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# WVE-N531 Clinical Trial Update

December 19, 2022

# Forward-looking statements

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# Today’s agenda

1. **Opening remarks**
   Paul Bolno, MD, MBA, President and CEO

2. **WVE-N531 clinical trial update**
   Anne-Marie Li-Kwai-Cheung, Chief Development Officer

3. **Closing remarks and Q&A**

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Paul Bolno, MD, MBA

President and CEO

# Third clinical trial in 2022 to achieve target engagement with PN chemistry-containing compound

## WVE-N531 Proof-of-Concept Trial

- Significant improvements in pharmacology compared with first-generation DMD program
  - Mean muscle concentration of 42 µg/g
  - 53% mean exon skipping and <1% (BLQ) mean dystrophin expression
  - WVE-N531 reaching the nucleus
  - All AEs mild except one COVID-19 infection of moderate intensity


- **PN chemistry translation and platform validation:** Third PN chemistry-containing compound with data to indicate target engagement:
  - WVE-N531 (DMD)
  - WVE-003 (HD)
  - WVE-004 (C9-ALS/FTD)
- Clinical data continue to support translation of preclinical datasets

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BLQ: Below the limit of quantification
ALS: Amyotrophic lateral sclerosis

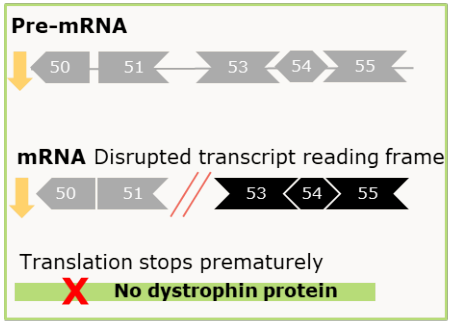
DMD: Duchenne muscular dystrophy
FTD: Frontotemporal dementia

HD: Huntington's disease

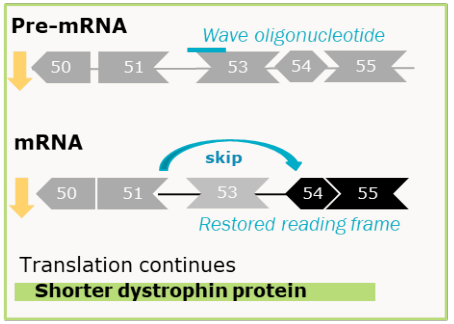
# Duchenne muscular dystrophy

- Genetic mutation in dystrophin gene prevents the production of dystrophin protein, a critical component of healthy muscle function
- Impacts approx. 1 in every 5,000 newborn boys each year; approx. 20,000 new cases annually worldwide
  - Approx. 8-10% are amenable to exon 53 skipping
- Dystrophin protein established by FDA as surrogate endpoint reasonably likely to predict benefit in boys[1] for accelerated approval in DMD
- Increasing amount of functional dystrophin expression over minimal amount shown with approved therapies is expected to result in greater benefit for boys with DMD

**Dysfunctional splicing (Disease)**



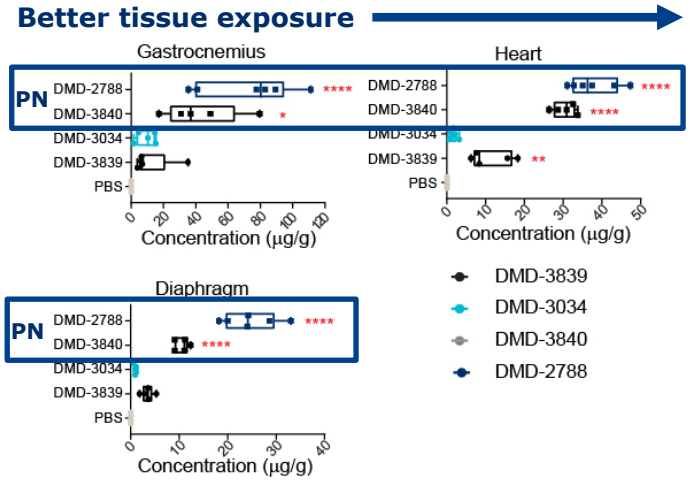

**Exon skipping (Partial Restoration)**



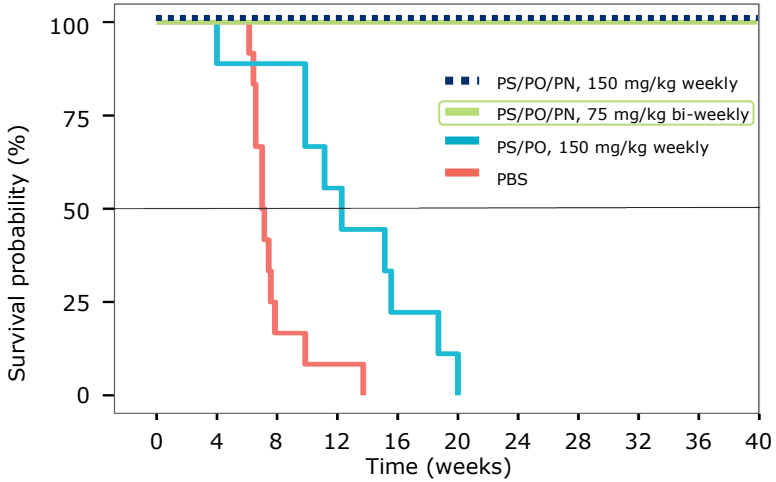

[1]Vyondys: www.fda.gov; viltepso; www.fda.gov; Exondys; www.fda.gov; Amondys: www.fda.gov

# PN chemistry improved muscle exposure and survival in preclinical mouse models

**PN increased muscle concentrations after single dose, which correlated with exon-skipping activity**




**Treatment with PN-modified molecules led to 100% survival of dKO mice at time of study termination**




Note: Untreated, age-matched mdx mice had 100% survival at study termination [not shown]

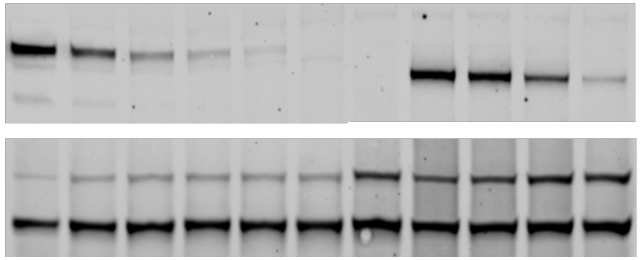
Kandasamy et al., 2022; doi: 10.1093/nar/gkac018

# WVE-N531: Dystrophin restoration *in vitro* and enhanced muscle distribution in NHPs

## Dystrophin protein restoration of up to 71% *in vitro*

**Western Blot normalized to primary healthy human myoblast lysate**

| Standard Curve (% WT lysate in D45-52 lysate) | | | | | | D45-52 Cells | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Mock | WVE-N531 | | | | |
| | | | | | | 0 | 10 | 3.3 | 1.1 | 0.3 | Conc [uM] |
| 100% | 50% | 25% | 12% | 6% | 0% | 0% | 71% | 65% | 37% | 9.5% | % Dystrophin |




## Enhanced muscle distribution in NHPs

- Plasma and tissue concentrations of WVE-N531 (PS/PO/PN) significantly higher than suvodirsen (first-generation PS/PO)
- WVE-N531 concentrations in heart and diaphragm substantially higher than skeletal muscle concentrations
- Higher plasma Cmax, AUC and Ctrough

**Preclinical data supported advancing proof-of-concept study to rapidly assess impact of PN chemistry in splicing oligonucleotides**

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Anne-Marie Li-Kwai-Cheung

Chief Development Officer

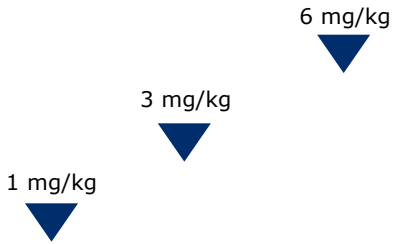
# In multidose portion of study, patients received three biweekly 10 mg/kg doses

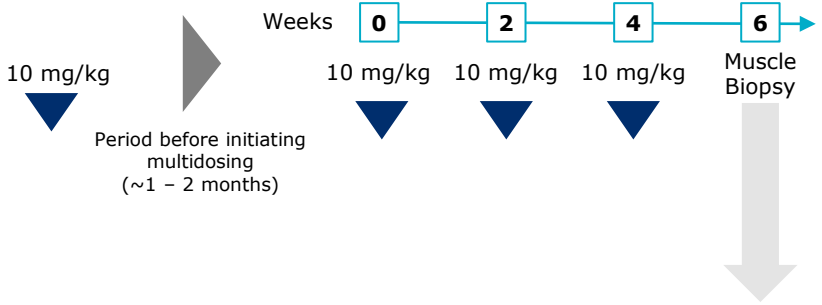
**Single ascending intra-patient doses**

**Multidosing at 10 mg/kg every other week**

**Initial cohort**

- **Boys with DMD amenable to exon 53 skipping**




**Data include:**

- WVE-N531 muscle concentrations
- WVE-N531 localization
- Exon skipping
- Dystrophin protein

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▼ Dose WVE-N531

# Baseline characteristics

| Characteristic | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Age (years) | 10 | 8 | 9 |
| BMI (kg/m^2) | 19.1 | 16.2 | 21.3 |
| Years since diagnosis | 3 | 4 | 7 |
| Mutation | del48-52 | del45-52 | del51-52 |
| Duration of steroid use (years) | 4 | 0.5 | 5 |
| NSAA (North Star Ambulatory Assessment) | 6 | 23 | 21 |

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# WVE-N531 appeared safe and well-tolerated

- All treatment-emergent adverse events (TEAEs) were mild, except one COVID-19 infection of moderate intensity
  - All adverse events (AEs) related to study drug (headache, pruritic rash) were mild, transient and resolved without sequelae
- No serious adverse events (SAEs)
- No events met stopping criteria
- No trend for an increase in TEAEs with single dose escalation from 1 to 10 mg/kg or three repeat doses at 10 mg/kg
- No evidence of class-related risks, such as thrombocytopenia, coagulation, complement activation, cytokine activation

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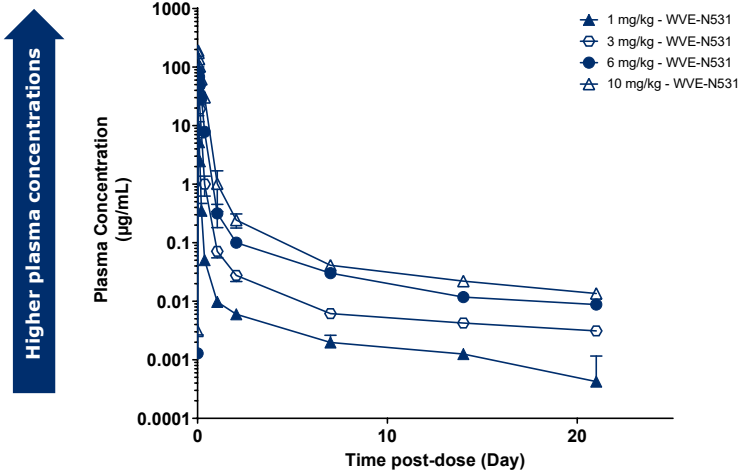
# Plasma pharmacokinetic profile enabling meaningful WVE-N531 tissue concentrations




- For 10 mg/kg dose level:
  - $C_{max}$: 191 (+/- 18.1) (µg/mL)
  - $AUC_{last}$ : 933 (+/- 103) (µg*h/mL)
  - $C_{trough}$ : 53 (+/- 10) (ng/mL)
  - $t_{1/2}$ : 25 days

Plasma concentrations and other PK parameters following a single dose of 10 mg/kg demonstrate a half-life of 25 days, which may support monthly dosing

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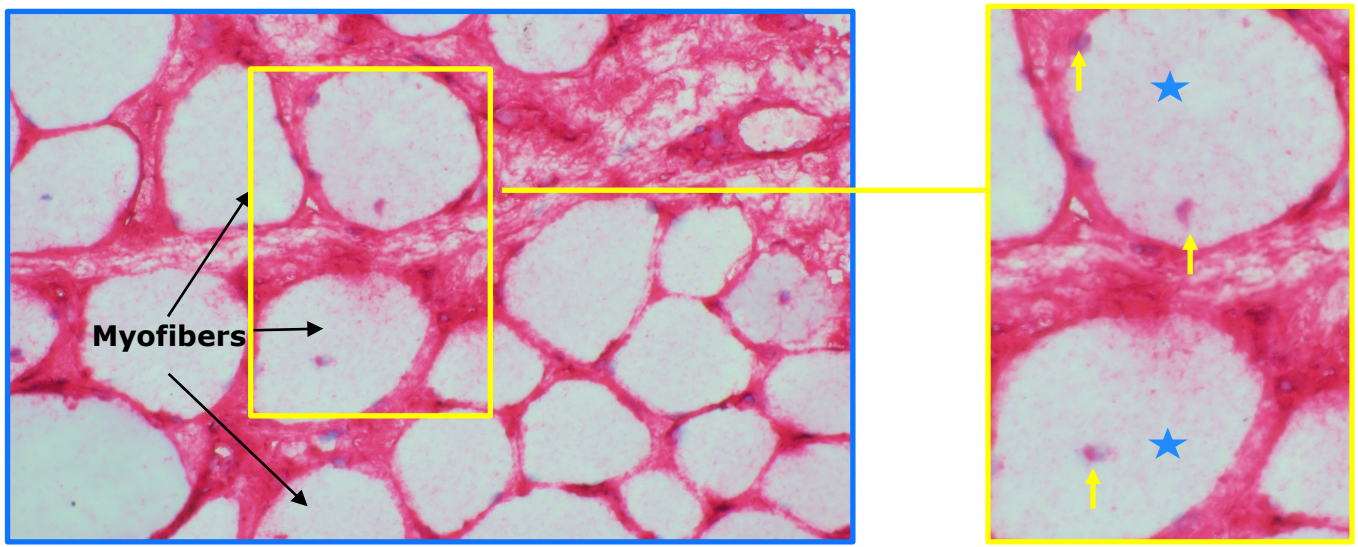
# Intracellular WVE-N531 enabling PD effects




WVE-N531 (in red) in myofiber cytoplasm (stars) and nuclei (yellow arrows)

Mag: 40x with an enlarged images

RNAscope (ISH – in situ hybridization)
Control Probes: Ubiquitin – Positive DapB – Negative

# High muscle concentration and exon skipping indicate WVE-N531 is engaging target

| Patient | Tissue Source | Tissue concentration (µg/g) | % Exon skipping by RT-PCR | Dystrophin by Western blot (% of normal) |
|---|---|---|---|---|
| 1 | Deltoid | 85.5 | 61.5 | 0.24 |
| 2 | Deltoid | 33.5 | 49.8 | 0.23 |
| 3 | Bicep | 8.3 | 47.9 | 0.34 |

Mean muscle concentration: 42 µg/g

Mean exon skipping: 53%

Mean dystrophin: 0.27% of normal (BLQ)

Biopsies collected ~2 weeks post-last dose (3 biweekly doses of 10 mg/kg)
BLQ: Below level of quantification (1%)

42 µg/g = 6.1 µM

# Conclusions & next steps

- Achieved proof-of-concept: High muscle concentrations of WVE-N531 and exon skipping observed following three biweekly doses at 10 mg/kg
- Planning underway to continue initial cohort to evaluate dystrophin
- Evaluating next steps for program in light of evolving regulatory environment
- Cash runway into 2025 remains unchanged

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# Q&A

# Realizing a brighter future for people affected by genetic diseases

For more information:

Kate Rausch, Investor Relations
InvestorRelations@wavelifesci.com
617.949.4827

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