Targeting pathological transcriptional variants in *C9orf72*-associated amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD): Initial results from the ongoing FOCUS-C9 clinical trial

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ENCALS Meeting

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Disclosures

Merit Cudkowicz, Jonathan D. Rohrer, Kenechi Ejebe, Ramakrishna Boyanapalli, Xiao Shelley Hu, Stephen Lake, Michael A. Panzara

- Michael Panzara is a full-time employee of Wave Life Sciences and is on the Board of Directors of Athira Pharma
- Merit Cudkowicz has provided consultation to Wave Life Sciences, RRD, Lilly, AB Science, Transposon, ALS Pharma, Immunity Pharma, Cytokinetics, Takeda, MTPC, Neurosense, Biogen, Regeneron, and Arrowhead
- Jonathan Rohrer is on the Medical Advisory Board of Alector and has provided consultation for Wave Life Sciences, Alector, Arkuda Therapeutics, Aviado Bio, Prevail Therapeutics, UCB, AC Immune, Astex Pharmaceuticals, Biogen, Takeda and Eisai
- All other authors are employees of Wave Life Sciences
- The data in this presentation are from preliminary analyses of an ongoing clinical trial

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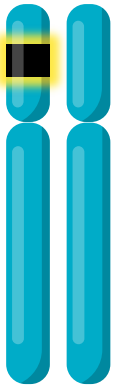
WVE-004 addresses each aspect of complex, but well described biology of *C9orf72*-associated ALS and FTD

C9orf72
Genetic mutation

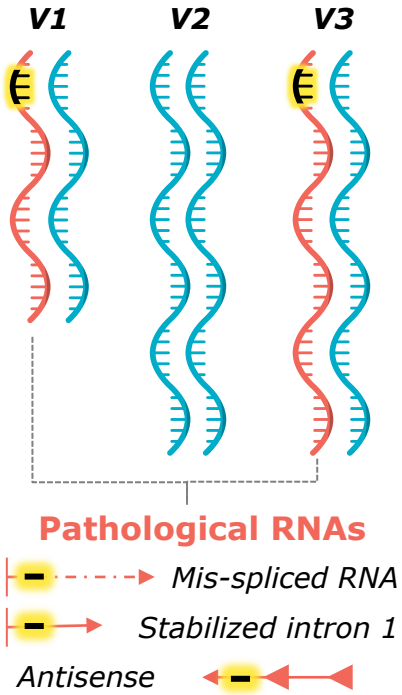
Repeat-expanded allele

Wild-type *C9orf72 allele*



Transcription

RNA variants



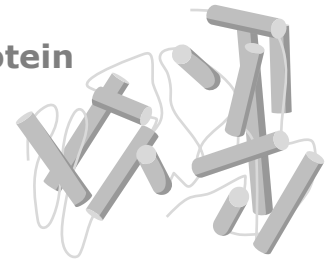
Disease drivers

Loss-of-function

1 *Reduced expression*

C9orf72 protein

Decrease in beneficial protein



Gain-of-function

2 *RAN translation*

Dipeptide repeat proteins (DPRs)

Sense: poly(GA), poly(GR)

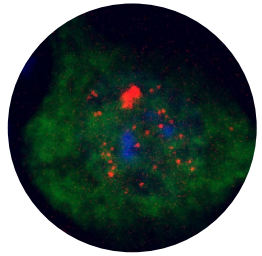
Antisense: poly(PR), poly(PA)

Sense & Antisense: poly(GP)

3 *Toxic RNA aggregation*

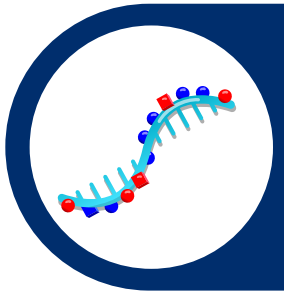
RNA foci

Sense & Antisense RNA



Poly(GP) biomarker selected as preferred DPR biomarker

- ✓ Abundant in CNS
- ✓ Most soluble
- ✓ Stable expression
- ✓ Only DPR derived from both sense & antisense RNAs



WVE-004 is designed to affect multiple drivers of toxicity

Variant-selective oligonucleotide, lowering V1 & V3 in preclinical studies[1]

Preserves C9orf72 protein expression; does not exacerbate potential loss-of-function driver of disease

Reduces toxic gain-of-function drivers of disease (RNA foci, DPRs)

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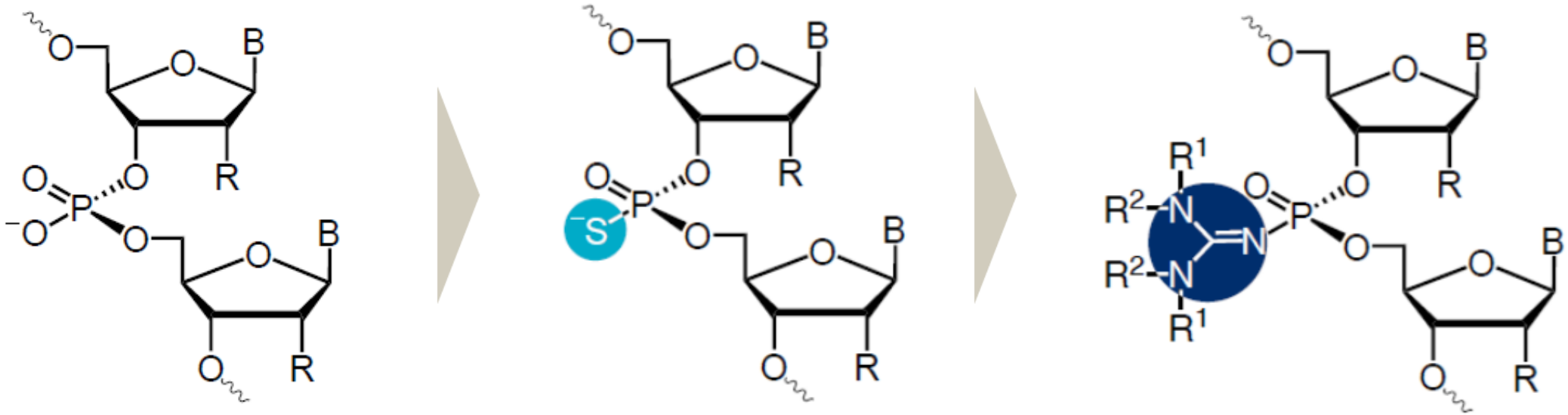
[1]**Liu et al., 2022** *Mol Ther Nuc Acids* doi: 10.1016/j.omtn.2022.04.007

Including PN chemistry in WVE-004 may increase potency and decrease frequency of dosing

- Stereopure oligonucleotides, which have a precisely controlled backbone stereochemistry, have been shown to outperform stereorandom oligonucleotides
- New PN chemistry has demonstrated enhanced potency, tissue exposure, and durability in preclinical studies[1]



Phosphodiester (PO)

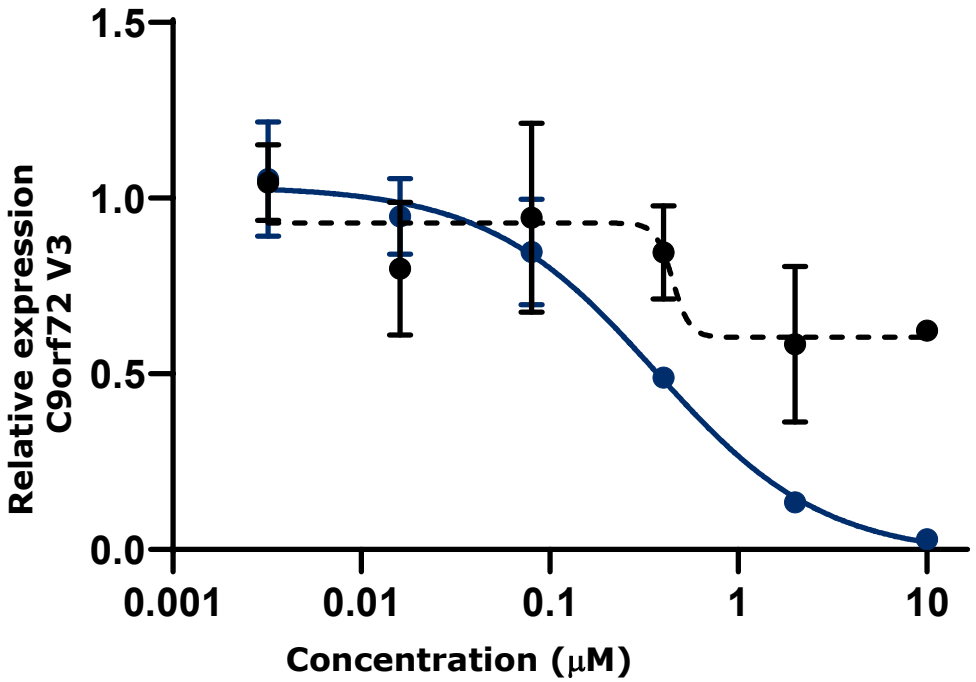
Phosphorothioate diester (PS)

Phosphoryl guanidine (PN)

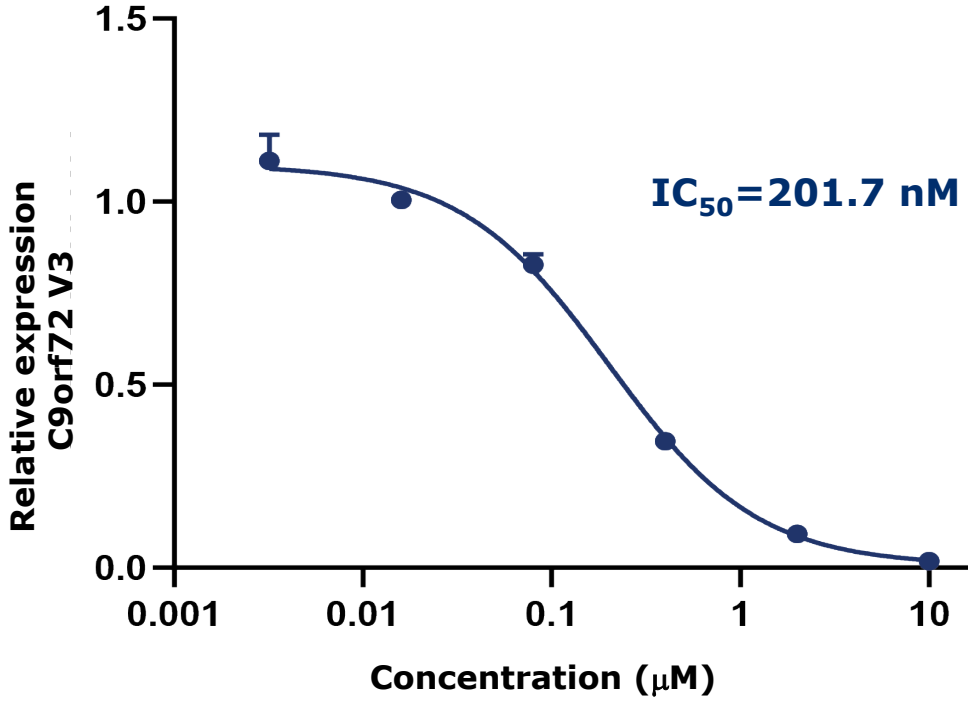
[1]**Kandasamy et al., 2022** *Nucleic Acids Res.*

WVE-004 potently depletes repeat-containing transcripts in patient-derived motor neurons

Comparison in *C9orf72* ALS iPSC-derived motor neurons



WVE-004 in *C9orf72* ALS iPSC-derived motor neurons[1]



- - Comparator[2]

— Early *C9orf72*-targeting lead compound

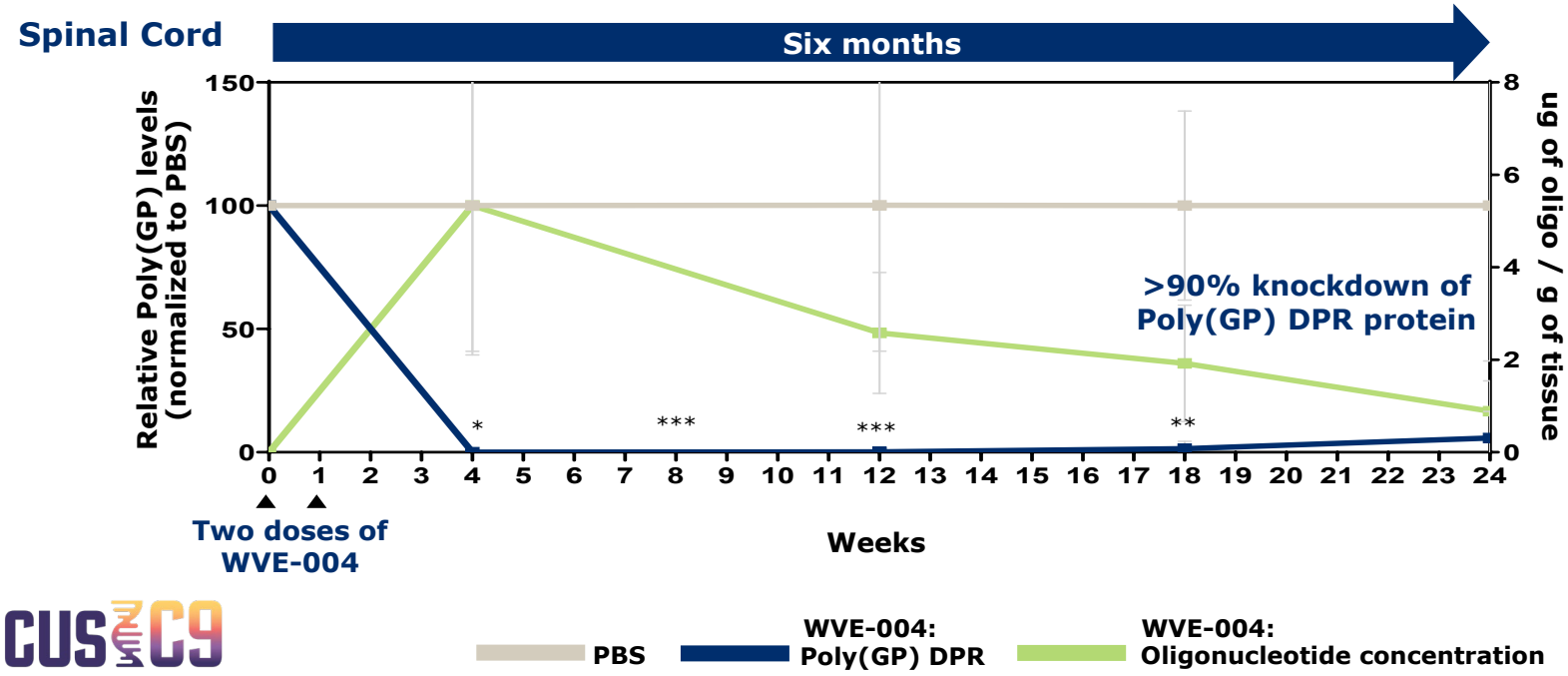
— WVE-004

[1]**Liu et al., 2022** *Mol Ther Nuc Acids doi: 10.1016/j.omtn.2022.04.007.* [2]**Biogen Patent** WO 2017/223258 BIIB 078.
IC50, half-maximal inhibitory concentration. V, variant. PN, phosphoryl guanidine.

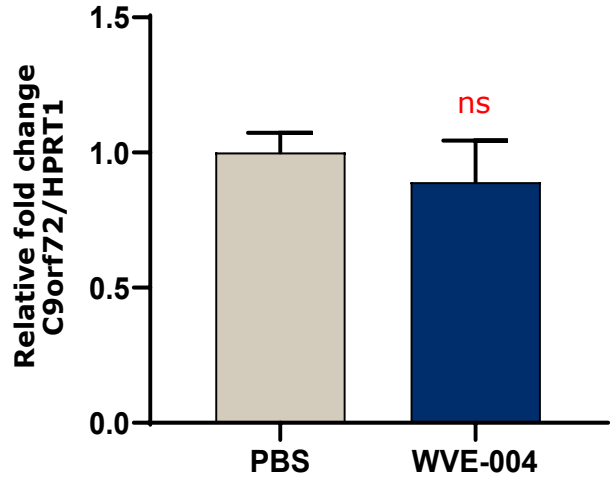
Preclinical data supported the development of WVE-004 as a potential treatment for *C9orf72* ALS and FTD

- WVE-004 treatment resulted in durable reduction of poly(GP) in spinal cord and cortex of C9 BAC mice[1,2]
- WVE-004 preserved expression of total C9orf72 protein in C9 BAC mice 6 months after dosing[1,2]

Change in poly(GP) and oligonucleotide concentration in C9 BAC mice over six months



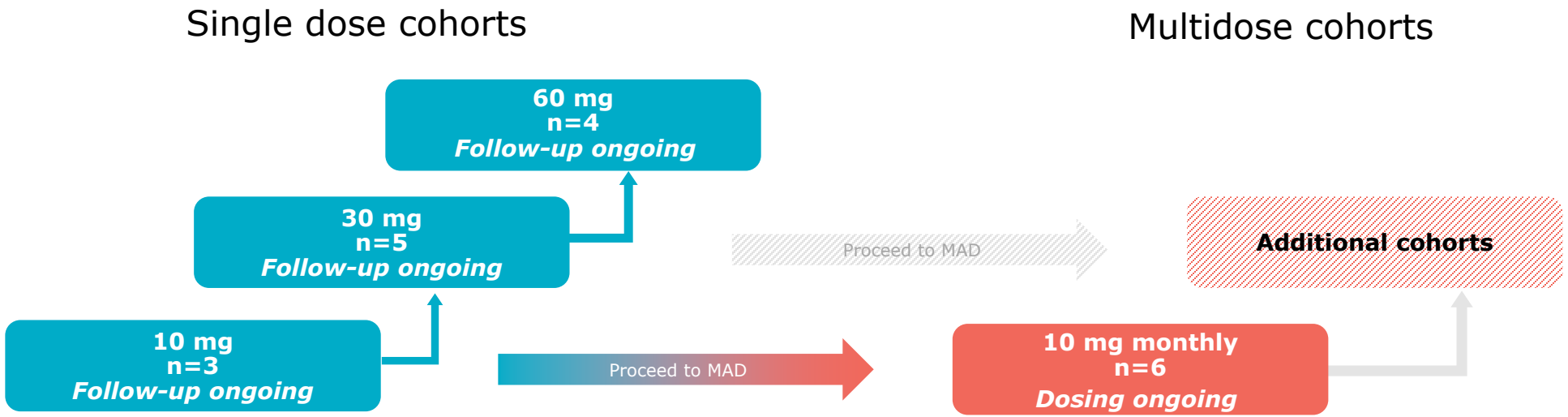
C9orf72 protein in C9 BAC mice unchanged at six months



*: p≤ 0.05, **: p ≤ 0.01, ***: p ≤ 0.001. DPR, dipeptide repeat protein. [1]**Liu et al., 2022** *Mol Ther Nucleic Acids*. [2]**Liu et al**. Poster i182 presented at ENCALS Meeting 2022. Poly(GP) assay: **Wilson et al., 2022** *J Neurol Neurosurg Psychiatry*.

Adaptive clinical trial designed to rapidly optimize dose level and frequency for WVE-004

Phase 1b/2a global, multicenter, randomized, double-blind, placebo-controlled trial



Single-ascending dose cohorts (SAD)*

Day	1-3	15	29	57	85
Dose	▼				
PK/Biomarker Samples	●	●	●	●	●
Clinical Evaluations	●		●	●	●

Multi-ascending dose cohorts (MAD)

Week	1	4	8	12	16	20	24
Dose	*Monthly or less frequent*						
PK/Biomarker Samples	●	●	●	●	●	●	●
Clinical Evaluations	●	●	●	●	●	●	●

*Six months of follow-up

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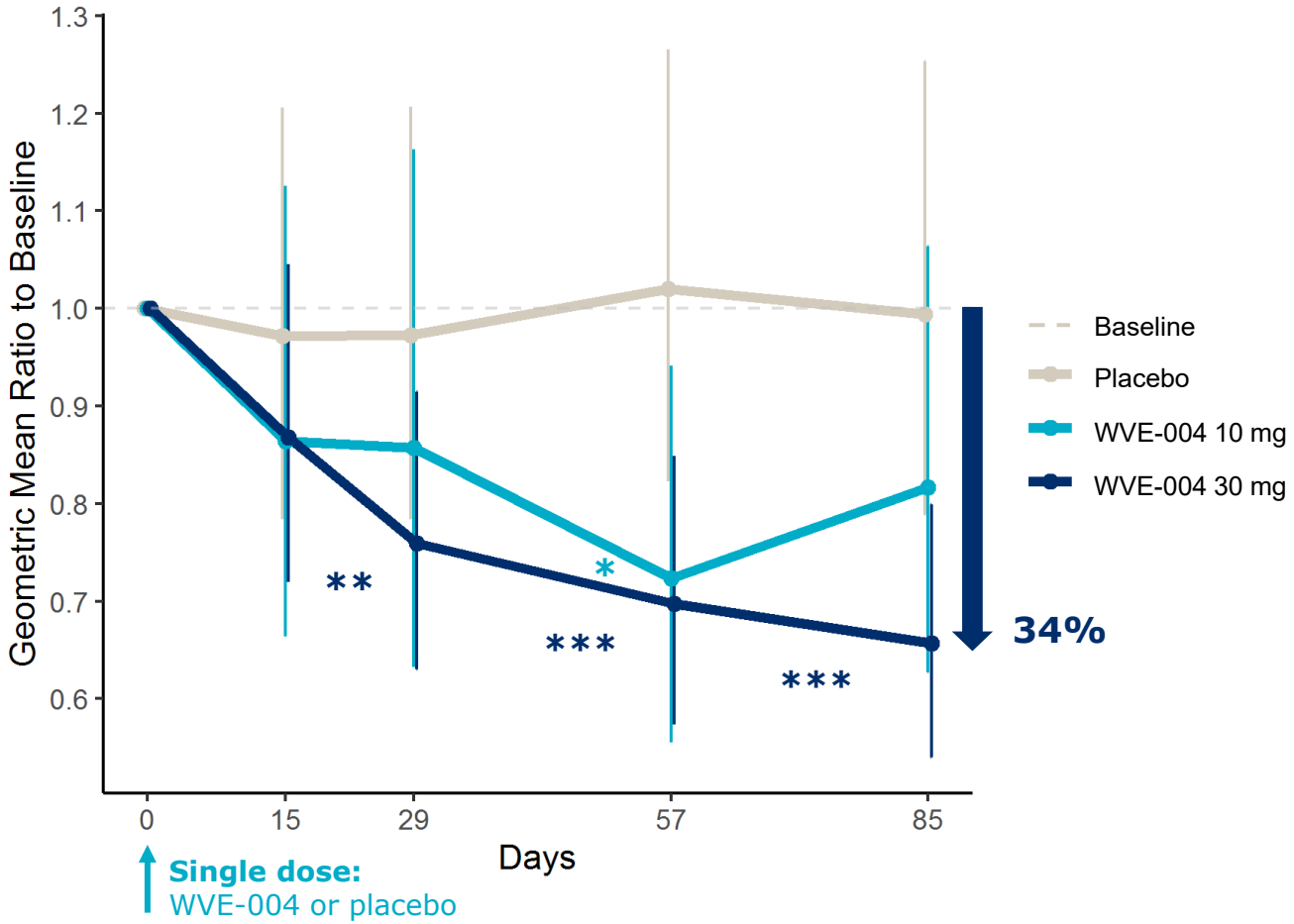
PK, pharmacokinetic

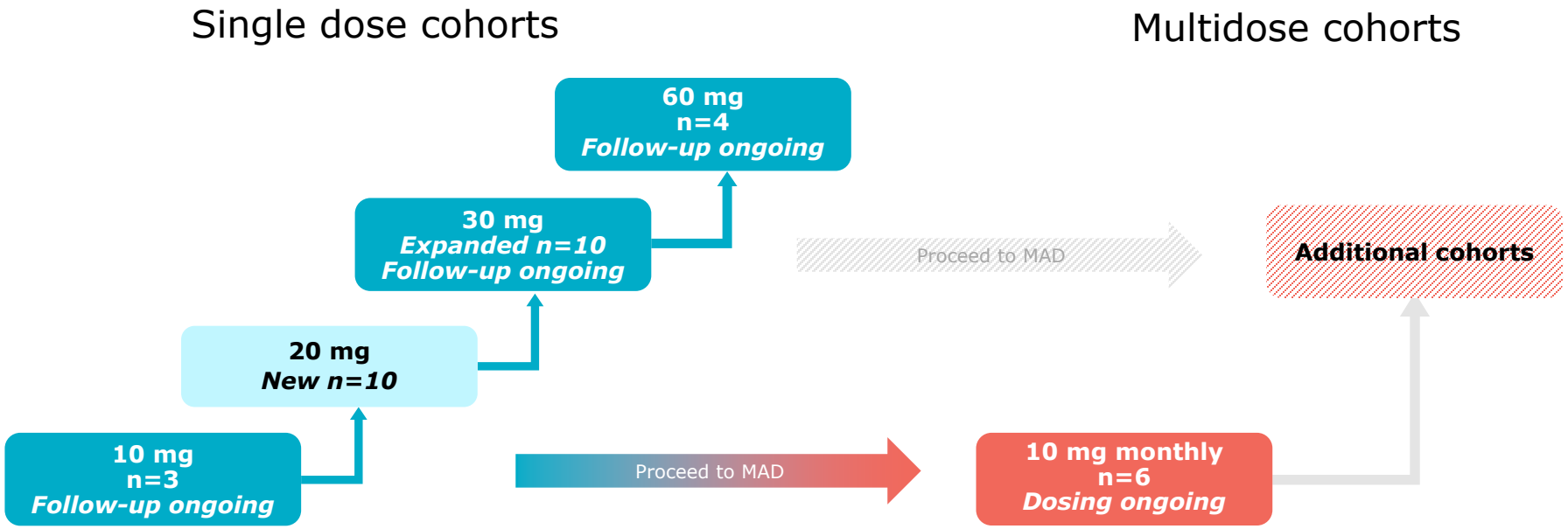
Low single doses of WVE-004 resulted in dose-dependent, potent and durable CSF poly(GP) reductions



- WVE-004 reduced poly(GP) vs placebo after **single** 10 mg and 30 mg doses, reaching statistical significance at day 57 (p=0.05 and p=0.015, respectively)
- Single 30 mg dose of WVE-004 **achieved 34% reduction of poly(GP) at day 85** (p=0.011) vs placebo
- Poly(GP) reduction does not appear to have plateaued following a single 30 mg dose

Mixed model for repeated measures used to estimate geometric mean ratio to baseline via least squares mean and to calculate p-values. P-values represented by asterisks are for within-dose group geometric mean ratios. *p≤0.05, **p≤0.01, ***p≤0.001.
Poly(GP) assay: **Wilson et al., 2022** *J Neurol Neurosurg Psychiatry* doi:10.1136/jnnp-2021-328710.

Adapting trial to rapidly optimize dose level, frequency and follow-up to enable discussions with regulatory authorities later in 2022

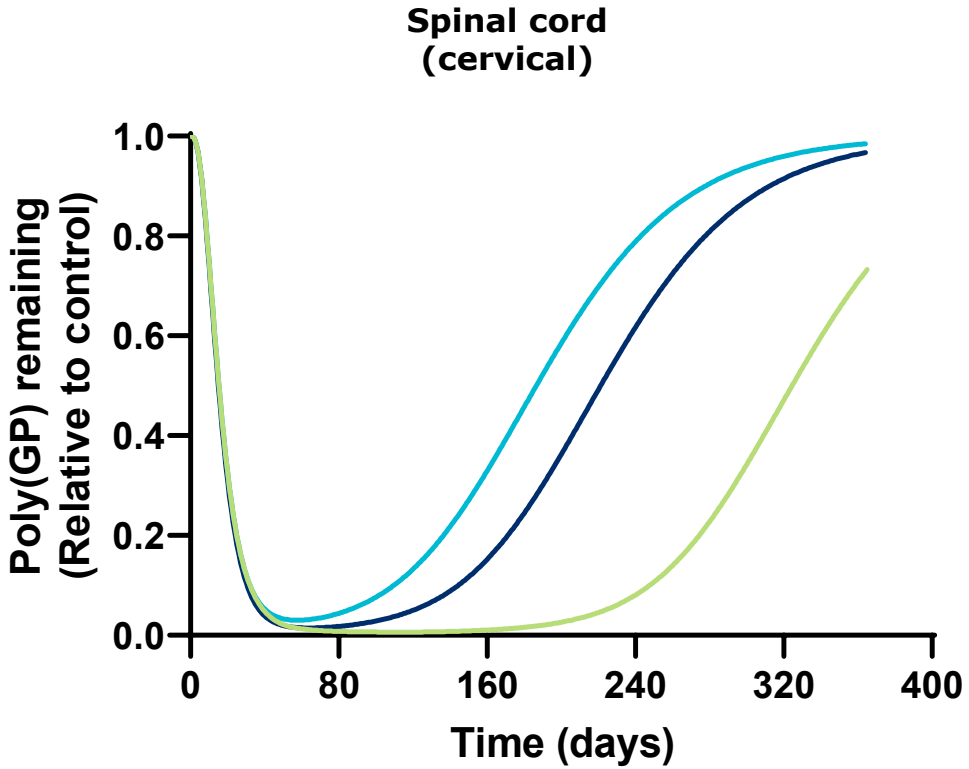


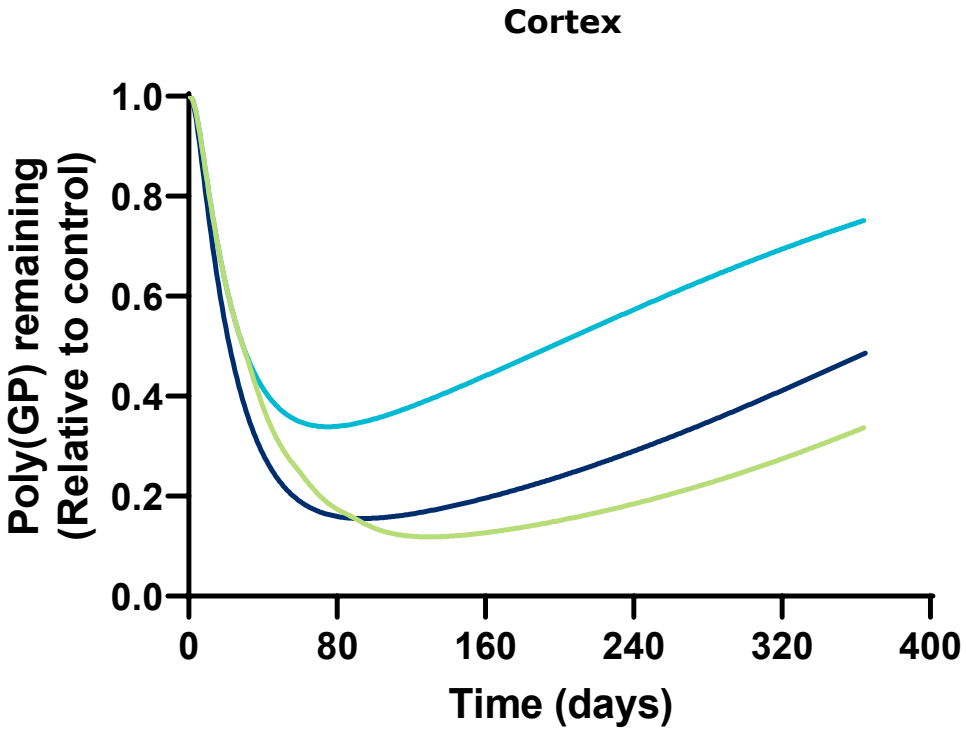
- Adaptations to the single-dose cohorts:
  - Dosing 10 patients at 20 mg dose level (4:1, active:placebo)
  - Expanding 30 mg cohort to include additional 5 patients
  - Extending observation period to six months from three months (day 85)

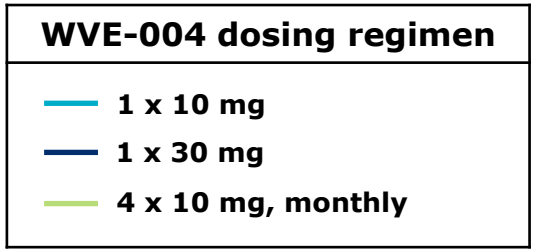
MAD, multiple ascending dose

Predicted further reduction of CSF poly(GP) with four monthly 10 mg doses of WVE-004

Modeling based on preclinical data and preliminary FOCUS-C9 data







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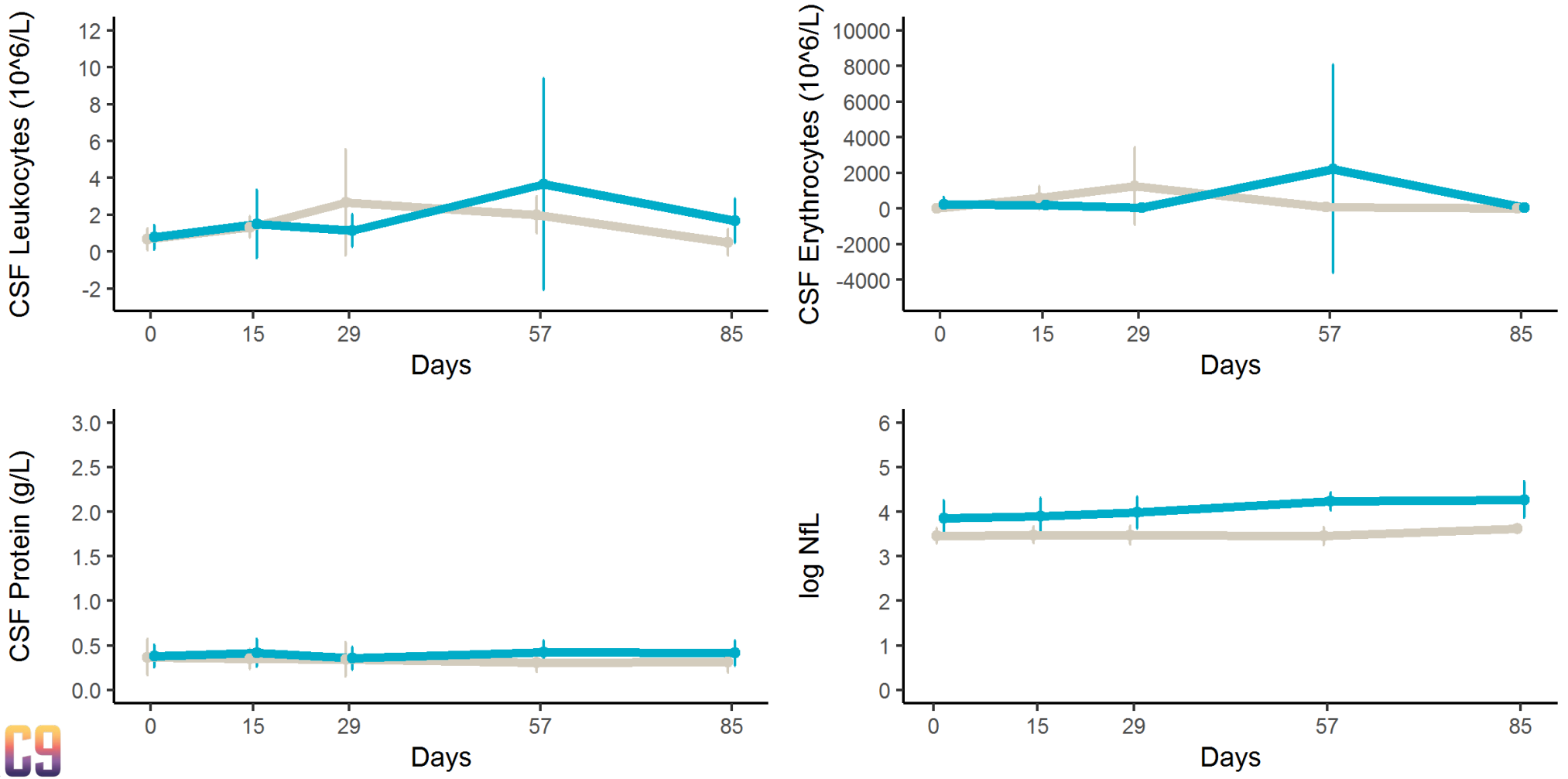
CSF cell counts, protein remained unchanged following treatment

NfL increased in some patients in the 30mg and 60mg cohorts



Graphs show mean ± SD for pooled treated and placebo groups. NfL (pg/mL) log-transformed per **Vacchiano et al., 2021** *Front Aging Neurosci.* CSF, cerebrospinal fluid. NfL neurofilament light.

Adverse events balanced across treatment groups

- All patients (n=12) in each single dose treatment group, including with placebo, experienced at least 1 adverse event (AE)
  - Most AEs were mild to moderate in intensity
  - Four patients (one placebo) experienced severe and/or serious adverse events
    - 1 severe choking (placebo)
    - 1 serious headache post lumbar puncture leading to overnight hospitalization (30 mg)
    - 1 respiratory failure in ALS patient after developing pneumonia post-placement of feeding tube (30 mg) leading to death post completion of single dose phase
    - 1 event reported as cerebellar syndrome with delirium, investigations ongoing (60 mg)
      - Only event reported by investigator to be related to study drug
- All events reviewed by independent data safety monitoring board (DSMB) that recommended continued dosing

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WVE-004 significantly reduced poly(GP) in patients with C9orf72 ALS and FTD, demonstrating target engagement and clinical proof of concept

- Potent, durable, dose-dependent target engagement observed following single, low doses
  - Modeling suggests continued decline in poly(GP) with continued observation and additional doses
  - Anticipate dosing no more frequent than every 3 months given pharmacology to date

- FOCUS-C9's adaptive trial design successfully enables rapid optimization of dose level and frequency
  - Observations & modeling from preclinical models translated well in clinic
  - Safety profile supports continued cohort expansion and dose exploration
  - Dosing in single and multiple dose cohorts underway

- Dataset & duration not yet sufficient to assess clinical effects

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Clinical Advisory Committee

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- Ammar Al-Chalabi
- Jeremy M Shefner

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Genetic FTD Initiative (GENFI)

Wave's scientists & study team

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Alzheimer's Drug Discovery Foundation

AFTD The Association for Frontotemporal Degeneration FIND HELP·SHARE HOPE

Forward looking statements

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