<table>
<thead>
<tr>
<th>Company/Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/ Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
<th>Employee</th>
<th>Other (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevail Therapeutics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
DESIGN OF THE FIRST-IN-HUMAN TRIAL OF NOVEL AAV9-BASED GENE THERAPY FOR PARKINSON’S DISEASE WITH PATHOGENIC GBA1 MUTATIONS

Olga Uspenskaya, Erin Mahoney, Lynne Verselis, Mark Lowrey, Jenny Velaga, Jeffrey Sevigny

Prevail Therapeutics, NY, USA

AAT-AD/PD™ 2020
April 4, 2020
Disclaimer

Certain information contained in this presentation and statements made orally during this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and Prevail Therapeutics Inc.’s (“Prevail”) own internal estimates and research. While Prevail believes these third-party sources to be reliable as of the date of this presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. While Prevail believes its internal research is reliable, such research has not been verified by any independent source.

This presentation contains forward-looking statements. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions our clinical trial results and other future conditions. All statements other than statements of historical facts contained in this presentation, including statements regarding our ongoing and planned clinical trials and the ability of our product candidates to treat patients with neurodegenerative diseases, are forward-looking statements. The words “may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “estimate,” “believe,” “estimate,” “predict,” “potential” or “continue” or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this presentation represent our views as of the date of this presentation. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements. New risk factors and uncertainties may emerge from time to time, and it is not possible to predict all risk factors and uncertainties.

Disclaimer
Disclosures

- PROPEL study is funded by Prevail Therapeutics
- OU, EM, LV, ML, JV, JS are employees and equity holders of Prevail Therapeutics
GBA1 mutations are the most common genetic risk factor for Parkinson’s disease

- Confirmed carriage of GBA1 mutation(s) increases risk for PD
- Risk observed even with mutations considered to be mild (e.g., N370S)
- Approximately 7-10% of PD patients worldwide have a GBA1 mutation
- Multiple known mutations
- Clinically PD-GBA patients tend to have earlier onset, progress more rapidly, and have a higher likelihood of dementia

Alcalay et al 2014; Gan-Or et al 2015; Liu et al 2016; Thaler et al 2017; Arkadir et al 2018
Gene dose effect of *GBA1* mutation(s) on GCase activity and clinical symptoms in Parkinson’s disease patients

- Homozygotes / compound heterozygotes have lower GCase activity than heterozygotes
- Heterozygotes have lower GCase activity than non-carriers

- Patients with two *GBA1* mutations present with more progressive cognitive changes than patients with one or no mutant alleles
- Among patients with one *GBA1* mutant allele, more severe mutations were associated with more cognitive dysfunction

---

**GCase activity**

**Cognitive decline**

Alcalay et al. Brain 2015

Liu et al., Annals of Neurology 2016
PR001 background

- PR001 is an investigational AAV9-based gene therapy that contains the codon-optimized human \textit{GBA1} transgene.

- In transgenic (4L/PS-NA) and CBE mouse models, treatment with PR001 increased GCase expression, reversed glycolipid accumulation, decreased neuropathology, improved behavioral abnormalities, and reduced \( \alpha \)-Synuclein accumulation.

- In NHPs, treatment with PR001 into the cisterna magna (clinical route of administration) resulted in broad CNS distribution of the \textit{GBA1} transgene and a significant elevation of GCase protein in brain tissue.

- No PR001-related safety events or adverse findings were observed in mouse or NHP studies.
AAV9 is well-suited to deliver functional genes or gene knockdown to the CNS

- AAV9-based therapy has shown transformative efficacy and safety and is now approved for SMA
- The effectiveness of AAV9-based therapies is due to its ability to distribute broadly across the CNS
- AAV9 manufacturing process is well-characterized and scalable
- Prevail has licensed exclusive WW rights to AAV9 from REGENXBIO to deliver the genes in our lead programs
How AAV-mediated gene therapy works

- Vector binds to cell surface receptors
- Transported via endocytic pathway; escapes endosome to nucleus
- Transgene (the payload) is released
- ssDNA is converted into dsDNA by host polymerase
- Form episomal concatemers
- Transgene expression (third party data suggests expression duration of >10 years*)

*Mingozzi and High Blood 2013, Li et al., Bioinsights 2019

ssDNA= single stranded deoxyribonucleic acid; dsDNA= double stranded deoxyribonucleic acid
PR001 mechanism of action in PD-GBA

Parkinson’s Disease WITH GBA1 MUTATION

PR001 Treated

INCREASED GCase

SUBSTRATE DECREASES (GLUCER, GLUSPH)

PRODUCT INCREASES

SECONDARY LIPIDS NORMALIZE

FUNCTIONAL LYSOsome

NEURODEGENERATION SLOWED OR STOPPED

INFLAMMATION REDUCED

PROTEIN AGGREGATION REDUCED
Goal of PR001 treatment is to restore GCase activity in PD-GBA patients

- Human genetics suggest increasing GCase activity by 20-30% of healthy levels expected to be clinically meaningful
- Similarly, mouse data suggests 20-30% increase in GCase activity corresponds to efficacy

Source: Liu et al., Annals of Neurology 2016; Thaler et al., Parkinsonism and Related Disorders 2017
PROPEL study

A Phase 1/2a Randomized, Double-Blind, Sham Procedure-Controlled, Ascending Dose Study to Evaluate the Safety of PR001 in Patients with Parkinson’s Disease with at Least One GBA1 Mutation

- N=16 subjects
- Two overlapping cohorts of 8 subjects/cohort
- Randomized (6:2) to receive one-time treatment with PR001 or undergo a simple sham procedure

PD-GBA Patients

PR001 Low Dose vs. Placebo (N=8, 6:2)

PR001 High Dose vs. Placebo (N=8, 6:2)
# Study objectives and endpoints

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Objectives</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>Safety and tolerability of 2 doses of PR001 administered via suboccipital injection into the cisterna magna</td>
<td>• Incidence and severity of treatment-emergent AEs and SAEs</td>
</tr>
<tr>
<td>(up to 5 years)</td>
<td>• Incidence of procedure or treatment-emergent safety findings as per brain MRI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>Effects of PR001 on:</td>
<td>Change from baseline in:</td>
</tr>
<tr>
<td>(up to 12 months,</td>
<td>• GCas levels in blood and CSF</td>
<td>• GluCer and GluSph levels, and GCase in CSF at Months 3 and 12</td>
</tr>
<tr>
<td>exploratory thereafter)</td>
<td>• Glycolipid panel (e.g. GluCer, GluSph) in blood and CSF</td>
<td>• GluCer and GluSph levels, and GCase in blood at Months 1, 2, 3, 6, 9, and 12</td>
</tr>
<tr>
<td></td>
<td>• PR001 immunogenicity in blood and CSF</td>
<td>• PR001 immunogenicity in blood at Day 14 and Months 1, 3, 6, 9, and 12; and in CSF at Months 3 and 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Exploratory</strong></td>
</tr>
<tr>
<td><strong>Exploratory</strong></td>
<td>Effects of PR001 on:</td>
<td>Change from baseline in:</td>
</tr>
<tr>
<td>(up to 12 months)</td>
<td>• Measures of clinical and daily function and quality of life</td>
<td>• CSF biomarkers of neurodegeneration at Months 3 and 12</td>
</tr>
<tr>
<td></td>
<td>• Selected biomarkers of neurodegeneration in CSF</td>
<td>• Clinical scales, LED</td>
</tr>
<tr>
<td></td>
<td>• Imaging patterns based on MRI and dopamine transporter single photon emission computed tomography (DaT-SPECT)</td>
<td>• DaT-SPECT at Month 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DTI and ASL MRI at Months 6 and 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Parameters captured by digital biomarker battery</td>
</tr>
</tbody>
</table>
## Patient population

<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
<th>Key Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men or women aged 40 to 75 years (inclusive)</td>
<td>Diagnosis of a significant CNS disease other than PD</td>
</tr>
<tr>
<td>Diagnosis of PD per UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria</td>
<td>MoCA score of &lt;14</td>
</tr>
<tr>
<td>At least 1 pathogenic GBA1 mutation confirmed by the central laboratory</td>
<td>Contraindication to intracisternal injection and/or general anesthesia/deep sedation</td>
</tr>
<tr>
<td>Hoehn and Yahr Stage III-IV (as determined in OFF state)</td>
<td>Concomitant disease or clinically significant abnormalities in laboratory test results precluding study participation</td>
</tr>
<tr>
<td>Stable use of background PD or GD medications at least 8 weeks prior to PR001 administration</td>
<td>History of deep brain stimulator placement, focused ultrasound, or surgery for PD</td>
</tr>
<tr>
<td></td>
<td>Any type of prior gene or cell therapy</td>
</tr>
<tr>
<td></td>
<td>Use of ambroxol within 8 weeks of dosing</td>
</tr>
</tbody>
</table>
**PROPEL schedule of assessments**

<table>
<thead>
<tr>
<th>MONTH</th>
<th>MRI</th>
<th>DaT SPECT</th>
<th>CLINICAL SCALES</th>
<th>DOD BIOMARKERS</th>
<th>CSF BIOMARKERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Brain" /></td>
<td><img src="image2.png" alt="DaT SPECT" /></td>
<td><img src="image3.png" alt="Score" /></td>
<td><img src="image4.png" alt="Test Tubes" /></td>
<td><img src="image5.png" alt="Test Tubes" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image1.png" alt="Brain" /></td>
<td><img src="image2.png" alt="DaT SPECT" /></td>
<td><img src="image3.png" alt="Score" /></td>
<td><img src="image4.png" alt="Test Tubes" /></td>
<td><img src="image5.png" alt="Test Tubes" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image1.png" alt="Brain" /></td>
<td><img src="image2.png" alt="DaT SPECT" /></td>
<td><img src="image3.png" alt="Score" /></td>
<td><img src="image4.png" alt="Test Tubes" /></td>
<td><img src="image5.png" alt="Test Tubes" /></td>
</tr>
<tr>
<td>6</td>
<td><img src="image1.png" alt="Brain" /></td>
<td><img src="image2.png" alt="DaT SPECT" /></td>
<td><img src="image3.png" alt="Score" /></td>
<td><img src="image4.png" alt="Test Tubes" /></td>
<td><img src="image5.png" alt="Test Tubes" /></td>
</tr>
<tr>
<td>9</td>
<td><img src="image1.png" alt="Brain" /></td>
<td><img src="image2.png" alt="DaT SPECT" /></td>
<td><img src="image3.png" alt="Score" /></td>
<td><img src="image4.png" alt="Test Tubes" /></td>
<td><img src="image5.png" alt="Test Tubes" /></td>
</tr>
<tr>
<td>12</td>
<td><img src="image1.png" alt="Brain" /></td>
<td><img src="image2.png" alt="DaT SPECT" /></td>
<td><img src="image3.png" alt="Score" /></td>
<td><img src="image4.png" alt="Test Tubes" /></td>
<td><img src="image5.png" alt="Test Tubes" /></td>
</tr>
</tbody>
</table>

**STUDY VISITS (10 TOTAL OVER 12 MONTHS)**

**SCREENING** (up to 45 days)

**DOUBLE BLIND PERIOD**

**FOLLOW UP VISITS EVERY 6 MONTHS** (4 years)
Intra cisterna magna administration provides most efficient delivery approach of PR001 into the CNS

AAV gene therapy may be delivered via different RoAs

Comparison of AAV9 biodistribution with IV versus IT lumbar versus IT ICM in NHPs

Figure 1: AAV9 biodistribution following intrathecal delivery in nonhuman primates. AAV9 was administered to six cynomolgus macaques at doses of 2.5-5 x 10^11 GC/kg by injection into the cisterna magna (n = 4) or the lumbar subarachnoid space (n = 2). An additional animal was treated intravenously with a high dose (2 x 10^12 GC/kg) of AAV9. All animals were sacrificed 2 weeks after injection and vector genomes were quantified in tissue samples by Taqman PCR.

Conclusions

- PR001 (AAV9-GBA1) is an investigational gene therapy supported by a comprehensive non-clinical package
  - Efficacy observed across multiple biochemical and neuropathological endpoints in two mouse models of disease (CBE and 4L/PS-NA)
  - Widespread CNS biodistribution of GBA1 and no PR001-related adverse events observed in NHPs treated with intra cisterna magna administration of PR001

- PROPEL study is the first clinical study of a potentially disease-modifying gene therapy for a genetically-defined PD patient population (PD-GBA)
  - Study in enrollment phase (ClinicalTrials.gov Identifier: NCT04127578)
  - Interim safety and biomarker data read out planned for late 2020

- Currently intend to initiate two Phase 1/2 clinical trials of PR001 in neuronopathic GD patient populations in mid-2020, the first for patients with Type 2 GD and the second for patients with Type 3 GD
Acknowledgments

We would like to thank all the clinicians, patient groups, patients and families that have helped support our progress thus far!

We would also like to acknowledge those who contributed to the development of PR001:

Asa Abeliovich  |  Franz Hefti
Zara Aziz       |  Sid Kamalakaran
Alissa Brandes  |  Ilan McNamara
Suzanne Burstein|  Stuart Nelson
Yong Dai        |  Jason Politi
Jennifer Daily  |  Patty Sheehan
Tim Fenn         |  Patricia Sondergaard
Swetha Garimalla|  Li Chin Wong
Jorge Haller     |  Zhao Hu Yang
Laura Heckman    |  Emily Minkow
Franz Hefti      |  Jeff Melzer

James Peluso
Thank you.