SUMMARY MINUTES

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

GASTROENTEROLOGY AND UROLOGY DEVICES PANEL

July 14, 2021

Via Zoom Videoconference

Attendees:

Chairperson

Steven Schwaitzberg, M.D.
University of Buffalo School of Medicine & Bio Science
Buffalo, NY

Voting Members

Jason A. Dominitz, M.D., M.H.S.
Puget Sound Health Care System
Seattle, WA

Susie Q. Lew, M.D., FACP
George Washington University Medical Center
Washington D.C.

Temporary Voting Members

Shaneeta Johnson, M.D., M.B.A., FACS, FICS, FASMBS
Morehouse School of Medicine
Atlanta, GA

Richard Lange, M.D., M.B.A.
Texas Tech University Health Sciences Center at El Paso
El Paso, TX

Jason Connor, Ph.D.
ConfluenceStat, LLC
Orlando, FL

Julie Heimbach, M.D.
Mayo Clinic
Rochester, MN

Kenneth D. Chavin, M.D., Ph.D., FACS
Cleveland Medical Center
Cleveland, OH

Lynt Johnson, M.D., M.B.A.
George Washington University
Washington D.C.

W. Ray Kim, M.D.
Stanford University School of Medicine
Stanford, CA

Mark A. Talamini, M.D., M.B.A.
Stony Brook Medicine
Stony Brook, NY

Steven Solga, M.D., AGAF
Penn Transplant Institute
Philadelphia, PA

Jennifer Lai, M.D., M.B.A.
University of California-San Francisco
San Francisco, CA

David Assis, M.D.
Yale School of Medicine
New Haven, CT

Colleen Gallagher, Ph.D., LSW, FACHE, HEC-C
University of Texas MD Anderson Cancer Center
Houston, TX

Industry Representative

Jacqueline N. Welch, M.D., Ph.D.
Teleflex, Inc.
Pleasanton, CA

Consumer Representative

Amy Price, D.Phil.
Stanford University School of Medicine
Stanford, CA

Patient Representative

Karen Hoyt
World Transplant Games Federation and Integris Liver Foundation

Designated Federal Officer

James Swink
Food and Drug Administration

CALL TO ORDER

Panel Chairperson Steven Schwaitzberg, M.D., called the meeting to order at 9:00 a.m. He noted the presence of a quorum and affirmed that the Panel members had received training in FDA device law and regulations. He announced that the Panel would be discussing, making recommendations, and voting on information related to the premarket application for the TransMedics Organ Care System (OCS) Liver System.

PANEL INTRODUCTIONS

Chairperson Schwaitzberg asked the Panel members and the FDA staff to introduce themselves.

CONFLICT OF INTEREST STATEMENT

James Swink, Designated Federal Officer, read the Conflict of Interest statement and reported that a conflict of interest waiver had been issued to Dr. Jennifer Lai.

He introduced Dr. Jacqueline Welch as the Industry Representative.

TEMPORARY VOTING MEMBER STATUS STATEMENT

Mr. Swink read the Appointment to Temporary Voting Member Status Statement and appointed Drs. Kenneth Chavin, Jason Connor, Colleen Gallagher, Julie Heimbach, Lynt Johnson, Shaneeta Johnson, Ray Kim, Richard Lange, and Mark Talamini as temporary voting members. He also appointed Ms. Karen Hoyt as temporary non-voting patient representative.

GENERAL ANNOUNCEMENTS

Mr. Swink then made general announcements regarding transcripts and speaker identification. He introduced Allison Hunt as the FDA press contact.

SPONSOR PRESENTATION

Introduction

Waleed Hassanein, M.D., presented background information on the TransMedics Organ Care System. He addressed the limitations of cold storage for liver transplantation, gave a device description, and played a brief video showing how the system works. He explained the clinical advantages of the OCS, summarized key results from the PROTECT trial, and outlined the remainder of the sponsor's presentation.

Clinical Needs in Liver Transplantation

Malcolm MacConmara, M.D., discussed current challenges in liver transplantation. He noted that one out of every three patients are delisted or die before receiving a transplant

due to the inadequate supply of donor livers, that post-transplant complications are common with cold static preservation, and that 75% of livers from deceased cardiac death donors end up being discarded. He cautioned that future trends in donor pool characteristics will exacerbate the issues with cold storage, and underscored the need for new technologies to improve outcomes and expand utilization.

PROTECT and PROTECT CAP Trial Design and Results

James Markmann, M.D., Ph.D., reviewed the study design and results from the PROTECT trial. He informed the Panel that the primary endpoint was met, that OCS was found to be superior to standard of care in reducing the incidence of early allograft dysfunction, that there was less reperfusion injury and ischemic biliary complications, and that the assessment capabilities of the system led to a significant increase in the utilization of DCD livers.

Pathology Results

Anthony J. Demetris, M.D., provided background information on hepatic ischemia-reperfusion injury, explained how histopathological assessments were performed in the PROTECT trial, and addressed concerns raised by FDA regarding lobular necrosis findings. He noted that IR injury is unavoidable regardless of the preservation method, that there was less lobular inflammation in the OCS group after transplant, and that the OCS revealed serious pre-existing issues that were not fully apparent in pre-preservation biopsies.

TransMedics Positions on FDA Discussion Questions

Dr. Hassanein addressed the panel discussion questions and made the following points in support of the sponsor's conclusions:

- The PROTECT trial met its primary endpoint, as well as the pre-specified safety analysis endpoint.
- The EAD definition used in the trial is a validated and clinically accepted endpoint in liver transplantation.
- Results from the secondary effectiveness endpoints provide further support that the system is safe and effective.
- The trial was powered to assess differences in EAD, and the results support its use as a surrogate for graft loss, mortality, and other unfavorable outcomes.
- Results were not impacted by donor or recipient screen failures nor by the low rate of device malfunctions.
- OCS assessment capabilities enabled higher utilization of DCD livers.
- There were significant reductions in ischemic biliary complications at 6 and 12 months post-transplant.

In response to questions regarding the proposed post-approval program, he noted that there is no evidence of bias in the conduct of the PROTECT trial and that two-year follow-up meets the regulatory standard for the intent of a post-approval study.

Clinical Perspective and Benefit-Risk Assessment

Parsia Vagefi, M.D., FACS, discussed the advantages of the OCS system over cold storage for long-distance organ retrieval, noting that its assessment capabilities will allow for optimization and assessment of donor livers outside the body to ensure the best possible clinical outcomes. He concluded that a significant reduction of ischemic damage to donor livers can be expected with the OCS, as well as reduced rates of EAD, ischemic biliary complications, and wait-list mortality.

SPONSOR Q&A

Questions from the Panel:

Jason A. Dominitz, M.D., M.H.S., asked when the third post-transplant liver biopsies were done.

Mark A. Talamini, M.D., M.B.A., asked if the pathologists were blinded as to when the samples were taken.

W. Ray Kim, M.D., asked why there was a higher rate of inflammation in the cold storage arm if there was no difference in necrosis.

Julie Heimbach, M.D., asked how far the lactate level has to rise before a liver is considered to be unusable.

Richard Lange, M.D., M.B.A., requested the following information:

- ALT data in addition to AST
- the numbers for each individual patient and the standard deviation
- a definition for post-transplant reperfusion syndrome
- clarification on two transplanted livers that did not show a decrease in lactate levels

Answers from the Sponsor:

Dr. Hassanein informed Dr. Dominitz that the third post-transplant biopsies were performed immediately after reperfusion in the OR for both groups.

- He affirmed that pathologists in the treatment arm were not aware of when the samples were taken.
- He presented data showing the progression of lobular necrosis, noting that the numbers were fairly consistent between the two arms and that further stratification revealed a significant difference in the DCD group as compared to DBD.

Dr. Demetris suggested that ingredients in the perfusate could have caused the

disconnect between necrosis and inflammation.

Dr. Vagefi confirmed that livers will not be used if no significant drop in the lactate level is observed within the first two hours of perfusion.

Dr. Hassanein presented combined AST/ALT results showing a connection between OCS and significant reduction of EAD.

- He verified that patients who were diagnosed with ischemic biliary complications underwent MRCP or ERCP analysis to substantiate their diagnoses.
- He explained the randomization process and why there were differences in DCD turndowns in the OCS arm.

FDA PRESENTATION

Indications for Use, Device Description, Summary of Nonclinical Information, OCS Principle of Operation, Clinical/Regulatory History, Panel Discussion Questions

Bridget Wildt, Ph.D., introduced the FDA review team and presenters. She reviewed the proposed indications for use, non-clinical testing information submitted by the sponsor, and the principle of operation for the OCS system. She also discussed the clinical and regulatory history, and FDA's study design considerations for the PROTECT trial.

Ex Vivo Animal Studies Conducted for IDE Approval and Device Design Changes

Diane Cordray, V.M.D., presented information from animal studies submitted prior to initiation of the PROTECT trial. Results from a Phase 3 ex vivo study showed that the OCS maintained stable perfusion parameters during preservations, and four additional studies validated the OCS liver design development. She informed the Panel that no in vivo testing was conducted to support the current PMA. She further noted that the Phase 3 study provided definitive safety data to support approval of the PROTECT trial, that the OCS maintained liver function better than standard of care over 12 hours of preservation followed by 24-hour simulated transplant, that bile production was equivalent between the OCS and standard of care arms, and that histology showed improved maintenance of liver and bile duct architecture in the OCS arm as compared to standard of care.

Trial Design, Trial Course, Donor Liver and Recipient Disposition

Min Min, Ph.D., described the pivotal study design. She informed the Panel that the primary effectiveness endpoint was incidence of early liver allograft dysfunction within the first seven postoperative days, that secondary effectiveness endpoints were defined as 30-day survival and survival after initial hospital discharge, and that the safety endpoint was frequency of liver graft-related serious adverse events up to 30 days following transplantation. She next discussed the sponsor's proposed multiplicity adjustment procedure and testing sequence, as well as the trial course. She pointed out that early randomization and re-randomization could increase the potential for bias and lead to complexities in data

interpretation. She then presented flow charts depicting data sources, donor and recipient disposition, and the sponsor-defined analysis populations.

Clinical and Benefit-Risk Analysis

Dr. Wildt presented results from PROTECT and the PROTECT continued access protocol study. She discussed the trial objective and conduct, randomization and screening failures, major protocol violations, and donor and recipient characteristics. She informed the Panel that observed recipient survival and other clinically relevant outcomes were similar for OCS livers as compared to cold storage; that there is uncertainty surrounding the benefits of reduced EAD, liver assessment, lessening of biliary complications, and reduction of post-reperfusion injuries; and that there is concern regarding the risks of device malfunctions, liver turndowns post-assessment, and non-ischemic biliary complications.

Post-Approval Considerations for the Panel Discussion

Lauren J. Min, Ph.D., apprised the Panel of the sponsor's post-approval study plans. An extended follow-up of the PROTECT and CAP cohorts is proposed for evaluation of long-term outcomes with a primary effectiveness endpoint of liver graft survival at two years post-transplant. She noted that a key limitation of this approach is that the potential for bias in the design and conduct of the premarket studies would persist in the extended follow-up studies. She further noted that FDA's recommendations include a new enrollment PAS to address questions that were raised in the PROTECT trial; high quality prospective data collection on device malfunctions, conversion to cold storage, and organ turndown; longer-term evaluation of clinically meaningful outcomes; and that the new PAS be conducted as part of the Thoracic Organ Perfusion Registry.

FDA Q&A

Questions from the Panel:

Chairperson Schwaitzberg pointed out that one way to mitigate Type 1 error for post hoc analysis is to lower the p-value. He asked Dr. Min Min if there is a p-value that she would find more acceptable than 0.05.

Jason Connor, Ph.D., remarked that he has never seen efficacy and safety share the same alpha and asked for further comment.

Amy Price, D.Phil., Consumer Representative, asked what the importance of superiority and inferiority are in terms of this study. She also asked for clarification as to how important the p-value is.

Jennifer Lai, M.D., M.B.A., asked for information on the characteristics of recipients who received DCD livers.

Answers from FDA:

Dr. Min Min explained that p-values should be pre-specified and cannot subsequently be lowered as a mitigation for Type 1 error.

Li Ming Dong, Ph.D., pointed out that lowering the p-value would not be a feasible way of dealing with the multiplicity issue since the data is already out and the results are known.

- She explained to Dr. Connor that since both endpoints had to be met, the alpha did not have to be split between safety and effectiveness.
- She noted that the secondary effectiveness endpoints are for labeling purposes.
- She specified that the p-value was mainly used as the decision threshold, that superiority is for the labeling claim, and that the study itself was designed for non-inferiority.

Ergun Velidedeoglu, M.D., addressed questions regarding EAD as a surrogate outcome, and interpretation of OCS data from a labeling perspective.

Arturo Hernandez, M.D., GACS, explained how decisions were reached regarding the safety and efficacy endpoints. He emphasized that it is impossible to define the two in organ preservation, and that they cannot be divided for these kinds of devices.

Dr. Wildt specified that the sponsors decide what the endpoints for safety and efficacy will be, and that the Agency gives recommendations.

OPEN PUBLIC HEARING

Meg Seymour, Ph.D., spoke on behalf of the National Center for Health Research. She pointed out that the OCS system has not been proven to be superior over cold storage with respect to graft or recipient survival at 30 days, 6 months, and 12 months post-transplant, and that it could cause additional harm to high-risk patients.

Chandra Bhati, M.D., told of his experience with the OCS device as a principal investigator for the CAP trial. He reported that marginal organs functioned well in the device and after transplant, that there was very little ischemia reperfusion injury, and that patients had shorter ICU and hospitalization stays.

Shane Ottmann, M.D., commented that the transplantation process is much smoother with DCD livers that have been on the pump, and that anything that can be done to convert more organs to a usable condition is imperative.

Shawn Pelletier, M.D., attested that the device is easy to use, simple to transport, and will improve the safety of marginal organs. He remarked that there is a great potential to expand the donor pool and that it will be possible to resuscitate livers that would otherwise be discarded.

Michael Rizzari, M.D., stated that he has seen less post-reperfusion syndrome with the OCS device, and that it will be beneficial for real-time assessment of marginal donors and DCD organs.

Mark Ghobrial, M.D., commented that machine perfusion will allow for greater accessibility, improve the quality of transplant organs, and enhance the lives of patients.

Francisco Cigarroa, M.D., confirmed that every OCS-perfused liver that he has transplanted has been highly successful with no evidence of cholangiopathy.

Robert Herriage shared his experience as an OCS liver recipient. He told the Panel that the surgery was completed in less than six hours, that he was in ICU for two days and was discharged from the hospital on the sixth day, and that his stay at a local hotel for continued observation and daily clinic visits was cut short because of his rapid progress and recovery. He further stated that he can now walk five miles without stopping, that he has been able to travel, and that he has resumed doing the activities that he has always loved to do.

Keith Weeks, a PROTECT trial participant, related that after he was diagnosed with liver failure, he underwent countless endoscopies, paracentesis procedures, and blood transfusions. He stated that after his transplant he lost 45 pounds of mostly fluid and that shortly thereafter he was doing a lot of walking, riding an exercise bike, and had more energy than he had in years. He further stated that if it had not been for the OCS, he would still be living a horrible life on the waiting list.

Kasey Sherman told the Panel that it took nine years for her to completely deteriorate after her diagnosis of primary biliary cholangitis. She stated that after her liver transplant, she had no more itching, her skin returned to a normal condition, that she is mobile with no body swelling, and that she is living her life again.

Mark Roberts, M.D., related that within one day of enrolling in the OCS trial, he was notified that he had a liver match. He stated that he spent 24 hours in the ICU and was discharged from the hospital on post-op day six. He recalled how amazed he was at his rapid recovery and how much better he felt. He stated that he is now able to work full time, participate in outdoor activities, and do anything that he wants to do without restrictions.

James Falconi told the Panel that he was diagnosed with cirrhosis in 2011 and that in 2017, a routine ultrasound revealed a tumor on his liver. He related that he had his transplant one day after enrolling in the OCS trial, that he was in the ICU for one day, that he was discharged from the hospital six days later, and that his life returned to normal over the next three to four months.

SPONSOR RESPONSE

Dr. Hassanein verified that inclusion criteria included donor age greater than 40, that

the oldest donor age in the study was 83, and that the percentage of donor age greater than 70 in both arms was around 4%.

In response to questions related to ischemic biliary complications, he explained how the diagnosis was made and addressed the issue of Type 1 error. He also informed the Panel that EAD was highly associated with relative risk of graft failure.

He reviewed the results of peak AST, expounded on the topic of DCD utilization, and presented data to support the sponsor's claim that EAD is already being used as a surrogate endpoint in recent and ongoing trials.

He then commented on the two cases in which the lactate level did not go down. He also affirmed that the sponsor never made claims related to post-transplant or quicker recovery.

Dr. Markmann explained why the Olthoff paper showed higher risk of graft and patient mortality as compared to the OCS.

Dr. MacConmara addressed concerns regarding the potential risk of infection or device malfunction.

FDA RESPONSE

Dr. Min Min presented a summary of mortality rates and the number of deaths for the ITT population. She noted that similar rates were observed between both arms at 6, 12, and 24 months.

Dr. Velidedeoglu expounded on the predictive value of EAD as a potential surrogate, noting that it has not yet been validated but is being used extensively.

Q&A

Dr. Hassanein showed a comparison of risk factors between the two study arms. He noted that they were nearly identical with the exception of a higher rate of DCD utilization in the OCS group.

He informed Dr. Talamini that the longest out-of-body time achieved in the PROTECT trial was just over 17 hours.

Dr. Kim asked if the study population adequately represents the potentially expandable donor pool. **Dr. Hassanein** replied that the OCS was associated with better clinical outcomes in EAD reduction in every subgroup analysis population. He pointed out that if the device is approved, additional studies will be conducted for different indications and that integration of the technology will be in the hands of surgeons.

He then reviewed post-approval study plans and explained how the OCS can be converted to cold storage in the event of a device failure. He also addressed questions regarding similarities in the discarded livers, maintenance protocols, device malfunctions, and the re-randomization process.

Dr. Dominitz requested information on livers with accessory vessels and non-

ischemic biliary complications. **Dr. Hassanein** informed him that there were 24 livers with accessory vessels in the OCS group and 15 in control.

Dr. MacConmara explained how the ischemic biliary complications were diagnosed.

Dr. Lai requested information on rates of acute kidney injury and renal replacement therapy post-transplant. **Dr. Hassanein** informed her that acute renal failure was 7.2% in the OCS arm and 5% in control, and that renal failure non-specified was an additional 1% in each arm.

He then addressed questions regarding the pathology of discarded DCD grafts, peak AST, and graft failures.

PANEL DELIBERATIONS

Dr. Connor explained to Dr. Talamini that the multiplicities do not matter because all of the non-inferiority components were reached, as well as superiority for both primary endpoints (mITT and per protocol).

Colleen Gallagher, Ph.D., asked if patients with early allograft dysfunction have worse outcomes. **Dr. Heimbach** replied that the only difference she is aware of is that they have longer hospital stays.

Lynt Johnson, M.D., M.B.A., commented that there is no information on patient-reported outcomes. He pointed out that patients with ischemic biliary complications have a very different experience than those who do not.

FDA QUESTIONS

Dr. Wildt read Question 1a: 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 non-inferiority 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 the 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.

Dr. Gallagher stated that it is acceptable.

David Assis, M.D., agreed that it meets the test for safety and effectiveness.

Dr. Dominitz stated that it is sufficient. He added that he would have preferred a stronger clinical outcome.

Dr. Lange stated that he is not convinced that differences in AST levels correlate with safety and effectiveness.

Dr. Connor stated that it is unclear as to whether EAD reflects the long-term endpoint.

Dr. Heimbach stated that she is unsure about effectiveness.

Dr. Lynt Johnson pointed out that it met both components and that the impact of some complications associated with ischemic disease was minimized.

Dr. Kim stated that the study criteria meet both endpoints. He added that he believes the predictive value of EAD for long-term outcomes may be partially dependent on organ quality.

Steven Solga, M.D., AGAF, remarked that EAD as a validated surrogate is overstated, but noted that it was greatly reduced in fatty livers and DCDs as compared to control.

Dr. Lai stated that she finds the data to be very compelling for biological plausibility and that it may also depend on recipient characteristics.

Chairperson Schwaitzberg summarized the Panel's response:

- A majority of the members feel that the parameters of EAD were sufficient to support the endpoint of reasonable assurance of safety and effectiveness.
- A certain degree of ambiguity was expressed by some of the members and one member said no.

Dr. Wildt read Question 1b: 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.

Susie Q. Lew, M.D., FACP, opined that the numbers may be overestimated since AST does come from other areas.

Shaneeta Johnson, M.D., M.B.A., observed that the results correlate with other clinical outcomes.

Dr. Lange stated that he is not convinced that a minimal change in enzymes would contribute to anything significant in long-term clinical outcomes.

Dr. Connor agreed. He stated that the inclusion of more minimal items may make it easier to achieve non-inferiority and superiority, but that it may also create more ambiguity without understanding each component's contribution to the long-term endpoint.

Dr. Lai emphasized that the endpoint was developed and validated as a composite and that she is not sure that it would be appropriate to analyze individual components.

Dr. Gallagher remarked that it is not very informative and that she agrees with Dr. Lange.

Chairperson Schwaitzberg summarized the Panel's response:

- One member is unsure and another expressed a negative viewpoint, but the majority is comfortable with the definition of EAD as used in the trial.

Dr. Wildt read Question 2: Secondary effectiveness endpoints included evaluation of:

- recipient survival at 30 days post-transplantation
- recipient survival at initial hospital discharge post-transplantation

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.

Dr. Lange stated that the survival data are strong and that they address the issue of safety and effectiveness.

Dr. Connor agreed that this is the most compelling data in support of safety and effectiveness.

Dr. Heimbach observed that the results clearly demonstrate safety without impacting the question regarding efficacy.

Dr. Lynt Johnson commented that the data definitely show non-inferiority.

Dr. Talamini stated that the survival results support a reasonable assurance of safety and effectiveness.

Chairperson Schwaitzberg noted that the Panel overwhelmingly feels that the data support a reasonable assurance of safety and effectiveness.

Dr. Wildt read Question 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?

Chairperson Schwaitzberg noted that a majority of the Panel feels that it is acceptable although not ideal, with the exception of two members who have a more negative point of view.

Dr. Wildt read Question 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.

Dr. Talamini stated that the data is acceptable in terms of safety regardless of the shortcomings outlined in the question.

Dr. Solga observed that the data is consistent with the indication of diminished ischemic complications in the OCS arm as compared to control.

Chairperson Schwaitzberg noted that there is strong consensus that the results demonstrate safety for the intended populations.

Dr. Wildt read Question 5: The PROTECT trial included:

- early randomization of recipients prior to donor liver retrieval
- re-randomization of dry run recipients whose designated organs were 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.

Dr. Dominitz stated that the design is acceptable, but very close to being fatally flawed.

Dr. Lew recognized the importance of DCD utilization. She stated that it was a difficult decision, but she is somewhat accepting of it.

Dr. Shaneeta Johnson agreed that it is problematic, but she would lean towards acceptance.

Dr. Lange remarked that there is a lot of uncertainty surrounding this issue. He pointed out that many of the dry runs could have been decided before randomization.

Dr. Connor stated that he is content with the design and feels that it is appropriate given the difficulty in resource utilization.

Dr. Heimbach pointed out that there is no other way that it could have been done. She stated that she is satisfied with it and accepts it.

Dr. Lynt Johnson agreed. He noted that these kinds of trials are very difficult and that there was no way of getting around it.

Dr. Talamini observed that this is what happens when strict intention-to-treat rules are applied to complex clinical trials.

Dr. Solga stated that the least burdensome approach was met and is consistent with regulatory expectation.

Dr. Lai agreed. She added that it would have been very wasteful to the general community as a whole.

Dr. Assis opined that this issue is inherent to some degree in these types of studies.

Dr. Gallagher surmised that some of the screen failures could have been avoided and that randomization could have been done differently.

Jacqueline N. Welch, M.D., Ph.D., Industry Representative, observed that it makes sense from a practical perspective.

Chairperson Schwaitzberg summarized the Panel's response:

- It is very difficult in these types of scenarios to create an ideal intention-to-treat study.
- The conduct of the study is acceptable and did not bias the results in a way to make them obscure.

Dr. Wildt read Question 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.

Dr. Heimbach commented that the sponsor has developed an excellent way of handling these types of issues.

Dr. Lynt Johnson stated that there should be clear instructions on what to do if a malfunction occurs.

Dr. Assis pointed out that the risk is low and that the malfunctions were dealt with appropriately.

Chairperson Schwaitzberg summarized the Panel's response:

- The safety concerns about malfunctions have been carefully addressed.
- The Panel is comfortable with the low incidence rate.

Dr. Wildt read Question 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.

Karen Hoyt, Patient Representative, revealed that she had two dry runs and was at

the point where she was willing to take anything. She stated that patients want options and they want to be able to make those decisions with their surgeons.

Dr. Welch said that she is not concerned about the turndowns.

Dr. Dominitz emphasized the importance of tracking and following patients. He pointed out that there is no way of knowing, based on the current data, if these patients would have been better off getting the livers or if they were saved by the OCS from getting a bad liver. He also said that the rate is low enough to cause him no concern.

Dr. Lew stated that the rate was very low and she is comfortable with it.

Kenneth D. Chavin, M.D., Ph.D., observed that the problem with using these organs is that the outcomes are unknown.

Dr. Lynt Johnson pointed out that it is not uncommon for organs to be turned down after they've been procured and that this is another tool to aid surgeons in evaluating the likely success of donor organs.

Dr. Kim stated that if the donor pool is to be expanded, these are the kinds of livers that will be seen more frequently. He emphasized the need for continued study of this population.

Dr. Talamini stated that he is not concerned about the low numbers and that long-term data collection will be important.

Dr. Assis concluded that when more of this data comes out, there will be questions about what the cutoff for suitability should be from both a clinical and legal perspective.

Chairperson Schwaitzberg summarized the Panel's response:

- A majority of the members feel that the low number of turndowns did not impact the suitability for approval for safety and effectiveness.
- This should be tracked moving forward as it could potentially help inform post-approval studies.

Dr. Wildt read Question 8a: 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?

Dr. Chavin stated that they are acceptable as markers, but are not adequate in and of themselves for making that determination. He added that other factors such as biopsy and donor history must also be considered.

Dr. Lynt Johnson stated that he is unsure and that no data has been presented to confirm the answer.

Dr. Talamini remarked that it is obvious they are not fully sufficient and that any one factor would never be adequate to determine the acceptability of a donor liver.

Dr. Assis observed that they are not a substitute for the clinical acumen that is necessary for making these decisions.

Drs. Gallagher, Dominitz, Lew, and **Shaneeta Johnson** agreed that this alone is not enough, that the information is inadequate, and that more data is needed.

Dr. Heimbach stated that these factors need to be followed to answer the question and that none of them alone would be sufficient.

Chairperson Schwaitzberg summarized the Panel's response:

- The decision to not transplant is a complex clinical determination.
- The data provided is part of the puzzle but is not fully sufficient for making the decision to turn down a liver.

Dr. Wildt read Question 8b: 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.

Dr. Lynt Johnson stated that it is sufficient to support their use.

Dr. Kim agreed that the information is acceptable. He added that more data would be helpful to determine what donor organs could be salvaged by the device.

Dr. Solga pointed out that these patients are sicker than the rest of the pool and that they do introduce some bias.

Dr. Price recommended additional post-market surveillance.

Dr. Dominitz emphasized the importance of further analysis due to the expansion of the donor pool.

Dr. Lange stated that concealed allocation is an issue with this small group and that he does not think the study supports an indication at this time.

Chairperson Schwaitzberg summarized the Panel's response:

- A majority of the members feel that the data is sufficient to support an indication for use that would include DCD livers.
- Further data collection is needed to clarify the benefits of the device.

Dr. Wildt read Question 8c: 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?

Courtney H. Lias, Ph.D., explained to the Panel that the questions are related to whether or not the labeling should include this information.

Dr. Shaneeta Johnson stated that more long-term data is needed to support the rationale for increased utilization.

Dr. Lange stated that he would be in favor of labeling that allows for expanded harvesting of DCD livers.

Dr. Connor pointed out that although there was a significant increase in utilization, there was also unblinding at the time, which could have introduced bias. He asserted that at this point, he would not recommend including it in the labeling.

Dr. Heimbach stated that she is also uncertain because of the unblinding.

Dr. Chavin remarked that whatever the biases were, more livers were used on the device and more people were transplanted. He added that this would be a reasonable point of clarity in the labeling.

Dr. Kim stated that the rigor with which the data were gathered does not meet the standard for inclusion in the labeling.

Dr. Talamini opined that the data offers the potential that this is true, but is not sufficient for it to be in the labeling.

Dr. Lai stated that she believes the data demonstrate improved utilization of DCD livers, but is uncomfortable with it going into the labeling since there are multiple factors that could be associated with it.

Dr. Assis observed that there are too many ambiguities to say that the device was designed to show this as one of the outcomes in the labeling.

Dr. Dominitz stated that he believes this is a post hoc analysis and would say no to its inclusion in the labeling.

Chairperson Schwaitzberg noted that a majority of the Panel members feel that the data are not sufficient to support language in the labeling.

Dr. Wildt read Question 8d: 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 pre-specified methodology to detect subtle subclinical cases.

Please discuss whether the data support a claim of reduction of ischemic biliary complications.

Dr. Solga stated that the data are not strong enough to support labeling.

Dr. Lai pointed out that it currently does not support a claim of reduction of ischemic biliary complications.

Drs. Assis, Gallagher, Welch, Price, Talamini, and **Ms. Hoyt** agreed.

Dr. Dominitz stated that he would say no because of the multiple comparisons issue.

Dr. Lew insisted that the data do not support it.

Drs. Lange, Connor, Heimbach, Chavin, Shaneeta Johnson, and **Lynt Johnson** agreed.

Dr. Kim stated that he is in favor of it because he believes the data are true.

Chairperson Schwaitzberg noted that the Panel, with the exception of one member, feels that the evidence is not sufficient to support a labeling claim.

Dr. Wildt read Question 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?

Dr. Heimbach stated that she would support enrolling new patients into the existing study design.

Dr. Chavin stated that the current patient pool is good. He suggested extending it to three years and opening it to others.

Dr. Lynt Johnson stated that extended follow-up and a two-year study would be sufficient, with the addition of patient-reported outcomes.

Dr. Kim emphasized the need for new patients.

Dr. Solga stated that two years of follow-up would be adequate.

Dr. Lai stated that a new enrollment PAS is necessary and should be limited to donors for whom the device is really intended. She also said that she would like to see acceptance data from surgeons, and recommended stringent collection of information on

ischemic biliary complications.

Dr. Assis stated that a less optimal pool of candidates should be enrolled and that more emphasis should be placed on biliary complications.

Drs. Gallagher and **Price** stressed the importance of patient-reported outcomes.

Dr. Welch stated that she supports a new enrollment study that would focus on less optimal DCD livers.

Dr. Dominitz suggested further study of higher-risk patients.

Dr. Lew recommended additional assessment of marginal and DCD livers.

Dr. Shaneeta Johnson proposed two years of follow-up with patient-reported outcomes, more information on screen failures, and additional data on biliary and non-biliary complications.

Dr. Lange insisted that a new study should be mandated.

Chairperson Schwaitzberg summarized the Panel's recommendations for Questions 9(a) and 9(b):

- new enrollment patients are needed
- two-year follow-up would be sufficient
- patient-reported outcomes should be included, as well as acceptance and rejection information from surgeons
- more emphasis should be placed on sicker patients and marginal livers
- the new study should be mandatory

The Panel then discussed Question 9(c) regarding the study design.

Dr. Kim suggested a single-arm registry with baseline covariates.

Dr. Lai acknowledged that an RCT would not be possible. She emphasized the need for more data on marginal livers.

Dr. Assis stated that a registry would be sufficient.

Chairperson Schwaitzberg noted that the Panel recommends a single-arm registry trial and that more data is needed.

SUMMATIONS

Dr. Lias commended the Panel members for their consistent answers, and thanked them for their recommendations and time.

Dr. Hassanein thanked the Panel members for their insights and feedback.

Marwan S. Abouljoud, M.D., highlighted beneficial changes that could result from the OCS system. He stated that cold storage is insufficient for meeting current organ demands and that it cannot reduce wait-list mortality. He recognized the work and achievements of the PROTECT trial, noting that the OCS has reduced ischemic perfusion injuries, as well as the consequences of early allograft dysfunction and biliary strictures. In addition, it has demonstrated that the system resuscitates livers and stabilizes organ function

before transplantation. He further stated that the OCS will improve the quality of liver preservation and associated clinical outcomes, expand the use of extended criteria livers, and provide flexibility to make the best donor/recipient matches regardless of travel time and distance.

FINAL COMMENTS

Ms. Hoyt thanked the Panel members and the sponsor.

Dr. Welch stated that she is hopeful for what this product will mean to patients and that there is a strong indication it will change things for the better.

Dr. Price commended all of the participants for their thoughtful discussion. She stated that the meeting came to an excellent conclusion and was well done.

PANEL VOTE

Mr. Swink read the safety and effectiveness definitions. He explained the voting procedure and read the voting questions.

Question 1: Is there reasonable assurance that the TransMedics Organ Care System (OCS) Liver is safe for patients who meet the criteria specified in the proposed indication?

The Panel voted unanimously 14 yes, 0 no.

Question 2: Is there reasonable assurance that the TransMedics Organ Care System (OCS) Liver is effective for use in patients who meet the criteria specified in the proposed indication?

The Panel voted unanimously 14 yes, 0 no.

Question 3: Do the benefits of the TransMedics Organ Care System (OCS) Liver outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

The Panel voted 12 yes, 1 no, with 1 abstention.

Chairperson Schwaitzberg asked the Panel members to discuss their votes.

Dr. Dominitz indicated that he voted yes on all three questions.

Dr. Lew indicated that she voted yes on all three questions.

Dr. Shaneeta Johnson indicated that she voted yes on all three questions.

Dr. Lange indicated that he voted yes on all three questions. He stated that this is the beginning of the data and not the end.

Dr. Connor indicated that he voted yes on all three questions.

Dr. Heimbach indicated that she voted yes on all three questions.

Dr. Chavin indicated that he voted yes on all three questions.

Michael Hyde informed the Chair that Dr. Lynt Johnson voted yes on all three

questions.

Dr. Kim indicated that he voted yes on the first two questions and abstained on the third.

Dr. Talamini indicated that he voted yes on all three questions. He stated that he's hopeful that this and future technologies will address some of the difficult and challenging problems associated with transplantation.

Dr. Solga indicated that he voted yes on all three questions.

Dr. Lai indicated that she voted yes on all three questions. She stated that it would be interesting to study the benefits from the time of listing to post-transplant.

Dr. Assis indicated that he voted yes on all three questions. He stressed the importance of focusing on marginal populations in a postmarketing study.

Dr. Gallagher indicated that she voted yes, yes, and no. She stated that she does not think the benefits have yet been proven.

ADJOURNMENT

Chairperson Schwaitzberg thanked the Panel, FDA, and the open public hearing speakers for their contributions to the meeting. He then adjourned the meeting at 6:22 p.m.

I certify that I attended this meeting on July 14, 2021 and that these minutes accurately reflect what transpired.

_____
James Swink
Designated Federal Officer

I approve the minutes of this meeting as recorded in this summary.

_____
Steven Schwaitzberg, M.D.
Chairperson

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