24 Hour Summary of the Pediatric Advisory Committee
Artificial Womb Technology
September 19, 2023

Introduction:

The Pediatric Advisory Committee (PAC) met on September 19, 2023, to discuss the appropriate development plans for establishing safety and effectiveness of artificial womb technology (AWT) devices, including regulatory and ethical considerations for first in human (FIH) studies.

AWT devices are intended to treat extremely premature infants (EPIs) to provide a bridge from extreme preterm birth to later gestation within a physiologic environment aimed at mimicking the womb.

Panel Deliberations/FDA Questions:

QUESTION #1:

Given that testing on large animal models (e.g., lamb, piglet, non-human primate) has limitations related to between-species differences in anatomy and physiology which may prevent direct representation of the use of AWT devices in the human neonate, please discuss key safety and proof-of-principle endpoints, including timepoint(s) of assessment (e.g., time of transition from AWT, longer term follow-up), that may be evaluated in animal studies to understand the potential benefits and risks of AWT in the human neonate.

The panel agreed that the choice of an animal model was important to allow information from animal studies to be translated to human clinical use but recognized that there is no one perfect animal model to simulate the human condition. Some panelists expressed uncertainty about timepoints of assessments, indicating that it was unclear whether the animal studies presented during the meeting, which vary in terms of duration of AWT therapy, are sufficient to demonstrate proof-of-concept to support clinical treatment durations that may be proposed for clinical application. However, a definitive timepoint for assessments was not largely agreed upon. In addition to assessment of organ growth and maturation, panelists noted that animal studies may provide value to understand the implications of differences in nutrient sources in uterine environments compared to AWT, including differences in natural amniotic fluid compared to investigational fluids intended to mimic amniotic fluid. Panelists also indicated that adverse events, especially those that could be attributed to the device, should be evaluated in animal studies and that there may be value in using animal studies to understand and prepare for potential emergencies (e.g., device malfunctions) in clinical use.

QUESTION #2:

Given the limitations of the animal models and the clinical experience data discussed, what additional, if any, existing clinical experience data may be leveraged to help inform the benefit risk assessment of enrollment in a first-in-human trial of an AWT?

Panelists generally agreed that global, diverse, and inclusive data sources on existing clinical experience with EPIs, including short and long-term outcomes, will be important to inform the benefit-risk assessment for enrollment considerations for a first-in-human trial of an AWT device. Panelists also noted that the use of datasets from diverse and inclusive populations may provide valuable information

regarding health equity considerations for trial enrollment. The panel also discussed the need for recent data on the outcomes of 23-week gestational age infants. Given the recognition that site variation exists with regards to outcomes in this population, panelists also discussed the need for local site-specific data to be considered in the context of any proposed study population.

QUESTION #3:

What challenges do you anticipate in obtaining effective informed consent for an AWT clinical trial? Please discuss potential strategies to address any anticipated challenges.

The panel acknowledged that obtaining informed consent and parental permission for an AWT clinical trial poses challenges given the urgent and emotional circumstances of preterm labor but felt that robust processes could be developed to ensure that the informed consent procedures meet the needs of the subjects and family members. The panel agreed that giving potential subjects and families sufficient time to understand and consider standard of care and investigational options available at their hospital would be critical. Suggestions were made regarding community outreach and targeted delivery of early information to high-risk populations (e.g., individuals with a history of preterm delivery). For community outreach, the importance of representation from diverse communities was emphasized to ensure conversations about AWT are inclusive of a variety of perspectives. Early and ongoing access to information on AWT systems and procedures is especially critical due to the novelty and complexity of these therapies, and several panelists commented that use of videos and animations may be helpful to facilitate understanding by potential subjects' families. Panelists also emphasized the importance of the availability of support and advocacy for eligible subjects and that this support should be provided by persons independent of the investigative team and should persist through the duration of AWT therapy and follow-up. The panel discussed factors that they believed to be important for the informed consent process for future first-in-human AWT trials, including complete accounting of potential adverse events related to AWTs, contemporary data regarding outcomes for EPIs for understanding of alternate treatment options (i.e., standard of care), considerations to ensure inclusivity of trial enrollment, and use of standardized nomenclature for therapy and patient-related terminology. The panel agreed that obtaining informed consent from the pregnant person would require discussion about the short- and long-term risks of a cesarian delivery to facilitate AWT, particularly when the procedure is not otherwise clinically indicated.

QUESTION #4:

Please discuss critical aspects of safety monitoring in an AWT first-in-human (FIH) trial:

a. What adverse events of special interest should be monitored in an AWT trial to assess subject safety?

b. FDA anticipates that a FIH trial would initially enroll and treat a single subject at a time. When considering enrollment of additional subjects, what safety endpoints, including timepoint(s) of assessment, should be considered before enrolling a subsequent subject(s)?

The panel generally agreed that it will be critical to develop key short-term endpoints to facilitate decisions regarding enrollment of subsequent subjects to maintain practical trial durations for FIH studies. The panel discussed several key short-term endpoints including mortality, growth rate, bleeding events, thrombosis, and infection. Additionally, panelists noted that FIH studies should ensure appropriate reporting on device-related complications, the ability of the device to function as intended, the ability for device-related procedures to be performed safely and evaluate how well patients tolerate

the procedures. When considering assessments to support enrollment of additional subjects, some panelists anticipated challenges interpreting data collected from a small number of subjects and discouraged stopping enrollment based on isolated events. This approach was suggested by several panelists due to the heterogeneity and expected adverse events in standard of care for EPIs that would further complicate decision-making based on isolated events. Panelists commented that while it will be important to collect long-term neurocognitive outcomes, that this should not serve as the basis for continuing enrollment in the FIH studies.