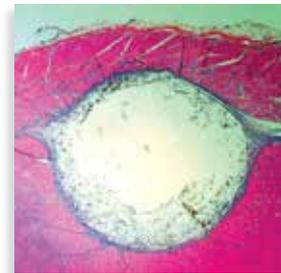


Cordis EXOSEAL[®]

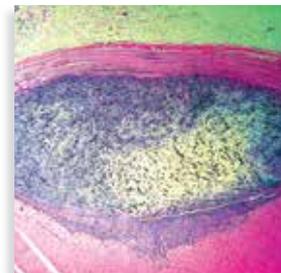
Vascular Closure Device

Polyglycolic Acid Plug (PGA)

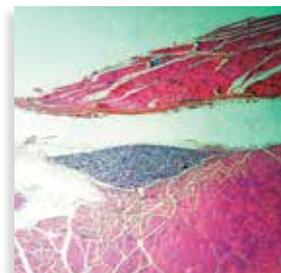
Material Absorption and Tissue Reaction Assessment



3 Days*



14 Days*



60 Days*



Polyglycolic Acid Plug

Material Absorption and Tissue Reaction Assessment

Rabbit-Intramuscular Model

Multiple animal studies have been conducted to evaluate the absorption profile and tissue reaction of the Cordis **EXOSEAL**® Vascular Closure Device bioabsorbable PGA plug. In addition to the plug absorption assessment conducted and described above under Series Number Two: Chronic Porcine Model Study (Gen 1.0), 60- and 90-day Intramuscular Implant Testing was conducted in the paravertebral muscles of rabbits, 90-day Implant Testing was conducted in the Rat Gluteal Flap Model, and 60-day Implant Testing was conducted in swine arteries. These non-clinical laboratory studies were performed in compliance with Good Laboratory Practice (GLP) per 21 CFR Part 58. The implant testing results are presented below.

This non-clinical laboratory study was performed by Northview Pacific Laboratories, Inc. (Hercules, CA) in accordance with ISO 10993-6 guidelines in the paravertebral muscles of the rabbit. The Cordis **EXOSEAL**® Vascular Closure Device bioabsorbable plug was implanted on Day 0 in the paravertebral muscles of six New Zealand White rabbits and remained implanted for either 60-days (n=3) or 90-days (n=3). At the end-of-study time-points, the implants and surrounding tissue were harvested and evaluated for evidence of haemorrhage, necrosis, discoloration, infection and encapsulation. An independent pathologist conducted histopathology assessments to assess the local tissue response and resorption properties of the plug.

All animals survived until their scheduled necropsies and there were no significant clinical findings or changes in body weights over the course of the study.

The results of this study demonstrate that the Cordis **EXOSEAL**® Vascular Closure Device bioabsorbable plug is biocompatible in the rabbit muscle under the conditions of this model with no gross evidence of local irritancy from the implant material at both the 60- and 90-days evaluations points. The 60-day study results demonstrated an advanced absorption response to the implant material with complete absorption at 90 days.



Polyglycolic Acid Plug

Material Absorption and Tissue Reaction Assessment

Rat - Gluteal Flap Model

This study was conducted to evaluate the absorption profile and tissue reaction of the Cordis EXOSEAL® Vascular Closure Device bio-absorbable Plug following implantation in a fascial pocket created above the gluteal muscle of a rat. Six (6) treatment groups of 2 to 5 female Long Evans rats were surgically implanted with the Cordis EXOSEAL® Vascular Closure Device bio-absorbable Plug in the fascial pocket above the gluteal muscles. The Plugs were implanted on Day 0 and remained implanted for a 3, 7, 14, 30, 60 (± 1), or 90 (± 1) day recovery period.

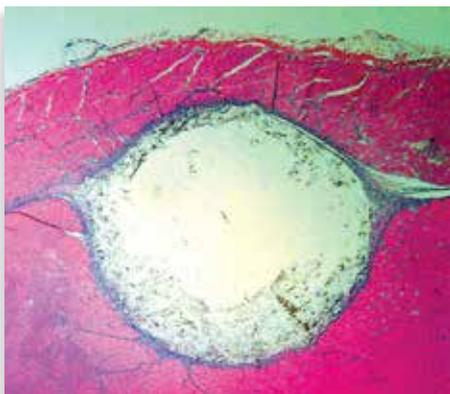
All animals survived until their scheduled necropsies and there were no significant clinical findings or changes in body weights over the course of the study.

Absorption of the polymeric fibers of the Plug progressed during the course of the study. The first indication of this process was a minor change in fiber staining at Day 7. By Day 60 there had been notable loss in fiber mass and at Day 90, 1 of the 2 evaluable sites was considered to have advanced absorption (little material remained at the site, but could still see extra-cellular material). The 7 implant sites that were not identifiable at trimming or histologically were considered to be "missing" sites, rather than implants that had undergone total absorption (majority of intracellular material was no longer recognizable as such, although there still may have been macrophages and chronic

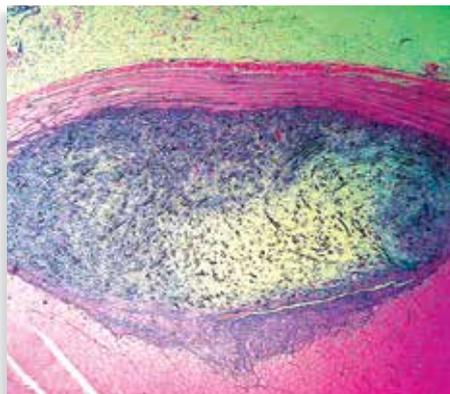
inflammatory cells at the site). There were no sites that showed features indicative of total implant absorption. Plug absorption progressed during the course of the study, but was not complete at Day 90. Average tissue reaction grades to the Plug were in the minimal range at 3, 7, and 90 days and in the slight range at 14, 30 and 60 days post-implantation. Overall tissue reaction grades ranged from minimal to "high" slight (1, Day 7 site). Minor (trace to slight) myocyte necrosis directly adjacent to the implant sites was limited to the acute (Day 3) period. Additional myocyte damage very suggestive of or definitely due to surgical (implantation) trauma was also noted in the majority of Day 3 sites (and as regenerating muscle in many later sites). There was no evidence of ongoing necrosis at any of the periods beyond Day 3. There was no notable apoptosis of inflammatory cells associated with any of the implants.

The results of this study demonstrate that the Cordis EXOSEAL® Vascular Closure Device bio-absorbable Plug is biocompatible in the rat gluteal muscle under the conditions of this model with no gross evidence of local irritancy from the implant material. Additionally, this study demonstrated that absorption of the Plug progressed over the course of the study with advanced absorption seen by 90 days. The slower absorption profile observed with the Plug in the rat gluteal flap model versus the rabbit paravertebral

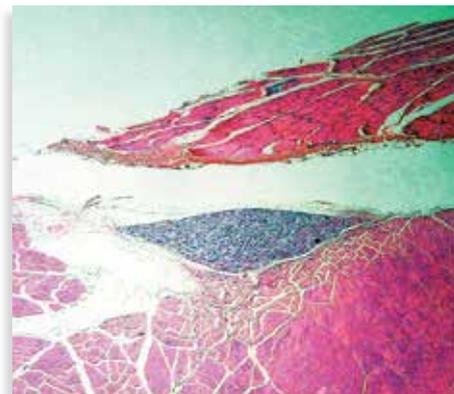
muscle model most likely reflects differences in the size of the Plug relative to the size of the implant sites and the amount of blood that the Plug is exposed to during the implant procedure. In the rat study, Plugs were implanted in pockets surgically created between the gluteal muscle and the fascia. The mass of the Plug is relatively large compared to the mass of the gluteal muscle and the thin fascia above it. In contrast, the mass of the Plugs is relatively small compared to the large paravertebral muscles of the rabbit into which they were implanted. Since the Plugs were completely surrounded by muscle in the rabbit, they were most likely exposed to more interstitial fluid and experienced more rapid cellular infiltration than the Plugs in the rat gluteal flap. Since the PGA material degrades by hydrolysis, the presence of a greater amount of interstitial fluid (i.e., water) and more rapid cellular infiltration would be expected to result in more rapid hydrolysis and absorption of the Plug in rabbit muscle. In addition, when the fascial pocket is created above the rat gluteal muscle there is very little if any bleeding. In contrast, when the Plugs are implanted in the rabbit paravertebral muscle with a hypodermic needle, there is considerable bleeding in the muscle and the Plugs most likely absorb more blood during the procedure than in the rat, which would also contribute to more rapid hydrolysis and absorption.



3 Days



14 Days



60 Days

Swine - Femoral Artery Model

This study was conducted to evaluate the absorption profile and tissue reaction of the Cordis **EXOSEAL**[®] Vascular Closure Device bio-absorbable Plug following arteriotomy closure in swine femoral arteries. Three treatment groups of 3 male Landrace-Duroc cross swine were surgically implanted with the Cordis **EXOSEAL**[®] Vascular Closure Device bio-absorbable Plug, via an arterial sheath inserted into the femoral arteries. The Plugs were implanted on Day 0, and remained implanted for a 14, 30 (± 1), or 60 (± 1) day recovery period.

Implantation of the Plugs was not associated with any unexpected mortality or changes in body weights or clinical pathology parameters. There were no macroscopic findings in the arteries implanted with the bio-absorbable Plug.

The Plug was not identified at Day 14 in 2 of 5 arteries in which the Plug was implanted. However, for the 5 arteries in which a Plug was implanted, the location from which the sections were obtained was correct, as the tissue reaction to the Plug was present. In the 2 arteries in which the Plug was not identified, the absence may have been due to complete absorption of the material, or the Plug may not have been captured in the histologic plane of the sections examined due to the small size of the device and shrinkage artifacts of fixation. Of the 3 arteries in which the Plug was identified, the Plug was not absorbed (i.e. most of the device was in the vessel wall or around the artery) in 2 of the arteries, but was in advanced absorption (i.e. the majority of implant was absorbed but with little extracellular and intracellular material remaining) in the third artery. In all arteries, the lumen was patent and completely endothelialised. In the arteries in which the Plug was present, the Plug fibers were located mostly in the adventitia of the artery and were embedded and surrounded by varying degrees of granulomatous inflammation, with many epithelioid macrophages and multinucleated giant cells, occasional

eosinophilic infiltration, and fibrosis. The site of arteriotomy was present in a few sections and included changes of haemorrhage, intimal hypertrophy/hyperplasia, and fibrin deposition. The arteriotomy site was healed but was not remodeled (i.e. did not return to the morphology of a normal, uninjured artery). Occasionally, there was also intimal mucinosis, mineralization, mononuclear cell infiltration, and neovascularisation.

The Plug was not identified at Day 30 in 3 of 6 arteries in which the Plug was implanted. However, the location from which the sections were obtained was correct, as the tissue reaction to the device was present in all sections examined. In the 3 arteries in which the Plug was identified, the Plug exhibited varying degrees of absorption ranging from partial (i.e., majority of implant present, but with some absorption) to essentially absorbed (i.e., majority of implant absorbed with only intracellular material remaining). In all arteries, the lumen was patent and completely endothelialised. In the arteries in which the Plug was present, the Plug fibers were located mostly in the adventitia of the artery and were embedded and surrounded by varying degrees of granulomatous inflammation, with many epithelioid macrophages and multinucleated giant cells and fibrosis. The site of arteriotomy was present in a few sections and included changes of haemorrhage, intimal hypertrophy/hyperplasia, and mineralisation. The arteriotomy site was healed, but was not remodeled. Occasionally, there was also mononuclear cell infiltration and neovascularisation.

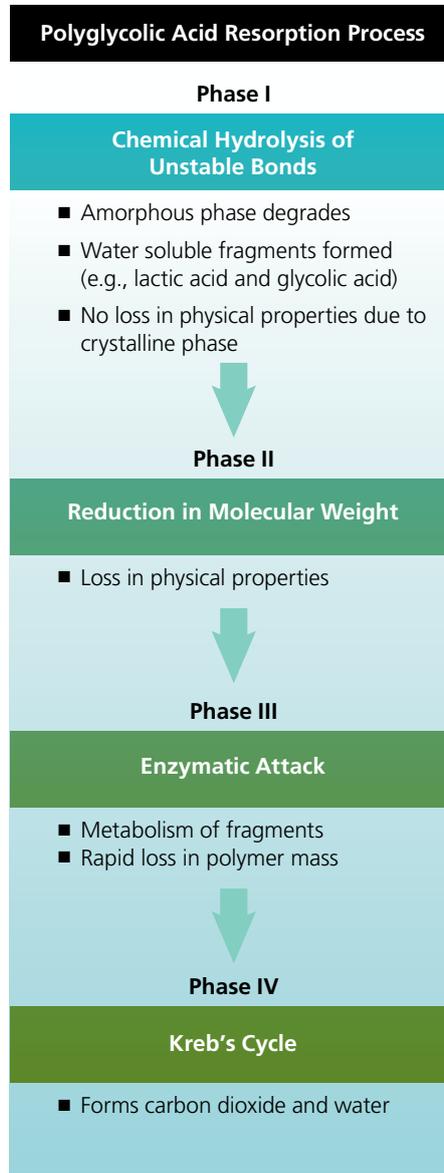
The Plug was not identified at Day 60 in 2 of 6 arteries in which the Plug was implanted. Of the 4 arteries in which the Plug was identified, the Plug was essentially absorbed in 3 of the arteries, and was in advanced absorption in the fourth artery. In 5 of 6 arteries the lumen was patent and completely

endothelialised. In 1 artery, the lumen was completely endothelialised, but there was advanced occlusion of the lumen due to medial and intimal fibrosis and mononuclear cell infiltration, which protruded into the lumen. There was no evidence of the Plug within the intimal fibrosis, but the possibility of the Plug being inadvertently implanted intravascularly cannot be excluded. In the arteries in which the Plug was present, the Plug fibers were located mostly in the adventitia of the artery and were embedded and surrounded by varying degrees of granulomatous inflammation, with many epithelioid macrophages, multinucleated giant cells and fibrosis. The site of arteriotomy was present in a few sections and included changes of mineralisation and intimal hypertrophy/hyperplasia. The arteriotomy site was healed, but was not remodeled. Occasionally, there was also mononuclear cell infiltration and neovascularisation.

The results of this study demonstrate that the Cordis **EXOSEAL**[®] Vascular Closure Device bio-absorbable Plug exhibited variable absorption following arteriotomy closure in swine femoral arteries. At 14 days post-implantation, 2 of 3 identifiable sites exhibited little or no absorption, while the third site exhibited advanced absorption. At 30 days, the 3 identifiable sites exhibited partial to advanced absorption. At 60 days, 3 of the 4 identifiable sites were essentially absorbed and the fourth site exhibited advanced absorption. During absorption, the Plug fibers were surrounded by varying degrees of granulomatous inflammation, with many epithelioid macrophages and multinucleated giant cells, and fibrosis (fibroblasts and collagen fibers), which is typical of a foreign body response. Therefore, based upon the histopathological evaluation, there were no adverse tissue reactions to the Plugs at 14, 30, or 60 days post-implantation. The Plugs were almost completely absorbed 60 days after arteriotomy closure in swine femoral arteries.

Absorption/Tissue Reaction Testing Conclusion

The results of the absorption profile and tissue reaction studies demonstrated partial to advanced absorption of the Plug at 30 days with complete absorption between 60 and 90 days following arteriotomy closure in swine femoral arteries and implantation in rabbit paravertebral muscles; in contrast, complete absorption of the Plug did not occur by 90 days following implantation in the rat gluteal flap model. However, as discussed previously, this most likely reflects differences in the rate of hydrolysis that the Plugs experience in the rat, rabbit, and pig models. Finally, it is important to remember that the Plugs produce an acceptable tissue response in all three species and that the Plugs were almost completely absorbed by 60 days following arteriotomy closure in swine femoral arteries, which is their intended use in humans.



Cordis **EXOSEAL**[®]

Vascular Closure Device