May 23, 2023

Dear ALS and FTD Communities,

We are sharing this update to keep you informed of Wave Life Sciences' FOCUS-C9 and FOCUS-C9 open label extension studies, which are Phase 1b/2a clinical trials investigating WVE-004 for people with C9orf72-associated amyotrophic lateral sclerosis (C9-ALS) and/or frontotemporal dementia (C9-FTD).

Background
WVE-004 is an investigational antisense oligonucleotide (ASO) designed to lower the unwanted, disease-causing proteins and preserve healthy C9orf72 protein in people with C9orf72-ALS and/or FTD. In April 2022, we shared data that WVE-004 demonstrated reductions in poly(GP), a key disease biomarker. This indicated that WVE-004 was acting as intended, and the reduction was observed across all active treatment groups after a single dose. Based on these findings, we adapted the FOCUS-C9 study to expand the single dose groups to optimize dose level and frequency and extend the follow-up period to enable further assessments, and we also advanced two multidose groups.

Data Update
After reviewing data from the multidose phase of the study, we have made the difficult decision to discontinue development of WVE-004**.** This decision was based on the following:

- We saw substantial reductions of poly(GP) with multiple doses.
- However, we did not see any evidence of clinical benefit on outcome measures for ALS or FTD.
- We also did not see any indication that poly(GP) was correlated with clinical outcomes.

WVE-004 was generally safe and well-tolerated.
- Most adverse events (AEs) presented as mild in intensity and the most common AEs were related to disease progression and administration.
- There was no evidence of inflammation in the CSF as there were no clinically meaningful changes in CSF protein or white blood cell count.
- Among WVE-004-treated participants, there was one SAE in the study reported by the investigator as related to study drug that occurred in the 60 mg single dose cohort, as previously reported in April 2022. There was also one SAE reported that was procedure related. All other SAEs were associated with disease progression.

We recognize that this news is difficult for the ALS and FTD communities and especially for those who took part in the study. On behalf of everyone at Wave, we want to sincerely thank the participants, their families, the clinical sites, investigators, and our clinical advisory committees who dedicated their time and effort over the past several years to advance these studies.

While the FOCUS-C9 study and FOCUS-C9 open label extension study have stopped dosing, we recognize that there is additional work to complete the studies such as follow-up visits and assessments. For those who are currently participating in the FOCUS-C9 studies, we expect that you will be having a conversation with your study site investigator or staff in the coming days to provide more specific information on this. We are working closely with the FOCUS-C9 investigators and clinical site staff as we navigate next steps.

We are deeply saddened to share this news and are truly grateful for the support from the ALS and FTD communities. Despite this outcome, the WVE-004 studies have resulted in a significant body of data which we are committed to sharing at an upcoming medical congress. It is our hope and belief that the learnings from this study can advance future research to benefit individuals with C9-ALS and C9-FTD.

Sincerely,
Chelley Casey, VP Patient Advocacy
Wave Life Sciences