On June 27th, 2022, Lexeo Therapeutics and Dr. Crystal from Weill-Cornell hosted a webinar to discuss their respective gene therapy programs to treat the cardiomyopathy associated with FA. Due to time limitations not all of the questions were addressed during the webinar, below are responses to the unanswered questions.

MRI exclusion include Baclofen pumps?

A cardiac MRI needs to be conducted to determine study eligibility. As such, certain devices may prevent a patient from having this assessment. We encourage patients and caregivers to discuss such devices, like the Baclofen pump, which may be impacted by the MRI, with the Study Doctor as part of the study eligibility process.

Other Phase 1 studies have involved multiple different doses with the initial doses being very low (likely to be safe but unlikely to have benefit) and then stepping dosage up… Since this is not like other drugs where the agent washes out or where the subject you can get a second or multiple doses, how did you determine the Cohort 1 low dose versus Cohort 2 high dose relative to the efficacy/toxicity data presented from the mouse models?

The low and high doses were selected based on safety obtained in long-term wild type mouse and NHPs, as well as efficacy studies conducted in MCK mice. Overall, the low dose showed improvements in body weight gain, survival, and led to human endogenous FXN levels that may achieve a clinical benefit. High dose also showed improvements in body weight gain, survival, along with cardiac function and produced higher human FXN endogenous levels in MCK mice. Thus, the doses selected are expected to potentially provide safety and efficacy in FA patients.

What next steps are necessary for FDA approval?

Both the LEXEO and Cornell programs have FDA clearance to proceed with the Phase 1/2 initial trials. As such, we want to ensure that this gene therapy is safe and has the potential for efficacy before testing the gene therapy in more individuals. When data from this study become available, we will share updates with the FA community and seek discussion with Regulatory Authorities (including FDA) on next steps for the AAVRH.10HFXN (LX2006) program in FA.

If you participate in this study, can you still participate in other studies that may come along during the duration?

To ensure that we are comprehensively assessing the safety and potential efficacy of this gene therapy, a participant in this study may not enroll or participate in any other studies throughout the duration of the entire study for all 5 years.

Not sure I understand the requirement to be "fully vaccinated" for COVID. Is this just the first two shots of Pfizer or does fully vaccinated mean the boosters too? If it includes the booster not sure why the COVID vaccine would be a relevant eligibility requirement, particularly when on the CDC website there is evidence of a higher risk of the boosters to heart thickening (particularly for young adult males). Was this considered? Not sure

why the COVID vaccine has anything to do with the purpose of your study. Seems like as a control at a minimum you would want some in the study that had the booster and some that didn't.

In line with guidance from the CDC and other scientific sources, COVID-19 vaccines available in the United States are effective at protecting people—especially those who are boosted— from getting seriously ill, being hospitalized, and even dying. As with other diseases, you are protected best from COVID-19 when you stay up to date with the recommended vaccine schedule, which includes booster(s). Given the higher vulnerability of FA patients to COVID-19 complications and need to ensure the safety of patients when receiving AAVRH.10HFXN (LX2006) , patients are required to be fully vaccinated for COVID-19 (including all recommended boosters by age) prior to dosing.

I wondered if the result of the adult clinical trial are favourable, what would be the timeframe for the paediatric trials?

As FA-related cardiomyopathy may be present in young individuals, clinical trials of AAVRH.10HFXN (LX2006) in pediatric patients may be performed in the future, once initial safety and evidence of efficacy are established in this initial clinical trial in adult FA patients.

Follow-up to my prior question about study dosing: Dr. Puccio's research has suggested, at least according to my understanding, that in order to rescue the FA mouse model from FA cardiomyopathy (or to prevent it if dosed early), around half the cardiac cells needed to receive the gene therapy. Did you do similar studies? Can you share how many of the cells received the gene in your animal studies (mice and NHP)? In determining study doses based on mouse model data, are you measuring for specific levels of frataxin in the tissues generally or measuring for a specific percentage of cells that received the therapy (or both)? Is there evidence that your proposed study dose(s) can provide benefit relative to number of cells receiving therapy- or that the dose is too low?

We anticipate the level of cardiomyocyte transduction is sufficient given the improvements of the FA disease related phenotype that was observed in MCK mice.

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Do we need to wait 5 years before the next trial (2/3)?

The goal of the first-in-human study is to determine initial safety and evidence of efficacy. Preliminary results of this study will be based upon findings from the initial 12-month study period. These results will help determine the timing and type of subsequent clinical trials of AAVRH.10HFXN (LX2006) in FA.

Can you pls elaborate on what sort of arrhythmias or treatments for arrhythmia might preclude one from taking part?

Patients who have unstable arrhythmias that require physician intervention are not able to participate in this trial. Patients are permitted to continue to receive anti-arrhythmic medications during the study. We encourage patients and caregivers to discuss such medications with the Study Doctor as part of the study eligibility process.