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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**
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)

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BLQ: Below the limit of quantification  
DMD: Duchenne muscular dystrophy  
HD: Huntington’s disease  
ALS: Amyotrophic lateral sclerosis  
FTD: Frontotemporal dementia
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

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**Dysfunctional splicing (Disease)**

- Pre-mRNA: 50 51 53 54 55
- mRNA: Disrupted transcript reading frame
- Translation stops prematurely (No dystrophin protein)

**Exon skipping (Partial Restoration)**

- Pre-mRNA: 50 51 53 54 55
- mRNA: Skipping exon 53
- Translation continues (Shorter dystrophin protein)

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\(^1\)Vyondys: [www.fda.gov](http://www.fda.gov); viltepso; [www.fda.gov](http://www.fda.gov); Exondys; [www.fda.gov](http://www.fda.gov); Amondys: [www.fda.gov](http://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

Better tissue exposure

Gastrocnemius

Heart

Diaphragm

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]
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

<table>
<thead>
<tr>
<th>Standard Curve (% WT lysate in D45-S2 lysate)</th>
<th>D45-S2 Cells</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mock</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
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</table>

Conc [μM] % Dystrophin

<table>
<thead>
<tr>
<th>Concentration (μM)</th>
<th>0</th>
<th>10</th>
<th>3.3</th>
<th>1.1</th>
<th>0.3</th>
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<tbody>
<tr>
<td>% Dystrophin</td>
<td>100%</td>
<td>50%</td>
<td>25%</td>
<td>12%</td>
<td>6%</td>
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</table>

Dystrophin

Vinculin

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

**Single ascending intra-patient doses**

- 1 mg/kg
- 3 mg/kg
- 6 mg/kg
- 10 mg/kg

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

- Weeks 0, 2, 4, 6

Period before initiating multidosing (~1 - 2 months)

**Data include:**

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

**Initial cohort**

- Boys with DMD amenable to exon 53 skipping
## Baseline characteristics

<table>
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<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>10</td>
<td>8</td>
<td>9</td>
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<tr>
<td>BMI (kg/m^2)</td>
<td>19.1</td>
<td>16.2</td>
<td>21.3</td>
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<tr>
<td>Years since diagnosis</td>
<td>3</td>
<td>4</td>
<td>7</td>
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<tr>
<td>Mutation</td>
<td>del48-52</td>
<td>del45-52</td>
<td>del51-52</td>
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<td>Duration of steroid use (years)</td>
<td>4</td>
<td>0.5</td>
<td>5</td>
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<tr>
<td>NSAA (North Star Ambulatory Assessment)</td>
<td>6</td>
<td>23</td>
<td>21</td>
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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
Plasma pharmacokinetic profile enabling meaningful WVE-N531 tissue concentrations

- For 10 mg/kg dose level:
  - $C_{\text{max}}$: 191 (+/- 18.1) (µg/mL)
  - $AUC_{\text{last}}$: 933 (+/- 103) (µg*h/mL)
  - $C_{\text{trough}}$: 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.
Intracellular WVE-N531 enabling PD effects

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

Mag: 40x with an enlarged images
High muscle concentration and exon skipping indicate WVE-N531 is engaging target

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tissue Source</th>
<th>Tissue concentration (µg/g)</th>
<th>% Exon skipping by RT-PCR</th>
<th>Dystrophin by Western blot (% of normal)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Deltoid</td>
<td>85.5</td>
<td>61.5</td>
<td>0.24</td>
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<tr>
<td>2</td>
<td>Deltoid</td>
<td>33.5</td>
<td>49.8</td>
<td>0.23</td>
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<tr>
<td>3</td>
<td>Bicep</td>
<td>8.3</td>
<td>47.9</td>
<td>0.34</td>
</tr>
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</table>

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
Realizing a brighter future for people affected by genetic diseases

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