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FOCUS-C9 clinical trial update

April 4, 2022

Today’s agenda

1. **Opening remarks -** Paul Bolno, MD, MBA, President and CEO
2. **C9orf72-associated ALS and unmet need –** Merit Cudkowicz, MD, MSc, Director of the Sean M. Healey & AMG Center for ALS, Chief of Neurology at Massachusetts General Hospital
3. **FOCUS-C9 clinical trial update -** Michael Panzara, MD, MPH, CMO, Head Therapeutics Discovery and Development
4. **Closing remarks and Q&A –** All

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Forward-looking statements

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WVE-004 target engagement provides clinical validation of Wave's novel oligonucleotide therapeutics

Innovative RNA therapeutics portfolio

WVE-004 ALS and FTD (C9orf72)	*Silencing*
WVE-003 HD (SNP3)	*Silencing*
WVE-N531 DMD (Exon 53)	*Splicing*
AATD program (SERPINA1)	*RNA editing*

Innovative RNA platform PRISM Stereochemistry, PN chemistry

Today's FOCUS-C9 (WVE-004) clinical trial update

- ✓ **Benefits of adaptive clinical trial:** Identify target engagement and adapt to optimize dose level and frequency
- ✓ **PN chemistry translation:** Potent activity and durable target engagement with low single doses
- ✓ **Platform validation:** Successfully predicted target engagement with PK/PD modeling, all pipeline programs leverage similar *in vivo* modeling work

WVE-003 and WVE-N531 clinical data for decision making also expected in 2022

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Kandasamy et al., NAR Breakthrough Article, 2022 doi: 10.1093/nar/gkac037; Kandasamy et al., 2022; doi: 10.1093/nar/gkac018

Dr. Merit Cudkowicz, MD, MSc

Dr. Merit Cudkowicz is the Chief of the Massachusetts General Hospital Neurology Service, Director, Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital, and the Julieanne Dorn Professor of Neurology at Harvard Medical School in Boston. She directs the Massachusetts General Hospital ALS Program and the Massachusetts General Hospital Neurological Clinical Research Institute (NCRI). Her passion for caring for people with ALS has enabled her to bring innovations to accelerate the development of treatments for people with ALS.

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C9orf72 repeat expansions: One of the most common genetic causes of ALS and FTD

Hexanucleotide (G_4C_2)- repeat expansions in C9orf72 gene are common autosomal dominate cause for ALS and FTD

Different manifestations across a clinical spectrum

Amyotrophic Lateral Sclerosis (ALS)

- Fatal neurodegenerative disease
- Progressive degeneration of motor neurons in brain and spinal cord
- C9-specific ALS: ~2,000 patients in US

Frontotemporal Dementia (FTD)

- Progressive neuronal degeneration in frontal / temporal cortices
- Personality and behavioral changes, gradual impairment of language skills
- C9-specific FTD: ~10,000 patients in US

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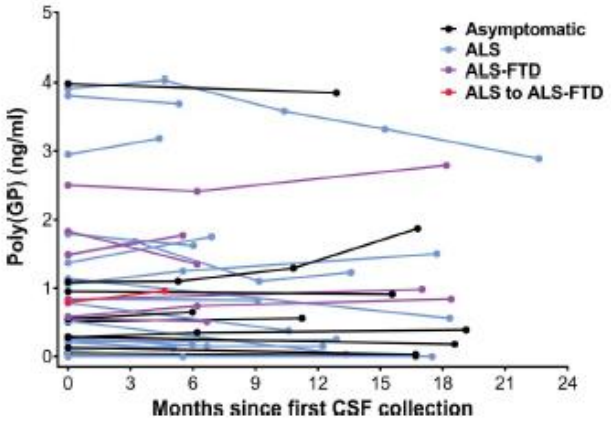
Sources: Balendra et al, EMBO Mol Med, 2017; Brown et al, NEJM, 2017, DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020, Stevens et al, Neurology 1998

Biofluid markers in C9ALS

- Dipeptide repeat proteins (DPRs) as a promising marker of target engagement for antisense therapy targeting G_4C_2 RNA
- CSF poly(GP) is stable over time (n=33 C9 carriers)



Gendron et. al. Science Translational Medicine 2017

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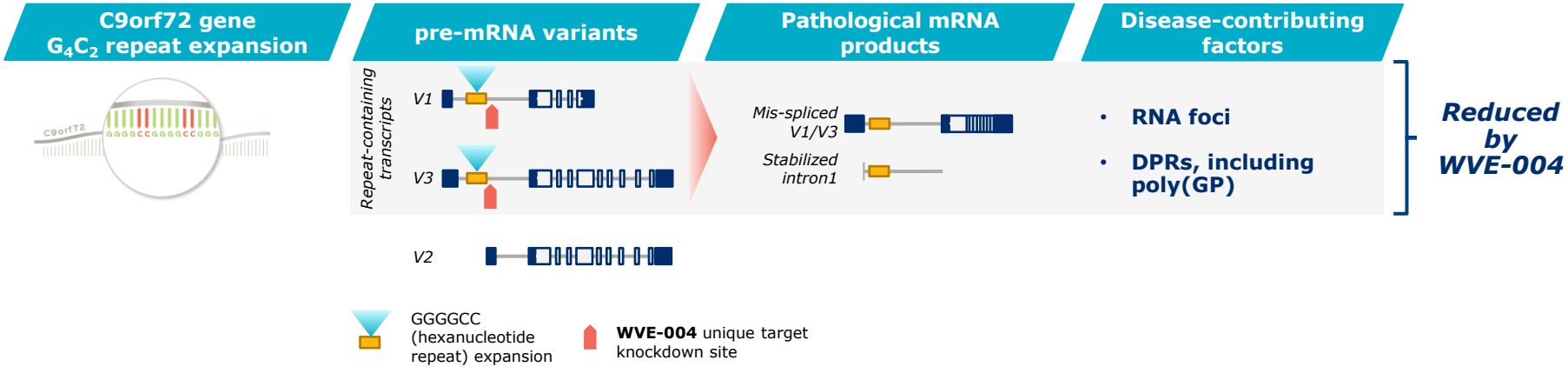
WVE-004 selectively targets repeat-containing transcripts to address multiple drivers of toxicity



- WVE-004 targets repeat-containing transcript variants that lead to production of pathological mRNA products and toxic DPR proteins and loss of normal C9orf72 function, which is important for normal regulation of neuronal function and the immune system
- Wave selected the poly(GP) DPR because it is a sensitive biomarker of target engagement and reductions of mRNA transcripts and other toxic proteins

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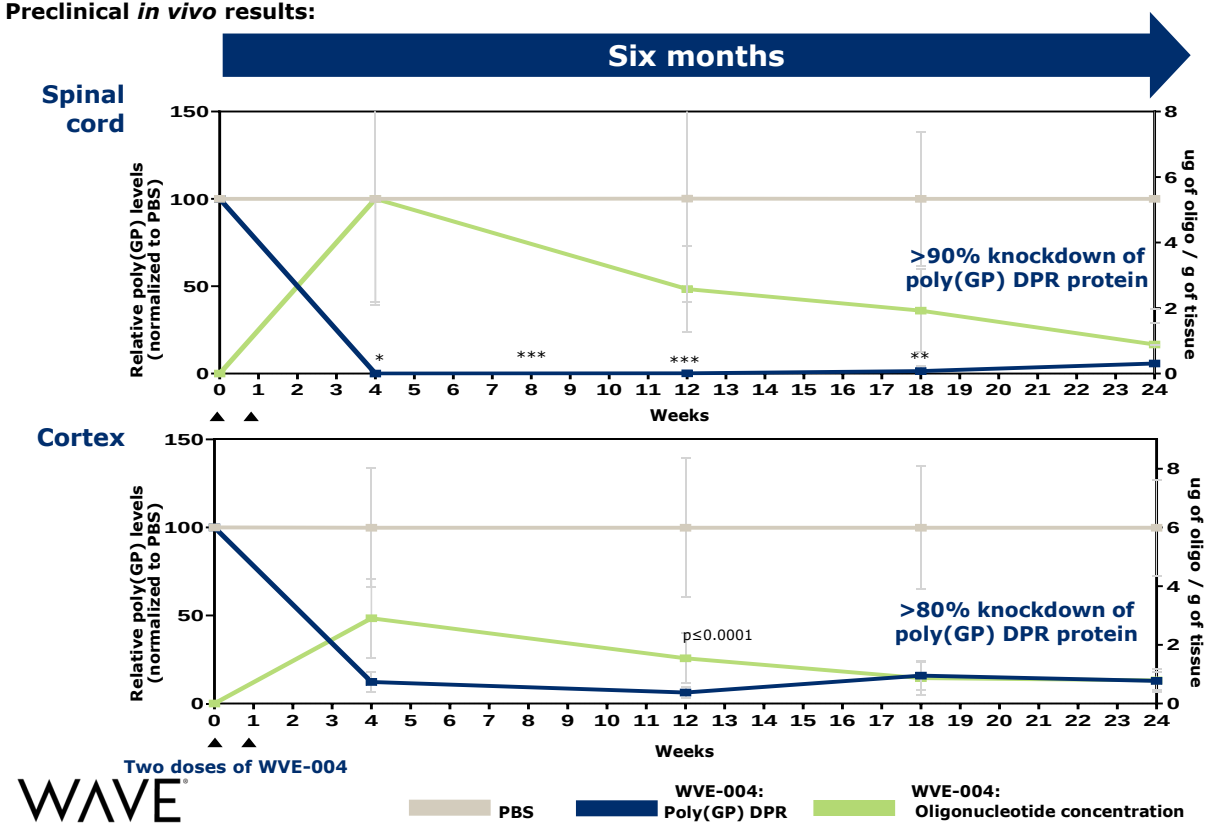
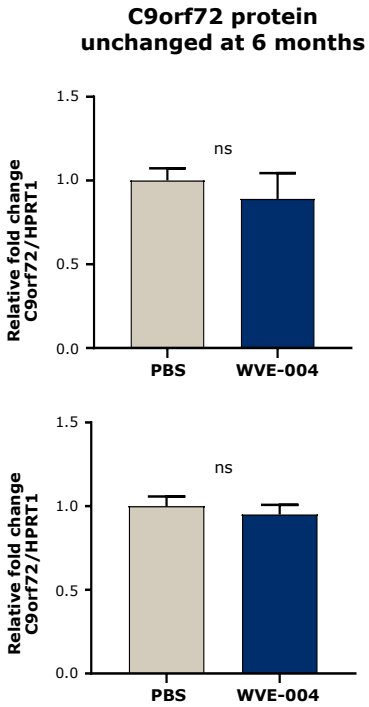
Liu et al, Nature Communications, 2021; DPRs: dipeptide repeat proteins

Preclinical studies with WVE-004 demonstrated durable reduction of poly(GP) in spinal cord and cortex 6 months after two doses

Preclinical *in vivo* results:





Full results presented at the 31st International Symposium on ALS/ MND (December 2020); 2 x 50 ug (day 0, day 7) dosed ICV; DPRs measured by poly(GP) MSD assay. *: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001. DPR: Dipeptide repeat protein

Preclinical PK/PD modeling successfully predicted therapeutically active starting dose of WVE-004

PK/PD modeling using preclinical *in vivo* models

- Achieved poly(GP) knockdown of >80% in cortex and >90% in spinal cord that persisted for at least 6 months in transgenic mice following two initial doses of WVE-004
- Achieved sufficient concentrations of WVE-004 in cortex and spinal cord of NHP for target engagement

Translation to clinic: Predict human target engagement with starting dose

- Based on PK/PD modeling, poly(GP) knockdown in humans was anticipated at the **starting 10 mg single dose** of WVE-004

PK/PD modeling to predict target dose facilitated by well-characterized PRISM-derived PN-containing stereopure compounds

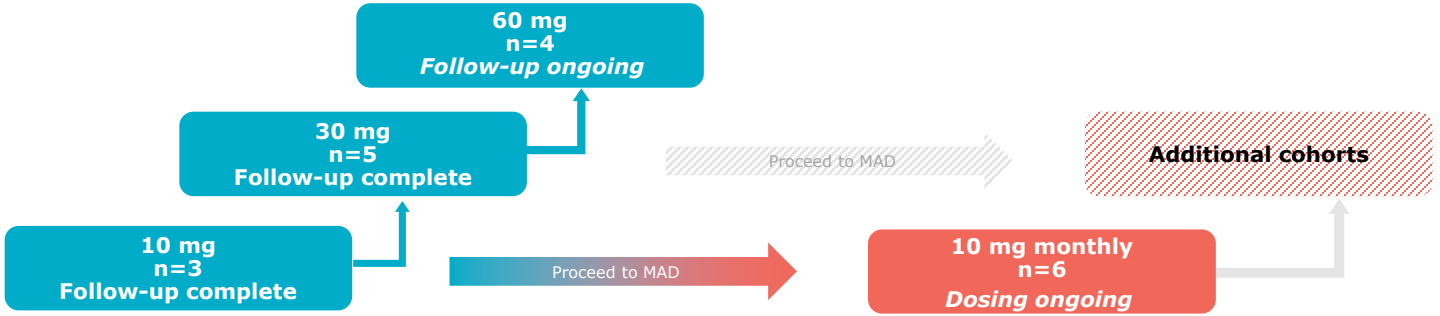
PK: pharmacokinetic PD: pharmacodynamic

FOCUS C9: Adaptive trial designed to rapidly optimize dose level and frequency based on early indicator of target engagement

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

Single dose cohorts

Multidose cohorts



Single-ascending dose cohorts (SAD)

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

Patients with C9-ALS, C9-FTD or mixed phenotype

Primary objectives

- Safety and tolerability

Secondary objectives

- Plasma and CSF PK profile
- Poly(GP) in CSF

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Baseline demographics and disease characteristics confirm recruitment of target patient population

- A total of 12 patients available for analysis in single dose cohorts
  - 9 patients with ALS, 3 patients with FTD (behavioral variant)
- Imbalance at baseline between treatment groups in functional status
  - 30 mg single dose patients younger, longer disease duration, higher pre-existing disability
    - ALSFRS-R, ALSAQ-40, FVC, CDR-FTLD sum of boxes used to assess function

Degree of poly(GP) knockdown from WVE-004 consistent, regardless of baseline status

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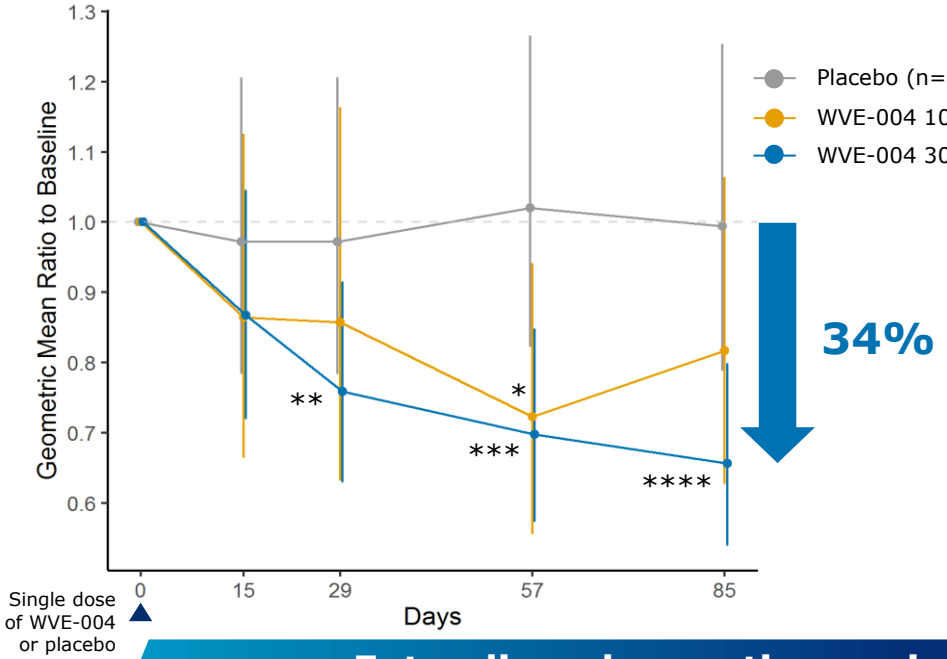
Single doses of WVE-004 resulted in dose-dependent, potent, and durable poly(GP) reductions

CSF poly(GP) reduction through day 85



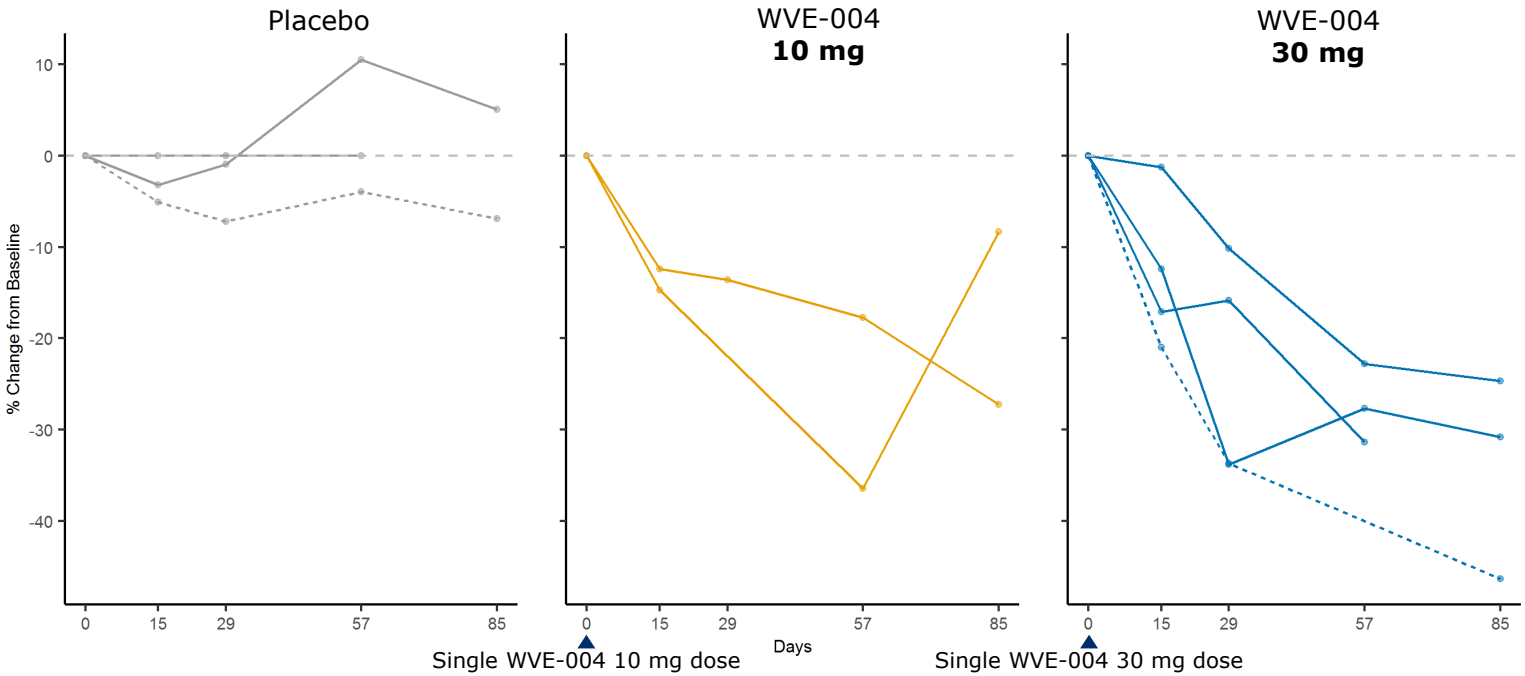
- WVE-004 reduced poly(GP) vs placebo after single 30 mg doses reaching statistical significance beginning at day 57 (p=0.015), **achieving 34% reduction at day 85** (p=0.011)
- Poly(GP) reduction does not appear to have plateaued at day 85 following single 30 mg doses

Extending observation period to identify maximum poly(GP) reduction and duration of effect

*p=0.020, **p=0.008, ***p=0.001, ****p<0.001, % change from baseline. Mixed model for repeated measures used for all statistical testing

Reductions in poly(GP) consistent in each patient dosed beginning as soon as 15 days after dosing

Percent change from baseline in CSF poly(GP) through day 85



PK/PD modeling predicts further poly(GP) reduction with multiple doses of WVE-004

Dashed line = FTD Solid line = ALS Follow-up data not yet available at all timepoints in 60 mg cohort

Exploratory assessments ongoing

- Refinement of PK/PD models
- CSF NfL elevations observed in some patients in the 30 mg and 60 mg single dose cohorts
- No meaningful changes in clinical outcome measures (ALSFRS-R, FVC), although the dataset and duration were not sufficient to assess clinical effects

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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
- No treatment-associated elevations in CSF white blood cell counts or protein and no other notable laboratory abnormalities were observed

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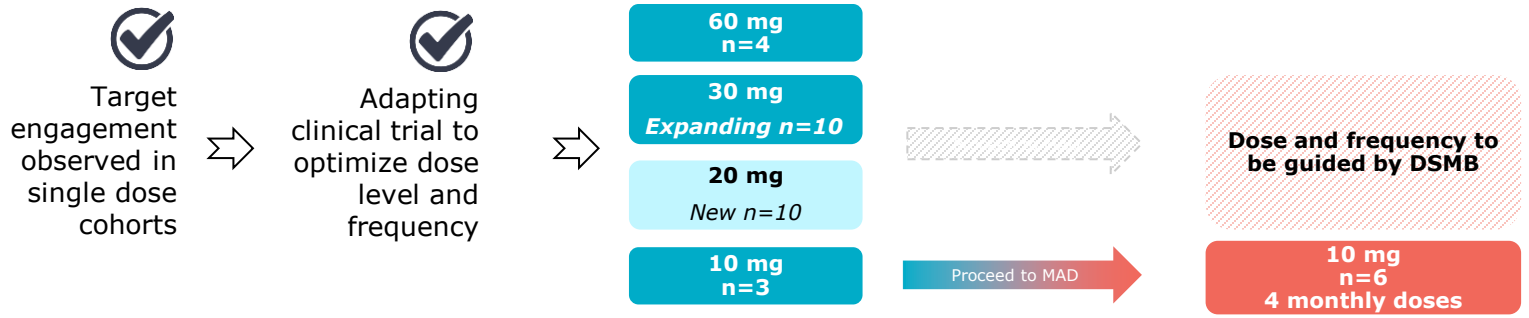
Adapting trial to rapidly optimize dose level, frequency and follow-up to enable discussions with regulatory authorities later in 2022



- Given potent and durable poly(GP) reduction with single 30 mg doses that do not appear to have plateaued at day 85, adapting the FOCUS-C9 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)
- Dosing in a multidose cohort (monthly) at 10 mg is well underway

Additional single and multidose data expected throughout 2022

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WVE-004 significantly reduced poly(GP) in C9-ALS/FTD patients, demonstrating target engagement and clinical proof of concept

- PN-containing stereopure compound enabled potent and durable target engagement at low single doses (10 mg and 30 mg)
  - Duration of effect opens potential for quarterly or less frequent dosing
- FOCUS-C9's adaptive trial design successfully provided early indications of target engagement and safety profile to enable rapid optimization of dose level and frequency
  - Observations and modeling from preclinical models translated well in clinic
  - Safety profile supports continued cohort expansion and dose exploration
- Clinical data expected in 2022 for ongoing clinical trials with WVE-003 (SNP3) for Huntington's disease and WVE-N531 (Exon 53) for Duchenne muscular dystrophy to enable decision making
  - Recent clinical pharmacology data for WVE-N531 demonstrates improved pharmacological profile with PN-chemistry compared to our first-generation compounds

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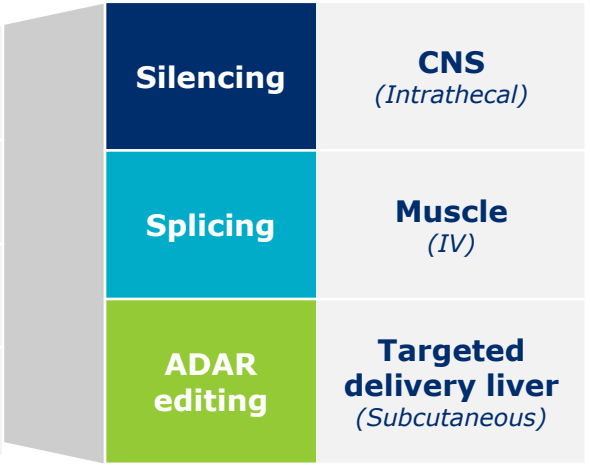
Delivered first clinical data demonstrating target engagement and translation of PN chemistry in CNS

WVE-004 C9orf72 ALS & FTD	• Additional single and multidose data throughout 2022 • Discussions with regulatory authorities regarding next phase of development later in 2022
WVE-003 HD SNP3	• Clinical data to enable decision making in 2022
WVE-N531 DMD Exon 53	• Clinical data to enable decision making in 2022
AATD program SERPINA1	• Select an AATD AIMer development candidate and initiate IND-enabling toxicology studies in 3Q 2022



Additional data generated in 2022 expected to inform future opportunities and unlock value

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WVE-004 FOCUS-C9 clinical trial (NCT04931862); WVE-003 SELECT-HD clinical trial (NCT05032196); WVE-N531 open-label clinical trial (NCT04906460)

Q&A

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