**FDA Gastroenterology and Urology Devices Panel**
**Advisory Committee Meeting on**
**TransMedics® Organ Care System™ (OCS) Liver System**

**July 14, 2021**

# FDA Discussion Questions

Safety and Effectiveness Endpoints

1. The primary effectiveness endpoint for this trial was the incidence of Early liver Allograft Dysfunction (EAD) and was defined as the presence of one or more of the following criteria:

   i. Transaminase (AST) level > 2000 IU/L within the first 7 postoperative days
   ii. Bilirubin ≥ 10 mg/dL on postoperative day 7
   iii. International Normalized Ratio (INR) ≥ 1.6 on postoperative day 7
   iv. Primary non-functioning graft within the first 7 days (defined as irreversible graft dysfunction requiring emergency liver re-transplantation or death, in the absence of immunologic or surgical causes).

   a. The primary effectiveness endpoint was that the OCS treatment is non-inferior to the Control with respect to EAD, with a noninferiority margin of 7.5%. The protocol specified that if non-inferiority were demonstrated, the results would be tested for superiority.

      The primary effectiveness endpoint was met under completer-case analysis in both mITT and PP populations: both non-inferiority and superiority were established for OCS arm compared to the Control arm.

      Please discuss whether the EAD results for the primary effectiveness endpoint support a reasonable assurance of the safety and effectiveness of the OCS Liver System.

| Population (Completers) | OCS Treatment % (n/N) | Control % (n/N) | %Difference (2-sided 90% UCB) (OCS-Control) | P-value | P-value |
|---|---|---|---|---|---|
| | | | | Non-inferiority Margin=0.075 | Superiority |
| mITT | 17.9 (27/151) | 32.4 (47/145) | -14.5 (-6.2) | <0.0001 | 0.0047 |
| PP | 18.0 (27/150) | 31.2 (44/141) | -13.2 (-4.9) | <0.0001 | 0.0096 |

   b. In the PROTECT trial, 63% of EAD cases in the OCS arm were only because of AST>2000, as were 77% in the Control arm. Please discuss the impact of EAD being mostly driven by AST on the interpretation of study results.

2. Secondary effectiveness endpoints included evaluation of
    - recipient survival at 30 days post-transplantation
    - recipient survival at initial hospital discharge post-transplantation

| Population | OCS Treatment % (n/N) | Control % (n/N) |
|---|---|---|
| | | |
| **Survival at Day 30** | | |
| mITT (N=298) | 99.3 (151/152) | 99.3 (145/146) |
| PP | 99.3 (150/151) | 99.3 (141/142) |
| | | |
| **Survival at Time of Initial Hospital Discharge Post Liver Transplantation** | | |
| mITT | 98.7 (150/152) | 98.6 (144/146) |
| PP | 98.7 (149/151) | 98.6 (140/142) |

In addition, Kaplan-Meier curves show similar probability of recipient and graft survival at 6, 12, and 24 months post-transplant for the ITT population.

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

3. Please discuss the importance of an improvement in EAD in the OCS arm over the Control, considering the similarity of observed survival in the OCS and Control arms. Is EAD an appropriate surrogate endpoint for survival?

4. Safety assessment was based on the number of liver-graft related serious adverse events (LGRSAEs) through 30 days post-liver transplantation per recipient, consisting of primary non-function, ischemic biliary complications, vascular complications, or liver allograft infections. LGRSAEs were also tracked at 6 months.

    Non-ischemic biliary complications were also reported at 30 days; there was no protocol to collect additional non-ischemic biliary complications after 30 days.

    Please discuss whether the results demonstrate device safety for the intended population.

LGRSAEs (AT Population, N=299)

| **Variable** | **OCS (N=153)** | | **Control (N=146)** | |
|---|---|---|---|---|
| | **Number of Recipients (%)** | **Number of Events** | **Number of Recipients (%)** | **Number of Events** |
| Recipients with at least one LGRSAE within 30 days post-transplant | 7 (4.6%) | 8 | 11 (7.5%) | 13 |
| | | | | |

| | | | | |
|---|---|---|---|---|
| Recipients with at least one LGRSAE within 6 months post-transplant | 9 (5.9%) | 10 | 23 (15.8%) | 28 |
| Non-functioning graft | 0 | 0 | 0 | 0 |
| Ischemic biliary complications | 2 (1.3%) | 2 (20%) | 12 (8.2%) | 12 (42.9%) |
| Vascular complications | 7 (4.6%) | 8 (80%) | 12 (8.2%) | 15 (53.6%) |
| Liver allograft infections | 0 | 0 | 1 (0.7%) | 1 (3.6%) |

Exploratory Analysis of Non-ischemic Biliary Complications (AT population, n=299)

| | **OCS (N=153)** | **Control (N=146)** |
|---|---|---|
| Non-ischemic biliary complications Diagnosed at 30 Days Post-Transplant | 13/153 (8.5%) | 6/146 (4.1) |

Uncertainty

5. The PROTECT trial included
   - early randomization of recipients prior to donor liver retrieval
   - re-randomization of dry run recipients who were organ that was not accepted for transplant.

   Given the trial randomization strategy and dry run/screen failures, please discuss how interpretation of the study results is impacted by the following:

   a. Among the 476 donor livers in the PROTECT trial, 176 (37%) were screen failures and were excluded from the study.

   b. Among the 429 consented recipients, 129 (30%) were excluded from the PROTECT trial and had no primary and limited secondary endpoint data collected. Of those excluded subjects, 49 (11%) were randomized and transplanted outside of the trial and not followed.

Device malfunctions and organ turndowns

6. Three device malfunctions were reported in the OCS arm, one of which resulted in the organ transfer to cold static storage for transplantation. These device malfunctions resulted in a protocol violation but did not cause any harm to the recipients involved. However, device malfunctions could result in liver damage or breach of organ sterility.

   Please discuss the significance of the device malfunctions.

7. Three livers were turned down after perfusion on the OCS device because of biopsy results or increasing lactate levels in their perfusion fluid. These three donor livers were all DCD livers that were initially assessed as "transplantable" following donor organ retrieval surgery but were deemed "non-transplantable" following OCS preservation.

   Please discuss the significance of the liver turndowns.

Labeling/claims

8. Please discuss whether the results of the PROTECT trial demonstrate the following.

   a. The OCS Liver System allows for *ex vivo* measurement of liver enzymes, lactate, and bile production. Are these measurements sufficient to determine that certain donor livers are not appropriate for transplantation?

   b. The sponsor has proposed an indications for use that specifies both liver allografts from donors after brain death (DBD) and liver allografts from donors after circulatory death (DCD) ≤55 years old.

      The PROTECT trial includes results for 41 recipients of DCD livers (28 OCS, 13 Control, mITT).
      - DCD donor risk factors indicate that these livers are suitable for transplantation
      - EAD rates were better in the OCS arm than in the Control (25.0% OCS, 84.6% Control, mITT)
      - Recipient survival at 12 months was better in the Control arm than in the OCS arm (4 OCS deaths, 1 Control death, ITT)
      - The three livers that were turned down for transplant after treatment were all DCD livers on the OCS Liver System

      Please discuss whether the data are sufficient to support an indications for use that includes DCD livers.

   c. Among the 106 DCD livers that were matched for transplantation (mITT), 50.9% (28/55) of the DCD livers randomized to OCS were transplanted, compared to 25.4% (13/51) of the DCD livers randomized to the Control group. The decisions to accept a DCD liver were made after the surgeon knew which study arm the liver would be used in.

      In the absence of validated criteria for assessment, is there rationale for increased utilization of DCD livers in the OCS arm? Has the study demonstrated improved utilization of DCD livers?

d. A lower rate of ischemic biliary complications was observed in the OCS arm compared to the Control. However, the protocol does not specify a definition of ischemic biliary complications or a prespecified methodology to detect subtle subclinical cases. Please discuss whether the data support a claim of reduction of ischemic biliary complications.

Post Approval Study

9. If the OCS Liver System is approved, TransMedics proposes to continue following participants in the OCS Liver PROTECT trial and in the OCS Liver CAP study up to 2 years post-transplant. FDA agrees with the PAS plan to continue follow-up of the pre-market cohorts, as this is the fastest way to collect longer-term data. However, with this approach, any limitations in the design and conduct of the PROTECT trial would persist in the extended follow-up studies.

   FDA also recommends a new enrollment study to better understand the safety and effectiveness of the OCS device on DCD donor organs, donor organ transplantability criteria, and device malfunctions. FDA recommends a longer-term evaluation of clinically meaningful outcomes, such as patient and/or graft survival post-transplant. FDA recommends leveraging the existing TOP Registry, which is an all-comers registry designed to collect real-world use data on OCS-perfused lungs and the patients who receive them.

   a. Please discuss whether a new enrollment PAS is needed.

   If so,

   b. Please comment on the key design elements of the study including the study objective, primary endpoint(s) and other endpoints, recipient follow-up duration, etc.

   c. Is it appropriate to leverage the existing TOP Registry to conduct a new post-approval study for the OCS Liver System?