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Treprostinil Administered to Treat Pulmonary Arterial Hypertension Using a Fully Implantable Programmable Intravascular Delivery System

Results of the DelIVery for PAH Trial

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BACKGROUND: The use of systemic prostanoids in severe pulmonary arterial hypertension (PAH) is often limited by patient/physician dissatisfaction with the delivery methods. Complications associated with external pump-delivered continuous therapy include IV catheter-related bloodstream infections and subcutaneous infusion site pain. We therefore investigated a fully implantable intravascular delivery system for treprostinil infusion.

METHODS: A multicenter, prospective, single-arm, clinical trial (DelIVery for Pulmonary Arterial Hypertension) was conducted by using an implantable intravascular delivery system. The implanted pumps were refilled percutaneously at least every 12 weeks. The primary end point was the rate of catheter-related complications using the new model 10642 catheter compared with a predefined objective performance criterion of 2.5 per 1,000 patient-days based on the literature.

RESULTS: Patients (n = 60) with severe PAH (World Health Organization group 1) receiving a stable dose of IV treprostinil for at least 4 weeks received an implant device and were followed up for 12.1 ± 4.4 months. Six catheter-related complications occurred, corresponding to a complication rate of 0.27 per 1,000 patient-days. The 97.5% upper one-sided confidence bound of 0.59 was less than the predefined criterion of 2.5 per 1,000 patient-days ($P < .0001$). Plasma treprostinil levels at 1 week postimplantation were highly correlated with baseline levels ($r = 0.91$; $P < .0001$). The delivery system management time as reported by the patients was 2.5 ± 1.7 hours per week preimplantation, and this time decreased to 0.6 ± 0.8 hour per week at 6 months' postimplantation ($P < .0001$). All patients rated overall satisfaction with the implantable system as good, very good, or excellent at 6 weeks and 6 months. There were no catheter-related bloodstream infections or catheter occlusions.

CONCLUSIONS: The implantable intravascular delivery system delivered treprostinil to patients with PAH with a low rate of catheter-related complications and a high rate of patient satisfaction.

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ABBREVIATIONS: 6MWD = 6-min walk distance; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; EQ-5D = European Quality of Life-5 Dimensions; FACIT-TS-G = Functional Assessment of Chronic Illness Therapy Treatment Satisfaction general questionnaire; NYHA = New York Heart Association; OPC = objective performance criterion; PAH = pulmonary arterial hypertension; QoL = quality of life

The development of targeted therapies for pulmonary arterial hypertension (PAH) has led to improved symptoms and outcomes.[1,2] Parenterally administered prostanoids are indicated in advanced PAH; however, prostanoid therapy is underused due to reluctance from patients and physicians. In a report by Farber et al,[3] 61% of patients with PAH whose condition deteriorated to New York Heart Association (NYHA) functional class IV were not receiving parenteral prostanoid therapy 90 days after their deterioration, despite an indication for this therapy based on guideline recommendations. In addition, indwelling central venous catheters increase the risk of bloodstream infections, which can be fatal.[4] Subcutaneous administration is associated with significant infusion site pain, which may preclude continued administration.

Limitations with current prostanoid delivery systems prompted a clinical trial (DelIVery for Pulmonary Arterial Hypertension) to determine if a fully implantable, programmable delivery system could safely administer treprostinil (Remodulin, United Therapeutics Corporation) to patients with PAH. Treprostinil was chosen because it is stable at body temperature[5] and has a longer plasma half-life (~4 h[6]) than epoprostenol.

Patients and Methods

DelIVery for Pulmonary Arterial Hypertension was a multicenter, prospective, single-arm clinical trial using an investigational implantable drug delivery system conducted at 10 US centers. The implantable drug delivery system consisted of the model 10642 Implantable Intravascular Catheter,[5] the model 8637 SynchroMed II implantable drug delivery pump, and the model 8840 N'Vision programmer (Medtronic, Inc). A key design intent of the model 10642 catheter was to prevent occlusion while delivering treprostinil at low flow rates.

Patients

Patients included in this trial had stable PAH (Word Health Organization group 1)[7] and were receiving continuous IV infusion of treprostinil by using an external infusion pump. Eleven patients (18%) were prescribed subcutaneous treprostinil within 3 months of pump implantation and were switched to IV treprostinil 41 ± 12 days (range, 30 to 71 days) prior to implantation. All patients were in stable condition, defined as NYHA functional class I, II, or III with no change in treprostinil dose for at least 4 weeks and no additional PAH treatment for at least 2 months before enrollment. The exclusion criteria included: age < 18 years; NYHA functional class IV; a recent (within 3 months) infection; unresolved infection; increased susceptibility to infection; chronic renal disease; an implanted pacemaker, implantable cardioverter-defibrillator, or spinal cord stimulator; or an existing external catheter that would remain in place after implantation of the system. Patients were also excluded if their body habitus was unacceptable for an 80-cm catheter or abdominal subcutaneous pump implantation.

This study was conducted in accordance with the amended Declaration of Helsinki. The institutional review boards at each center approved the protocol, and written informed consent was obtained from all patients (e-Table 1).

Study End Points

The primary end point was the rate of catheter-related complications per 1,000 patient-days using the implantable system compared with an objective performance criterion (OPC) of 2.5 complications per 1,000 patient-days. A complication was an adverse event that required an invasive intervention (e-Table 2). In addition, because pneumothoraces are known complications due to venous access and/or central venous catheter placement,[8] these were conservatively included as part of the primary end point. The OPC was calculated based on published complication rates in populations with PAH that included central venous catheter systemic bloodstream infections (0.43-1.13 per 1,000 patients-days[9,10]), site infections (0.26-0.87 per 1,000 patient-days[11,12]), and complications from catheter thrombosis, mechanical dysfunction, or catheter dislocation in the general central venous catheter population (0.36-0.51 per 1,000 patient-days[8,13,14]). The sum of the upper rates for these three complications was used as the OPC (2.5 per 1,000 patient-days). An independent Adverse Events Advisory Committee reviewed all adverse events and deaths to determine their relatedness to the study procedures or system components. Adverse Event Advisory Committee structure and duties are shown in e-Tables 1 and 2.

The ancillary end points included changes from baseline in plasma treprostinil levels, 6-min walk distance (6MWD), NYHA functional class, quality of life (QoL), treatment satisfaction, and delivery-system management time. QoL was assessed by using the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), a PAH-specific questionnaire.[15] Generic health status was assessed with the European Quality of Life-5 Dimensions (EQ-5D) Summary Health Score.[16] Treatment satisfaction was assessed with the Functional Assessment of Chronic Illness Therapy Treatment Satisfaction general questionnaire (FACIT-TS-G).[17] Delivery system management time

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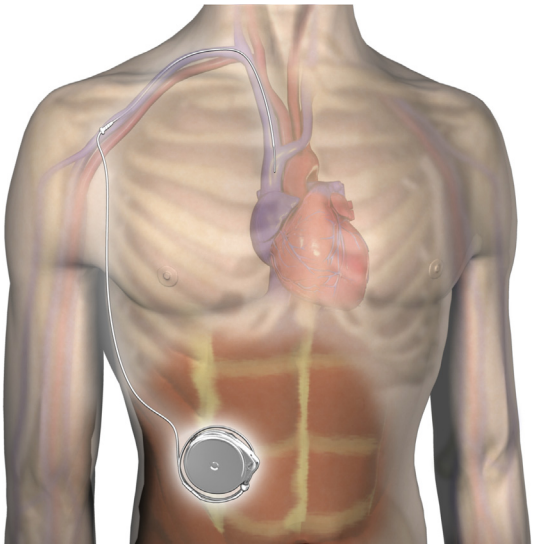

Figure 1 – *Implantation location of the drug delivery system.*

was assessed before and after implantation by asking patients to estimate how many hours per week were spent managing their delivery system, including time spent in travel to and from, as well as in, the PAH clinic.

Study Procedures

Baseline assessment of plasma treprostinil, 6MWD, NYHA functional class, QoL, and delivery system management time were performed, and the system was implanted within 2 weeks of enrollment. Prior to implantation (≥ 1 day), the existing external central venous catheter was removed and replaced with a temporary peripheral IV or a peripherally inserted central catheter. Implantations were performed by experienced operators (cardiologists, anesthesiologists, or surgeons) following specialized training overseen by the study sponsor. During system implantation, the investigational catheter was introduced into the superior vena cava via a subclavian, cephalic, jugular, or axillary puncture/cutdown and sutured to the venotomy site using the anchoring sleeve. An incision was made to create a pocket in the abdomen for pump placement, and the catheter was tunneled under the skin between the venous access site and the pump pocket, and connected to the infusion pump (Fig 1). The implanted pump was then programmed to deliver a priming bolus followed by continuous infusion of treprostinil from the pump reservoir through the implanted catheter, and the external IV infusion pump was discontinued.

Patients were discharged from the hospital approximately 24 h after surgery with their implantable pump programmed to deliver the same dose of treprostinil as their external pump. One week after surgery, safety assessments were performed, and blood samples were collected to determine treprostinil concentrations. Adverse events, NYHA functional class, 6MWD, QoL, delivery system management time, pump refill data (if necessary), and device interrogations were assessed at 6 weeks' and at 3, 6, and 12 months' postimplantation. The FACIT-TS-G treatment satisfaction survey was administered at 6 weeks and 6 months' postimplantation.

The implanted pump was refilled with treprostinil via percutaneous needle access to the pump reservoir. Refills occurred when the drug volume in the pump reservoir was low at an interval dependent on patient dose (up to 12 weeks). At the time of a refill, any drug remaining in the pump reservoir was removed and discarded, and fresh drug was injected into the pump. Study procedures for the refills of the fully implanted system were similar to those for commercially available systems.[18] The pump refill process took approximately 15 min when performed by a trained and experienced clinician (typically a physician, physician's assistant, or nurse). Noncoring needles are used to pierce the self-sealing silicone septum of the reservoir during the refill process. The flow rate was initially programmed using the pump programmer to deliver the same dose of treprostinil as delivered by the external pump, but it could be adjusted up or down based on the clinical assessment of each patient.

Statistical Analysis

The number of patient-days contributed by each patient toward the primary end point was obtained from the last date of known follow-up minus the date of implantation. Sample size calculations were performed based on the OPC determined from complication rates in previous studies,[8-14] and it was estimated that 22,000 days of follow-up among 60 patients undergoing implantation would be required to ensure 90% power. A one-sample exact test for the Poisson rate was used to obtain the 97.5% one-sided upper confidence bound of the catheter-related complications. StatXact version 9 (Cytel, Inc) was used to generate the Poisson rate CI.

Continuous variables are reported as the mean ± SD, and a paired *t* test was used to determine the significance of changes in these variables from preimplantation to postimplantation. For all analyses, a P value $<.05$ was considered significant.

Results

Patients

Patients (n = 64) were enrolled from June 2011 through November 2012. Four patients were enrolled but did not undergo implantation: two patients developed infections from their external treprostinil delivery catheters between enrollment and scheduled implantation, one patient had insufficient body size to accommodate the implantable pump, and one patient was withdrawn due to worsening PAH. All 60 procedures were successful, and the mean follow-up time was 12.1 ± 4.4 months. Baseline demographic and clinical characteristics are provided in Table 1.

Treprostinil Dose

The mean dose of IV treprostinil at baseline was 71.4 ± 27.8 ng/kg/min, which is similar to previously reported doses.[19,20] The implantable pump can be programmed by using telemetry for flow rates of 0.048 to 24 mL/d. In the present study, a treprostinil concentration of 10 mg/mL was primarily used. The average refill interval was 47.2 days (range, 19.5 to 94.3 days). The refill interval was dependent on body size, dose, treprostinil concentration, low-reservoir alarm setting, and the pump reservoir size.

Primary End Point

The primary end point (catheter-related complications) was assessed once all patients completed their 6-month

TABLE 1] Baseline Patient Characteristics

Characteristic	Patients Undergoing Implantation (N = 60)
Age, y	50.1 ± 13.5
Male sex	20%
Race/ethnic origin	
Asian	3%
Black or African American	5%
Hispanic or Latino	13%
White or Caucasian	78%
Height, cm	165 ± 11
Height, in	65 ± 4.3
Weight, kg	75.6 ± 16.9
Weight, lb	167 ± 37
Classification of PAH	
Idiopathic	58%
Heritable	3%
Associated	38%
Preimplantation IV treprostinil dose, ng/kg/min	71.4 ± 27.8
Time on dose at implantation, wk	71.9 ± 96.7
NYHA functional class	
I	17%
II	50%
III	33%
No. receiving SC treprostinil switched to IV treprostinil within 12 wk of implantation[a]	11 patients (18%) (on IV 41 ± 12 days; range, 30-71 days)

Data are presented as mean ± SD unless otherwise indicated. NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; SC = subcutaneous.
[a]All patients met study inclusion criteria.

follow-up visit and there were at least 22,000 patient-days of follow-up. This criterion was met in June 2013 with a total of 22,013 patient-days accumulated. Six catheter-related complications were observed in five patients and included three catheter dislocations (two patients), one episode of venous stenosis, one episode of mechanical catheter damage, and one episode of pneumothorax (Table 2). No catheter-related bloodstream infections or occlusions occurred. The complication rate was 0.27 per 1,000 patient-days, and the 97.5% upper one-sided confidence bound (0.59 per 1,000 patient-days) was significantly less than the OPC of 2.5 per 1,000 patient-days ($P < .0001$). In addition, a post hoc analysis showed that the observed complication rate (0.27 per 1,000 patient-days) was significantly less ($P < .0001$) than the sum of the three lower rates reported in the literature (1.05 per 1,000 days).

Complications

All complications that were related to the catheter, implant procedure, pump, and pump refill process are listed in Table 2. Some complications were adjudicated by the Adverse Events Advisory Committee as related to multiple system components and/or procedure steps, and these are listed based on their primary relatedness. Multiple associated complications during a single hospitalization (eg, infection that led to sepsis and renal failure) were counted as a single complication. There were a total of 16 complications in 14 patients.

Three pump refill-related complications were reported in three patients; these were defined as local and/or systemic symptoms and adverse effects of treprostinil delivery soon after an implanted pump refill procedure requiring an invasive intervention. Local adverse effects included pain, erythema, and/or swelling near the pump refill site. Systemic symptoms included flushing, headache, nausea, and/or a decrease in blood pressure. The rate of refill-related complications (based on three complications) was 0.7% per refill and was attributed to a small amount of drug exiting the needle as the needle was withdrawn from the pump reservoir.

Deaths

Three deaths occurred among the 60 patients undergoing implantation. None was adjudicated to be related to the system, procedure, or treprostinil. One patient experienced a fatal pulmonary thromboembolism 4 months' postimplantation due to a leg injury in a motor vehicle accident. A second patient died 3 months' postimplantation after hospital admission for refractory heart failure. The patient was treated with palliative care, and all medications were discontinued, including treprostinil. The third death occurred when the patient was admitted to the hospital with severe gastrointestinal bleeding and underwent hemoclipping of a Dieulafoy lesion. The patient died 10 months' postimplantation of right-sided heart failure due to excessive fluid resuscitation.

Ancillary End Points

Plasma treprostinil levels at 1 week postimplantation were highly correlated with baseline levels ($r = 0.91$; $P < .0001$) (Fig 2).

The QoL results are summarized in Table 3. CAMPHOR scores of mean changes in the symptom scale and QoL

TABLE 2] Complications Related to the Procedure or System During 22,013 Patient-Days of Follow-up

Complication and Relatedness	No. of Occurrences	Comment
Implant procedure related		
Atrial fibrillation	1	Prior to catheter insertion Resolved by cardioversion
Fever, unknown origin	1	Admitted for observation; negative culture results
Pump pocket infection	1	Resolved after surgical modification and antibiotics
Legionella pneumonia with septic shock, renal failure, and DVT at the PICC line site	1	Subject recovered after 34-day hospitalization
Urinary retention	1	Urinary catheterization required
Catheter related (primary end point)[a]		
Catheter dislocations	3	Dislocated catheters removed and replaced via surgical procedures
Venous stenosis	1	187 days' postimplantation
Damaged catheter	1	Catheter migrated over the refill port and was pierced with the needle during refill
Pneumothorax	1	Associated with subclavian venous access; required chest tube; discharged 2 days; postimplantation
Pump-related		
Pump pocket seroma	2	Fluid from pump pocket in 2 subjects aspirated at 13 and 70 days after implantation
Pump refill process related		
Refill reactions	3	3 subjects treated due to local and/or systemic reaction shortly after refill
Programmer related	0	
Total system-related complications	16	

PICC = peripherally inserted central catheter.
[a]Six catheter-related complications is a 0.27 per 1,000 patient-days complication rate (95% upper confidence bound = 0.59; $P < .0001$).

scale from baseline to 6 months were not significant ($P = .41$ and $P = .22$, respectively); however, there was a small significant increase in the activity scale ($P = .02$).

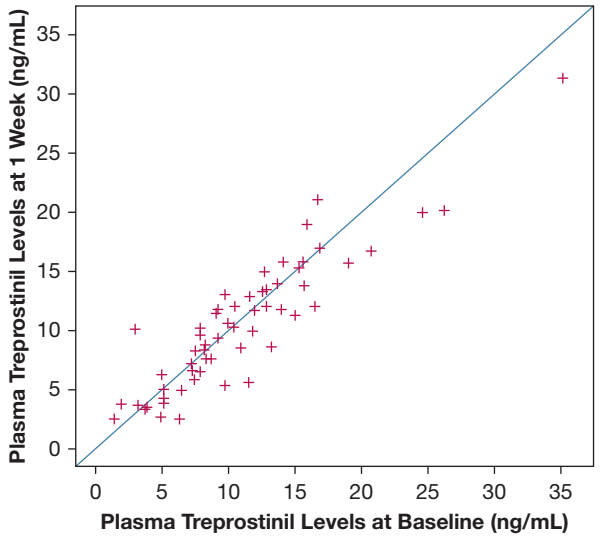

Figure 2 – *Plasma treprostinil levels at baseline and 1 week post-implantation ($r = 0.91$; $P < .0001$).*

The mean EQ-5D score did not change from baseline to 6 months ($P = .43$). At 6 weeks, according to the FACIT-TS-G, patients were satisfied with the therapy; they had a mean treatment satisfaction score of 94.7 ± 13.9 and a mean recommendation score of 98.3 ± 9.1 (of 100). Patients were asked, "How do you rate this treatment overall?" All patients answered good, very good, or excellent at both 6 weeks and 6 months (n = 60 at 6 weeks; n = 58 at 6 months). Furthermore, 79% felt that the effectiveness of the treatment was better than expected at 6 months.

Compared with baseline, the increase in 6MWD at 6 months was 1.7 ± 21.6% for 56 patients with paired data (Table 3); this difference was not significant ($P = .56$). Similarly, there was no significant change in NYHA functional class from preimplantation to postimplantation ($P = 0.99$). The mean delivery system management time was 2.5 ± 1.7 h per week preimplantation and decreased significantly ($P < .0001$) to 0.6 ± 0.8 hour per week at 6 months.

TABLE 3] Change in Efficacy Variables Between Baseline and 6 Months' Postimplantation

Variable	CAMPHOR (n = 57)			EQ-5D (n = 58)	NYHA (n = 58)	6-Min Walk Distance (% change) (n = 56)
	Symptom Scale	Activity Scale	QoL Scale			
Change, mean ± SD	−0.4 ± 3.5	1.0 ± 3.1[a]	−0.5 ± 3.1	−0.01 ± 0.10	0.00 ± 0.56	1.7 ± 21.6
95% CI	−1.3 to 0.5	0.2 to 1.8	−1.3 to 0.3	−0.04 to 0.02	−0.15 to 0.15	−4.1 to 7.5
Change (at least 2 points)						
Better	19 (33%)	10 (18%)	18 (32%)	NA	NA	NA
No change	24 (42%)	26 (46%)	29 (51%)			
Worse	14 (25%)	21 (37%)	10 (18%)			

Higher CAMPHOR scores and lower EQ-5D scores indicate worse quality of life. CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; EQ-5D = European Quality of Life-5 Dimensions; NA = not applicable. See Table 1 legend for expansion of other abbreviation.
[a]Only the change in the activity scale was significant ($P = .02$).

Discussion

This study describes a novel implantable treprostinil delivery system to treat patients with PAH. Successful implantation was achieved with minimal catheter-related complications. The study patients showed no change in 6MWD or NYHA functional class, which was expected because treprostinil has been proven effective in previous studies,[19,20] and postimplantation dosing was based on each patient's clinical condition. Furthermore, the target dose was achieved by the implantable system, as plasma treprostinil levels at 1 week were highly correlated with baseline levels.

Patients were satisfied with their implanted delivery system at both 6 weeks and 6 months, as supported by findings from the FACIT-TS-G treatment satisfaction survey. Moreover, patients spent 75% less time managing their delivery system (average of 0.6 hour per week) at 6 months compared with the external system that they used prior to implantation (average of 2.5 hours per week). The low catheter complication rate, reduced delivery system management time, and the high rate of patient satisfaction in this study suggest that the implanted delivery system may be an important new option for patients with PAH who require parenteral treprostinil.

The observed catheter dislocations occurred within 1 month of implantation and resulted in complete displacement of the catheter from the vasculature. Dislocations were identified following patient complaints of pain along the subcutaneous catheter track and/or within the pump pocket, resulting from local delivery of treprostinil. Detailed analysis revealed that the dislocations likely occurred because of inadequate compressive force exerted on the catheter by the sutures tied on the anchoring sleeve. Additional training was given to operators performing the implantations, and there were no further dislocations in 39 subsequent procedures.

Adverse events associated with the priming bolus resulting in hypotension occurred when transitioning patients from an external system to the implantable delivery system. Hypotension and other systemic adverse effects from excess treprostinil were observed during delivery of a priming bolus into the implanted catheter in three of the first four procedures. Excess dosing during the transition was remedied by reducing the drug volume used to prime the implantable delivery system, while extending the drug delivery time via the external pump. With the 57 new procedures and three system modifications performed with this revised method, no episodes of hypotension were observed during the priming bolus.

This study has important limitations. There was no parallel control group with patients receiving treprostinil through an external pump. Given the novel technology evaluated, enrollment was limited to patients already shown to tolerate systemic treprostinil and who were receiving a stable dose. As such, the use of the delivery system cannot be recommended during initial drug titration in patients with PAH. In addition, patient size and dosing must be considered to avoid the need for excessively short refill intervals.

Conclusions

The fully implantable programmable intravascular delivery system delivered treprostinil to patients with PAH, with a low rate of catheter-related complications and a high rate of patient satisfaction. The use of this system maintained NYHA functional class and 6MWD but significantly shortened the delivery system management time.

Primary Study Results Addendum

At the end of the prespecified primary results analysis period, all active study subjects continued to receive treprostinil via the implanted delivery system. As part of the clinical study, the amount of residual drug in the pump reservoir was estimated by withdrawal into a syringe prior to each refill and recorded as the ratio of that estimated residual volume to the amount that was programmed to remain in the pump reservoir (ie, the accuracy ratio). During the primary study period, the accuracy ratio remained within prespecified boundaries set based on earlier experience with the pump. However, starting within 6 months after the primary study period, it was observed that, over time, the delivery system tended to deliver slightly less drug than the programmed amount, and the decrease in delivered drug was related to the total volume of drug delivered over the lifetime of the pump. This discrepancy is attributable, in part, to an increased "back" pressure from the investigational catheter (relative to catheters used with the implanted pump in other applications in which this discrepancy is not observed). No adverse events reported to date have been attributed to this observation, physicians continue to dose treprostinil based on PAH symptoms, and no trend has been identified between the apparent delivered dose reduction and symptom-related changes in treprostinil dose adjustments. Given these facts, the study Steering Committee, the study Data Monitoring Committee, and all study investigators have elected to continue the study with ongoing review of the safety and accuracy of this route of prostanoid delivery.

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Author contributions: R. C. B. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. A. B. W., M. G.-M., J. C., M. M., M. T., L. P., and L. J. R. contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. S. M. S., J. H. T., D. L. Z., J. P. F., M. M. C., R. P. F., and F.T. contributed substantially to the data acquisition and interpretation, and the writing of the manuscript.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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