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XYMPHONY™

Contour Adapting Resorbable Membrane

Xymphony™ Contour Adapting Resorbable Membrane
In Vivo And In Vitro Testing Summary

Summary Of In Vivo Use Of Bioresorbable Xenograft Materials
In The Treatment Of Intrabony Three-Wall Defects In
A Canine Model & Follow-Up Comparative In Vitro
Suture Tear Resistance Testing

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ABSTRACT:

The in vivo study evaluated two bioresorbable xenograft barrier membranes (Salvin Xymphony™ Contour Adapting Resorbable Membrane and Geistlich Bio-Gide®) to evaluate local tissue response and membrane resorption profile when implanted over a three-wall periodontal defect model in canines. An intrabony three-wall defect was created in the buccal wall of the mandible bilaterally at the extraction sites of the second and fourth premolars (P2 and P4). Each defect site was filled with marketed bone void filler Bio-Oss® (Geistlich) and two defects per animal were covered with either Xymphony™ Contour Adapting Resorbable Membrane or Bio-Gide®. The study evaluated local tissue response, resorption profile, and barrier function in beagle dogs at 2, 4, 9, 16, 24 and 33 weeks. Xymphony™ was last detected overlying the defect sites at four weeks while Bio-Gide was detected at all time points. By nine weeks, the fibrous tissue infiltration into the defect site was similar between Xymphony™ and Bio-Gide®, and remained similar at the 16, 24, and 33 week time points. Barrier function, as determined by new bone formation, was similar between the two membranes at all time points after two weeks, and new bone formation may have trended slightly higher at the Xymphony™ sites at 33 weeks. Time five minutes and time 24 hours in vitro suture tear resistance testing revealed that Xymphony™ had greater than twice the suture tear resistance when compared to the Bio-Gide® membrane at both time periods.

Materials

Barrier Membrane Materials:

Xymphony™ Contour Adapting Resorbable Membrane is a resorbable porcine derived extracellular matrix (ECM) barrier membrane manufactured using a proprietary process called OPTRIX, that gently removes cellular components and inactivates viral agents that may be present in the starting material, while maintaining the natural structure of the source tissue without cross-linking. Xymphony™ Contour Adapting Resorbable Membrane is intended for guided tissue and bone regeneration in dental applications. Xymphony™ is placed between bone graft material and soft tissue to maintain a barrier between the healing defect and healthy tissue, retarding fibrous tissue ingrowth, allowing bone or tissue regeneration at the defect site. Xymphony™ has an average thickness of 0.14 mm (140 microns) (Figure A) with an overall porosity of 76%. Xymphony™ is provided sterile via ethylene oxide, in a double pouch configuration.

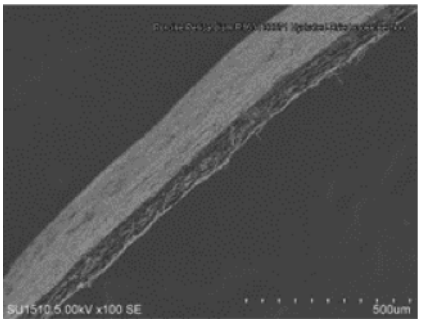


Figure A:
SEM Image - Cross-Section - 100X

Bio-Gide® is a porcine-derived non cross-linked collagen membrane processed by standardized, controlled manufacturing techniques that remove non-collagenous components. Bio-Gide® has a bilayer structure: A porous surface on one side and a dense surface on the other. Bio-Gide® has an average thickness of 0.64 mm (640 microns) (Figure B) with an overall porosity of 86%. Bio-Gide® is provided sterile via gamma irradiation in double blisters.

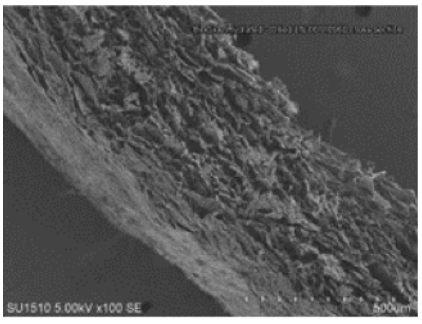


Figure B:
SEM Image - Cross-Section - 100X

Bone Void Filler Material:

Bio-Oss® is a granular porous bone mineral matrix produced by removal of organic components from bovine bone. Bio-Oss® is physically and chemically comparable to the mineralized matrix of human bone. Bio-Oss® is sterilized by gamma-irradiation.

Methods for In Vivo Study:

In Vivo Study Subjects:

Eighteen adult beagle dogs were included in the study providing six defects per treatment group per time point for evaluation. Within three days prior to the surgical procedures, a detailed observation and an oral health examination was conducted. The day before surgery, each animal was weighed and fasted. On the day of surgery, each animal was pre-anesthetized with an intramuscular dose of acepromazine maleate (0.2 mg/kg). General anesthesia was induced by intravenous propofol (4 mg/kg, to effect). An intravenous catheter was placed in a forelimb for intravenous access and a saline drip for hydration. A subcutaneous injection of buprenorphine (analgesic) dosed at 0.02 mg/kg was administered. A non-medicated ophthalmic ointment was applied to both eyes of each animal as necessary to protect the corneas from drying. Each animal was intubated and placed on isoflurane inhalant anesthetic for continued general anesthesia. A full-mouth scaling was performed on each animal. All teeth were scaled and planed using an ultrasonic scaler. Following scaling, the teeth were polished. Radiographs were taken of the second (P2) and fourth (P4) pre-molars in each mandible to confirm root morphology and to document mandible condition prior to tooth extraction/defect creation.

In Vivo Study Surgical Procedure:

The buccal and lingual gingiva were elevated and a full thickness gingival flap (buccal side) was created to expose the mandibular bone. Following tooth extraction, a defect was created in the buccal wall which spanned the extraction site. The three-wall defects measured 2mm deep x 7mm long x 5mm wide. Bio-Oss® was hydrated with sterile saline per the manufacturer's IFU and formed into the intrabony defect, including any empty root socket in the area of the defect. Xymphony™ was hydrated in sterile saline for a minimum of five minutes and placed over a corresponding defect site. Bio-Gide® was prepared and implanted over a corresponding defect site per the manufacturer's IFU; the dense surface printed with "UP" facing the soft tissue, and the rough surface facing the bone. The membranes were placed at the lingual side between the mandible and the gingival tissue, and then pulled over the defect to the buccal side with an overlap of the defect walls by at least 3mm to allow for complete defect coverage. The final dimensions of the membranes were measured and recorded. While the membranes were expected to self-adhere to the gingival tissue, two Salvin Bone Tacks were placed on the buccal side to aid in fixation of membrane corners. The gingival flap was closed with 4-0 PDS suture. Suture tension was minimized to prevent dehiscence. After suturing, the surgical site was rinsed with 0.12% chlorhexidrine solution. At the end of surgery, Tramadol was orally administered at a dose of 3-5mg/kg and the antibiotic Clindamycin was orally administered at a dosage of 7-11mg/kg. Tramadol continued to be administered twice daily for the next four days, and Clindamycin continued once daily for the next six days.

In Vivo Study Evaluations:

At the completion of each time point (2, 4, 9, 16, 24 and 33 weeks) implant sites were isolated, decalcified, and embedded in paraffin. Two slides were prepared as transverse sections; one slide was stained with hematoxylin and eosin (H&E) and the other was stained with Masson's trichrome. These slides were provided to a board certified veterinary pathologist for histological evaluation.

Cellular Response - The H&E stained sections at 2, 4, 9, 16, 24 and 33 weeks were evaluated for cellular response to the membranes. Cellular response at the rostral, middle, and caudal regions of each defect were graded according to Tables E.1 and E.2 in ISO 10993-6, Annex E.

Resorption and Barrier Function - Performance of Xymphony™ and Bio-Gide® was evaluated using Masson's trichrome stained sections at 2, 4, 9, 16, 24, and 33 weeks. Device performance in the animal study was evaluated based on the membrane degradation, the extent of fibrous tissue infiltration into the bony defect, and the amount of new bone formed in the defect at each time point. The rostral, middle, and caudal regions of each defect were graded for membrane degradation, fibrous tissue infiltration, and new bone formation.

Results for In Vivo Study:

Cellular Response:

Overall, no significant adverse gingival health observations were noted. Typical mild focal gingival inflammation was seen for both Xymphony™ and Bio-Gide® at the two week time point along with histologic appearance of neutrophils and macrophages, which are expected to be present in an early host response to a resorbable implant. At the four week time point both clinical and histologic signs of inflammation were largely resolved and both articles were considered non-irritant. This non-irritant classification continued for both Xymphony™ and Bio-Gide® through the rest of the study time points.

Resorption Profile:

Xymphony™ was no longer histologically identifiable in any study animal by the nine week time point. Bio-Gide® was histologically identifiable throughout the 33 week time point in all animals. Occasionally Bio-Gide® was not visible directly over the defect, however it was present overlying adjacent bone at all time points.

Barrier Function (New Bone Formation):

Both the Xymphony™ Membrane and the Bio-Gide® Membrane maintained their barrier function and retarded fibrous tissue infiltration throughout the 33 week time period. New bone growth was seen to increase at all time points for both membranes through the 24 week time point and volume of new bone was similar between Xymphony™ and Bio-Gide®. (See Figure C & D) Barrier function, as determined by new bone formation, was similar between the two membranes at all time points after two weeks, and new bone formation may have trended slightly higher at the Xymphony™ sites at 33 weeks.

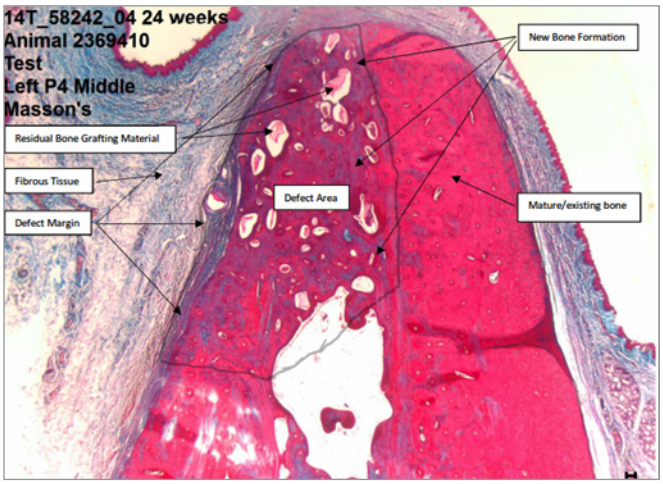


Figure C:
Test Article - Xymphony™ - 24 Weeks Post-Op

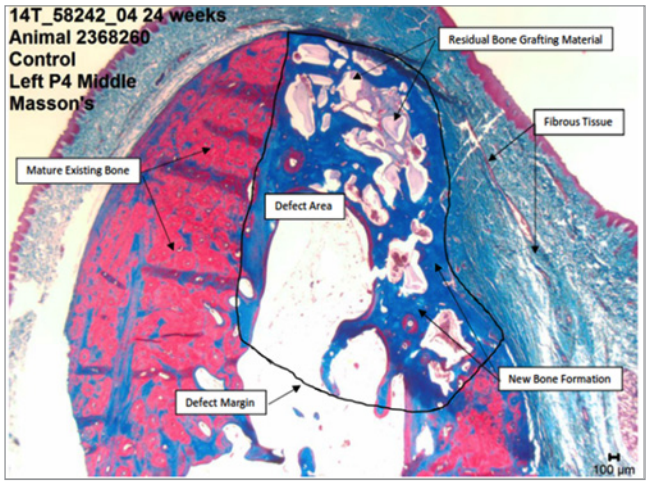


Figure D:
Control Article - Bio-Gide® - 24 Weeks Post-Op

Methods for In Vitro Study:

In Vitro Study Suture Tear Resistance Procedure:

A side-by-side comparison of Xymphony™ and Bio-Gide® was performed to evaluate the membranes' ability to withstand suture tear when sutured to maintain device positioning. All samples were hydrated in saline. Thirty samples of Xymphony™ after five minute hydration were evaluated, and fifteen samples of Xymphony™ after 24 hour hydration were evaluated. Fifteen samples of Bio-Gide® after five minute hydration were evaluated, and fifteen samples of Bio-Gide® after 24 hour hydration were evaluated. Testing was performed by loading the sample devices into pneumatic grips of an Instron Test Stand after hydration for the prescribed minimum five minutes or 24 hours, and applying 0.5N at 125.00 mm/min to record the suture tear resistance strength.

Results for In Vitro Study

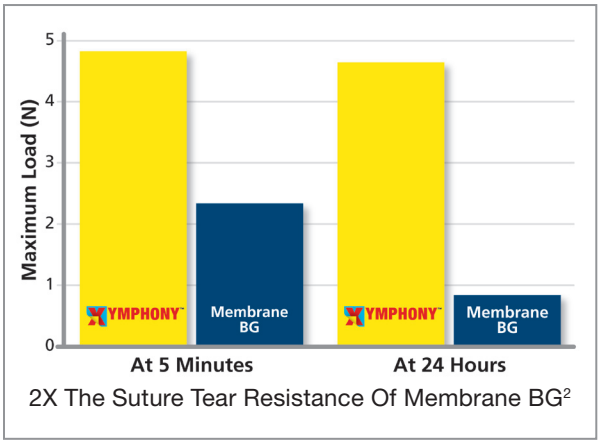
In Vitro Study Suture Tear Resistance:

Suture tear resistance testing was performed on Xymphony™ and Bio-Gide® to compare the suture tear resistance strength of each device, with summary data available in Table A and Figure E. A five minute hydration test simulated suture tear resistance at device implantation. Xymphony™ demonstrated a significantly higher suture tear resistance strength than Bio-Gide®. A 24 hour hydration / incubation test was included to represent suture tear resistance 24 hours post-implantation. Again, Xymphony™ demonstrated significantly higher suture tear strength compared to Bio-Gide®. Both devices experienced decreases in average suture strength between the five minute and 24 hour time point. However, Xymphony™ did not have a significant change over the 24 hours, which demonstrates that the initial suture tear resistance is maintained 24 hours post-implantation.

Table A: *Suture Tear Resistance Over Time*

	5-Minute Hydration		24-Hour Hydration		5-minute vs. 24-hour Comparison: **Percent Decrease**	
	Xymphony™	Bio-Gide®	Xymphony™	Bio-Gide®	Xymphony™	Bio-Gide®
Average	4.802 ± 1.53 N	2.363 ± 0.49 N	4.774 ± 0.99 N	0.845 ± 0.26 N	0.59%	64.25%

Figure E: *Suture Tear Resistance Over Time*



2X The Suture Tear Resistance Of Membrane BG[2]

Discussion

The Xymphony™ Membrane, manufactured using the proprietary OPTRIX process, is 1/4th the thickness of the Bio-Gide® membrane. Even though substantially thinner, testing shows that Xymphony™ Membrane has twice the suture tear resistance in comparison to Bio-Gide® after five minutes of hydration, and after 24 hours of hydration, Bio-Gide® lost 64% of its original suture tear resistance strength compared to only 0.5% loss of original suture tear resistance strength for Xymphony™.

Both Xymphony™ and Bio-Gide® maintain barrier function through 33 weeks as evidenced by the comparable fibrous tissue infiltration and new bone formation. However, Bio-Gide® can still be seen within the surgical site at 33 weeks, while the Xymphony™ barrier resorbed in less than nine weeks, without loss of barrier function during the 33 week study.

It is apparent from the above summary of in vivo and in vitro testing that use of the OPTRIX process results in a natural extracellular matrix with unique handling and strength characteristics. This is specifically evidenced by in vivo study results showing that Xymphony™ was indistinguishable from the surrounding tissue at nine weeks post implantation, while at the same time, maintaining barrier functionality.