FORWARD-LOOKING STATEMENTS

This press release contains forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995 and other federal securities laws. The use of words such as "expect," "estimate," "may" and other similar expressions are intended to identify forward-looking statements. For example, all statements Sio makes regarding costs associated with its operating activities, funding requirements and/or runway to meet its upcoming clinical milestones, and timing and outcome of its upcoming clinical and manufacturing milestones are forward-looking. All forward-looking statements are based on estimates and assumptions by Sio’s management that, although Sio believes to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that Sio expected. Such risks and uncertainties include, among others, the impact of the Covid-19 pandemic on our operations; the actual funds and/or runway required for our clinical and product development activities and anticipated upcoming milestones; actual costs related to our clinical and product development activities and our need to access additional capital resources prior to achieving any upcoming milestones; the initiation and conduct of preclinical studies and clinical trials; the availability of data from clinical trials; the development of a suspension-based manufacturing process for Axo-Lenti-PD; the scaling up of manufacturing, the expectations for regulatory submissions and approvals; the continued development of our gene therapy product candidates and platforms; Sio’s scientific approach and general development progress; and the availability or commercial potential of Sio’s product candidates. These statements are also subject to a number of material risks and uncertainties that are described in Sio’s most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission on June 9, 2021, as updated by its subsequent filings with the Securities and Exchange Commission. Any forward-looking statement speaks only as of the date on which it was made. Sio undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.
THREE CLINICAL-STAGE PROGRAMS
- Balanced pipeline leveraging both AAV and in vivo lentiviral vector systems
- Classical applications of AAV-based gene therapy in monogenic diseases and extension of gene therapy potential into more prevalent indications like Parkinson’s disease

LEADING DEVELOPMENT POSITION
- All programs have potential best-in-class and first-to-market profiles in their respective indications
- All programs are in clinical development and generating data

STRENGTHENED BALANCE SHEET
- $119 million of cash and cash equivalents as of March 31, 2021
- Cash runway extends into Q4 2022, beyond the expected dates of major upcoming milestones for the AXO-AAV-GM1 program
Unique CNS delivery capabilities
• Neurosurgical delivery with infusion to cisterna magna and deep brain structures
• Intravenous delivery with demonstrated BBB penetration and widespread neuraxial distribution

Hybrid manufacturing strategy
• Two-pronged approach pairs in-house analytical development capabilities with external CDMO relationships
• Scalable HEK293 manufacturing systems
• Partnered with Andelyn, AskBio (Viralgen) and Oxford Biomedica

Strong product-indication fit across 3 clinical-stage programs
• Well-validated targets with established POC in large animal models of disease
• Modality-agnostic approach utilizes both LVV and AAV capsids to meet the needs of each indication

Optimized vector design and approach to immunosuppression
• Current pipeline consists of 2nd and 3rd generation vector systems
• Promoters and transgenes optimized for safety, potency, and durability
• Dual suppression of T- and B-cell mediated immunity
PROVEN LEADERSHIP TEAM POSITIONED TO EXECUTE ON OUR VISION

Pavan Cheruvu, MD
Chief Executive Officer

David Nassif, JD
Chief Financial Officer & General Counsel

Gavin Corcoran, MD FACP
Chief R&D Officer

Parag Meswani, PharmD
Chief Commercial Officer

Frank Torti, MD
Chairperson

Senthil Sundaram
Board Member

Berndt Modig
Board Member

Pavan Cheruvu, MD
Board Member

Atul Pande, MD
Lead Independent Director

Eric Venker, MD, PharmD
Board Member

Kristiina Vuori, MD, PhD
Board Member

Strong Investor Base

Guangping Gao, PhD
Chief AAV Scientific Advisor

Horae (红瑞)
Gene Therapy Center
### THREE CLINICAL-STAGE GENE THERAPY PROGRAMS

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Indication</th>
<th>Vector/Gene</th>
<th>Phase</th>
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<tbody>
<tr>
<td>AXO-AAV-GM1</td>
<td>GM1 gangliosidosis</td>
<td>AAV9/GLB1</td>
<td>Phase 1/2</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>Geographic rights:</td>
<td>Worldwide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FDA Designations:</td>
<td>GM1 gangliosidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Orphan Drug Designation</td>
<td>AAV9/GLB1</td>
<td></td>
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<tr>
<td></td>
<td>Rare Pediatric Disease Designation</td>
<td></td>
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</tr>
<tr>
<td>AXO-AAV-GM2</td>
<td>Tay-Sachs/Sandhoff disease</td>
<td>AAVrh.8/HexA + HexB</td>
<td>Phase 1/2</td>
</tr>
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</tr>
<tr>
<td>AXO-Lenti-PD</td>
<td>Parkinson’s disease</td>
<td>Lentivirus/TH, CH1, AADC</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Geographic rights:</td>
<td>Worldwide</td>
<td></td>
</tr>
</tbody>
</table>

**Upcoming Events**

2H 2021: 12-month data from low-dose cohort
Q1 2022: 12-month data from high-dose cohort
1H 2022: FDA meeting re: registrational pathway
Mid-2022: 24-month data from low-dose cohort

2021:
Continued enrollment in dose-escalation Stage 1

Ongoing:
Development of suspension-process manufacturing enabling QP certification of clinical trial material
LEAD PROGRAMS REPRESENT SIGNIFICANT MARKET OPPORTUNITY

- **Broad and balanced pipeline of best-in-class gene therapies create sustainable gene therapy business model**

- **Sio has full commercial rights to all indications in all markets**

1 Management estimate of addressable population in major reimbursable markets based on published incidence and prevalence. PD number represents estimate of the global prevalence; GM1/GM2 numbers represent US/EU prevalence only.
Rare fatal pediatric diseases

First clinical-stage gene therapies for GM1 gangliosidosis, Tay-Sachs and Sandhoff diseases
GM1 GANGLIOSIDOSIS AND GM2 GANGLIOSIDOSIS (TAY-SACHS/SANDHOFF DISEASE): IDEAL TARGETS FOR GENE THERAPY

- GM1 Ganglioside: β-galactosidase
- GM2 Ganglioside: β-Hexosaminidase A (α-β heterodimer)
- GM3 Ganglioside

Underlying neurobiology supports the use of gene therapy for long-term enzyme restoration.

Able to leverage cross-correction to achieve broad distribution via one-time administration.

Well-established natural history of both GM1 gangliosidosis, Tay-Sachs, and Sandhoff Disease.
Clinical course illustrates rapidly progressive and uniformly fatal nature of both diseases

- Dysphagia Requiring Feeding Tube
- Lose Head Control
- Cannot Sit Alone
- Blindness
- Osteoporosis

~50% mortality by 3.5 years
~75% mortality by 5 years

Life expectancy curve derived from natural history study in GM2 patients

AXO-AAV-GM1 PROGRAM HIGHLIGHTS

RATIONALE
AAV9 IV administration delivers a functional copy of the *GLB1* gene to address multi-organ manifestations with proof-of-concept from large animal models.

SAFETY
Safe and well-tolerated at low dose, supported enrollment at high dose with no observed complications to date.

CLINICAL OUTCOMES
Positive six-month enzyme activity and preliminary outcomes with first evidence of disease stabilization.

MILESTONES
- H2 2021: 12-month durability data from low-dose
- Q1 2022: 12-month data from high-dose cohort
- 1H 2022: FDA meeting re: registrational pathway
GM1 GANGLIOSIDOSIS IS A PROGRESSIVE, PEDIATRIC LYSOSONAL STORAGE DISEASE WITH MULTISYSTEM MANIFESTATIONS AND NO APPROVED TREATMENTS

- Fatal, pediatric lysosomal storage disorder with monogenic autosomal recessive inheritance
- Single gene (GLB1) defect leads to decreased β-galactosidase enzyme activity and ganglioside accumulation
- Disease hallmark is progressive neurodegeneration due to storage of GM1 ganglioside in lysosomes
- Type and Type II have decreased life expectancy
- Currently no treatments available
- Successful treatments will address multisystem manifestations of disease
GM1 GANGLIOSIDOSIS SEVERITY VARIES ACROSS DISEASE TYPES

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Onset</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (Infantile)</td>
<td>Onset &lt;6 mo</td>
<td>Skeletal dysplasia, Hepatosplenomegaly, Developmental arrest, Hypotonia, Cherry red macula, Seizures, Death at &lt;2 years</td>
</tr>
<tr>
<td>Type II (Late-Infantile)</td>
<td>Onset 1-2 yrs</td>
<td>Difficulty walking, Variable skeletal disease, Decreased cognition, Seizures, Death in mid-teens</td>
</tr>
<tr>
<td>Type II (Juvenile)</td>
<td>Onset 2-5 yrs</td>
<td>Impaired ambulation, Dysarthria, Variable skeletal disease, Decreased cognition, Survival into 3rd decade</td>
</tr>
<tr>
<td>Type III (Adult)</td>
<td>Adult onset</td>
<td>Gait disturbance, Dystonia, dysarthria, Decreased cognition, Age at death variable</td>
</tr>
</tbody>
</table>

Focus of AXO-AAV-GM1
**AXO-AAV-GM1: DIFFERENTIATED GENE THERAPY FOR GM1 GANGLIOSIDOSIS**

**APPROACH**

- **AAV9 vector system** delivers a functional copy of the *GLB1* gene via IV administration
- **AAV9** has been shown to cross the blood-brain barrier, allowing meaningful transduction of CNS and peripheral tissues in GM1 mouse and feline models.\(^1\)\(^,\)\(^3\)-\(^4\)
- **Broad transduction along with cross-correction of neighboring cells** has the potential to address the multisystem manifestations.\(^5\)
- **Only gene therapy** to demonstrate restoration of wild-type survival in a naturally-occurring GM1 feline model

<table>
<thead>
<tr>
<th>βgal = β-galactosidase gene; CB = chicken β-actin promoter; CMV En = cytomegalovirus immediate early enhancer; ITR = inverted terminal repeat; pA = poly A; SA = splice acceptor; SD = splice donor</th>
</tr>
</thead>
</table>


**OUTCOMES**

- **Positive six-month biomarker and preliminary clinical outcomes data** in Type II children treated with \(1.5 \times 10^{13}\) vg/kg dose
- **CSF GM1 ganglioside reduction** suggests ability to address systemic and neurological manifestations of GM1 gangliosidosis
- **High dose cohort** \((4.5 \times 10^{13}\) vg/kg\) initiated after DSMC review
- **7 children treated** as of June 2021
ONLY GENE THERAPY TO DEMONSTRATE RESTORATION OF WILD-TYPE SURVIVAL IN A GM1 FELINE MODEL

GM1 Felines Treated with 1.5E13 vg/kg via Intravenous Injection at 5 Weeks of Age

Clinical Rating Score

Age (months)

1: UMass Data on File; WPRE included in construct administered to felines
Note: Felines were treated with the first-generation construct and the AXO-AAV-GM1 vector has been optimized prior to dosing patients in the ongoing clinical trial.
INDEPENDENT STUDY CONFIRMS AAV9 IV ROUTE OF ADMINISTRATION HAS SUPERIOR CNS DISTRIBUTION IN GM1 FELINES

All feline animals were treated with 1.5e13 vg/kg and used a similar vector backbone

1: Data from Auburn University.
Note: Felines were treated with a vector that includes a WPRE component; AXO-AAV-GM1 does not include this component.
INDEPENDENT STUDY DEMONSTRATES AAV9 GENE THERAPY WITH IV ROUTE OF ADMINISTRATION IS MOST EFFECTIVE IN EXTENDING SURVIVAL AND IMPROVING CLINICAL FUNCTION

All feline animals were treated with 1.5e13 vg/kg and used a similar vector backbone

1: Data from Auburn University.
Note: Felines were treated with a vector that includes a WPRE component; AXO-AAV-GM1 does not include this component.
**AXO-AAV-GM1**: FIRST-IN-HUMAN, PHASE 1/2 STUDY CONDUCTED AT NIH

**STAGE 1: Dose Ranging**
*Goal is to assess safety & identify optimal dose*

- **Low-Dose** (5 patients)
  - $1.5 \times 10^{13}$ vg/kg
- **High-Dose** (up to 3 patients)
  - $4.5 \times 10^{13}$ vg/kg

**STAGE 2: Efficacy & Safety Study**
*Goal is to assess how well the optimal dose works*

- **Low-Dose** (up to 3 patients)
  - $1.5 \times 10^{13}$ vg/kg
- **High-Dose** (up to 3 patients)
  - $4.5 \times 10^{13}$ vg/kg

**Registralional Study using Optimal Dose from Stage 1**

**Key Study Endpoints**
- Safety and tolerability
- Markers of disease progression in serum & CSF
- Change in disease severity
- Motor function
- Developmental changes and disease progression
- Change in brain volume *(after 1 year)*

All subjects received immune modulation with rituximab, sirolimus and glucocorticoids
NCT03952637 on ClinicalTrials.gov
### AXO-AAV-GM1: CLINICALLY MEANINGFUL ASSESSMENTS OF THERAPEUTIC RESPONSE

| Safety and Tolerability | Adverse event collection  
Focused ongoing surveillance of gene therapy |
|-------------------------|-----------------------------------------------|
| Vineland-3 Adaptive Behavior Assessment | Measure of adaptive behavior widely used to address  
Intellectual ability |
| Clinical Global Impression Scale | Rates severity and improvement based on clinical  
opinion |
| Biomarkers of Disease Activity | Level of residual enzyme correlates inversely with  
disease severity |

**Vineland-3 Adaptive Behavior Assessment (VABS-III)** evaluates communication, daily living and social skills.

**Clinical Global Impression Scale (CGI)** measures severity and improvement since initiation of treatment.

**Biomarkers** measured across plasma and CSF to evaluate enzyme activity and substrate levels.
AXO-AAV-GM1: 6-Month Data Readout

Safety
Biomarkers
Clinical and Functional Outcomes
OVERALL SAFETY SUMMARY (6-MONTH DATA)

• AXO-AAV-GM1 was generally safe and well-tolerated at the low dose (1.5x10^{13} \text{ vg/kg}) delivered intravenously in Type II (late-infantile and Juvenile) patients.

• There have been no serious adverse events (SAEs) related to gene therapy.
  o One SAE was described: a single patient experienced bacterial sepsis due to a PICC line infection, which was considered to be unrelated to the investigational drug product, and which resolved within a few days following line removal and administration of IV antibiotics.

• The most common adverse events were considered mild to moderate. Transient AST elevations were observed in 4 subjects, none of which required clinical intervention or had associated clinical sequelae. There were no other adverse events indicative of impaired liver function including serum bilirubin, GGT, and ALT. No clinically relevant changes were observed in platelet count.

• The favorable safety profile in the low-dose cohort supports continued enrollment of patients in the high-dose cohort (4.5x10^{13} \text{ vg/kg}), in which two patients have now been dosed without complications.
# Adverse Events Occurring in ≥ 1 Patient

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Events, n</th>
<th>Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Any serious adverse event <em>(Bacterial sepsis due to PICC line, unrelated to AXO-AAV-GM1)</em></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Any treatment emergent adverse events</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Elevated Aspartate Aminotransferase (AST)*</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Elevated Blood Cholesterol</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Decreased Fibrin D Dimer*</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Decreased Platelet Count* <em>(lowest level 148K)</em></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bacterial Line Sepsis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Possibly related to AXO-AAV-GM1, resolved without intervention
ENZYME ACTIVITY RESTORED TO 23-57% (mean: 38%) OF NORMAL* REFERENCE LEVELS AT MONTH 6

β-galactosidase ACTIVITY IN SERUM BY SUBJECT

Therapeutics strategies for GM1 gangliosidosis do not need to completely normalize Beta-gal activity to prevent disease progression.

Entire range of clinical phenotypes for GM1 gangliosidosis, ranging from severe to relatively mild are clustered within a narrow range of residual lysosomal Beta-Gal activity, from 0-15% of normal control levels.

*The reference level was defined by the lowest level of enzyme activity in serum from 30 healthy adult volunteers using the same validated assay of beta-galactosidase enzyme activity as was used to assess the patients in the study.
SERUM AND CSF BIOMARKERS OF DISEASE PROGRESSION OR STABILIZATION

33%-128% Increase in β-galactosidase in Serum

% Change from Day 0 to Day 180
-40%  -49%  -19%  +37%  -18%

Mean levels in pediatric population1-3

Impact on GM1 Ganglioside in CSF demonstrate signs of CNS penetration

% Change from Day 0 to Day 180
-49%  -19%  +19%

Pt1: Juvenile; Pt2-5: Late infantile
LLN= Lower limit of normal from 30 serum samples of 30 presumed healthy adults
VINELAND-3: COMMUNICATION SUBDOMAIN SCORES STABILIZATION AT MONTH 6

<table>
<thead>
<tr>
<th>Growth Scale Value Score</th>
<th>Communication</th>
<th>Daily Living Skills</th>
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<tbody>
<tr>
<td>Age in Months</td>
<td>Pt1 Pt2 Pt3 Pt4 Pt5</td>
<td></td>
</tr>
<tr>
<td>Pt1</td>
<td></td>
<td></td>
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<td>Pt2</td>
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<tr>
<td>Pt3</td>
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<tr>
<td>Pt4</td>
<td></td>
<td></td>
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<tr>
<td>Pt5</td>
<td></td>
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</tr>
</tbody>
</table>

Visit Schedule:
Screening, Baseline, Day 180

[1] Domestic, Community and Written subdomains are applicable to subjects 3 years and older.
Subject 004 turned 3 years old between Day 90 and Day 180.
VINELAND-3: BEHAVIOR AND MOTOR SUBDOMAIN SCORES STABILIZATION AT MONTH 6

Visit Schedule:
Screening, Baseline, Day 180

Age (in Months)
AXO-AAV-GM1: Foundational Commercialization & Launch Activities Already in Progress

**Disease State Awareness and Stakeholder Engagement**
- Identify and connect with Key Opinion Leaders (KOLs) to increase disease and product awareness and drive faster diagnosis timelines
- Early and ongoing collaboration with advocacy groups to increase disease and gene therapy awareness, drive faster diagnosis, and support clinical trial recruitment

**Manufacturing Strategy & Development**
- Partnered with Viralgen, a leading CDMO built as a joint venture between AskBio and Columbus Venture Partners
- Secured cGMP capacity and resources to support development and commercialization

**Patient Identification**
- Facilitate faster diagnoses for children with GM1 gangliosidosis and Tay-Sachs/Sandhoff disease
- Partnered with Invitae to offer access to genetic testing and counseling at no charge to patients suspected of having a lysosomal storage disease, or LSD

**Payer Engagement**
- Early engagement to foster familiarity with the disease, gene therapy, and help elucidate any specific evidence requirements in support of market access
**RATIONALE**
AAVrh8 vector encoding *HEXA* and *HEXB* genes directly to the CNS with large animal model proof-of-concept

**SAFETY**
Therapy has been generally well-tolerated to date, with no serious adverse events

**FIRST IN THE CLINIC**
January 2021: first patient dosed in AXO-AAV-GM2 trial

**MILESTONES**
Expect to continue patient identification, screening, and enrollment in Stage 1 of the study throughout 2021
GM2 GANGLIOSIDOSIS: TAY-SACHS / SANDHOFF DISEASE

**Disease Background**

- **Fatal, pediatric** lysosomal storage disorder with monogenic autosomal recessive inheritance pattern
- **Caused by** a mutation in the *HEXA* or *HEXB* genes, which prevents β-hexosaminidase A enzyme formation
- Well-characterized natural history demonstrating **developmental regression, blindness and epilepsy** with focal seizures
- **Infantile (Type I)** is the most common form of the disease; patients have a life expectancy of **3-4 years**
- Currently **no treatments** available

**Natural History of Infantile Tay-Sachs and Sandhoff Disease**

Most early motor milestones are gained and subsequently lost within a ~1-year time frame

- **Sitting without propping**
- **Transfer from hand to hand**
- **Head control**
- **Reach for object**
- **Seizure onset**
- **Blindness**
- **Deafness**
**AXO-AAV-GM2: DIFFERENTIATED GENE THERAPY FOR GM2 GANGLIOSIDOSIS**

The Only Gene Therapy in Development That has Already Been Tested in Human Patients Through an Expanded Access Protocol

**APPROACH**

- **One-time delivery** of two vectors using AAVrh8 vector encoding *HEXA* and *HEXB* genes **directly to the CNS**
- **Dual** intrathalamic and intrathecal **routes of administration** allow for **transduction** across **entire neuraxis** to address neurological manifestations
- **Well-characterized natural history** demonstrating developmental regression, blindness and epilepsy with focal seizures

**OUTCOMES**

- Only gene therapy in development tested in children with Tay-Sachs disease through expanded access protocol
- **IND clearance** received November 2020
- January 2021: **first patient dosed** in AXO-AAV-GM2 clinical trial
- Therapy has been generally **well-tolerated to-date**, with no serious adverse events
AXO-AAV-GM2: COMBINED INTRAPARENCHYMAL AND CSF DOSING DELIVERS OPTIMAL OUTCOMES

Bilateral Thalamic + Unilateral ICV (BiTh/ICV) Injections in SD Cats Transduce Entire Neuraxis and Dramatically Improve Function with Significantly Increased Survival (P < 0.0001)

Neuraxial Distribution of Reconstituted Enzyme with Combination Delivery (cross sections stained for HEXA enzyme activity)
**AXO-AAV-GM2: CLINICAL STUDY DESIGN**

**STAGE 1: Dose Ranging**
*Goal is to assess safety & identify optimal dose*

- **Starting Dose**
  - 1.42E+14 vg
  - (n=1)

- **Low-Dose**
  - 1.95E+14
  - (n=3)

- **Mid-Dose**
  - 2.18E+14
  - (n≈3)

- **High-Dose**
  - 3.56E+14
  - (n≈3)

**STAGE 2: Efficacy & Safety Study**
*Goal is to assess how well the optimal dose works*

Registralional Study using Optimal Dose from Stage 1

**Key Study Endpoints**
- Safety and tolerability
- Enzyme activity in CSF and serum
- GM2 ganglioside levels in CSF
- Changes to MRI/MRS
- Motor function and disease severity
- Exploratory objectives include other systemic and CSF biomarkers and neurological symptoms

**Type I (infantile-onset): 1-year assessment; 4-year long term follow-up**

**Type II (juvenile-onset): 2-year assessment; 3-year long term follow-up**

NCT04669535 on ClinicalTrials.gov
Adult neurodegenerative disease

Parkinson’s disease
**Moderate to Advanced Parkinson’s disease**

- Progressive and chronic disease that impacts more than **1 million patients** in the US
- 50% of people with PD develop motor problems after 5 years, despite best medical treatment
- >80% experience ON/OFF fluctuations
- Levodopa, the gold standard therapy, causes treatment **side effects** such as *dyskinesias* and has a high pill burden with modest improvements of 4-8 points in UPDRS III “OFF” Scores
- Substantial opportunity to improve motor function and **quality of life**

**AXO-Lenti-PD**

- **One-time treatment using a lentiviral vector** with **three key genes** to produce **endogenous dopamine**
- Development plan integrates robust preclinical and clinical data from 1st generation vector, ProSavin
- **SUNRISE-PD Cohort 1**: **17-22 point improvement** from baseline in UPDRS III “OFF” scores at 6 and 12 months
- **Cohort 2**: Positive 6-month data demonstrating **21-point improvement** from baseline in UPDRS III “OFF” score
- Addressable market of **> 200k patients**
- **Next steps**: development of suspension-process manufacturing

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**Clinical Data From 21 Patients Across 5 Different Dose Cohorts**

- **Dose Dependent Efficacy and Favorable Safety Profile**
AXO-Lenti-PD: THE ONLY GENE THERAPY CANDIDATE FOR PD CAPABLE OF DELIVERING ALL THREE ENZYMES REQUIRED FOR DOPAMINE PRODUCTION

**AXO-Lenti-PD encodes three enzymes required for endogenous dopamine synthesis**
- Tyrosine hydroxylase (TH) and Cyclohydrolase 1 (CH1): converts tyrosine to L-dopa
- Aromatic L-amino acid decarboxylase (AADC): converts L-dopa to dopamine

Tyrosine $\xrightarrow{\text{TH}}$ Levodopa $\xrightarrow{\text{CH1}}$ Dopamine

**Utilizes a lentiviral vector with large gene packaging capacity to accommodate all three genes**

**Stereotactic delivery via one-time infusion directly into the putamen**
- Neuroimaging with MRI performed before and after procedure to ensure localization
- No intraoperative MRI required for localization
**AXO-LENTI-PD: RE-ENGINEERED VECTOR LEVERAGES PROSAVIN NONCLINICAL AND CLINICAL EXPERIENCE**

### VECTOR DESIGN

#### ProSavin

- SIN LTR
- CMVp
- TH
- AADC
- CH1
- IRES
- IRES
- SIN LTR

#### AXO-Lenti-PD

- SIN LTR
- CMVp
- TH
- CH1
- AADC
- IRES
- IRES
- SIN LTR

**ProSavin → AXO-Lenti-PD**

- CH1 moved closer to promoter to enhance expression
- TH and CH1 joined by flexible linker to ensure co-localization

### PRE-CLINICAL DATA

- 5-10x improvement in dopamine production *in vitro* with AXO-Lenti-PD
- Enhanced PK and PD observed *in vitro* and *in vivo* with AXO-Lenti-PD
- Evidence of dose-dependent efficacy and biomarker activity vs. control observed in animal models of disease (MPTP macaque monkeys)
- Long-term studies showed no evidence of carcinogenicity in multiple species

### PROSAVIN CLINICAL EFFICACY

**Mean UPDRS-III OFF Change from Baseline to 12 Months**

- **Cohort 1:** -7 points (-27%)
- **Cohort 2:** -11 points (-29%)
- **Cohort 3:** -15 points (-29%)

15 patients treated with ProSavin to inform AXO-Lenti-PD’s development plan

### PROSAVIN - PHASE 1/2 STUDY

- **Cohort 1**
  - 1.9 x 10^7 TU
  - n=3

- **Cohort 2**
  - 4.0 x 10^7 TU
  - n=6

- **Cohort 3**
  - 1.0 x 10^8 TU
  - n=6

---

**AXO-LENTI-PD CLINICAL DEVELOPMENT PLAN**

**Single-arm Dose Escalation**

- **Cohort 1**
  - $4.2 \times 10^6$ TU
  - 600 µL total infusion volume

- **Cohort 2**
  - $1.4 \times 10^7$ TU
  - 600 µL total infusion volume

- **Cohort 3**
  - $4.2 \times 10^7$ TU
  - 1800 µL total infusion volume

**Randomized, Controlled Trial**

Randomized, double-blinded clinical trial with optimal dose vs. sham surgical procedure

**Key Enrollment Criteria**

- Advanced, idiopathic Parkinson Disease
- Age: 30-70
- Hoehn & Yahr (H&Y) OFF Stage: 3-4
- UPDRS Part III (motor) OFF score: 30-60
- Levodopa equivalent daily dose (LEDD): $\geq 900$ mg
- $\geq 2.5$ hours diary OFF time (Cohort 2)
### SYSTEMATIC DATA COLLECTION EVALUATING PATIENT OUTCOMES

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety and Tolerability</td>
<td>Adverse event collection</td>
</tr>
<tr>
<td></td>
<td>Focused ongoing surveillance of gene therapy</td>
</tr>
<tr>
<td>Motor Function</td>
<td>Hauser Patient Diary</td>
</tr>
<tr>
<td></td>
<td>UPDRS Part III OFF</td>
</tr>
<tr>
<td>Activities of Daily Living</td>
<td>UPDRS Part II OFF</td>
</tr>
<tr>
<td>Effect on Current Medication Regimen</td>
<td>Levodopa Equivalent Daily Dose (LEDD)</td>
</tr>
</tbody>
</table>

**Hauser Diary** is completed by the patient at home every 30 mins over 3 consecutive days.
- OFF
- ON without troublesome dyskinesia
- ON with troublesome dyskinesia
- ON without dyskinesia
- Sleep

**UPDRS II and III evaluations**
Objective scale completed by a trained neurologist after a 12-hour Levodopa washout to evaluate patients without the effects of background medical therapy.

**LEDD:** calculated based on patient’s daily medication doses of Levodopa & other dopamine agonists.
**TOTALITY OF **AXO-LENTI-PD** DATA ACROSS COHORTS SUGGESTS CONSISTENT PATIENT BENEFIT**

<table>
<thead>
<tr>
<th>Safety and Tolerability</th>
<th>Generally well-tolerated with no serious adverse events related to therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved Motor Function</td>
<td>17-21-point mean improvement in the UPDRS Part III (motor) OFF score at 6 months</td>
</tr>
</tbody>
</table>
| Improved Dyskinesias    | • Increase in “Good” ON time” and decrease in “OFF” time  
                          • Increased ON time without dyskinesia and ON time with non-troublesome dyskinesia  
                          • Decrease in ON time with troublesome dyskinesia |
| Improved Quality of Life | • Improvement in UPDRS Part II (activities of daily living) OFF score  
                          • Decrease in LEDD |
AXO-LENTI-PD: POTENTIALLY TURNING BACK THE CLOCK FOR PATIENTS WITH PARKINSON’S DISEASE

CHANGE FROM BASELINE ON UPDRS PART III “OFF” SCORE

*UPDRS III Off score is expected to worsen by 3-4 points per year as the PD progresses; Palfi, et al. Lancet. 2014
AXO-LENTI-PD CLINICAL DEVELOPMENT PLAN: PROPOSED NEXT STEPS

**Single-arm Dose Escalation**

- **Cohort 1 (n=2)**
  - 4.2 x 10^6 TU
  - 600 µL total infusion volume

- **Cohort 2 (n=4)**
  - 1.4 x 10^7 TU
  - 600 µL total infusion volume

- **Cohort 2 (n=2)**
  - 1.4 x 10^7 TU
  - Evaluate new surgical procedure

**Randomized, Controlled Trial**

- **Cohort 3**
  - 4.2 x 10^7 TU
  - 1800 µL total infusion volume

**Dependencies**
- Completion of GMP manufactured clinical trial material
- Filing of IMPD update

Randomized, double-blinded clinical trial with optimal dose vs. sham surgical procedure
### AXO-LENTI-PD MANUFACTURING UPDATE AND NEXT STEPS

**Our goal:** Move from an adherent process to a suspension process to develop a reproducible, scalable GMP manufacturing process that can generate sufficient clinical trial material (CTM) to supply future dose-escalation and pivotal studies.

<table>
<thead>
<tr>
<th>Adherent Process</th>
<th>Process and Analytical Development</th>
<th>Suspension Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adherent material used for CTM for the initial cohorts 1&amp;2 of the dose ranging study</td>
<td>• EIAV vector had not previously been scaled up at OXB</td>
<td>• Manufacturing of 200L in GMP suite has commenced at OXB</td>
</tr>
<tr>
<td>• Transfer to a serum-free, suspension process required to enable the development of a scalable commercial supply</td>
<td>• Process and analytical development for scale from 50L to 200L</td>
<td>• QP certification of clinical trial material expected in Q4 2021 following the successful manufacturing of both drug substance and drug product</td>
</tr>
<tr>
<td></td>
<td>• Basis of the process to be tested at the 200L scale</td>
<td>• Comparability protocol in place</td>
</tr>
</tbody>
</table>

CTM = Clinical Trial Material  
OXB = Oxford Biomedica  
QP = Qualified Person
THREE CLINICAL-STAGE PROGRAMS

- Balanced pipeline leveraging both AAV and in vivo lentiviral vector systems
- Classical applications of AAV-based gene therapy in monogenic diseases and extension of gene therapy potential into more prevalent indications like Parkinson’s disease

LEADING DEVELOPMENT POSITION

- All programs have potential best-in-class and first-to-market profiles in their respective indications
- All programs are in clinical development and generating data

STRENGTHENED BALANCE SHEET

- $119 million of cash and cash equivalents as of March 31, 2021
- Cash runway extends into Q4 2022, beyond the expected dates of major upcoming milestones for the AXO-AAV-GM1 program