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Pre-clinical Implants of the Levitronix PediVAS® Pediatric Ventricular Assist Device – Strategy for Regulatory Approval

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Abstract

The PediVAS blood pump is a magnetically levitated centrifugal pump designed for pediatric bridge-to-decision or bridge-to-recovery in pediatric patients from 3–20kg in weight. In preparation for submission of an investigational device exemption (IDE) application, we completed a final six-animal series of pre-clinical studies. The studies were conducted under controlled conditions as prescribed by the recently released FDA guidance document for animal studies for cardiovascular devices. Three 30-day chronic left ventricular support studies were completed in a juvenile lamb model to demonstrate the safety and hemocompatibility of the PediVAS pump. Three additional 8-hour acute biventricular support studies were performed to demonstrate the feasibility of this approach from a hemodynamic and systems standpoint. It is estimated that 50% of pediatric patients who require left ventricular support also require right ventricular support. All studies were successfully completed without complications, device malfunctions, or adverse events. End-organ function was normal for the chronic studies. We noted small surface lesions on one kidney from each chronic study as well as the presence of ring thrombus on connectors, as expected for these types of studies in animal models. The strategy and challenges imposed by performing a controlled cardiovascular device study in a juvenile lamb model are discussed. We believe that these successful implants demonstrate safety and performance for the PediVAS device for support of an IDE application to initiate human clinical trials and provide a roadmap for other researchers.

Keywords

Pediatric; Ventricular Assist Device; Regulatory Submission; In vivo

Introduction

There are currently over 3,200 pediatric patients listed for heart transplantation in the United States. The current median wait time is 80 days and continues to grow as more patients compete for donor organs. Pediatric patients <15 kg have the highest transplant wait mortality of any age group (Schure and Kussman 2010). Further, there is a growing body of evidence that pediatric patients may have a greater propensity for organ recovery and thereby not require transplantation with successful mechanical circulatory support (Fan et al.

2010; Bryant et al. 2010). Until recently the options for pediatric cardiac support were extracorporeal membrane oxygenation (ECMO), a small centrifugal pump, and pediatric intraaortic balloon pump. These technologies are limited in their application time (days to weeks) and the risk of complications as time progresses. The pediatric IABP is indicated for moderate to severe left ventricular dysfunction where recovery is anticipated. These patients are often post-operative cardiectomy patients from atrial septal defects (ASD), anomalous left coronary artery from the pulmonary artery (ALCAPA), and mitral valve repair among others (Paul Collison and Singh Dagar 2007). ECMO is most useful for biventricular dysfunction which is often associated with additional pulmonary dysfunction. These therapies can be used as bridge to recovery and bridge to decision, but once the decision for heart transplantation occurs, the median wait times dictate that another long-term device is warranted. To date, only one FDA approved product (DeBakey Child VAD) is available for patients less than 1.2 m² body surface area, and only one pediatric heart assist device is undergoing a U.S. clinical trial – the Berlin Heart EXCOR VAD, which is a pneumatically driven paracorporeal blood pumping system. Like all pneumatically driven systems, the Berlin Heart EXCOR VAD requires the use of valves to control flow, with a high risk of thrombus development and potential for strokes (Potapov et al. 2007). Recently, Levitronix has developed a smaller version of the widely used CentriMag[®] pump, which is an extracorporeal magnetically levitated (MagLev) centrifugal pump based on the bearingless motor concept where the drive, magnetic bearing, and pump rotor are combined into a single unit with a single moving part without valves, seals, or mechanic bearings (Zhang et al. 2007; Dasse et al. 2007). Designed to provide circulatory support for pediatric patients, the PediVAS is an extracorporeal miniaturized MagLev blood pump with a 14 mL priming volume and superior hydraulic efficiency owing in large part to its closed impeller design (Zhang et al. 2007). The PediVAS system is CE Mark approved and is used extensively in Europe for extracorporeal membrane oxygenation applications (Ressler et al. 2009).

On July 29, 2010, the FDA released a non-binding guidance document for animal studies and cardiovascular devices (Center for Devices and Radiological Health 2010). In what appears to be an initial effort by the Agency to improve the standards for cardiovascular medical device development testing, comparable to that required for drugs and biological devices, this document outlines the “best practices” which the FDA reviewers, device manufacturers and their associated contract research organizations should adhere to for preparation and review of for Investigational Device Exemption (IDE), 510K, or Premarket Approval (PMA) applications.

Although the document released by the FDA is non-binding for industry, the recommendations of the Agency are quite important to medical device manufacturers and university researchers alike as they present an official set of “expectations” for the submission of an IDE application (see Table 1). A key point of this document is the expectation that studies should be performed under Good Laboratory Practice (GLP) which is outlined in 21 CFR part 58 (Food and Drug Administration 1980). Such stringent regulations are required for all pharmaceutical applications, and are now being strongly recommended for cardiovascular devices. What is important to note, however, is that because the application of cardiovascular devices in animal models often requires very specialized laboratories, the use of non-GLP institutions is taken into consideration, given that an explanation of the specific expertise critical to the conduct of these studies is provided. In addition, it is required that the participating laboratories also maintain the highest standards of data collection integrity, and an overall Quality System is expected during the pre-clinical testing and application processes.

The purpose of this report is to describe our pre-clinical study of the PediVAS system, which represents our first study that adheres to the recommendations outlined by the FDA in

their Guidance document. This study may also provide some guidance for the upcoming pre-clinical studies that will occur through the newly established Pumps for Kids and Infants (PumpKIN) contract from the National Heart Lung and Blood division of the National Institutes of Health (Baldwin 2009). We performed a study with three acute (8 hours) and three chronic (30 days) animals to satisfy our objectives of demonstrating safety for left ventricular (LVAD) and biventricular (BVAD) applications of the PediVAS device. The data from the six successful implants described will be used to supplement data from eight animals (6 LVAD and 2 BVAD) previously submitted to the FDA in support of an Investigational Device Exemption application for the PediVAS pediatric VAD. Minor changes were made in the VAD circuit and protocols for the final series of six animals, and the studies were conducted following discussions with the FDA.

Methods

All animal testing was performed under an approved protocol from the University of Pittsburgh Institutional Animal Care and Use Committee (IACUC). Cheviot breed lambs (20–40 kg) were utilized for the acute and chronic studies. This animal is a small, slow-growing breed, ideal for long-term studies and has been well-described for pediatric cardiology with a physiology similar to that of the human child (Kajino et al. 2002; Nau et al. 2002; Yu and Lumbers 2002). In addition, the juvenile ovine model provides a rigorous test-bed for biocompatibility as ovine red blood cells are more fragile and platelets more easily activated than bovine or human cells. (Kamenewa et al. 1994). Since the intended patient size is up to 20 kg, the age and size of the animal were a compromise between selection of a small pediatric animal model and use of an established model to achieve the study purpose of demonstrating safety.

Upon entrance to the facility, vital signs were measured by the attending veterinarian, and a complete blood count and serum chemistry values (see Online Resource 1) were sent for analysis to an outside facility (IDEXX, Pittsburgh, PA). Because the animals were derived from a local farm, they were required to be negative for Q-fever and parasite surveillance was performed upon arrival and weekly using the fecal float method. Positive fecal analysis was immediately treated with Ivermectin (300 µg/kg). Acceptance, care, and acclimation were identical for both the acute and chronic animal subsets. The left ventricular application of the PediVAS was performed in a chronic 30 day study to assess the long-term safety, hemocompatibility and effect on organ function. Biventricular application of the PediVAS device was performed in an acute setting to demonstrate the stability of the cardiovascular system because of the challenges of performing heart surgery without the benefit of cardiopulmonary bypass or use of a sternotomy.

Surgical Procedure

All devices were placed via a left thoracotomy in the 3rd intercostal space since a sternotomy in a quadruped is difficult if recovery is desired. Amiodarone (5mg/kg) was given following placement of indwelling catheters in the carotid artery and jugular vein, which were used to monitor arterial blood pressure, central venous pressure, and administer fluid and medications. The PediVAS circuit was comprised of a 14 Fr. right angled metal inlet cannula (Medtronic, Minneapolis, MN), 12 Fr. straight outlet cannula (Medtronic), 120 cm of medical grade polyvinylchloride tubing (Medtronic), and the PediVAS pump. The blood contacting surfaces of all components of the circuit except the pump were heparin bonded by the manufacturer. Following heparinization to achieve an activated clotting time (ACT) greater than 300 seconds, the inlet cannula was placed in the right and/or left atrium using dual purse string sutures for BVAD and LVAD configurations. The outlet cannulae were similarly placed in the pulmonary artery and/or aorta for BVAD and LVAD configurations. The PediVAS pump and tubing were pre-primed in a sterile field using a custom prime pack

(Medtronic). The pump and tubing were flushed with CO₂ for 5 minutes at 1 L/min before being filled with warm PlasmaLyte(Baxter). The primed circuit was tunneled through the skin and connected to the cannula. Flow initiated at 0.75 L/min while the thoracic space was open. The thoracotomy was closed in layers after insertion of a chest tube, the pump speed was gradually increased to achieve approximately 1 L/min, and maintained in the range of 0.7 to 1.5 lpm for the duration of the study in accordance with the intended clinical flow range of the pump. For the BVAD animals, the right ventricular assist device (RVAD) speed (RPM) was set to achieve a flow rate approximately 0.1 L/min lower than the LVAD. For the 30-day LVAD animals, the pump was placed in a modified backpack to protect the tubing and pump throughout the test period.

Post-Operative Monitoring

For the BVAD animals post-operative monitoring was performed hourly with documentation of vital signs (heart rate and blood pressure), pump parameters (speed and flow rate), and arterial blood gas values (pH, pCO₂, pO₂, [Hb], and [HCO₃⁻]) for the duration of the 8 hour study. Normal saline was given as necessary for decreases in central venous pressure (CVP; target 2 -- 9 mmHg) attributed to volume loss. For the chronic LVAD animals, following discontinuation of anesthesia and extubation, the animal was transported to the intensive care unit and placed in an IACUC approved stanchion that permitted vertical movement of the animal. Vital signs (heart rate, arterial blood pressure [ABP], CVP, respiratory rate) and device parameters (pump speed, flow rate, pre-set alarm limits) were monitored hourly. Arterial blood gas values were monitored every 4–6 hours. High flow oxygen was administered through nasal cannula for the first postoperative day, and weaned as the blood oxygenation normalized. Plasma free hemoglobin, fibrinogen, and total plasma protein were measured daily throughout the study using established techniques (Kameneva et al. 1994). Serum chemistry values (see Online Resource 1) were measured daily for three days post-operatively and then weekly thereafter.

Anticoagulation

For the BVAD studies, anticoagulation was maintained with heparin sodium bolus for ACT > 300 seconds. For the LVAD studies, both heparin and intravenous Coumadin were administered following the protocol outlined in Table 2–3. Anticoagulation effectiveness was monitored using both the activated partial thromboplastin time (aPTT) and prothrombin time (PT). For all studies, an outsourced laboratory value was used to monitor anticoagulation. Individual baseline PT values were used to form the PT ratio (PTR), which served as the basis for adjusting the Coumadin dose. Heparin was not administered until at least sixteen hours post-operatively when chest tube drainage was minimal. Unfractionated heparin (UH) was started at 15 U/kg/hr and maintained according to Table 2. Coumadin was withheld until fibrinogen levels and platelet counts normalized following surgery (usually 7–14 dayspost operative) and then initiated at 0.2 mg/kg. Heparin administration continued until the PTR was within the expected range as indicated in Online Resource 1. The target range for the aPTT was calculated as 1.5 – 2.3 times a 30 sec control value.

Necropsy

After 30 days of LVAD support, a weaning trial was performed using low flow conditions anticipated during the weaning process for a pediatric patient in accordance with guidelines developed for clinical users. These guidelines address anticoagulation and the gradual reduction in VAD flow to assess recovery of ventricular function. A heparin bolus was given prior to the reduction in flow, consistent with standard clinical practice to reduce the risk of thrombus formation in the circuit during the period of reduced flow. Once the ACT exceeded 300 seconds, the pump flow rate was reduced by 0.1 L/min every 15 minutes until a final flow rate of 0.5 L/min was achieved. This flow rate was maintained for 4 hours until

euthanasia. For all animals, euthanasia was performed in accordance with accepted IACUC practices. Briefly, heparin was administered to achieve an ACT greater than 400 seconds, 500 mg of Beuthanasia[®] was administered followed by 60 mL of concentrated potassium chloride to ensure full cardiac arrest. Simultaneously, the PediVAS device was stopped, and the outflow tubing clamped. Following euthanasia, the animals were weighed, exsanguinated, and a full necropsy was performed to demonstrate the safety of the PediVAS device. Photographs and tissue samples were taken from skin exit sites, cannula paths through tissue, and cannulation sites (atria, pulmonary artery and aorta) as well as the solid organs (heart, lung, kidney, liver). Tissue samples were sent to a contract pathology lab at Texas A&M University for detailed evaluation. The PediVAS circuit was photographed and any deposits or abnormalities were noted. The cannula and pump were immersed in a buffered formalin solution for storage to provide additional pump circuit information if requested by the FDA.

Performance of the study under controlled conditions

The University of Pittsburgh, like many other academic institutions, conducts device studies under strict controls and documentation consistent with GLP standards, but is not formally GLP certified. Thus, a significant effort for the planned conduct of the PediVAS testing was made in the development of the Study Protocol and continual development of a Quality System based on continual process improvement through the use of Standard Operating Procedures and the training of support personnel. In adherence to internal Quality System requirements, identification and assignment of the roles and responsibilities for study personnel supporting the effort was established in conjunction with the Test Facility Management, Study Director and the Medical Director (see Figure 1).

Unlike pharmaceutical studies, which are usually undertaken with a single principle investigator who is the medical or veterinary director of a research program, cardiovascular device studies are often performed by a multidisciplinary team including engineers, clinicians, and veterinary staff. For this current study, a Study Director and Medical Director were identified, instead of a single Study Director. These Directors are more senior faculty responsible for the overall study design and conduct. The purpose of having a Medical and Veterinary Director in addition to the Study Director reflects the highly technical nature of cardiovascular device testing in animal models. Our Medical Director is a pediatric cardiothoracic surgeon who is well qualified to make decisions about the cardiovascular impact of the device and any associated medications, while the Veterinary Director makes decisions on pain management intricacies of ruminants and overall day-to-day care. In addition to the three Directors, two Study Coordinators were used for day-to-day study oversight and data collection. A dual Study Coordinator model was employed where the Primary Study Coordinator was also the Principle Engineer responsible for device operation and data collection. The Secondary Study Coordinator was an on-site Lead Veterinary Technician whose primary duties involved assisting with data collection and documentation and provided the Primary Study Coordinator with necessary information for proper communication among the Study Director, Device Sponsor and the Veterinary and Medical directors.

The Device Sponsor utilized a Point of Contact (POC) within their organization to disseminate the necessary information coming from the Test Facility to the appropriate personnel in their organization. This POC functioned similarly to the Test Site Study Coordinator by being the primary issuer and recipient of requests for data and updates on the conduct of the study. The Device Sponsor also utilized a Quality Assurance (QA) team to ensure that the proper policies and procedures were being followed by personnel at the Device Sponsor, Test Site and Contract Laboratories. This was accomplished by pre-study and in-study audits of the facilities to identify any aspect of the study which could be called

into question by the FDA. To effectively communicate with the FDA and Test Facility the Device Sponsor QA team must not only be experienced in the regulatory submission process from the Device Sponsor's standpoint, but also have an understanding of the day-to-day operations of the Test Site.

An additional component to this particular study was the use of Contract Laboratory Services. These contracted services included the serum chemistry (IDEXX), histopathology (Texas A&M) and hemocompatibility (Kamenewa) laboratories. The Test Site Study Coordinator coordinates the communication between the Test Facility and study personnel. Like the Test Site, the Contract Laboratory Services must be able to demonstrate a Quality System that maintains data integrity and reproducibility. Depending on the location, these laboratories are inspected by either the Test Site Quality Systems Team or the Device Sponsor QA Team.

Concurrent with the creation of the roles and responsibilities, the Study Protocol and Standard Operating Procedures were developed based upon the recommendations of FDA officials, the objectives of the study, and the FDA guidelines. Once finalized, the Study Protocol was reviewed and approved by the Device Sponsor, Test Site Management; and then signed by the Study Director, initiating the in-vivo testing. The conduct of the Study Protocol was governed by an approved Study Schedule providing a timeline of deliverables and specific study actions (outlined within the Study Protocol), and controlled by a set of Standard Operating Procedures (SOPs). As intended the Study Protocol, Study Schedule, and SOPs provided a clear set of instructions for the conduct of the study, while allowing for flexibility in decisions related to management of the animal's condition since this can be quite variable.

A major component to the conduct of the study was appropriate and controlled documentation. When immediate decisions or actions taken in response to a medical situation were required which were not addressed in the study protocol or laboratory standard operating procedures, the Study Director, Medical Director, Study Coordinator and/or the Attending Veterinarian were immediately notified with a Study Project Official Communication (SPOC), which was circulated to the appropriate personnel. The purpose of the SPOC is to describe the circumstances surrounding a specific event, the actions taken by study personnel, the impact (if any) these events have on the integrity of the data or study (as assessed by the Study Director), and corrective actions followed by any necessary preventative actions (if necessary). All SPOCs required signatory review and directed action prior to approval from the Study Director and subsequent archival with the study Master File. In our hands, the SPOC proved to be very effective for creating a closed-loop communication system to ensure that all parties are in communication, aware of changes or actions taken, and that there are no unresolved issues.

In-Study Internal Quality Reviews

Throughout the Study, an independent representative designated by Test Site Facility Program Management was charged with insuring adherence to internal Quality Systems. This Quality Unit provided documented review and oversight of each study segment, data collection requirements, and procedural performance according to the Study Protocol. Reviews were conducted in accordance with specific events in the Study Timeline and adhered to established SOPs with all findings being reported directly to Test Facility Management and the Study Director in documented form. Findings reported included suggested corrective actions and any preventative actions as needed.

Results

Acute Study

All three animals implanted with biventricular PediVAS devices were successfully supported for the 8 hour acute study. There were no complications during the course of the study. Hourly blood pressures and heart rates are depicted for each of the three animals in Figure 2. No arrhythmias, which were not attributable to surgery or manipulation of the heart, were detected during initiation of biventricular support or at any time during the course of the study. Pump flow rates for each pump and animal (S007-10, S014-10, S015-10) as well as plasma free hemoglobin values are depicted in Figure 3. The steady decline in plasma free hemoglobin during the 8 hour study period was attributed to hemodilution from intraoperative bleeding at pump initiation, and fluid administration throughout the procedure.

Following each 8-hour experiment, a full necropsy was performed as noted previously. There were no significant or unexpected findings in the heart, liver, kidneys, or spleen. There was mild atelectasis in the lungs of each animal from the extended ventilation time and from the animal remaining on its right side for the duration of the study. Representative images of the organs are found in Figure 4. Inspection of the PediVAS pump and tubing revealed minor ring thrombi on several connectors as well as small blood deposits (< 1 mm in diameter) at the junction of the blades to the rotor.

Chronic 30-Day Study

All three implants survived to the expected 30-day study termination. There were no complications in the post-operative period for any animal. All PediVAS systems were operated between 3000 and 3300 RPM to maintain flow rates of approximately 0.75–1.25 L/min for the duration of the study (see Figure 5A). Serum chemistry values are presented as the 30-day average + standard deviation with the baseline values (as available) in parenthesis in Online Resource 1. Certain enzymes, including AST, ALT, LDH, and CK, and other serum parameters such as fibrinogen all showed a significant spike after surgery, followed by a decline to baseline values. This is the common inflammatory response for these enzymes as a result of surgical insult. An important facet of the study is the excellent hemocompatibility of the PediVAS. Plasma free hemoglobin remained near baseline levels for the duration of the study (see Figure 5B) and is similar to data on animals undergoing the same operative and post-operative procedures but without implantation of a pediatric ventricular assist device. In these “sham” animals, the median plasma free hemoglobin was 9.8 mg/dL with a range of 7.1 – 13.4 mg/dL for the 40 day post-operative period (Maul et al. Under Review).

Anticoagulation proved to be a challenge in this juvenile ovine model as has been reported by others (Carney et al. 2009; Yamanaka et al. 2006; Weiss et al. 2005). Coumadin administration to achieve a PTR >1.5 was rare (see Figure 6A) with the Coumadin anticoagulation protocol used, and concurrent heparin administration continued for the 30-day study for each of the animals. The daily PTT values are presented in Figure 6B for each animal.

After 30-days of support, a 4 hour weaning of the flow was performed with increased levels of heparin anticoagulation (ACT > 300 seconds). Weaning resulted in a significant decrease in heart rate (30%, $p < 0.05$) in two of the three animals, and a significant increase in respiratory rate (80%, $p < 0.05$) for one of the three animals although these changes were within the normal physiological limits for the animals. The animal with a significant increase in respiratory rate was the lone animal that did not exhibit a significant decrease in heart rate.

A full necropsy was performed for each of the three chronic animals. There were no significant or unexpected findings in the heart, lungs, liver or spleen (representative images shown in Figure 7). In each of the animals, there was evidence of cortical infarction on one kidney (see Figure 8). These infarctions were superficial and represented <1% of the total area of the affected kidney. The largest was 2 mm in diameter. The source of these infarctions is unknown as they appear old and well-healed; we speculate they may have arisen during implantation from a missed air bubble during connection of the primed tubing to the cannula, cannulation, or from a thromboembolism from the pump during the initial postoperative period without anticoagulation. Ring thrombi were observed at most of the tubing-connector junctions (see Figure 7F). Custom connector fittings were used on all connectors, which are designed to “pinch” the tubing near the connector and reduce the step change in diameter from the edge of the tubing connectors near the cannula and at the inlet and outlet of the PediVAS pump.

Discussion

Overall, the three acute BVAD and three chronic LVAD animals are considered to be successful. Survival of all animals with no evidence of clinical sequelae support the key assertion that the PediVAS pump is safe for 30 days use as a pediatric left ventricular assist device. Overcoming the challenges of the ovine animal model, particularly the propensity for arrhythmias, fragile red blood cells, and difficulty in achieving prolonged prothrombin time for the PediVAS device, give evidence that human clinical use will provide a safe modality for bridge-to-decision or recovery. The presence of ring thrombus on the barbed connectors may have contributed to the presence of minor renal surface lesions, which are common in the study of cardiovascular devices in the ovine models (Kilic et al. 2007; Tuzun et al. 2007) and bovine models (Macha et al. 1997; Yamazaki et al. 1997), but it should be stressed that there were no clinical sequelae from these lesions. Animal health remained normal with no effect on creatinine, BUN or urine output. The presence of ring thrombus on these types of connectors is also common, particularly in animal models that are difficult to achieve therapeutic anticoagulation levels (Savage et al. 1999; Noon et al. 1983).

The BVAD studies were designed as acute studies for two primary reasons. First, we were initially unsure whether implantation of the BVAD could be performed either from a single lateral thoracotomy or via a sternotomy. In the latter case, from our experience there would be no feasible way for a ruminant to recover from a sternotomy, and therefore, this approach was rejected. Second, we hypothesized that the addition of a second pump for “right sided” support would not have an adverse impact on the biocompatibility of the system. This plan was presented and agreed to by the FDA prior to initiation of the study.

We subsequently learned during a pilot study that placement of the BVAD through a thoracotomy was feasible. Implantation became routine with experience, and recovery of animals in future studies was consistently successful. This approach may provide an interesting model to study the long-term effects of a diminished pulse on pulmonary perfusion and oxygenation. From our acute studies, there was no evidence that the addition of the continuous flow PediVAS to the right heart circulation impacted the ability of the animal to oxygenate. However, previous studies have shown some evidence of renal hyperplasia in continuous flow systems (Kihara et al. 2003), but none have been performed on right-heart circulation. The PediVAS system might be a suitable model for studying the potential for such phenomenon.

Challenges of Controlled Studies in Large Animals

A major challenge in this study was to design a controlled study with six animals, three in each arm, which would be acceptable to the FDA. These types of studies have been

performed at contract research organizations for many pharmaceutical and implant materials, but few have been performed on cardiovascular devices such as the PediVAS. An initial challenge was determining the appropriate study protocol. To assist with this, communication with the sponsor and the FDA prior to the initiation of the study was essential. The participants of these meetings included representatives from the study sponsor, as well as the technical experts from the laboratories and the Quality Systems team. All parties were necessary to provide their individual expertise that ultimately shaped the Study Protocol as well as established the basic foundation for the development of a Quality System for the conduct of the studies. The formulation of the protocol went through three revisions, one of them occurring in-study, during the first chronic device implant. This in-study change to the protocol was brought about by the challenge of anticoagulation monitoring in this animal model. Without an in-house capability of frequent PTT and PT measurement, we opted to contract with an outside laboratory (IDEXX) that could provide daily values for of PTT and PT. However, as the change was made during the first chronic study, all animals were able to be monitored with the same protocol.

Another major challenge is creation of Quality Systems in the ancillary testing facilities. In order for the data generated by the study to be acceptable to the FDA, the main test center must ensure that the data generated from any outsourced testing facilities is also created in a standard, reproducible and documented manner. Therefore, we had to work with our University of Pittsburgh partners to ensure that similar Quality Systems were established, in anticipation of a potential audit by the FDA as part of the IDE submission process.

Preparation of Animal Study Results for FDA Regulatory Submission

The preparation and presentation of the animal study results is an essential component of the Investigational Device Exemption (IDE) application submitted to the FDA for the purpose of requesting approval to commence human implants. Prior to release of the FDA Guidance for Animal Studies for Cardiovascular Devices each sponsor was limited by their individual experience in preparing regulatory submissions. The FDA Guidance document has provided a template for submissions for both industry and the FDA reviewers. While the document is “non-binding” for industry, the FDA has stated that it will serve as the standard for FDA review of “animal study protocols, methods, data, and reports provided in regulatory submission to demonstrate the safety and performance of cardiovascular devices”(Center for Devices and Radiological Health 2010).

The essential elements of the animal study (outlined in Table 1) should be addressed in regulatory submissions to the FDA. While the FDA has provided considerable detail in their Guidance document on each of the key elements, historically, emphasis has been placed on several key sections. These key sections include the protocol and data supporting or assembled into individual reports. These key elements or reports (outlined in Table 4) include the surgery, animal health, medical and veterinary care, device performance, necropsy, histopathology, and summary reports.

The animal study documentation must be complete, organized and clearly support that adequate safety has been demonstrated to commence human use for the application proposed. While analysis of the data and preparation of the current PediVAS study regulatory submission is ongoing, the data presented herein supports the conclusion that the PediVAS System is safe and performs satisfactorily for use up to 30 days in a juvenile ovine model. All six animal validation implants achieved the planned durations of LVAD and BVAD support. Ring thrombus and minimal fibrous depositions were observed at the connections between the VAD circuits and pumps, which is consistent with the step change in diameter from the barbs to the tubing and is found on other devices containing these types of connections. Hemodynamic performance of the pumps was within design specifications

for the intended clinical use. Hemolysis remained within acceptable limits at near baseline values. No adverse events, malfunctions, or device failures were observed. Indicators of animal health, end organ function, based on review of renal, hepatic, and other laboratory parameters monitored remained within acceptable physiologic limits. The pre-study “success” criteria were met, end organ function remained normal, there were no device failures, and there were no animal deaths. Overall the devices performed as designed and the IDE application to the FDA will support that the PediVAS System is suitable for testing in a U.S. clinical study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Flow chart of personnel involved and the flow of communication for the study. Demonstration of the flow of information is an important component to a controlled study, particularly in a non-GLP environment. POC=Device Sponsor Point of Contact

A)

B)

Figure 2.

(A) Heart rate and (B) mean arterial pressure for the acute BVAD studies.

Figure 3.

(A) Pump flow rates for the acute BVAD studies. All RVAD flows are depicted by dashed lines (B) Plasma free hemoglobin values during the course of the BVAD studies.

Figure 4.

Representative necropsy photos from the 8-hour acute studies. (A) Heart-lung block with two sets of cannulae, (B) Lungs, (C) LVAD Inflow cannula (D) LVAD Outflow cannula (E) Kidney, (F) Liver (G) PediVAS inlet connector

Figure 5.

(A) Hourly flow rates for each of the three animals implanted with the PediVAS LVAD for 30 days. The significant reduction in flow during the last day of support reflects the simulated weaning protocol. (B) Measured plasma free hemoglobin for the chronic PediVAS LVAD animals. (POD = post-operative day)

Figure 6.

(A) PTR and (B) PTT values for the three chronic PediVAS implants. PTT values at 120 seconds are out of measurement range and actually exceed 120 seconds. (POD = post-operative day)

Figure 7.

Representative necropsy photos from the 30-day chronic studies including images of the (A) heart, (B) atrial cannulation, (C) aortic cannulation, (D) lungs, (E) liver, (F) pump housing with small ring thrombus on a tubing connector, and (G)-(I) close-up images of ring thrombi from each of the studies.

Figure 8.

Images of the surface infarctions for the kidneys of 30 day implant animals: (A) S003-10, (B) S010-10, and (C) S011-10. Dissection pins mark the position of the surface lesions. Only one kidney from each animal demonstrated evidence of such lesions.

Table 1

Key elements of an animal study for a cardiovascular device application(Center for Devices and Radiological Health 2010)

Key element	Brief explanation
Introduction, including a rationale for the selection of the particular animal model	The animal and its related environmental and physiologic attributes should provide a test system that offers a best attempt at simulating the clinical setting
Study assurances	An independent Quality Assurance Unit is required under 21 CFR part 58.35 (Good Laboratory Practices)
Purpose and objectives of each test protocol	The main objective should be to evaluate the risks predicted from the design of the device, any known risks of the product class, and any new risks that may have emerged in feasibility studies or bench testing.
Study schedule	A strict schedule identifying the key elements and milestones should be kept. Variability in the animal model may require adjustments, which should be documented.
Methods and procedures utilized in the study	Describe when protocol deviations have occurred, and how any new safety concerns have been or will be addressed. Maintenance and validation of any study related equipment used in study conduct should also be documented and archived.
Characterization of the test articles and test systems	The test article should be in near final production format (prototype, sterilization, etc) and justification should be provided when that is not the case.
In-vivo study results;	Descriptions of monitoring, data collection, and necropsy should be detailed and demonstrate a similar level of care to human intensive care settings
Ex-vivo article characterization	Additional post-mortem testing of the device including scanning electron microscopy or radiography should demonstrate the effects of the in vivo environment on the device itself
Ex-vivo tissue characterization	A full histopathologic assessment of tissue in direct contact with the device as well as other vital organs should detail device related and unrelated changes from normal
the relevant study conclusions,	Limitations from the choice of the animal model and any amendments and deviations from the protocol should be detailed

Table 2

Heparin anticoagulation management protocol for chronic LVAD studies.

Heparin Anticoagulation Management Protocol		
aPTT (sec)	Bolus	Infusion Titration
<35	50 U/kg	Give 50 units/kg bolus and/or increase infusion by 15%
35–45	None	Increase infusion by 10%
46–70	None	No change
71–90	None	Decrease infusion by 10%
> 90	None	Interrupt infusion for 1 hr and/or then decrease infusion by 15%

Table 3

Coumadin anticoagulation management protocol adapted from Andrew et al. (Andrew et al. 1998)

Coumadin Loading Protocol (Days 2–4)	
If PTR is	Action
1.1–1.4	Repeat initial loading dose
1.5–3.0	50% of initial loading dose
3.1–3.5	25% of initial loading dose
>3.5	Hold until PTR <3.5, then restart at 50% less than previous dose
Coumadin Maintenance Protocol	
If PTR is	Action
1.1–1.4	Increase by 20% of dose
1.5–1.9	Increase by 10% of dose
2.0–3.0	No change
3.1–3.5	Decrease by 10% of dose
>3.5	Hold until PTR <3.5, then restart @ 20% less than previous dose

Table 4

Key sections in the study results accompanying an FDA regulatory submission

Key Element	Brief Explanation
Surgery Records	The surgery and anesthesia records document implantation of the device in accordance with accepted standards for animal care and the approved protocol. These records are expected to show a stable animal model during the surgery and implantation of the cardiovascular device, with minimal or no complications.
Animal Health Records	These records include all of the standard animal health parameters (laboratory, hemodynamic, vital signs, etc.) outlined in the protocol and are to demonstrate study of an acceptable animal model and maintenance of an acceptable level of health for the duration.
Medical and Veterinary Care Records	These records are intended to demonstrate that, as part of the quality control systems of the laboratory, qualified medical and veterinary care providers are actively involved in the daily care and management of the animal to insure that standards are met.
Device Performance Records	The performance records detail the performance of the device as outlined in the study protocol, and demonstrate performance of the in accordance with design and clinical expectations for use. For a ventricular assist device this includes pressures, flows, and device specific parameters such as RPM without malfunctions.
Necropsy and pathology Reports	No cardiovascular device is without adverse effects and the assist device is expected to have verifiable acceptable biocompatibility with minimal effect on applicable tissue and the major organs.
Individual Animal and Study Executive Summaries	The data collected for each animal is summarized in an individual animal report, and in turn the individual reports are summarized in the executive summary for the study. The executive summary reviews the objectives of the study, provides evidence that the study was conducted in accordance with the prescribed institutional and regulatory standards, and objectives were met.