Design of an Adaptive Phase 1b/2a Randomized Controlled Trial of WVE-004 in Patients with *C9orf72*-ALS/FTD

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Summary

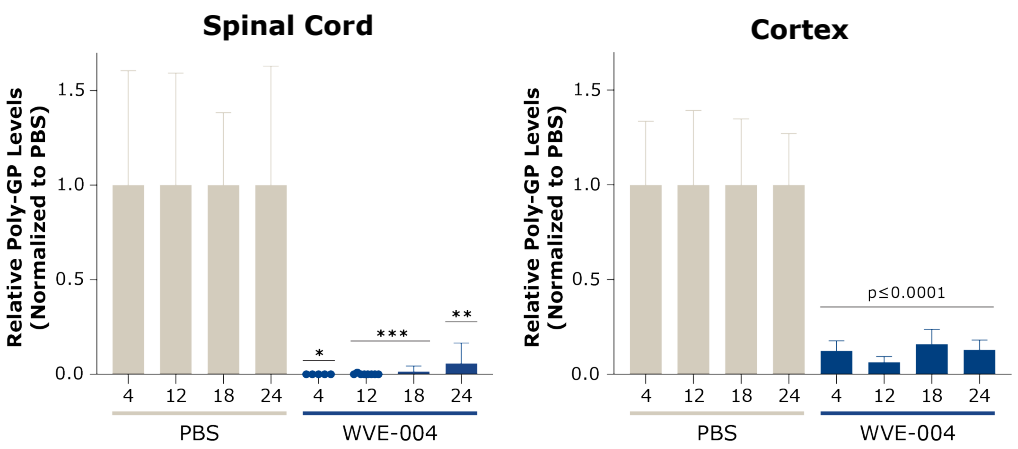
- WVE-004 is an investigational stereopure oligonucleotide for the treatment of *C9orf72*-associated ALS or FTD
- Evaluation of WVE-004 in C9orf72 BAC transgenic (C9BAC) mice demonstrates that WVE-004 selectively depletes pathogenic transcriptional variants (those containing the hexanucleotide (G_4C_2)-repeat expansion in *C9orf72*), preserves expression of C9orf72 protein and leads to durable effects in the CNS
- Wave is advancing WVE-004 into a phase 1b/2a global, multicenter, randomized, double-blind, placebo-controlled trial in ALS, FTD, or mixed phenotype patients with *C9orf72* mutation
- This trial, called FOCUS-C9, is an adaptive clinical trial that may allow for rapid assessment of the safety, tolerability and pharmacodynamic (PD) effects of WVE-004

Introduction

- G_4C_2-repeat expansions found in the *C9orf72* gene are one of the most common genetic causes of the sporadic and inherited forms of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD).[1]
- WVE-004 is a variant-selective stereopure oligonucleotide that was designed to decrease expression of pathogenic *C9orf72* transcripts and thereby address the genetic root cause of *C9orf72*-associated ALS or FTD.[2]
- WVE-004 incorporates Wave's new PN backbone chemistry, which has been shown to improve the pharmacologic profile of oligonucleotides in preclinical studies.

Results

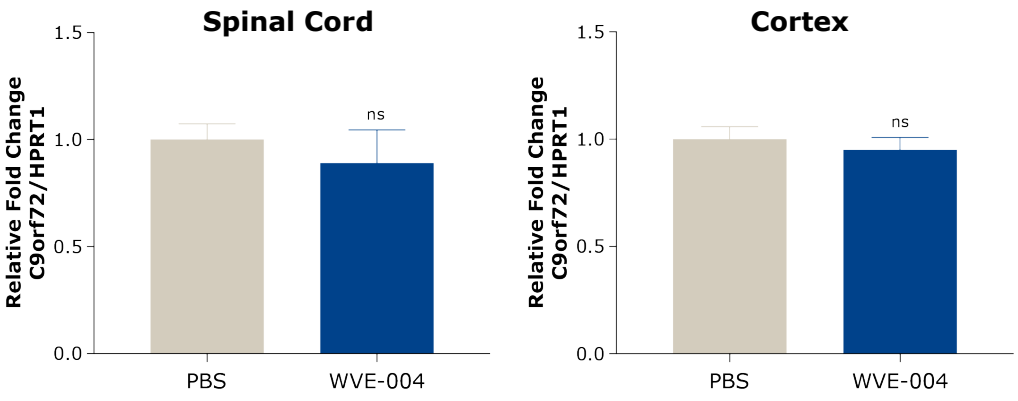
Figure 1. WVE-004 shows durable knockdown of Poly-GP in CNS of C9BAC mice



C9BAC mice (n=7-8) received 2 x 50 µg (day 0, day 7) dosed by intracerebroventricular injection; Poly-GP was measured by Meso-scale discovery assay. Stats *: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001, 1-way ANOVA. PBS: phosphate-buffered saline.

- WVE-004, an investigational oligonucleotide, has potential as a disease-modifying therapy for patients with *C9orf72*-associated ALS or FTD, a single genetic disorder that manifests across a clinical spectrum.
- Poly-glycine-proline (Poly-GP) is a dipeptide-repeat protein produced from pathogenic *C9orf72* transcripts and a biomarker for *C9orf72*-target engagement.[1]
- Based on evidence from patients and preclinical studies, decreases in Poly-GP are expected to reflect reductions in pathogenic transcripts and their downstream sequela.[3]
- By 1-month post-administration in C9BAC mice[4], WVE-004 substantially depleted pathogenic transcriptional variants (not shown) and Poly-GP from spinal cord and cortex, and the knockdown persisted for at least 6 months in both tissues (**Figure 1**).

Figure 2. WVE-004 preserves expression of total C9orf72 protein in CNS of C9BAC mice



WVE-004 was administered to C9BAC mice (n=7-8) as described. C9orf72 protein was quantified by capillary immunoassay and normalized to Hprt1. ns: not significant; PBS: phosphate-buffered saline.

- It is important to preserve the expression of C9orf72 protein, which is expected to protect against neurodegeneration associated with C9orf72 haploinsufficiency.[2,5] WVE-004 is designed to be selective, sparing the most abundant *C9orf72* transcript.
- In C9BAC mice treated with WVE-004, C9orf72 protein expression was comparable to mice treated with PBS for up to 6 months after treatment in spinal cord and cortex, indicating that WVE-004 executes the desired selective mechanism in mice (**Figure 2**).

Figure 3. Key inclusion criteria

Key Inclusion Criteria for Enrollment

- Patient must have the ability to provide written informed consent
- Forced vital capacity (FVC) of >50% predicted
- Documented mutation (G_4C_2-repeat expansion) in the first intronic region of the *C9orf72* gene
- ≥18 and ≤80 years of age at screening visit

ALS-phenotype specific

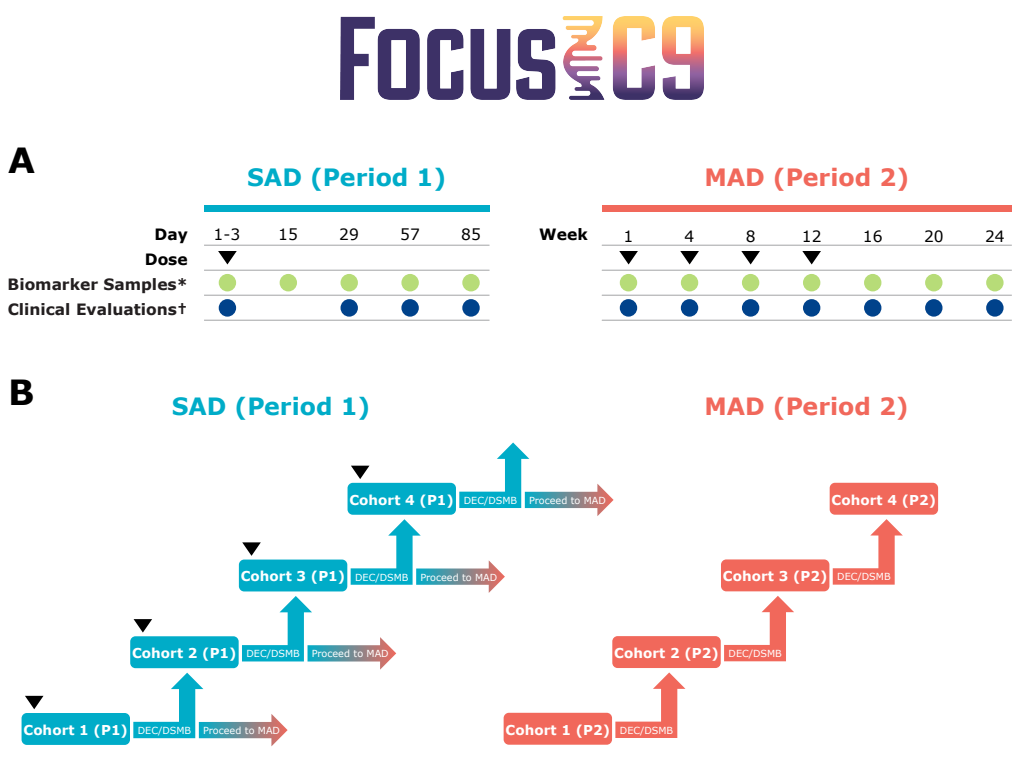
- Diagnosis of ALS based on clinical manifestations
- Can remain on other treatments if treatment regimen is stable for ≥1 month

FTD-phenotype specific

- Global Clinical Dementia Rating – Frontotemporal Lobar Degeneration (CDR® plus NACC FTLD) score of 0.5 or 1

- Wave is advancing WVE-004 as a potential disease-modifying therapy for the treatment of patients with *C9orf72*-associated ALS or FTD.
- WVE-004 will be tested in a global, multicenter, randomized, double-blind, placebo-controlled phase 1b/2a clinical trial, called FOCUS-C9, which is planned to target approximately 50 patients with ALS, FTD, or mixed phenotypes who have a documented G_4C_2-repeat expansion in *C9orf72* (**Figure 3**).

Figure 4. FOCUS-C9, an adaptive first-in-human Phase 1b/2a study of WVE-004



*Biomarker samples: CSF: Poly-GP, Neurofilament light chain, White blood cell; Plasma: WVE-004 PK; Urine: $p75NTF^{ECD}$.
†Clinical evaluations may include: ALSFRS-R, CDR-FTLD, C-SSRS.

- The trial is designed to be adaptive. It includes single- (SAD) and multiple-ascending dose (MAD) portions (**Figure 4A**). Initially, patients will receive a single dose of WVE-004 administered intrathecally (IT) by lumbar puncture.
- At defined points throughout the study, the Dose-Escalation Committee (DEC) will make recommendations regarding dose escalation in Period 1 and initiation of multiple doses in Period 2 upon review of blinded safety and pharmacokinetic (PK) data (**Figure 4B**).
- An independent Data Safety Monitoring Board (DSMB) will review the DEC's recommendations, as well as unblinded safety, PK and pharmacodynamic (PD) data to determine dose level in the next Period 1 cohort and whether to initiate the MAD portion of the study in Period 2 (**Figure 4B**).
- This same DEC/DSMB review process will determine dose frequency in Period 2 (**Figure 4B**).
- For Cohort 1 (Period 2), WVE-004 will be administered monthly (**Figure 4A**). Dosing frequency in subsequent MAD cohorts will be determined by the DSMB.

Figure 5. FOCUS-C9 objectives

1 Primary Objectives

- Safety and tolerability of WVE-004

2 Secondary Objectives

- Plasma and CSF PK profile of WVE-004
- PolyGP in CSF

Exploratory Objectives

Biomarkers

- $p75NTR^{ECD}$ in urine
- NfL in CSF

Clinical Endpoints

- ALSFRS-R
- FVC
- CDR-FTDLD
- HHD

- The primary objectives of FOCUS-C9 are to assess the safety and tolerability of WVE-004 (**Figure 5**).
- PK and PD will also be evaluated, including Poly-GP — a biomarker of target engagement and PD effect — that is elevated in *C9orf72*-associated ALS and FTD.[1]
- The adaptive design will enable rapid evaluation of multiple WVE-004 dosing regimens, possibly enabling rapid assessment of the safety, tolerability and PD effects of WVE-004 in *C9orf72*-associated ALS and FTD.

References: 1. Balendra, R. et al., 2017. Specific biomarkers for *C9orf72* FTD/ALS could expedite the journey towards effective therapies. *EMBO Mol Med.* 9(7), 853-855. doi:10.15252/emmm.201707848; 2. Liu, Y. et al., 2021. Variant-selective stereopure oligonucleotides protect against pathologies associated with *C9orf72*-repeat expansion in preclinical models. *Nat Commun.* 12(1), 847. doi:10.1038/s41467-021-21112-8; 3. Gendron, T. F. et al., 2017. Poly(GP) proteins are a useful pharmacodynamic marker for *C9ORF72*-associated amyotrophic lateral sclerosis. *Sci Transl Med.* 9(383). doi:10.1126/scitranslmed.aai7866; 4. O'Rourke, J. G. et al., 2015. *C9orf72* BAC transgenic mice display typical pathologic features of ALS/FTD. *Neuron.* *88*(5), 892-901. doi:10.1016/j.neuron.2015.10.027; 5. Shi, Y. et al., 2018. Haploinsufficiency leads to neurodegeneration in *C9orf72* ALS/FTD human induced motor neurons. *Nat Med.* *24*(3), 313-325. doi:10.1038/nm.4490. **Acknowledgments:** The authors are grateful to Eric Smith and Amy Donner (Wave Life Sciences) for graphical and editorial support, respectively.