Date: June 13, 2016

Prof. Ibrahim Al Janahi
Executive Director of Research
Medical Research Center
Hamad Medical Corporation

Dear Prof. Al Janahi,

This letter is in reference to the HMC's submission of the clinical trial titled "An Open-Label Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of ISIS 396443 Delivered Intrathecally to Subjects with Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy" / NURTURE study. We acknowledge receipt of your submission dated May 24, 2016. We have completed our review of the below submitted documents:

Research proposal	Reviewed Document
15162/15	1. 15162_15_Biogen_DSMB_v15Jul2015_29Pages 2. 15162_15_Biogen_IB_28Jan2016_107Pages 3. 15162_15_Biogen_ICF_Ara_v12Mar2015_10Pages 4. 15162_15_Biogen_ICF_Eng_v12Mar2015_11Pages 5. 15162_15_Biogen_ICF_Future_Scientific_Research_Ara_v11Mar2015_06Pages 6. 15162_15_Biogen_ICF_Future_Scientific_Research_Eng_v11Mar2015_06Pages 7. 15162_15_Biogen_Motor_Milestone_Card_Ara_v16Oct14_02Pages 8. 15162_15_Biogen_Motor_Milestone_Card_Eng_v16Oct14_02Pages 9. 15162_15_Biogen_Protocol_v18Dec2014 _64Pages 10. 15162_15_Biogen_Travel_Policy_v04Sep2015_03Pages 11. 15162_15_Biogen_Ventilatory_Support_Tracker_Ara_v11Nov2014_08Pages 12. 15162_15_Biogen_Ventilatory_Support_Tracker_Eng_v11Nov2014_08Pages 13. 15162_15_CaseReportForm_V2_25Feb15_690Pages 14. 15162_15_InsuranceCertificate_14Jan16_01Page 15. 15162_15_JustificationOfInclusionOf Minors_Signed10Feb15_02Pages 16. 15162_15_PatientKit_V1_25Feb15_01Page 17. 15162_15_SubjectIDAndEmergencyCard_Ara_V1_14Nov14_01Page 18. 15162_15_SubjectIDAndEmergencyCard_Eng_V1_11Nov14_01Page 19. 15162_15_VisitReminderCard_Ara_V_11Nov14_01Page 20. 15162_15_VisitReminderCard_Eng_V1_11Nov14_01Page 21. 15612_15_StudyLabels_V1_03Oct14_01Page

Please be noted that the Ministry of Public Health (MoPH) supports the conduct of this clinical trial. This support is conditioned by maintaining the following responsibilities:

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- **It is HMC-IRB's responsibility to:**

1. Conduct periodic reviews throughout the trial's duration. Continuing reviews may take place at least once a year and include the entire trial, not just changes.

2. Report all unanticipated problems including adverse events to the MoPH.

3. Keep IRB meeting minutes in order for inspection purposes.

4. Monitor the work conducted by Quintiles-DSMB.

- **It is the DSMB coordinated by Quintiles's responsibility to:**

1. Periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy.

2. Make recommendations concerning the continuation, modification, or termination of the trial.

3. Ensure that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants.

4- Report adverse events to the IRB, the sponsor, and MoPH.

- **It is the HMC's Principal Investigator**, Dr. Tawfeg Ben-Omran's responsibility to ensure that this Clinical Trial is conducted in compliance with MoPH regulations and the principles of International Conference of Harmonization (ICH) - Good Clinical Practice (GCP) which include, but are not limited to, the following:

1. Conduct the research in accordance with the protocol and the principles of research ethics as set forth in the Belmont Report.

2. Submission of any and all proposed change to this Clinical Trial (e.g., protocol, recruitment materials, consent form, status of the study, etc.) to HMC-IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the HMC-IRB as unanticipated problem.

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3. Submission of continuing review submissions for re-approval of the project prior to expiration of HMC-IRB approval and a final continuing review submission when the project has been completed.

4. Submission of any and all unanticipated problems, including adverse event(s) in accordance with the HMC-IRB's policy on reporting unanticipated problems including adverse events.

5. Obtaining informed consent from subjects or their legally authorized representative prior to initiation of research procedures.

6. Ensure that prior to performing study-related duties, each member of the research study team has had training in the protection of human subjects appropriate to the processes required in the approved protocol.

7. Informing all investigators and study staff listed on the project of changes and unanticipated problems, including adverse events, involving risks to subjects or others.

Sincerely yours,

Dr. Eman Sadoun
Manager, Human Research
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