Data and Safety Monitoring Board Meeting Summary
November 16, 2010
Teleconference

RE: Efficacy and Mechanisms of Glutamine Dipeptide in the SICU
U01 DK069322

ATTENDEES:

DSMB Members:
Stephen McClave, MD, Chairperson
Bruce Bistrian, MD, PhD
Feng Gao, PhD
Khursheed Jeejeebhoy, MBBS, PhD, FRCPC
Frederick Moore, MD

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK):
Carolyn Miles, PhD., Outgoing NIDDK Project Scientist
Mary Evans, PhD, Incoming NIDDK Project Scientist
Patricia Robuck, PhD, MPH, NIDDK Program Official
Rebecca Torrance, RN, MS, Executive Secretary to the DSMB
Rebekah Van Raaphorst, MPH, Alternative Secretary to the DSMB

Representing the Investigators:
Thomas Ziegler, MD, Principal Investigator (PI)
George Cotsonis, MS, Statistical Programmer
Kirk Easley, MS, Data Coordinating Center (DCC) Director
Gautam Hebbar, MBBS, MPH, Lead Study Coordinator
Traci Leong, PhD, unmasked Statistician
Thandeka Tutu-Gxashe, MPH, Project Monitor
Nana Freret, RN, Project Monitor
Seegar Swanson, Database Administrator

This was the ninth meeting of the Data and Safety Monitoring Board (DSMB). The agenda for the meeting included review of the status of the study, including review of the response to the previous DSMB recommendations. Dr. Miles opened the meeting by thanking the DSMB members for their ongoing service to the NIDDK as members of the DSMB and informing the DSMB that she is retiring from Federal service at the end of December, 2010. She introduced Dr. Mary Evans, who will be assuming the role of NIDDK Project Scientist for the GLND study and Dr. Patricia Robuck who will be serving as the NIDDK Program Official for GLND. Dr. Miles explained that NIDDK is revising their system of providing support for projects funded as cooperative agreements; now the NIDDK Project Scientist will be involved in the conduct of the study and a separate NIDDK Program Official will make decisions regarding funding and other

administrative issues. Previously, one NIDDK program staff member (Dr. Miles) had performed both roles.

No conflicts of interest were disclosed at the meeting, and none were disclosed on the forms on file with the NIDDK. All DSMB members were reminded of the confidentiality of the information regarding all aspects of the study. The meeting was chaired by Dr. McClave, DSMB Chairperson.

Dr. Ziegler reviewed his response to the recommendations from the previous (March 31, 2010) DSMB meeting and Mr. Easley provided an update on the status of the study.

Key points from the discussion of the response to previous DSMB recommendations included:

- Data on participants who are in skilled nursing facilities (SNF) or nursing homes six months following enrollment in the trial are now being collected. The investigators concur with the DSMB recommendation to include residence in a SNF or nursing home as a secondary endpoint.
- Analysis of Sequential Organ Failure Analysis (SOFA) scores will include the techniques suggested by the DSMB.
- Normal heat shock protein (HSP) values will not be determined by a validation study as was suggested at the previous DSMB meeting. Dr. Ziegler reiterated that absolute quantification of HSP levels is not perfect and normal ranges for these proteins have not been well-defined. The issue of normal HSP ranges will not be addressed as part of the GLND study, but the investigators will have descriptive data on the actual HSP values in GLND participants.
- Data on insulin requirements is now being recorded.

Highlights of the update on the status of the study included the following:

- As of October 29, 2010 (the date the database was locked for preparation of the DSMB report), 130 participants had been enrolled. Full enrollment of 150 participants is anticipated within the next six months.
- Retention data are good for follow-up contact with the participants who remain hospitalized; however, participants who have been discharged from the hospital prior to the 21 and 28-day time points are not consistently returning for blood collection. The rate of compliance for blood collection at 14, 21, and 28 days is 71%, 50%, and 47%, respectively, essentially unchanged from the previous DSMB report six months prior. More than 90% of the expected follow-up phone calls to determine vital status are being completed.
- Participant characteristics, blood glucose monitoring and other clinical data were reviewed in aggregate in open session and by treatment group during closed session.
- A total of 130 serious adverse events (SAEs) have been reported. Thirty-nine participants have died; twenty-seven within the first 28 days following their index surgery. Adjudication of deaths to assure consistency in reporting has been initiated per the DSMB's recommendation.
- The timeliness and quality of data being submitted to the Data Coordinating Center remains high. All sites are prompt in responding to data queries. No problems have been identified with the data quality and timeliness of submission at this time.

- Adjudication of nosocomial infections is underway; summarized incident infection data using standardized rates was provided and reviewed. To date, infections in all 130 participants have been adjudicated.

Dr. Leong presented the data by treatment group in closed session.

The DSMB deliberated in executive session and unanimously recommended continuation of the study. No safety issues were identified at this time.

The DSMB once again complimented the Data Coordinating Center on the quality of the report provided to the DSMB, and their responsiveness in providing the data requested. The investigators were also again complimented on the consistency of the patient care and compliance with the protocol across all clinical sites. All concerns raised by the DSMB at the previous DSMB meeting have been satisfactorily addressed by the investigators.

Specific recommendations regarding the conduct of the trial included:

1. The DSMB expressed concern with the recent decrease in enrollment and urges the investigators to redouble their efforts to fully enroll this trial in a timely manner.
2. The DSMB hopes that oral intake is being documented, noting that this data may have an impact on six-month mortality. Specifically, the DSMB wonders:
    a. Are the investigators collecting documentation of the oral caloric intake as TPN is tapered and subsequently discontinued?
    b. How long after the discontinuation of TPN is oral caloric intake being documented? Will these data be included in the analysis of six-month mortality?

Looking ahead at the analysis of the data following completion of the study, the DSMB made the following suggestions:

1. Regarding the secondary endpoints for the study; the DSMB wishes to clarify their recommendation that the investigators analyze the data using death as a secondary endpoint, and residence in a SNF or nursing home as a separate composite endpoint, using this endpoint as a surrogate for functional status. It may be worthwhile to create a third composite endpoint that combines death with the other composite endpoint.
2. Consider the possibility that body mass index (BMI) may impact response to glutamine. The DSMB suggests that the nutrition, infection, and mortality data be analyzed with respect to BMI.

The DSMB congratulated Dr. Miles on a successful and highly productive Federal career and expressed their very best wishes to her for a long and happy retirement. They further commended her work with GLND project and expressed their confidence in the incoming NIDDK team of Drs. Evans and Robuck to continue the tradition of excellence established by Dr. Miles.

The DSMB will meet next in six months by teleconference.

The Principal Investigator of this study, Dr. Ziegler, has assumed responsibility for assuring that all DSMB recommendations are forwarded to all co-investigators and that all IRBs responsible

for this study also receive this summary and the final recommendation letter from NIDDK that accompanies this summary.

This meeting summary has been reviewed and approved by the DSMB.

Rebecca J. Torrance, RN, MS
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