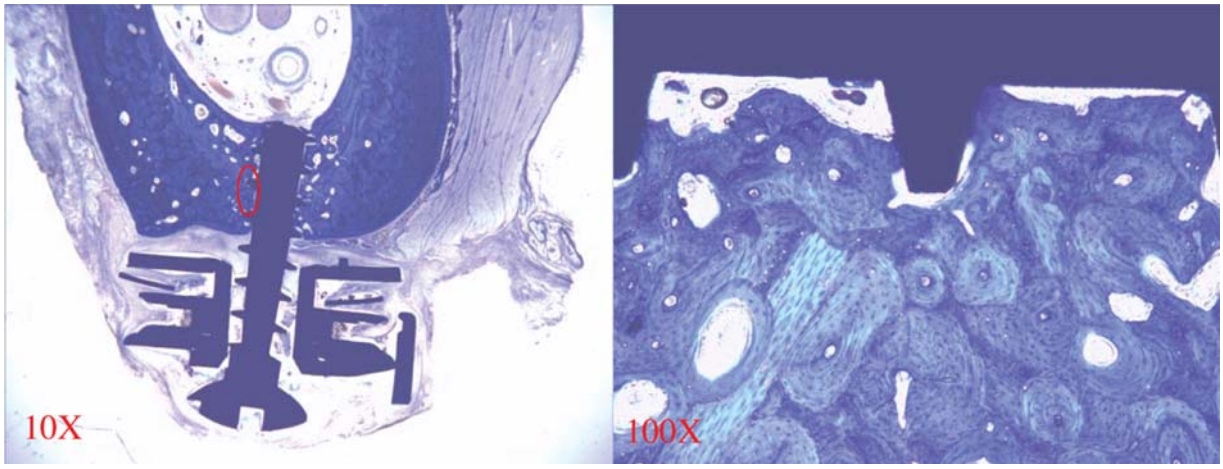

Figure 4. Bone anchor 150 days: **left:** early development bone anchor (527939), 10X magnification, **right** 100X magnification. Toluidine blue stained. Bone remodeling was observed by the presence of bone resorption and bony proliferation adjacent the of the screw and the mandible and on the periost.

Results

Implant procedure

All 21 implant procedures were successfully completed without complications. No device failures or malfunctions were observed at the time of implantation. The average procedure time was 53.5 minutes (range: 36-81 minutes). The average incision length was 27.5 mm (range: 20-43 mm). The tissue anchor was advanced an average of 13.5 mm (Range: 6.7-22.3 mm). The average depth of implantation (canula insertion) was 6.6 cm (range 5.5-7.5 cm).

During the procedure, no complications were observed such as: perforation of the oral cavity, difficulty inserting trocar or delivery system into tongue, vessel perforation, excessive bleeding, damage to the mandible, fracture or failure of any part of the implant or delivery system, excessive force required or other difficulty with titration. The implanting investigator was able to palpate the delivery system and successfully deliver the tissue anchor in the desired location.

Retrieval procedure

The feasibility of attaching the tether winder to the suture, the feasibility and safety of accessing the tissue anchor with the dilator and the recapturing of the tissue anchor into the recapture tube was rated clinically acceptable in all cases. All tissue anchors were intact after retrieval.

Follow up evaluation

During the early follow-up periods (up to 30 days), five of the canines showed wound infection and four showed a seroma at the surgical incision site. All the infections and seromas resolved with antibiotic treatment without the need for surgical intervention. None of the canines demonstrated any other significant health issues during the in-life phase of the study. All canines vocalized normally, ate normally, and showed no signs of distress or pain that might be indicative of damage to or impingement on nerves. No device extrusions into the oral cavity or through the skin have been noted at any time point in any of the implanted animals. On gross examination, the tongue, oral cavity and mandible implan-

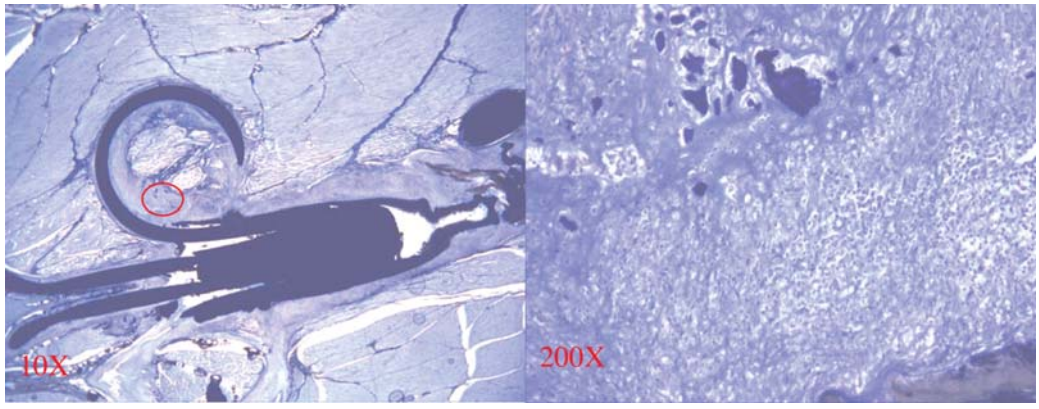

Figure 5. Tissue anchor at 150 days: **left:** early development lingual anchor (527939), 10X magnification, **right:** 200X magnification. Toluidine blue stained. The tissue anchor is incorporated in the tongue muscle with a thin fibrous covering without inflammation outside this fibrous layer.

Bone Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**	**Bone Growth**	**Bone Lysis**
518174	1	1	1	1	1	1	1
518611	3	3	2	2	3	3	2
518786	1	1	1	0	2	1	1
Tissue Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**		
518174	2	1	2	1	1		
518611	4	2	4	1	2		
518786	1	0	2	2	1		

Table 4. Histopathology scores on bone and tissue anchors – Group B.

tation areas appeared normal during the in-life follow-up examinations and at the time of their removal for histology.

Of the 14 bone anchors secured with two fixation screws in this study, only one bone anchor showed signs of instability. In this animal, the central screw affixing the bone anchor was not adequately seated and tightened at the time of implantation. Four out of seven bone anchors secured with a single fixation screw loosened during the study period.

Histology

Group A: early development

The samples of 2 canines were harvested at 122 days (533335) and 150 days (527939). The tissue reaction to the bone anchor was similar and mild in both animals, while the lingual anchors had large variations in the amount of lymphocyte and the presence of giant cells.

Results of histologic evaluation is presented in Table 3. Figures 4 and 5 show histologic images of the bone anchor and tissue anchor at 150 days after implantation.

Group B: development

The samples of three canines were harvested at 84 days. The tissue reactions to the bone anchor and lingual anchor had large variations in all parameters. Animal 518611 contributed the most to the variations, while the other two had mostly mild tissue reactions. Bone growth and lysis in that case might have resulted from the tissue reactions.

Results of histologic evaluation is presented in Table 4. Figures 6 and 7 show histologic images of the bone anchor and tissue anchor at 84 days after implantation.

Group C – Pre-clinical single fixation screw

Two of the five samples (529427 and 541672) had a single fixation screw and were harvested at 30 days. The other three samples (537900, 543608 and 543888) were harvested at 30 days and were originally implanted with a single fixation screw and had a second screw added in a revision surgery. The tissue reactions to the bone anchor and lingual anchor had large variations in all parameters among these five samples.

Results of histologic evaluation is presented in Table 5. Fig-

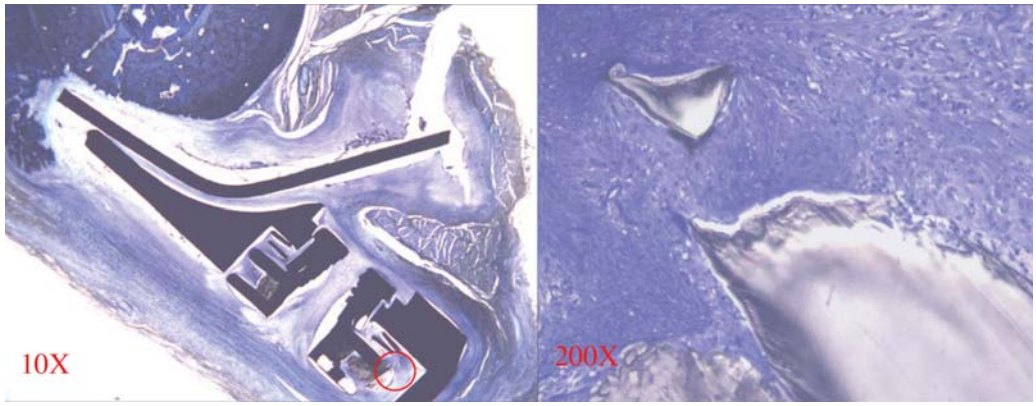

Figure 6. Left: pre-study development bone anchor at 84 days (518174), 10X magnification, **right:** 200X magnification. Toluidine blue stained. A dense fibrous layer is observed between the bone anchor and the mandible.

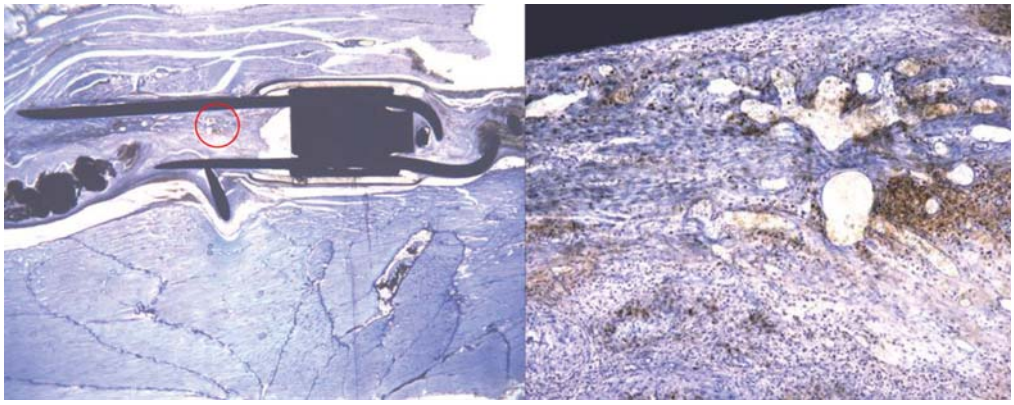

Figure 7. Left: pre-study development lingual anchor at 84 days (518174), 10X magnification. **Right:** 100X magnification. Toluidine blue stained. A fibrous layer of 1 mm encapsulates the tissue anchor (left). No inflammation is seen outside this fibrous layer. Moderate inflammation is observed within the interior portions of the fibrous layer (right). Brown staining is red blood cells which did not get stained due to the thick ground section.

Bone Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**	**Bone Growth**	**Bone Lysis**
529427	1	1	1	0	2	2	0
541672	2	2	1	0	2	2	2
537900	1	2	2	1	1	2	1
543608	2	2	3	1	2	1	2
543888	1	2	1	1	1	1	1
Tissue Anchor							
Animal ID	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**		
529427	4	4	2	1	2		
541672	4	2	4	2	2		
537900	3	3	3	1	2		
543608	1	1	1	2	1		
543888	4	1	3	1	1		

Table 5. Histopathology scores on bone and tissue anchors – Group C.

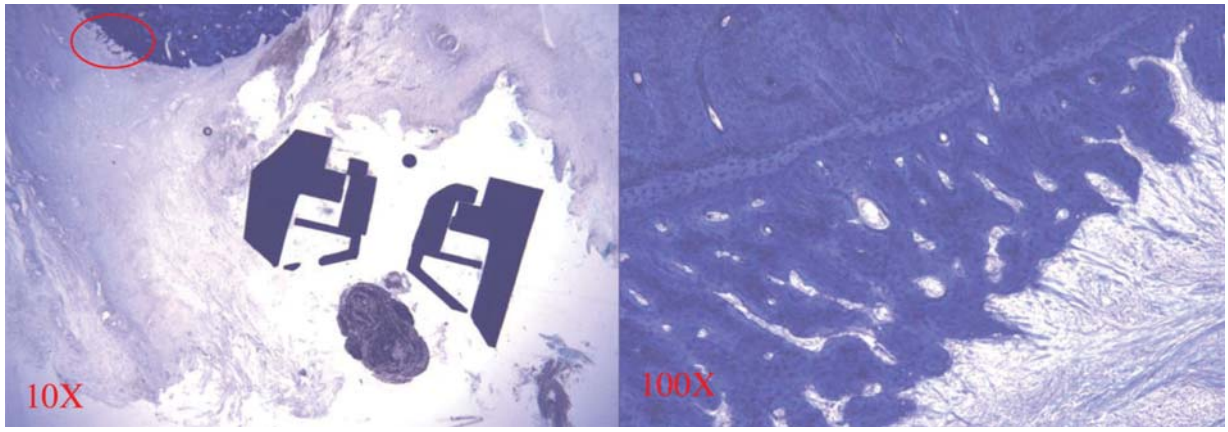

Figure 8. Left: pre-clinical single fixation screw bone anchor at 30 days (529427), 10X magnification. **Right:** 100X magnification. Toluidine blue stained. The original cortical bone is located at top. A band of lighter blue stained bony tissue separates the newly formed woven bone that is perpendicular to the band. Strings of Sharpey's fibers can be seen from the surface of newly formed bone.

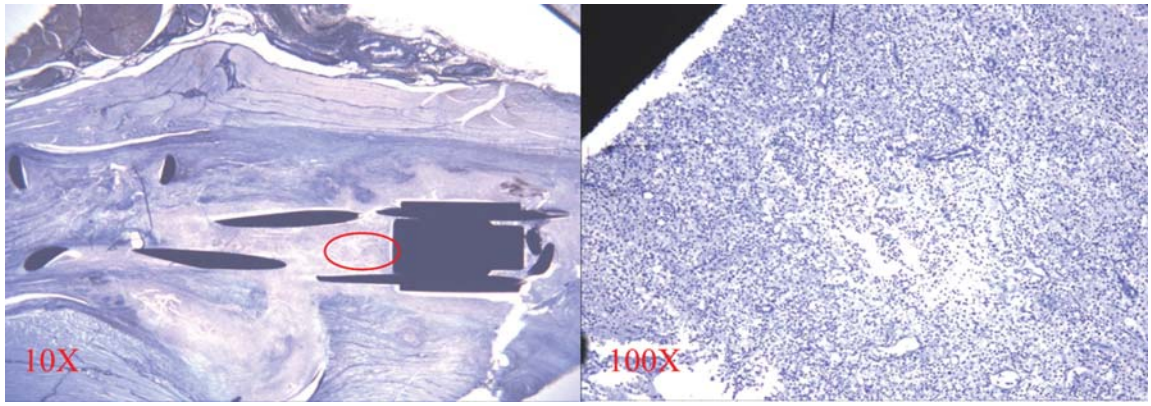

Figure 9. Left: pre-clinical single fixation screw lingual anchor at 30 days (541672), 10X magnification. **Right:** 100X magnification. Toluidine blue stained. The implant part is seen at the top left corner. The tissues seen around the implant part contain many newly formed vessels and obvious infiltration of inflammatory cells.

ures 8 and 9 show histologic images of the bone anchor and tissue anchor at 30 days after implantation.

Group D – Pre-clinical multiple fixation screws

Eleven animals were implanted with the Advance device utilizing two fixation screws. Of these animals, two were sacrificed at 30 days, five at 90 days, and four at 180 days post-implantation. Results of histologic evaluation of the bone anchor is presented in Table 6. Figures 10 and 11 show histologic images of the bone anchor at 90 and 180 days after implantation.

Bone anchor histology

A dense fibrous layer was seen between the bone anchors and the mandible (Figure 6) with direct bone apposition to the screws and/or implant seen in most of the slides at the 90 (Figure 10) and 180 (Figure 11) day timepoints. A 2 to 8 mm thick tissue reaction zone was seen around the bone anchors at 30 days. Outside this reaction zone, normal tissues were present without signs of inflammation. In addition, the width of the zone reduced to a thin layer at 180 days from about 2 mm to 8 mm at 30 days. Bone remodeling was demonstrated at 150 days by bone resorption adjacent the interface of the bone anchor and mandible and bony proliferation on the lateral periosteal and ventral endosteal surfaces (Figure 4 and figure 8).

Results of histologic evaluation of the tissue anchor is presented in Table 7. Figures 12 and 13 show histologic images of the tiisue anchor at 30 and 90 days after implantation.

Tissue anchor histology

Grossly, the tongue and mandible appeared normal in all the samples submitted for analysis. After dissection and slide

Bone anchors pre-clinical evaluation Group								
Animal ID	**Time Points**	**Lymphocytes**	**PMN**	**Macrophages**	**Giant cells**	**Fibrosis**	**Bone Lysis**	**Bone Growth**
544990	30	1	0	1	1	3	1	3
MOVF34152	30	2	2	1	0	2	0	2
30 day average		**1.5**	**1.0**	**1.0**	**0.5**	**2.5**	**0.5**	**2.5**
2X128	90	1	0	1	1	3	0	1
35153	90	2	3	2	1	1	3	3
85125	90	1	2	2	1	1	0	4
34189	90	1	0	2	2	3	1	1
54253	90	2	3	2	1	1	1	3
90 day average		**1.4**	**1.6**	**1.8**	**1.2**	**1.8**	**1.0**	**2.4**
24253	180	1	3	2	1	2	1	2
545031	180	1	0	1	1	3	0	2
34325	180	1	0	1	1	3	0	2
24382	180	1	0	1	1	1	0	1
180 average		**1.0**	**0.8**	**1.3**	**1.0**	**2.3**	**0.3**	**1.8**

Table 6. Histopathology evaluation on bone anchors – Group D.

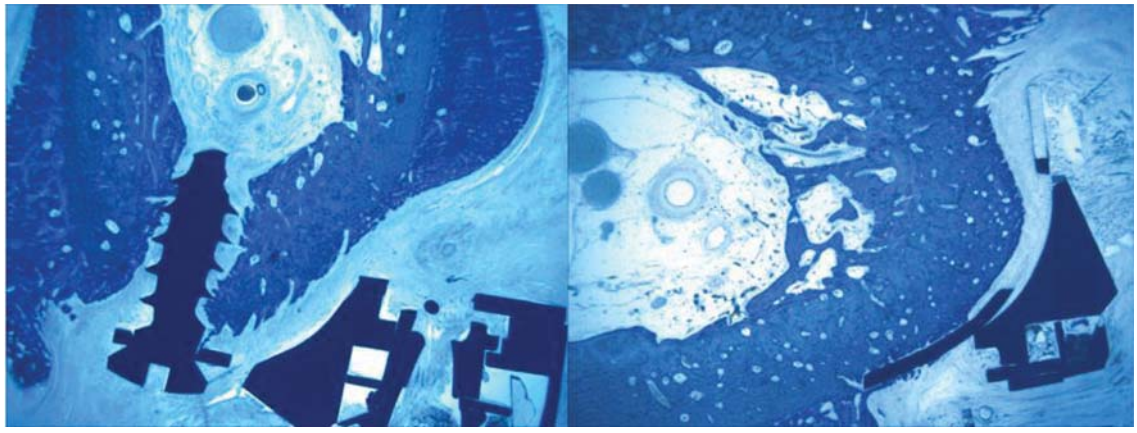

Figure 10. Bone anchor at 90 days. **Left:** screw with fibrous tissue and some bone attachment. **Right:** direct bone apposition to implant.

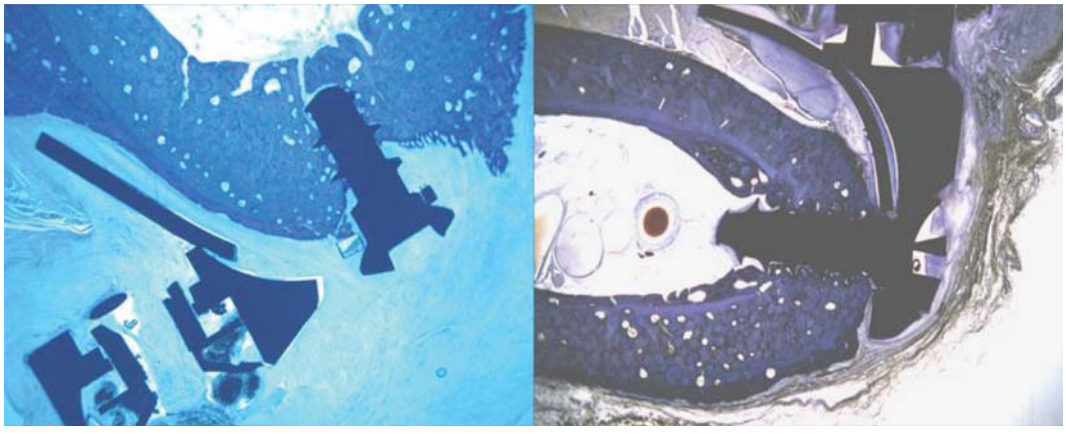

Figure 11. Bone anchor at 180 days. Seamless screw-bone apposition is seen in both slides and bone proliferation in response to mechanical stresses.

Tissue anchors pre-clinical evaluation Group						
Animal ID	**Time Points**	**Lymphocytes**	**PMN**	**Macrophages**	**Giant Cells**	**Fibrosis**
544990	30	1	0	2	1	1
MOVF34152	30	4	1	4	1	2
30 day average		**2.5**	**0.5**	**3.0**	**1.0**	**1.5**
2X128	90	1	1	2	2	2
35153	90	3	2	3	1	1
85125	90	3	1	3	2	2
34189	90	1	0	2	1	1
54253	90	3	2	3	1	1
90 day average		**2.2**	**1.2**	**2.6**	**1.4**	**1.4**
24253	180	1	1	1	1	1
545031	180	1	0	1	1	1
34325	180	1	0	1	1	1
24382	180	1	0	1	1	1
180 day average		**1.0**	**0.3**	**1.0**	**1.0**	**1.0**

Table 7. Histopathology evaluation on tissue anchors – Group D.

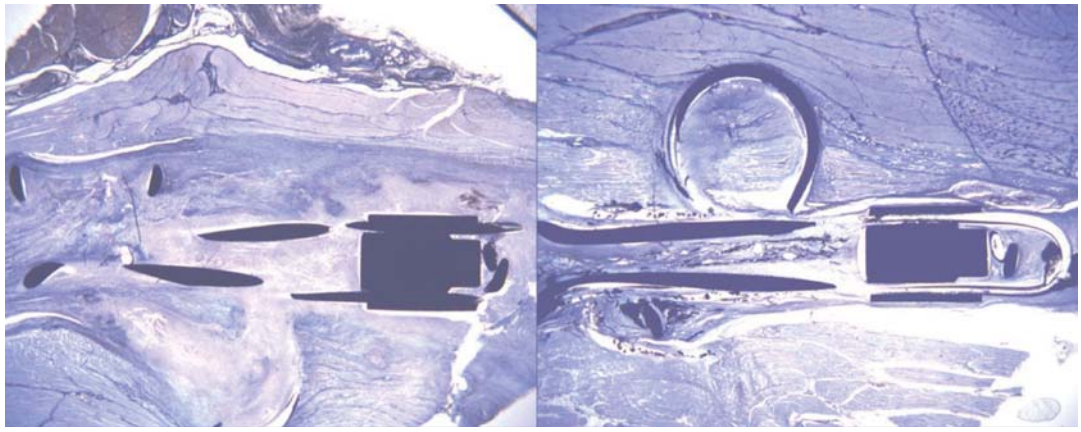

Figure 12. Tissue anchor at 30 day. Tissue anchor is incapsulated in thin layer of fibrous tissue surrounded by normal muscular tissue.

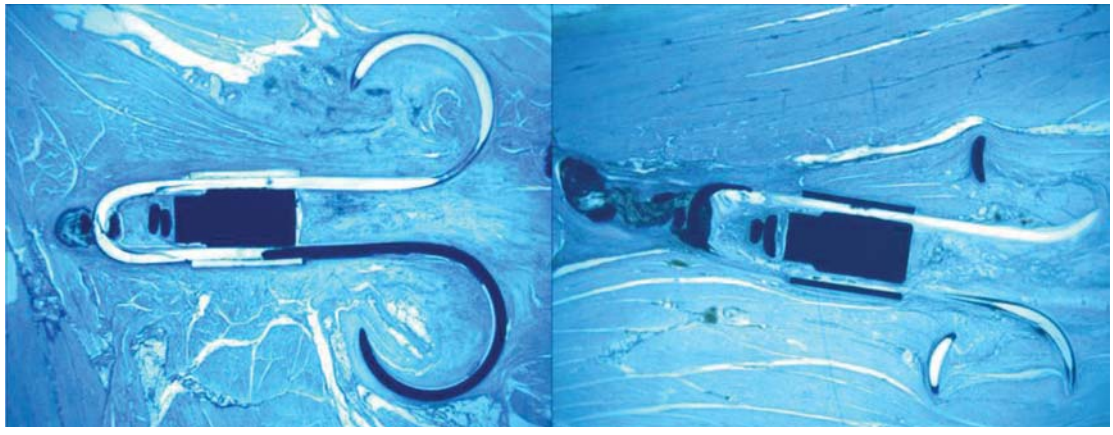

Figure 13. Tissue anchor at 90 days. Tissue anchor is incapsulated in thicker layer of fibrous tissue surrounded by normal muscular tissue.

preparation, histopathological analysis of the tissue anchor showed similar tissue components at all three time points, and the severity of the tissue reactions reduced with time. A thin 0.5 to 1.0 mm thick fibrous layer encapsulated the tissue anchor at each time point (Figure 5 and figure12). Histologically normal striated muscle was seen surrounding the encapsulated tissue anchor. The tissue anchor is incorporated into the tongue muscle with a thin fibrous covering without inflammation of the tongue muscle outside the fibrous layer and mild to moderate inflammation observed within the interior portions of the fibrous layer (Figure 7 and figure 9). The points of the tissue anchor barbs did not appear to cause any clinically significant effects such as erosion or chronic irritation of the muscle tissue. The lack of residual fibrous tissue dorsal to the tissue anchor indicates the tissue anchor was stable in the tongue muscle with no evidence of migration through the tongue or other instability. The tissue anchor was well-tolerated within the tongue muscle and was well-healed in all the samples at 180 days.

Discussion

This study is an evaluation of the feasibility and safety of a new tongue implant for the treatment of obstructive sleep apnea. Histologic analysis of the two parts of the implant was performed to evaluate tissue reaction and stability of the implant in canines.

The fact that all procedures were performed successfully and no device failures or complications were reported resulted in a new procedure for treatment of obstructive sleep apnea that is safe and feasible in humans.

Some canines showed wound infection or seroma. These infections were related to difficulty in wound management and cleanliness of the surgical site in the canine model.

The seromas appeared to be related to the inability to place a suitable drain in the snout of the canine due to the attending increase in infection risk associated with the placement of drains in canines.

One bone anchor secured with 2 fixation screws showed signs of instability. Four bone anchors secured with one single screw loosened during the study period. In the final design of the bone anchor for human implantation, the bone anchor will be secured with three screws which will further enhance the stability.

Histologic evaluation of the bone anchor and tissue anchor showed only limited inflammation at 30 days. This inflammation decreased over time.

The tissue anchor was incapsulated in a fibrous layer. This finding is in accordance with other studies evaluating titanium biocompatibility[12]. The surrounding muscle tissue was free of inflammation. These findings support the biocompatibility of the implant. The implant is well tolerated by the canine tongue.

Around the bone anchor, bone reformation and remodelling could be in favor of the stability of the implant fixed in the mandible. This remodeling is apparently in response to the biomechanical loading of the bone anchor and mandible due to the tension supplied by the tissue anchor connection. The strings of Sharpey fibers are probably the result of the traction of the bone anchor on the mandible. Bone matrix was particularly abundant and thick at 150 days, indicating progressive mineralization and maturation of remodeled bone matrix and compatibility of the implant[13].

Local inflammation around the bone anchor and tissue anchor are mild and decrease over time (Table 4). Foreign body reaction around both parts of the implant are mild in the early phase after implantation, have the tendency to increase at 90 days and decrease again at 180 days. The presence of giant cells was observed by other investigators using titanium bone screws in the mandible[14].

Conclusion

The implantation of the Advance System is safe in the canine model. Technical success was achieved in all dogs clinically. There were no procedural complications observed that required revision. The seromas and infections noted during the *in vivo* portion of the study did not appear to adversely affect the healing of the implanted components nor involve or originate from the implants.

The implant devices are well-tolerated in the canine as evidenced by gross examinations in-life and post-mortem as well as histopathological examination of the explanted tissues and devices. No adverse health consequences or other complications on the mandible or tongue of the canines related to the implant were evident with up to 16.5 mm of advancement. Infections and seromas observed within the study are related to wound management difficulties specific to the canine model which are not relevant to human clinical cases. Histological evaluation indicates good healing responses for both the tissue and bone anchors. The bone anchor appeared to be stable in position to the mandible in all cases where the bone screws were sufficiently secured in the intended places, and the mandible exhibited a remodeling response accommodative to the biomechanical loading of the bone anchor. Histology of the tissue anchors showed a thin fibrous layer encapsulating the tissue anchor, and a lack of tissue anchor migration at time points up to 180 days as evidenced by a lack of a residual trail of fibrous tissue distal to the anchor. The components of the Advance System were found to be benign, well-tolerated, and suitable for implantation in the tongue.

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