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October 12, 2022

RE: Rate of Progression of PCDH15-Related Retinal Degeneration in Usher Syndrome 1F (RUSH1F)

Dear Investigator,

This Protocol Administrative Change Letter (PACL) is to notify you of the following administrative changes and clarifications to the RUSH2A protocol; version 1.0 December 21, 2020. The edit described below is to clarify an inconsistency in the text of the protocol and provide an administrative change that does not impact the safety of subjects, the scope of the trial, or the scientific quality of the study. Therefore, this does not qualify as an amendment.

This PACL makes the following changes:

Page 21, Section 2.3.1.1 Participant Criteria, states that *"Must meet one of the Genetic Screening Criteria, defined below:*

- *Screening Group A: At least 2 disease-causing variants in the PCDH15 gene which are homozygous or heterozygous in trans, based on a report from a clinically certified lab.*
- *Screening Group B: Only 1 disease-causing variant in the PCDH15 gene, based on a report from a clinically certified lab.*
- *Screening Group C: At least 2 disease-causing variants in the PCDH15 gene which are unknown phase, based on a report from a clinically certified lab".*

To clarify, the intention of the protocol criteria is to confirm that the mutations on the *PCDH15* gene are the cause of the retinal degeneration. Currently the protocol requires segregation analysis to provide enough evidence. However, for participants who are syndromic, diagnosed with hearing loss, coupled with having two (2) mutations of unknown phase, this is sufficient evidence to demonstrate that the mutations on *PCDH15* are the cause. Therefore, the following note will be added to the next amendment "The Genetics Committee will review unique cases where segregation analysis is not feasible to determine eligibility".

If this protocol requires substantial changes in the future, the changes described in this letter will be incorporated into the amended protocol. Please inform your institutional review board and/or independent ethics committee of these changes, as required.

If you have any questions, please feel free to contact me via email at aayala@jaeb.org.

Sincerely,

Allison Ayala

Digitally signed by Allison Ayala
DN: cn=Allison Ayala ou=North Wing
Reason: I am approving this document
Location:
Date: 2022-10-14 10:15:04-00

Allison Ayala, MS
RUSH1F Project Director