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]

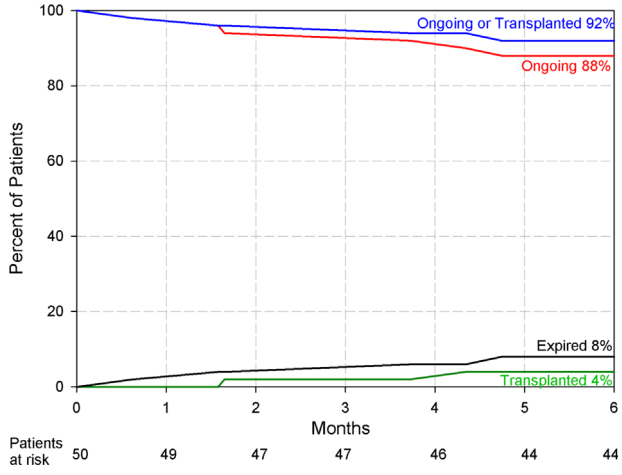

Figure 1 HeartMate 3 CE mark study. Competing-outcomes analysis through 6 months.[13]

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,

Table 1 All Adverse Events Through 6 Months for the 50 Patients Enrolled in the HeartMate 3 CE Mark Clinical Trial[13]

	Days 0 to 30 ($n = 50$)			Days >30 ($n = 49$)			All ($n = 50$)		
Adverse event	Patients (n)	Patients (%)	Number of events	Patients (n)	Patients (%)	Number of events	Patients (n)	Patients (%)	Number of events
Bleeding	15	30	19	8	16	16	19	38	35
Requiring surgery	6	12	6	2	4	2	7	14	8
GI bleeding	2	4	2	3	6	4	4	8	6
Cardiac arrhythmias	14	28	14	3	6	3	17	34	17
Infection	10	20	14	12	24	14	18	36	28
Sepsis	4	8	4	4	8	4	8	16	8
Drive-line	1	2	1	4	8	4	5	10	5
Stroke[a]	2	4	2	4	8	4	6	12	6
Ischemic	2	4	2	2	4	2	4	8	4
Hemorrhagic	0	0	0	2	4	2	2	4	2
Neurologic dysfunction other[b]	2	4	2	2	4	2	4	8	4
Device thrombosis	0	0	0	0	0	0	0	0	0
Device malfunction	0	0	0	0	0	0	0	0	0
Hemolysis	0	0	0	0	0	0	0	0	0
Psychiatric episode	1	2	1	2	4	2	3	6	3
Renal dysfunction	5	10	5	0	0	0	5	10	5
Hepatic dysfunction	1	2	1	0	0	0	1	2	1
Respiratory failure	7	14	7	1	2	1	8	16	8
Right heart failure	4	8	4	1	2	1	5	10	5
Requiring RVAD	2	4	2	0	0	0	2	4	2
Wound dehiscence	2	4	2	2	4	2	3	6	3
Other event[c]	18	36	35	19	39	25	27	54	60

GI, gastrointestinal; INR, international normalized ratio; RVAD, right ventricular assist device.

[a]Includes 3 procedural-related events: 1 implant issue (difficulty engaging inflow conduit); 1 after anaphylactic shock from contrast media; and 1 after transcatheter aortic valve implantation procedure.

[b]Seizure ($n = 2$) and transient ischemic attack ($n = 2$).

[c]Other adverse events include pleural effusion ($n = 1$), volume status ($n = 5$), and high/low INR ($n = 7$) and various ($n = 10$).

comparing the HM3 LVAS with the HMII LVAS in advanced-stage heart failure patients (Figure 5). The study will enroll 1,028 patients in up to 60 centers throughout the USA.

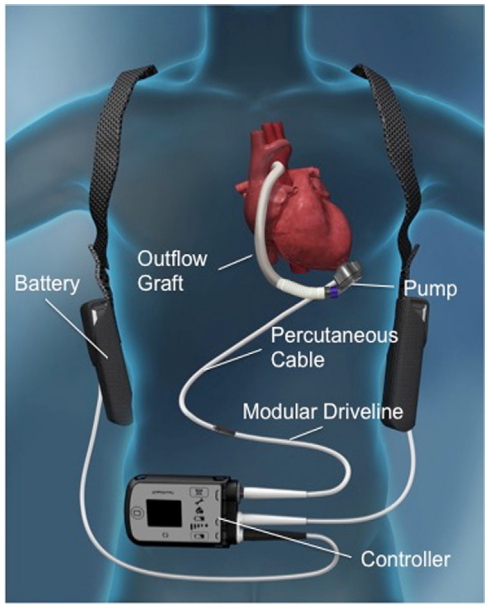

Figure 2 The HeartMate 3 LVAS.

The MOMENTUM 3 trial proposes a paradigm shift for regulatory bodies on the basis of today's clinical reality. It diverges from previous clinical studies and has an innovative trial design with the following characteristics:

1. It is an all-comer study, with patients enrolled in the trial under a single inclusion and exclusion criteria, regardless of the intended use of the device (short-term [ST], such as BTT, and long-term [LT], such as DT).
2. There is a pre-specified safety phase (N = 30) in lieu of a pilot study while maintaining randomization.
3. There is an ST cohort consisting of the first 294 patients for evaluation of outcomes to 6 months of support, powered to demonstrate the non-inferiority of the HM3 compared with the HMII.
4. There is an LT cohort consisting of the first 366 patients for evaluation of outcomes to 2 years of support, powered to demonstrate the non-inferiority of the HM3 compared with the HMII.
5. There is ongoing enrollment of a further 662 patients (to a full sample size of 1,028) for evaluation of a secondary end-point of pump replacement at 2 years, powered to demonstrate the superiority of the HM3 over the HMII.
6. The study has an adaptive design, with an interim pre-specified analysis conducted by an independent

Table 2 Comparison of HeartMate II and HeartMate 3 Devices

Characteristic	HeartMate II	HeartMate 3
Pump (flow)	Axial	Centrifugal
Bearing	Mechanical (blood washed)	Magnetic
Hydraulic capacity	Up to 10.0 liters/min	Up to 10.0 liters/min
Implantation location	Extrathoracic	Intrathoracic
Typical clinical speed range	8,000 to 10,000 rpm	5,000 to 6,000 rpm
Textured surfaces (sintered titanium)	Yes	Yes
Inflow graft	14-mm sealed Vascutek	None
Outflow graft	14-mm sealed Vascutek	14-mm sealed Vascutek
Quick pump attachment	No	Yes
Modular drive-line	No	Yes
Electronics incorporated in pump	No	Yes
Software incorporated in pump	No	Yes
Artificial pulse	No	Yes
Flow estimator hematocrit adjustment	No	Yes
Power efficiency (battery run-time)	—	20% longer than that of HMII

statistician to determine ongoing power and sample size requirements.

Study objectives and end-points

The primary objective of the MOMENTUM 3 study is to evaluate the safety and effectiveness of the HM3 LVAS by demonstrating its non-inferiority to the HMII when used for the treatment of advanced, refractory heart failure. Secondary objectives include: assessment of adverse events; quality of life as measured by the EuroQol-5D-5L and Kansas City Cardiomyopathy Questionnaire; functional status as measured by the 6-minute walk test and New York Heart Association (NYHA) class; assessment of device malfunction rates; and determination of need for reoperation or rehospitalization. The study will also be powered to evaluate a secondary end-point to determine whether the incidence of pump replacement at 24 months is significantly different between treatment arms (superiority analysis).

The primary end-point is a composite of survival free of debilitating stroke (modified Rankin score >3) or the need for a pump exchange. The ST end-point will be assessed at 6 months and the LT end-point at 24 months. Patients who are urgently transplanted due to a device complication before a pre-specified end-point will be considered study failures. All other transplants or device explants due to myocardial recovery that occur before a pre-specified end-point will be considered study successes.

Study population

All patients meeting the study entry criteria will be enrolled regardless of the planned use of the device (BTT or DT). Patients with advanced heart failure classified as NYHA Class III with dyspnea upon mild physical activity, or

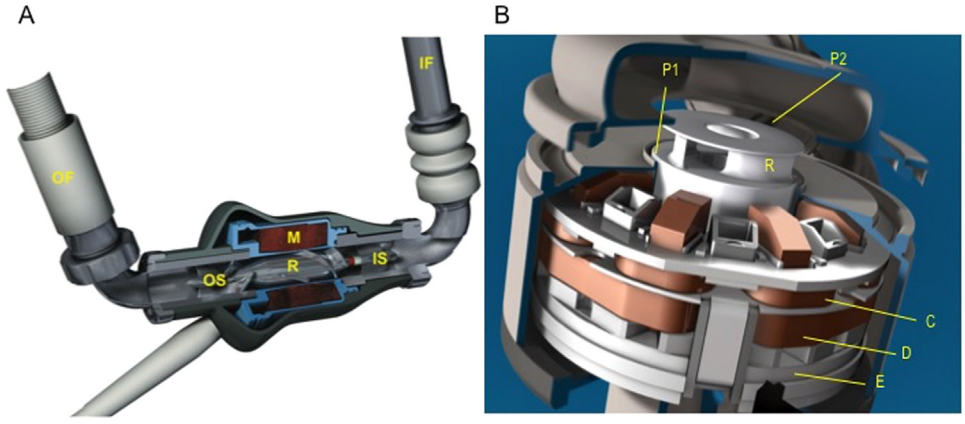

Figure 3 (A) Cross-section of the HeartMate II. Arterial blood passes from the left ventricle into the pump through the inflow (IF) conduit; blood flow direction is straightened by the inflow stator (IS); the rotor (R) controlled by the motor (M) spins to generate the needed force for blood to pass through the outflow stator (OS), then through the outflow (OF) conduit. (B) Cross-section of the HeartMate 3. The rotor (R) is magnetically levitated via electromagnetic coils (C) and rotated via motor drive coils (D). The levitated rotor produces wide recirculation passages radially (P1) and axially (P2). A second axial passage beneath the rotor is hidden in this view. Motor electronics (E) are incorporated into the implantable pump.

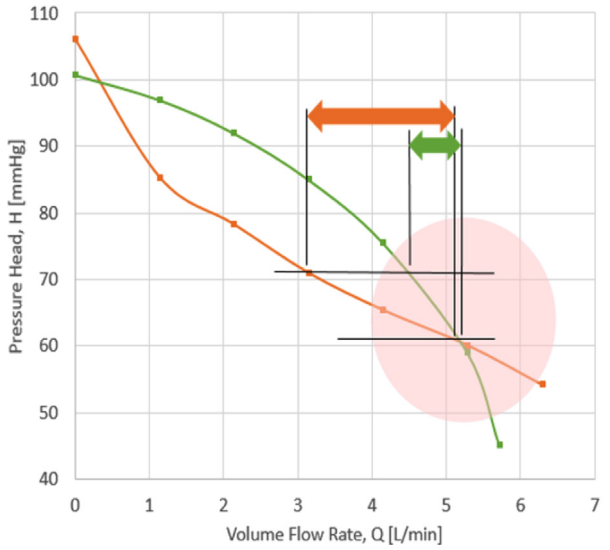

Figure 4 HeartMate 3 pressure head, H, versus volume flow rate, Q. The orange circle covers the typical usage range. HeartMate II typical speed, 9,000 rpm (orange curve), and HeartMate 3 typical speed, 5,400 rpm (green curve), shown passing through the design point (center of the orange circle). A change in pressure head across the pump, for example, from 60 to 70 mm Hg, results in a greater change in flow for the HeartMate II (orange arrow) than for the HeartMate 3 (green arrow).

NYHA Class IV who are refractory to advanced heart failure management are candidates for the study. A detailed listing of the study inclusion and exclusion criteria is shown in Table 3.

Qualified study candidates will be randomized 1:1 between the HMII and the HM3. The randomization will be stratified by study center and blocked to maintain the 1:1 ratio over time. Randomization will be implemented through the electronic data capture (EDC) system (Merge Healthcare, Morrisville, NC). Study centers will be allowed a maximum of 50 randomized patients. Patients will be considered enrolled in the study upon signing informed consent; all randomized patients will be included in the intent-to-treat analysis.

Early assessment for safety

The investigation will be conducted as a staged, pivotal study that includes a pre-specified early assessment for safety that is consistent with the FDA's new guideline for a staged approval process.[15] The study was initially limited to 5 study sites during the early safety assessment. Safety data were analyzed when the first 10 patients, randomly assigned to HM3, achieved 30 days of support. Data included the status of each patient, a summary of adverse events, and a description of any device malfunction. The data were presented to an independent data safety monitoring board (DSMB) and the FDA, with a request to expand the trial to up to a total of 60 study centers. The first 5 study sites continued to enroll and randomize up to a total of 30 patients during the FDA review of the safety data. This phase began in October 2014 and, after review of the initial data, the FDA granted unrestricted expansion to the planned 60 sites. Thus, the expanded phase of enrollment began in April 2015 and is ongoing.

Sample size and power calculations

A total of 1,028 patients will be enrolled in the study. Three hundred sixty-six patients (randomized 1:1) will be enrolled and randomized to evaluate the primary end-point for assessment of non-inferiority. Of these, the first 294 patients will be evaluated at 6 months for the primary end-point. An

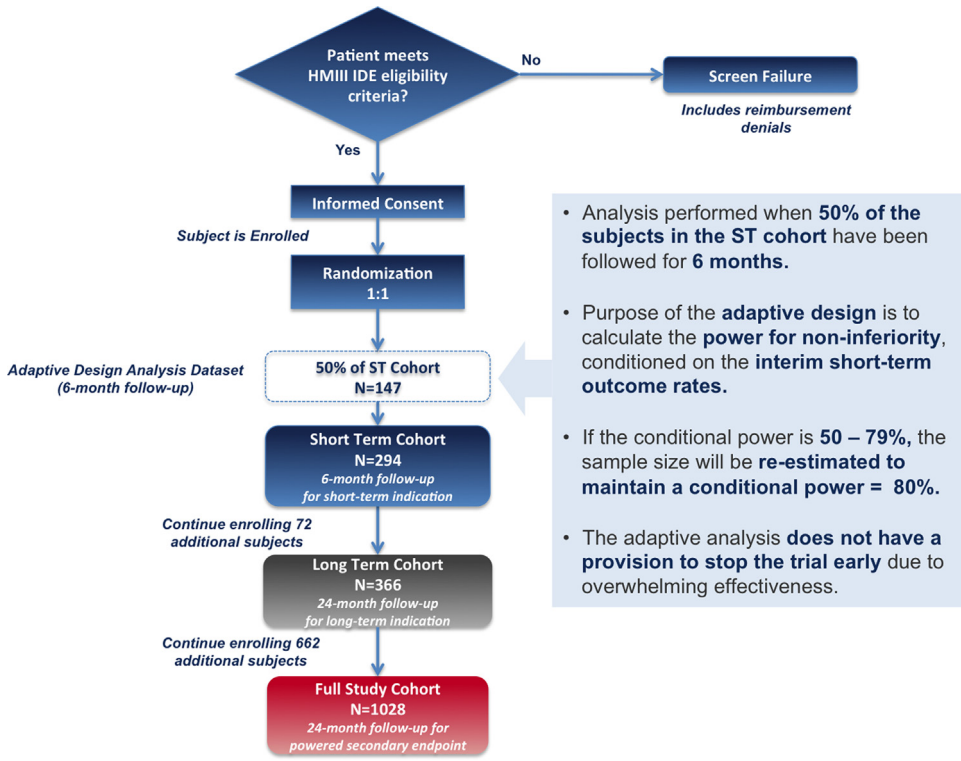

Figure 5 MOMENTUM 3 study flowchart.

Table 3 Study Inclusion and Exclusion Criteria

Inclusion criteria:

1. Subject or legal representative has signed ICF.
2. Age $\geq$18 years.
3. BSA $\geq$1.2 m^2.
4. NYHA Class III with dyspnea upon mild physical activity or NYHA Class IV.
5. LVEF $\leq$ 25%.
6. (a) Inotrope-dependent; OR (b) CI $<$2.2 liters/min/m^2, while not on inotropes and subjects must also meet one of the following:
   - On optimal medical management, based on current HF practice guidelines for at least 45 of the last 60 days and are failing to respond.
   - Advanced heart failure for at least 14 days and dependent on IABP for $\geq$7 days.
7. Females of childbearing age must agree to use adequate contraception.

Exclusion criteria:

1. Etiology of HF due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis or restrictive cardiomyopathy.
2. Technical obstacles which pose an inordinately high surgical risk, in the judgment of the investigator.
3. Existence of ongoing MCS other than IABP.
4. Positive pregnancy test if of childbearing potential.
5. Presence of mechanical aortic cardiac valve that will not be either converted to a bioprosthesis or oversewn at the time of LVAD implant.
6. History of any organ transplant.
7. Platelet count $<$ 100,000 $\times$ 10^3/liter ($<$100,000/ml).
8. Psychiatric disease/disorder, irreversible cognitive dysfunction or psychosocial issues likely to impair compliance with the study protocol and LVAS management.
9. History of confirmed, untreated AAA $>$5 cm in diameter within 6 months of enrollment.
10. Presence of an active, uncontrolled infection.
11. Intolerance to anti-coagulant or anti-platelet therapies or any other peri-/post-operative therapy that the investigator will require based upon the patient's health status.
12. Presence of any one of the following risk factors for indications of severe end-organ dysfunction or failure:
    - An INR $\geq$2.0 not due to anti-coagulation therapy.
    - Total bilirubin $>$43 μmol/liter (2.5 mg/dl), shock liver, or biopsy-proven liver cirrhosis
    - History of severe COPD defined by $FEV_1/FVC < 0.7$, and FEV_1 $<$50% predicted.
    - Fixed pulmonary hypertension with a most recent PVR of $\geq$8 Wood units that is unresponsive to pharmacologic intervention.
    - History of stroke within 90 days prior to enrollment, or a history of cerebrovascular disease with significant ($>$80%) uncorrected carotid artery stenosis
    - Serum creatinine $\geq$221 μmol/liter (2.5 mg/dl) or the need for chronic renal replacement therapy.
    - Significant PVD accompanied by rest pain or extremity ulceration.
13. Patient has moderate to severe aortic insufficiency without plans for correction during pump implant.
14. Pre-albumin $<$150 mg/liter (15 mg/dl) or albumin $<$30 g/liter (3 g/dl) (if only one available); pre-albumin $<$150 mg/liter (15 mg/dl) and albumin $<$30 g/liter (3 g/dl) (if both available).
15. Planned Bi-VAD support prior to enrollment.
16. Patient has known hypo- or hypercoagulable states such as disseminated intravascular coagulation and heparin-induced thrombocytopenia.
17. Participation in any other clinical investigation that is likely to confound study results or affect the study.
18. Any condition other than HF that could limit survival to $<$24 months.

AAA, abdominal aortic aneurysm; Bi-VAD, biventricular assist device; BSA, body surface area; CI, cardiac index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HF, heart failure; IABP, intra-aortic balloon pump; ICF, informed consent form; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; NYHA, New York Heart Association; PVD, peripheral vascular disease; PVR, pulmonary vascular resistance.

additional 662 patients will be randomized to achieve the total of 1,028 needed for the powered secondary superiority end-point analysis.

Primary end-point, ST indication

On the basis of a review of recent data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and Thoratec, it is assumed that the HMII population will achieve a composite success rate of 85% at 6 months.[16,17] It is also assumed that the HM3 population will have a composite success rate of 87% due to fewer pump replacements at 6 months caused by thrombus or drive-line problems. We estimate that 138 patients in each group will be required to achieve 80% power to demonstrate that the HM3 is non-inferior to HMII at a margin of non-inferiority of –10% (= Δ in the previously noted null and alternative hypotheses) using the Farrington–Manning risk difference approach to non-inferiority with a one-sided $\alpha = 0.025$.

INTERMACS data were reviewed from 26 sites likely to participate in the study. Eight hundred twenty (820) patients

were implanted with an HMII in 2012 at these sites, and 52 (6%) received a transplant or explant due to myocardial recovery before 6 months. Based on this, and to have sufficient data to evaluate the 6-month success rate, an additional 9 patients will be randomized per arm (6% of 138) to account for these early outcomes. This requires 147 patients to be randomized in each arm (294 total patients) for the ST cohort analysis.

Primary end-point, LT indication

On the basis of the results from the HMII destination therapy IDE study, it is assumed that 50% of the HMII patients will successfully achieve the composite primary end-point.[18] It is also assumed that the HM3 patients will have a composite success rate of 55% due to fewer pump replacements at 24 months caused by thrombus or driveline–related complications. It will require 174 HM3 and 174 HMII patients (348 total patients) to achieve 80% power to demonstrate that the HM3 is non-inferior to the HMII when the margin of non-inferiority ($= \Delta$ in the above null and alternative hypotheses) is –10% using the Farrington–Manning risk difference approach to non-inferiority with a one-sided $\alpha = 0.025$. The 9 additional patients added per treatment arm for the ST indication will result in a total of 183 patients randomized in each arm (366 total patients). Thus, the LT indication will include the 294 patients from the ST indication plus 72 additional patients. To have a sufficient number of patients available to assess the LT indication, at least 75 patients randomized to HeartMate 3 must survive to 24 months free of debilitating stroke on their original device before data can be analyzed for the LT indication. Sequential non-inferiority followed by superiority testing will be conducted for the primary end-point analyses.

Secondary end-point

In addition to primary outcomes, the study will be powered to test whether the HM3 pump is superior to the HMII by analyzing the incidence of pump replacements. If we assume the HMII pump replacement rate at 24 months will be reduced by half with the HM3, then 1,028 patients (514 per treatment arm) will provide 80% power ($\alpha = 0.05$, two-sided). Once the 366 patients needed for the LT indication are enrolled, the study will continue to randomize 662 additional patients for the secondary analysis.

Clinical assessments

Baseline assessments include patients' demographics, blood chemistry, hemodynamics, medical and cardiac history, current medications, functional capacity and quality of life. Follow-up assessments will be performed post-implant at Week 1; at the time of discharge; and then at 1, 3, 6, 12, 18 and 24 months. Pre-defined adverse events, reoperations, readmissions to the hospital and device malfunctions will be reported as they occur.

Statistical analysis

Continuous data will be presented as the number of patients, mean with standard deviation, median and minimum/maximum values. Categorical data will be reported as frequencies and percentages. Adverse events will be reported as events per patient-year. Adverse events that occur with and after the implant procedure will be analyzed. Survival data will be presented using the Kaplan–Meier product limit method. Data will be analyzed using the intent-to-treat (ITT) method, defined as all randomized patients. Every effort will be made to avoid cross-over; however, in the event of cross-over, data will also be analyzed "as randomized" for efficacy analysis and "as treated" for safety analysis and all other secondary end-points. Missing primary end-points will be imputed using multiple imputation techniques. A one-sided 0.025 level of significance or a two-sided 0.05 level of significance will be used to declare statistical significance. The LT indication will be performed only if the ST indication has been achieved; therefore, multiplicity adjustments will not be required. Once non-inferiority is proven, the data will be analyzed for superiority using closed testing methods via the *Z*-test of proportions, with the normal approximation to the binomial distribution. Statistical analysis will be performed using SAS version 9.1 (or higher).

Interim analysis

A pre-specified, unblinded interim analysis will be performed when the first 147 patients enrolled in the study have achieved an outcome or 180 days of support, whichever occurs first. An independent statistician will perform this analysis and the results will be presented to the DSMB. The purpose of the interim analysis is to calculate the power for non-inferiority, conditioned on the difference between treatments with respect to ST outcome rates and on the non-inferiority margin of 10%. Based on the result of the analysis, an adjustment to the sample size may occur. The interim analysis will not be used to stop the trial for overwhelming effectiveness, and thus no adjustment of the significant level for the final analysis is required.

Pre-specified subgroup analyses will be conducted for gender, ethnicity, and intended use of the device at the time of implant. These analyses are considered secondary and hypothesis-generating. Similarly, a learning curve analysis to assess outcome differences between early and later implants as a function of center volume and duration of experience will be developed.

Data management

Centers will enter data into a validated internet-based EDC system that is compliant with Title 21 Code of Federal Regulations Part 11 (21 CFR Part 11). Unique usernames and passwords will be assigned and maintained by St. Jude Medical, Inc., for all study personnel. Site users will be permitted only data entry rights to use the system and only after database training has been completed.

An independent clinical events committee (CEC) blinded to the randomization will adjudicate all events. They will also adjudicate the severity and device relationship of these adverse events. An independent DSMB will perform regular review of the clinical safety data and may recommend study discontinuation or modification as per pre-approved charter.

Ethics considerations

All sites participating in this study will obtain approval from their institutional review board (IRB) before enrolling patients. All sites will follow the reporting requirements of their IRB. Informed consent will be obtained for all patients enrolled in the study. If new information becomes available that may affect a patient's participation, then investigators will be required to update and revise the informed consent as necessary, and all patients will be re-consented by the site. All revisions to the informed consent must be approved by the IRB before re-consenting.

Study status and summary

Enrollment of the MOMENTUM 3 study began on September 4, 2014 at 5 centers that were enrolling in the safety phase. Subsequent to review of the 30-day safety data in the first 10 patients by the DSMB, the FDA provided complete approval to expand to all study sites on April 1, 2015. The study is currently enrolling and, as such, is the largest randomized comparison between two LVASs. It will afford valuable insights into the performance of the novel HM3 when compared with an established LVAS, beyond previously conducted smaller studies. The size of the study will allow for useful insights into important pre-specified subgroups and sub-analyses, thus providing an opportunity for establishing data-driven guidelines for LVAS therapy. Importantly, the trial seeks to establish the use of LVAS therapy in appropriately selected advanced-stage heart failure patients, irrespective of primary intent (BTT or DT), in an effort to reflect contemporary clinical reality.[19]

Disclosure statement

G.H., P.S. and D.M. are employees of St. Jude Medical, Inc.; D.G. reports consulting relationships with St. Jude Medical, Inc., HeartWare, Medtronic and Sunshine Heart; N.U. reports relationships with St. Jude Medical, Inc., HeartWare, Abiomed and Medtronic; J.C. reports grant support from St. Jude Medical, Inc., and HeartWare; D.M. reports consulting relationships with St Jude Medical, Inc., HeartWare, Medtronic, Boston Scientific, Stealth Biopeptides, Johnson and Johnson and Teva. The authors thank Tim Myers for preparation of the manuscript and Kevin Bourque, PhD, for providing the technical details of the HeartMate 3.

Appendix

The MOMENTUM 3 Study Group consists of: Stephen H. Bailey (Allegheny General Hospital, Pittsburgh, PA); John Ransom, Jr. (Baptist Health Medical Center, Little Rock, AR); Akinobu Itoh, Shane LaRue and Muhammad Massod (Barnes-Jewish Hospital, St. Louis, MO); Shelley Hall and Brian Lima (Baylor University Medical Center, Dallas, TX); Marc Katz (Bon Secours Health System, Richmond, VA); Michael Givertz (Brigham and Women's Hospital, Boston, MA); Martin Strueber (Spectrum Health Butterworth, Grand Rapids, MI); Sanjeev Gulati and Eric Skipper (Carolinas Medical Center, Charlotte, NC); Francisco Arabia (Cedars-Sinai Medical Center, Los Angeles, CA); Antone Tatooles (Advocate Health Care, Oak Lawn, IL); Nadar Moazami and Randall Starling (Cleveland Clinic, Cleveland, OH); Yoshifumi Naka and Hiroo Takayama (Columbia Presbyterian, New York, NY); Carmelo Milano (Duke University, Durham, NC); Scott Silvestry (Florida Hospital, Orlando, FL); Jeffrey Morgan and Celeste Thomas Williams (Henry Ford, Detroit, MI); Walter Pae (Hershey Medical Center, Hershey, PA); Pavan Atluri and Joyce Wald (Hospital of the University of Pennsylvania, Philadelphia, PA); Shashank Desai and Ramesh Singh (Inova, Fairfax, VA); James Long and Douglas Horstmanshof (INTEGRIS Baptist Medical Center, Oklahoma City, OK); Jeffery Wang (Methodist Hospital–Indiana University Health, Indianapolis, IN); Mark Slaughter (University of Louisville, Louisville, KY); John Stulak (Mayo Clinic, Rochester MN); Igor Gregoric (Memorial Hermann, Houston, TX); Brian Bruckner and Mathias Loebe (Methodist, Houston, TX); Ulrich Jorde (Montefiore Medical Center, Bronx, NY); Anelechi Anyanwu and Sean Pinney (Mt. Sinai Hospital, New York, NY); Meredith Brisco (Medical University of South Carolina, Charleston, SC); Margarita Camacho (Newark Beth Israel, Newark, NJ); Allen Anderson (Northwestern Memorial Hospital, Chicago, IL); Aditya Bansal (Ochsner Medical Center, New Orleans, LA); Ahmet Kilic (Ohio State University Medical Center, Columbus, OH); Frederick Tibayan (Oregon Health & Science University, Portland, OR); David Dean (Piedmont Hospital, Atlanta, GA); Michael McGrath (Sentara Heart Hospital, Norfolk, VA); Juan Aranda and Charles Klodell (University of Florida–Shands Hospital, Gainesville, FL); Robert Adamson (Sharp Memorial Hospital, San Diego, CA); Mary Walsh (St. Vincent Hospital, Indianapolis, IN); Francis Downey and Vinay Thohan (Aurora St. Luke's Medical Center, Milwaukee, WI); Don Chomsky (St. Thomas Hospital, Nashville, TN); Richard Ha (Stanford University, Palo Alto, CA); Christiano Calderia (Tampa General, Tampa, FL); Steve Singh (Texas Heart Institute, Houston, TX); John Entwistle (Thomas Jefferson Hospital, Philadelphia, PA); Jay Bhama (University of Iowa, Iowa City, IA); Sirtaz Adatya (University of Chicago, Chicago, IL); Andreas Brieke (University of Colorado, Denver, CO); Francis Pagani (University of Michigan, Ann Arbor, MI); Rebecca Cogswell and Ranjit John (University of Minnesota, Minneapolis, MN); Brian Lowes and John Um (University of Nebraska, Omaha, NE); Brett Sheridan (University of North Carolina, Chapel Hill, NC); Leway Chen (University of Rochester, Rochester, NY); John Kern (University of Virginia, Charlottesville, VA); Claudius Mahr and Nahush Mokadam (University Washington, Seattle, WA); Shahab Akhter and Ravi Dhingra (University of Wisconsin, Madison, WI); Eric Adler (UC San Diego, San Diego, CA); Mary Keebler and Ashish Shah (Vanderbilt University, Nashville, TN);

Vigneshwar Kasirajan and Rachit Shah (Virginia Commonwealth University, Richmond, VA); David Majure (Washington Hospital, Washington, DC); and Abeel Mangi (Yale University, New Haven, CT).

References

1. Frazier OH, Rose EA, McCarthy P, et al. Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. Ann Surg 1995;222:327-36.
2. Frazier OH, Rose EA, Macmanus Q, et al. Multicenter clinical evaluation of the HeartMate 1000 IP left ventricular assist device. Ann Thorac Surg 1992;53:1080-90.
3. Frazier OH, Rose EA, Oz MC, et al. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. J Thorac Cardiovasc Surg 2001;122: 1186-95.
4. Farrar DJ, Hill JD, Pennington DG, et al. Preoperative and postoperative comparison of patients with univentricular and biventricular support with the Thoratec ventricular assist device as a bridge to cardiac transplantation. J Thorac Cardiovasc Surg 1997;113:202-9.
5. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med 2001; 345:1435-43.
6. Rose EA, Moskowitz AJ, Packer M, et al. The REMATCH trial: rationale, design, and end points. Ann Thorac Surg 1999;67:723-30.
7. Aaronson KD, Slaughter MS, Miller LW, et al. Use of an intrapericardial, continuous flow, centrifugal pump in patients awaiting heart transplantation. Circulation 2012;125:3191-200.
8. Goldstein DJ, Naftel D, Holman W, et al. Continuous-flow devices and percutaneous site infections: clinical outcomes. J Heart Lung Transplant 2012;31:1151-7.
9. Coffin ST, Haglund NA, Davis ME, et al. Adverse neurologic events in patients bridged with long-term mechanical circulatory support: a device-specific comparative analysis. J Heart Lung Transplant 2015;34: 1578-85.
10. Stewart GC, Givertz MM, Mehra M. Pump thrombosis redux. J Heart Lung Transplant 2015;34:1511-4.
11. Stulak JM, Davis ME, Haglund N, et al. Adverse events in contemporary continuous-flow left ventricular assist devices: a multiinstitutional comparison shows significant differences. J Thorac Cardiovasc Surg 2016;151:177-89.
12. Schmitto JD, Hanke JS, Rojas SV, et al. First implantation in man of a new magnetically levitated left ventricular assist device (HeartMate III). J Heart Lung Transplant 2015;34:858-60.
13. Netuka I, Sood P, Pya Y, et al. Fully magnetically levitated left ventricular assist system for the treatment of advanced HF: a multicenter study. J Am Coll Cardiol 2015;66:2579-89.
14. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007; 357:885-96.
15. U.S. Department of Health and Human Services; Food and Drug Administration; Center for Devices and Radiological Health; Center for Biologics Evaluation and Research. Draft guidance for industry and Food and Drug Administration staff: adaptive designs for medical device clinical studies. CDRH-Guidance@fda.hhs.gov, May 18, 2015.
16. Kirklin JK, Naftel DC, Pagani FD, et al. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant 2015;34: 1495-504.
17. John R, Naka Y, Smedira NG, et al. Continuous flow left ventricular assist device outcomes in commercial use compared with the prior clinical trial. Ann Thorac Surg 2011;92:1406-13.
18. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241-51.
19. Teuteberg JJ, Stewart GC, Jessup M, et al. Implant strategies change over time and impact outcomes: Insights from the INTERMACS (interagency registry for mechanically assisted circulatory support). J Am Coll Cardiol. Heart Fail 2013;1:369-78.