ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

MAJOR CLNICAL TRIAL DESIGN

Clinical trial design and rationale of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) investigational device exemption clinical study protocol

Gerald Heatley, MS,[a] Poornima Sood, MD, MBA,[a] Daniel Goldstein, MD,[b] Nir Uriel, MD, MSc,[c] Joseph Cleveland, MD,[d] Don Middlebrook,[a] Mandeep R. Mehra, MD[e] and on behalf of the MOMENTUM 3 Investigators

From the [a]St. Jude Medical, Minneapolis, Minnesota, USA; [b]Department of Cardiothoracic Surgery, Montefiore Medical Center, New York, New York, USA; [c]Division of Cardiology, University of Chicago, Chicago, Illinois, USA; [d]Department of Surgery, University of Colorado Anschutz Medical Center, Denver, Colorado, USA; and the [e]Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, Massachusetts, USA.

KEYWORDS:
HeartMate 3;
MOMENTUM 3;
MagLev;
LVAD;
advanced heart failure

The HeartMate 3 left ventricular assist system (LVAS; St. Jude Medical, Inc., formerly Thoratec Corporation, Pleasanton, CA) was recently introduced into clinical trials for durable circulatory support in patients with medically refractory advanced-stage heart failure. This centrifugal, fully magnetically levitated, continuous-flow pump is engineered with the intent to enhance hemocompatibility and reduce shear stress on blood elements, while also possessing intrinsic pulsatility. Although bridge-to-transplant (BTT) and destination therapy (DT) are established dichotomous indications for durable left ventricular assist device (LVAD) support, clinical practice has challenged the appropriateness of these designations. The introduction of novel LVAD technology allows for the development of clinical trial designs to keep pace with current practices. The prospective, randomized Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) clinical trial aims to evaluate the safety and effectiveness of the HeartMate 3 LVAS by demonstrating non-inferiority to the HeartMate II LVAS (also St. Jude Medical, Inc.). The innovative trial design includes patients enrolled under a single inclusion and exclusion criteria , regardless of the intended use of the device, with outcomes ascertained in the short term (ST, at 6 months) and long term (LT, at 2 years). This adaptive trial design includes a pre-specified safety phase ($n = 30$) analysis. The ST cohort includes the first 294 patients and the LT cohort includes the first 366 patients for evaluation of the composite primary end-point of survival to transplant, recovery or LVAD support free of debilitating stroke (modified Rankin score >3), or re-operation to replace the pump. As part of the adaptive design, an analysis by an independent statistician will determine whether sample size adjustment is required at pre-specified times during the study. A further 662 patients will be enrolled to reach a total of 1,028 patients for evaluation of the secondary end-point of pump replacement at 2 years.

J Heart Lung Transplant 2016;35:528–536

Reprint requests: Gerald Heatley, MS, St. Jude Medical, 23 Fourth Avenue, Burlington, MA 01803. Telephone: +781 272 0139. Fax: 781-852-8320.

E-mail address: jerry.heatley@thoratec.com

http://dx.doi.org/10.1016/j.healun.2016.01.021

Early clinical trials of durable left ventricular assist device (LVAD) support prospectively included bridge-to-transplant (BTT) candidates and compared them to historical or parallel control patients who did not undergo device implantation.[1–3] After nearly a decade of successful BTT experience, the Thoratec paracorporeal VAD system and the HeartMate I devices (IP-LVAD and VE-LVAD; Thoratec Corporation, Pleasanton, CA) were commercially approved by the United States Food and Drug Administration (FDA) for this indication.[1,3,4] The limited donor supply and consequent strict transplant candidacy criteria generated a need for such therapy in transplant-ineligible candidates with advanced heart failure who could potentially benefit from permanent, lifetime LVAD support. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, the first randomized, controlled trial with an LVAD, was thus conceived and led to FDA approval for the indication of "destination therapy" (DT).[5,6] On the basis of these approved indications, the Centers for Medicare and Medicaid Services in the USA established criteria for reimbursement, and the regulatory agencies used similar criteria for center accreditation. Accordingly, all successive clinical trials with new LVADs targeted these distinct BTT and DT indications. Thus, the ADVANCE trial of the HeartWare HVAD (HeartWare, Inc., Framingham, MA) enrolled a BTT population and compared outcomes with registry-derived patients implanted contemporaneously with commercially available devices.[7] The HeartMate II LVAS (St. Jude Medical, Inc., formerly Thoratec Corporation, Pleasanton, CA) is currently approved for BTT and DT, whereas the HVAD remains indicated for BTT alone and trials examining the use of an HVAD in DT populations await completion. Despite improved survival and quality of life, long-term success with current devices remains partially limited by adverse effects, including infections, neurologic complications and pump thromboses.[8–11]

The HeartMate 3 LVAS is a centrifugal-flow pump engineered to optimize fluid dynamics and developed with wider blood-flow passages with the intent to avert thrombogenesis. The HeartMate 3 was first evaluated in humans in 50 patients in a single-arm, prospective, non-randomized clinical study outside of the USA to meet the Conformité Européenne (CE) mark requirements.[12,13] Figure 1 presents the competing outcomes analysis, and Table 1 presents the adverse event data from this first-in-humans experience through 6 months of follow-up.[13]

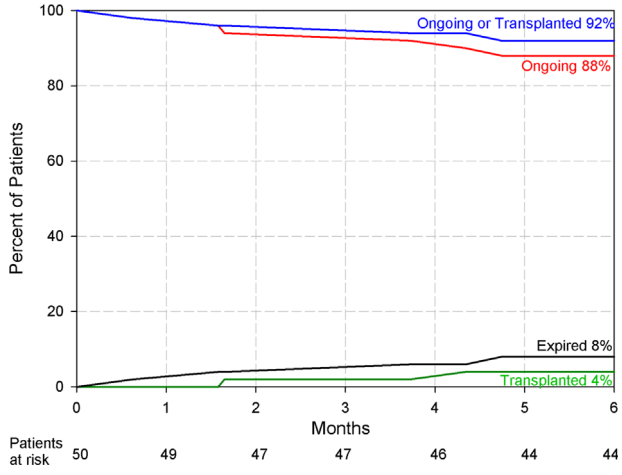

Figure 1 HeartMate 3 CE mark study. Competing-outcomes analysis through 6 months.[13]

The MOMENTUM 3 (Multicenter Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3) investigational device exemption (IDE) randomized, pivotal clinical trial aims to evaluate the safety and effectiveness of the HeartMate 3 LVAS by demonstrating non-inferiority to the HeartMate II LVAS when used for the treatment of advanced, refractory left ventricular heart failure, irrespective of the primary implant strategic intent.

HeartMate 3 LVAS—Device characteristics

The HeartMate 3 LVAS includes an implanted blood pump, a modular drive-line and external power and control components (Figure 2). With the exception of the system controller, all external components are identical for both the HeartMate II (HMII) and HeartMate 3 (HM3). The design strategy for the HM3 involved adopting successful elements of the HMII while pursuing a different technological path to address hemocompatibility factors associated with most clinically significant adverse events with mechanical circulatory support. Comparisons of the fundamental characteristics of the HMII and HM3 are provided in Table 2 and Figure 3. A description of the HMII has been provided elsewhere.[14]

The engineering technology in the HM3 involves a magnetically levitated rotor and wide blood-flow passages that are designed with the intent to reduce blood shear stress exposure. In addition, the wide blood-flow passages facilitate rapid rotor speed changes, allowing for the introduction of an artificial pulse. The artificial fixed pulse is intended to disrupt regions of stasis within the pump and to provide a degree of physiologic normalcy in cases of otherwise chronically attenuated native pulsatility. These engineering differences also alter the hemodynamic pressure and flow relationships in the HM3 as compared with the HMII pump. Both devices demonstrate the expected inverse relationship between the pressure head across the pump and flow through the pump, and generally follow the convention that the slope of this relationship is steeper for the axial-flow HMII than for the centrifugal HM3 (Figure 4). However, a closer examination near the typical design point suggests the opposite. Thus, within the typical ranges of clinical operation, a change in pressure head across the pump results in a greater change in flow for the HMII than for the HM3. The clinical effects of these engineering and technological characteristics in the HM3 will be validated in the MOMENTUM 3 study and other mechanistic trials.

Study design

The MOMENTUM 3 IDE clinical trial is an ongoing, prospective, multicenter, randomized, pivotal study,