24 Hour Summary of the Circulatory System Devices Panel Meeting
TransMedics Organ Care System (OCS) Heart System
April 6, 2021

Introduction:

The Circulatory System Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on April 6, 2021 to discuss and make recommendations on the PMA application for the TransMedics Organ Care System (OCS) Heart System, including whether the device demonstrates a reasonable assurance of safety and effectiveness in perfusing and transporting donor hearts with the following indications for use:

The sponsor has proposed the following Indications for Use:

The TransMedics® Organ Care System (OCS™) Heart System is a portable extracorporeal heart perfusion and monitoring system indicated for the resuscitation, preservation, and assessment of donor hearts in a near-physiologic, normothermic and beating state intended for a potential transplant recipient. OCS Heart is indicated for donor hearts with one or more of the following characteristics:

- Expected cross-clamp or ischemic time ≥4 hours due to donor or recipient characteristics (e.g., donor-recipient geographical distance, expected recipient surgical time); or
- Expected total cross-clamp time of ≥2 hours PLUS one of the following risk factors:
  - Donor Age ≥55 years; or
  - Donors with history of cardiac arrest and downtime ≥20 minutes; or
  - Donor history of alcoholism; or
  - Donor history of diabetes; or
  - Donor Left Ventricular Ejection Fraction (LVEF) ≤50% but ≥40%; or
  - Donor history of Left Ventricular Hypertrophy (LVH) (septal or posterior wall thickness of >12 and ≤16 mm); or
  - Donor angiogram with luminal irregularities but no significant coronary artery disease (CAD).

Panel Deliberations/FDA Questions:

Question 1: Impact of Study Design limitations and Study Conduct on assessing safety, effectiveness and benefit/risk for the OCS Heart System.

The panel was frustrated by the lack of sufficient animal studies to assess safety; by the small study size (underpowered); the performance goal of 65% for the primary endpoint; the lack of a valid comparator; and by the absence of a traditional clinical events committee (rather than a single medical monitor that was used in the clinical studies) for event adjudication (and thus the primary endpoint). The Panel also felt that the inclusion criteria were too liberal and would have liked to see more specific elements (e.g., travel distance instead of time) that would have made the study more clinically interpretable.

Question 2: Whether the EXPAND donor heart study inclusion criteria also captured standard donor hearts, and if so, considering the results of PROCEED II, how this may impact the availability of acceptable donor hearts for transplantation and long-term survival.

The panel expressed concern about indication creep (i.e., OCS Heart use with standard criteria donor hearts), which could result in reduced long-term survival. Identifying a set of inclusion criteria where benefit is likely may be difficult. Some examples that were discussed include expected cross clamp time (ECCT) ≥4 plus other risk factors, mileage, and consideration of the number of refusals to assure that the donor heart would otherwise be discarded.

Question 3: The use of lactate as the principle determinant for transplantability

The panel agreed that lactate should not be the sole determinant for transplantability. There was no consensus on a lactate level threshold to define an acceptable donor heart for transplant. It was suggested that additional animal studies may help in that determination. It was accepted that the recipient should not undergo a sternotomy unless it is known that the donor heart is going to be transplanted.

Question 4: (a) is there a long-term survival benefit of preserving donor hearts on the OCS System; (b) the impact of the use of the OCS System on wait-times in the context of post-transplantation long-term survival; (c) reasonable assurance of safety and effectiveness with donor hearts considered "non-standard" based on anticipated prolonged preservation time only (i.e., ECCT ≥4).

(a) The panel had difficulty determining whether there was a long-term benefit due to limited long-term data (1 to 2 years at best) and no comparator group. The >10% survival difference as compared to SRTR, and > 25% of OCS subjects on mechanical circulatory support (MCS) post-transplant suggests uncertainty about long-term survival, since early post-transplant problems usually adversely affect long-term outcomes.

(b) Although difficult to determine impact of wait times without a control, the panel indicated that use of the device will most likely shorten waiting time. This might be favorable if it prevents the recipient from getting an LVAD but not if it means that the recipient will receive a suboptimal donor heart resulting in worse outcomes. One panelist suggested that a potential concurrent control group could be recipients willing to trade a shorter wait time for a suboptimal heart vs recipients who would rather wait for a standard heart.

(c) The panel had a diversity of opinion regarding safety and effectiveness for the sole inclusion criterion of ECCT ≥4 hours. Some indicated that unknown effects of total ischemic time (cold and warm) for the OCS System, and/or potential injury (e.g., 25% MCS post-transplant) do not support safety and effectiveness for extended out of body times, while others pointed to the greater miles travelled and higher cross-clamp times for the OCS-supported hearts as compared to SOC hearts. There was also additional discussion around how to better define prolonged perfusion or assure that the donor heart represented an acceptable definition of expanded criteria heart (e.g., >4 hours ischemic time based on mileage, plus number of refusals).

Question 5: Potential myocardial injury to the heart by the OCS System.

Due to lack of sufficient pre-clinical data (as brought up in the discussion of earlier questions), and limited clinical data, a definitive answer regarding whether the OCS Heart System is causing myocardial injury to some hearts is unable to be determined. Some panelists believe that the OCS System isn't injuring hearts but may be identifying hearts that shouldn't be transplanted; while others

believe that due to the significantly higher use of post-transplant mechanical circulatory support in subjects receiving an OCS heart, as well as the turn-down rate, especially in the randomized PROCEED II study, myocardial injury due to the OCS System cannot be ruled out.

Question 6. (a) are the identified inclusion criteria in the indications for use statement objective enough to define "extended hearts," and if so, will this result in an increase in donor heart utilization and acceptable survival; (b) is there a reasonable assurance of safety and effectiveness for each of the individual donor heart inclusion criteria.

(a) The panel believes that there will be an increase in donor heart availability, however, they are concerned with indication creep [*i.e., into standard heart criteria*]. The donor hearts should be defined to assure hearts that would not otherwise be used (e.g., prolonged perfusion based on distance and maybe another criterion). Defining a high-risk recipient was discussed; however, matching a high-risk recipient with a high-risk heart may be problematic. A suggestion was made that animal studies should be performed to better understand the final condition of OCS supported hearts especially for a high risk recipient population.

(b) The panel suggested that the second part of the donor heart inclusion criteria are arbitrary and could lead to indication creep (*i.e., use in standard hearts*). Inclusion criteria should be focused on prolonged out of body times and use of these extended hearts in the right recipient population.

Question 7. Benefit-Risk Profile

There was overall agreement that safety and effectiveness could not be determined for ischemic times <4 hours (based on PROCEED II). However, there may be benefit for hearts that won't be used (e.g., ischemic times ≥4 hours with other criteria) but is challenging to define, and given the limited number of sites (1 or 2) that enrolled a majority of subjects, translatability to smaller sites across the country is of concern. Some said it's difficult to say whether there's benefit, and also questioned whether it might be better to wait for a standard heart transported via standard of care.

Question 8. Post-Approval Study (PAS)

The panel agreed that the proposed post-approval study is not adequate. They recommended: significantly more enrolled subjects; a prospective concurrent comparator (e.g., patients who want an OCS "extended" heart vs. those who want to wait for a standard criteria heart; or comparison to 4 hour ischemic time SOC hearts); use of donor hearts that would not otherwise be used (e.g., rejection rate of 90-100), and where the recipient is on the transplant list should be a consideration. Also, the PAS needs to define device performance characteristics that affect long-term outcomes such as ischemic time and others to be identified and confirmed in PAS.

Vote

Voting Question 1, regarding whether there is reasonable assurance that the TransMedics OCS Heart System is **safe** for use in patients who meet the criteria specified in the proposed indication, the panel voted:

- Yes: 9

- No: 7
- Abstain: 2

Voting Question 2, regarding whether there is reasonable assurance that the TransMedics OCS Heart System is **effective** for use in patients who meet the criteria specified in the proposed indication, the panel voted:

- Yes: 10
- No: 6
- Abstain: 2

Voting Question 3, regarding whether **the benefits outweigh the risks** of the TransMedics OCS Heart System for the proposed indication, the panel voted:

- Yes: 12
- No: 5
- Abstain: 1