GASTROENTEROLOGY AND UROLOGY DEVICES PANEL
of the
MEDICAL DEVICES ADVISORY COMMITTEE

TransMedics Organ Care System™ (OCS) Lung System
TransMedics, Inc.

May 17, 2017

Discussion Questions

When addressing the discussion questions regarding the OCS Lung System and its clinical outcomes, the panel is asked to consider the benefits and risks of currently available devices or alternative forms of treatment.

Primary Analyses

1. The modified primary effectiveness endpoint presented by TransMedics was survival at 30 days post transplantation and absence of PGD (primary graft dysfunction) 3 ***within*** 72 hours post transplantation, using the ***per protocol*** (PP) population. This was modified from the initially approved primary effectiveness endpoint, which was survival at 30 days post transplantation and absence of PGD 3 ***at*** 72 hours post transplantation, using the ***modified intent to treat*** (mITT) population. Both endpoints were analyzed based on a non-inferiority comparison of success proportions in the two treatment groups, with the non-inferiority margin 0.04.

   FDA advised TransMedics against changing the primary effectiveness endpoint, because 71% of the originally planned 320 subjects had already been transplanted, and TransMedics may have been influenced by their monitoring of data. In addition, FDA has consistently recommended the mITT as the main analysis population due to potential bias associated with the PP population. Furthermore, PGD grading at T0 may be susceptible to confounding, e.g., volume status if cardiopulmonary bypass was used or post-cross-clamp ventricular dysfunction.

a. Please discuss whether these results support a reasonable assurance of the safety and effectiveness of the OCS Lung System.

Table 1 – Primary Effectiveness Endpoint

Population	SOC control % (n/N)	OCS Treatment % (n/N)	% Difference (95% UCB) (SOC – OCS)	p-value[1] Non-inferiority Margin= 0.04
Modified primary effectiveness endpoint **Survival at Day 30 post-transplantation and absence of ISHLT PGD 3 *within* the first 72 hours**				
mITT[2]	71.2 (131/184)	73.3 (121/165)	-2.1% (5.8%)	0.1003
PP	71.1 (128/180)	78.6 (121/154)	-7.5 (0.3%)	0.0077
Initially approved primary effectiveness endpoint **Survival at Day 30 post-transplantation and absence of ISHLT PGD 3 *at* 72 hours**				
mITT[2]	94.5 (173/183)[3]	87.9 (145/165)	6.7% (11.8%)	0.8084
PP	95.0 (170/179)[3]	91.6 (141/154)	3.4 (8.0%)	0.4162

1: normal approximation Wald test for non-inferiority, and Chi-square test for superiority
2: Turn-down (b) imputed as failure
3: The N is smaller in the Initially approved primary effectiveness endpoint due to missing data in PGD grading at 72 hours

b. The observed difference in rates of PGD 3 grading within 72 hours was driven predominantly by T0 gradings. Please discuss the impact of T0 PGD 3 episodes on the interpretation of study results.

2. Despite 1:1 randomization, there were disproportionately more screen failures and major protocol violations among OCS-randomized subjects compared to SOC-randomized subjects. 64% of "screen failures" were transplanted "off-study." The disproportionate removal of subjects jeopardized the property of randomization and may have introduced selection bias into the safety and effectiveness analyses.

Table 2 – Screen Failures and Protocol Violations

	SOC control		**OCS Treatment**	
Randomized (True ITT)	199		208	
Total Screen Failures	15		43	
Donor screen failures		10		31
Logistic screen failures		1		10
Recipient screen failures		4		2
Modified ITT (mITT)	184		165	
Total Protocol Violations	4 subjects	4 violations	10 subjects	12 violations
User error				7
Procedural error		3		2
Donor eligibility		1		3
Device Failure / turn down			1	
Per Protocol (PP)	180		154	

a. Please comment on the impact of post-randomization patient screening failures and protocol violations on trial interpretability, and the relative significance of the mITT and PP analysis populations.

b. Given the number of donor screen failures, is additional clarity needed to define which lungs should be accepted for treatment with the OCS system?

c. The 7 user errors identified in the table above were all primary effectiveness endpoint failures and included 2 deaths by 30 days post-transplant. Furthermore, while turn-down of conventionally preserved donor lungs is usually a rare event, at least one turn-down appears to have been the direct result of device malfunction.

   Please comment on the benefit-risk of the OCS Lung System in the context of the device's complexity and reliability, and the impact on donor lung utilization.

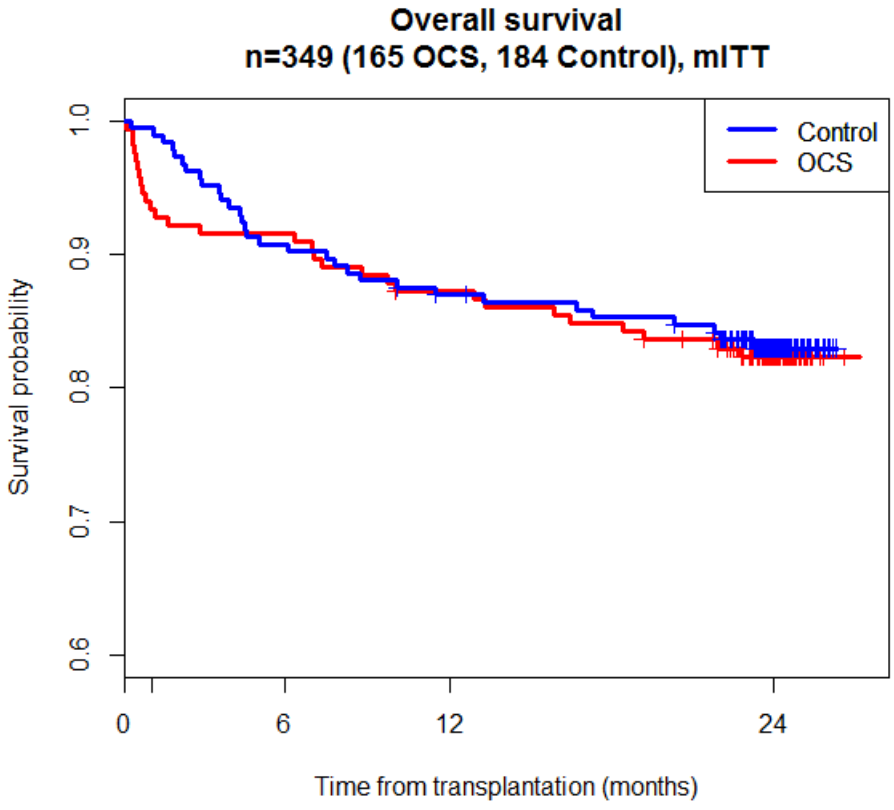
3. FDA believes the PGD grading scheme used by TransMedics does not represent the pre-specified criteria (2005 ISHLT Consensus Statement); specifically:

   - Assigning PGD 3 in the setting of "prophylactic" ECMO may not adequately account for post-operative pulmonary dysfunction superimposed on the pre-operative ECMO indication. Note that prophylactic ECMO was used primarily at one site, and this site enrolled 24% of all study patients.

   - Parsing PGD grading on the basis of intubation status is not a part of the Consensus Statement grading scheme.

   Please comment on the impact of the unplanned modification to the PGD grading scheme on the interpretability of the trial's effectiveness results.

4. The OCS Lung System did not demonstrate a survival benefit compared to control. Rather, an apparent increased risk of death in the early post-transplantation period seemed to be associated with the OCS device. Please comment on the clinical implications of the early OCS-associated mortality, given the later equilibration of overall survival.



5. The safety endpoint was based on the average number of four pre-specified lung-graft related serious adverse events (SAEs), per patient, up to 30 days following transplantation. The average number was 0.26 in the OCS arm compared with 0.29 in the SOC arm. The treatment difference (OCS-SOC) was -0.031 with the upper one sided 95% CI of 0.06, which met the non-inferiority margin of 0.07.

Table 3 – Safety Endpoint

	SOC control		OCS treatment	
	Subjects (N=184)	**Events (N=55)**	**Subjects (N=164)**	**Events (N=45)**
Lung – graft-related serious adverse events up to the 30-day follow-up after transplantation	45 (24.5%)	55 (100.0%)	40 (24.4%)	45 (100.0%)
Acute Rejection	4 (2.2%)	4 (7.3%)	2(1.2%)	2 (4.4%)
Respiratory failure*	16 (8.7%)	16 (29.1%)	23 (14.0%)	24 (53.3%)
Bronchial Anastomotic Complication	4 (2.2%)	4 (7.3%)	0 (0.0%)	0 (0.0%)
Major Pulmonary-Related infection	29 (15.8%)	31 (56.4%)	18 (11.0%)	19 (42.2%)

* *Respiratory failure: Impairment of respiratory function requiring reintubation, tracheostomy or the inability to discontinue invasive ventilatory support within 4 days (96 hours) post-transplant. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.*

a. Please discuss the appropriateness of the four pre-specified lung-graft related SAEs and the 30 day time point for assessing device safety, and the use of average number of events as the primary safety endpoint.

b. Please comment on the clinical significance of increased incidence of respiratory failure in the OCS arm related to the risk of mortality.

c. Please comment on the clinical implications of the safety endpoint and its 4 components.

Post-hoc and Adjunctive Analyses

6. Although Bronchiolitis Obliterans Syndrome (BOS) was not one of the safety endpoints, the protocol specified the accrual of data on the diagnosis of BOS at 6, 12 and 24 months. The inferences regarding BOS development are somewhat limited due to the unadjudicated nature of the data. TransMedics suggests a favorable decrease in BOS with use of the device. FDA failed to identify a clearly meaningful decrease in BOS at 24 months, and rates of patient survival to 2 years without BOS appeared to be comparable between the two study arms.

Please discuss the significance of the BOS findings in relation to the OCS Lung System.

7. TransMedics seeks marketing approval for its device with use of the OCS Lung Solution. TransMedics provided documentation indicating the OCS Lung Solution is equivalent to [redacted]. The INSPIRE pivotal study was conducted using both OCS Lung Solution and [redacted] Please discuss the appropriateness of assessing safety and effectiveness of the OCS Lung system based on the entire cohort of study subjects.

Post-Approval Study

8. The primary effectiveness endpoint in the new enrollment Post Approval Study (PAS) is 5-year survival. TransMedics proposes to conduct a hypothesis test to demonstrate that 5-year survival in this PAS is greater than 38.4% (performance goal of 50.4% with a 12% margin). The survival rate of 50.4% was based on OPTN (Organ Procurement and Transplantation Network) data of double lung transplants performed between 1997 and 2004.

   A 2015 annual report from OPTN reported a 5-year patient survival rate of approximately 60% in patients who underwent a double-lung transplant between 2008 and 2010. Based on these data, FDA recommends that a point estimate of 60% is more appropriate in this PAS.

   Please discuss what would be an acceptable point estimate to which 5-year survival in this PAS cohort should be compared, and what would be an acceptable margin that will not be clinically different from the point estimate.

9. TransMedics proposes to collect data on the following additional endpoints: short-term and long-term survival; PGD grade 3 ***within*** 72 hours post lung transplantation; and long-term assessment of BOS. While FDA supports collection of PGD data at all key time points up to and including 72 hours, FDA recommends that PGD 3 outcome assessment be based on measures at 72 hours. Please discuss the appropriateness of the proposed outcomes and follow-up assessment in order to evaluate the short-term and long-term safety and effectiveness of the device.

10. TransMedics did not specify a primary safety endpoint for the new enrollment PAS. FDA recommends that the incidence of lung graft-related adverse events up to 90 days or more post-transplant is a clinically meaningful measure. FDA recommends these events include acute rejection, respiratory failure, infection, and bronchial anastomotic complications. Please discuss an appropriate primary safety outcome, including the time period and the acceptable margin.