

# Cyclerion: Pioneering a New Era in Neuropsychiatric Therapies

Investor Call  
September 24<sup>th</sup>, 2025, 10:30am EST



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# Relaunching Cycleron:

## A new, pioneering neuropsychiatric-focused company

### Strong Company Fundamentals

- ✓ Built on opportunity for patient impact and shareholder value creation
- ✓ Driven by lean, nimble team with world-class neuropsychiatric and biopharma experience
- ✓ Plan to focus on disciplined advancement through de-risked value inflection points

### Strategic Pipeline Focus

- ✓ Tech-enhanced therapies to optimize patient benefit
- ✓ Significant neuropsychiatric market potential with patients requiring new treatment options
- ✓ Novel, improved or first-in-class therapies
- ✓ Validated modes of action with potentially rapid path to clinical Proof-of-Concept (POC)

**Clear strategic plan to advance programs through de-risked inflection points to drive shareholder value**

# Cyclerion's neuropsychiatric expertise and agility in action

Leveraging experience to efficiently drive success focused completely on therapeutic solutions



## Deep Industry Expertise with Strong Relationships

from early research to late commercialization

### Officers



**Regina Graul, PhD; CEO**  
EQRx, Ironwood,  
Cyclerion



**Rhonda Chicko; CFO**  
Scholar Rock, Editas,  
Ironwood

### Board of Directors



**Errol De Souza, PhD, Chair**  
Neurocrine,  
Royalty Pharma



**Steven Hyman, MD**  
Broad Institute of  
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NIMH\*\* Director



**Peter Hecht, PhD**  
Tisento, Cyclerion,  
Ironwood



**Michael Higgins**  
Voyager  
Therapeutics,  
Camp4, Polaris  
Partners, Ironwood



**Regina Graul, PhD**  
EQRx, Ironwood,  
Cyclerion



**Dina Katabi, PhD**  
MIT, Emerald  
Innovations,  
MacArthur Fellow

### Key Advisors



**Husseini Manji, MD, FRCPC**  
Development leader;  
Yale, Oxford, J&J,  
Director NIMH, UK  
Govt



**Linda Carpenter, MD**  
Neuropsychiatry  
leader; Brown,  
Director of  
BRaIN\*\*\*



**Laeben Lester, MD**  
Anesthesiology leader;  
Johns Hopkins



**Erika De Boever, DDS, MPH, PhD**  
Clinical Development;  
U of Michigan



**Lawrence Olanoff, MD, PhD**  
R&D; MUSC, Forest,  
Celsion



**Lisa Loram, PhD**  
Regulatory Affairs; U of  
Colorado, Boulder



**Andy Parratt**  
New Product  
Planning &  
Commercialization;  
Karuna, AlgavitaBio



**Jessica Duda**  
BD Advisor;  
Red Sky



**Michael Madden**  
Medical Device  
Development;  
Mountain Medical



\*Massachusetts Institute of Technology

\*\*National Institute of Mental Health

\*\*\* Brain Research and Interventional Neurotherapeutics (BRaIN) program at Butler Hospital

# Building a pipeline of innovative therapies focused on neuropsychiatric disorders



**Foundational Platform:** Pioneering the potentially first-in-class option for anesthetic-based therapy

- **Lead indication: potential to be an improved therapy for 3M patients with Treatment-Resistant Depression (TRD) in the US with high unmet need and few treatment options**
- Developing a proprietary, tech-enabled, personalized delivery system using biofeedback to potentially optimize treatment
- Known mode of action with three POC clinical trials supporting use of specific common anesthetics in TRD
- Leveraging the same PACU\* setting and HCPs\*\* while potentially overcoming limitations with existing treatments
- Rapid path to clinical POC: Phase 2-ready product, expect to initiate trial next year
- Key Intellectual Property (IP) secured from MIT



**Additional Indications:** Potential for expansion into other neuropsychiatric diseases



**Additional Therapies:** Core platform with optionality to add pipeline-enhancing, strategically relevant therapies



**Leveraging legacy assets:** for potential non-dilutive capital to drive pipeline development

**Akebia** THERAPEUTICS **Praliguat** – Licensed for kidney disease  
Up to \$560M in future milestones + royalties<sup>1</sup>



**Olinciguat** - Exclusive option agreement for cardiovascular diseases

**Tisento** THERAPEUTICS **10% equity ownership**

# Treatment-Resistant Depression is a **growing crisis\***

## 3 Million TRD Patients

Of the **21 Million Major Depression Disorder (MDD) Patients** in the U.S....

**1 in 7**  
are treatment-resistant

### Major clinical burden

- **2-10x** incidence of suicide or suicide attempts;
- **23%** higher all-cause mortality for TRD vs. MDD patients
- Significantly higher prevalence of psychiatric comorbid conditions

### Massive cost burden

Health care, unemployment, & the productivity burden

MDD Cost Burden

**\$40B**  
a year

**TRD**  
**\$20B**  
a year

The 14% that progress to TRD represent 50% of the \$40B yearly cost.

# The pressing need for better approved treatment options for the 3M patients that progress to TRD

## Treatments

## Electroconvulsive Therapy (ECT)

## ECT + Invasive Therapies



### Cyclerion Foundational Therapy Candidate

Potentially safe and effective treatment through personalized delivery of common anesthetics



### Spravato

Recently approved drug, but carries safety warnings, potential risk for abuse and misuse \*

### rTMS \*\*

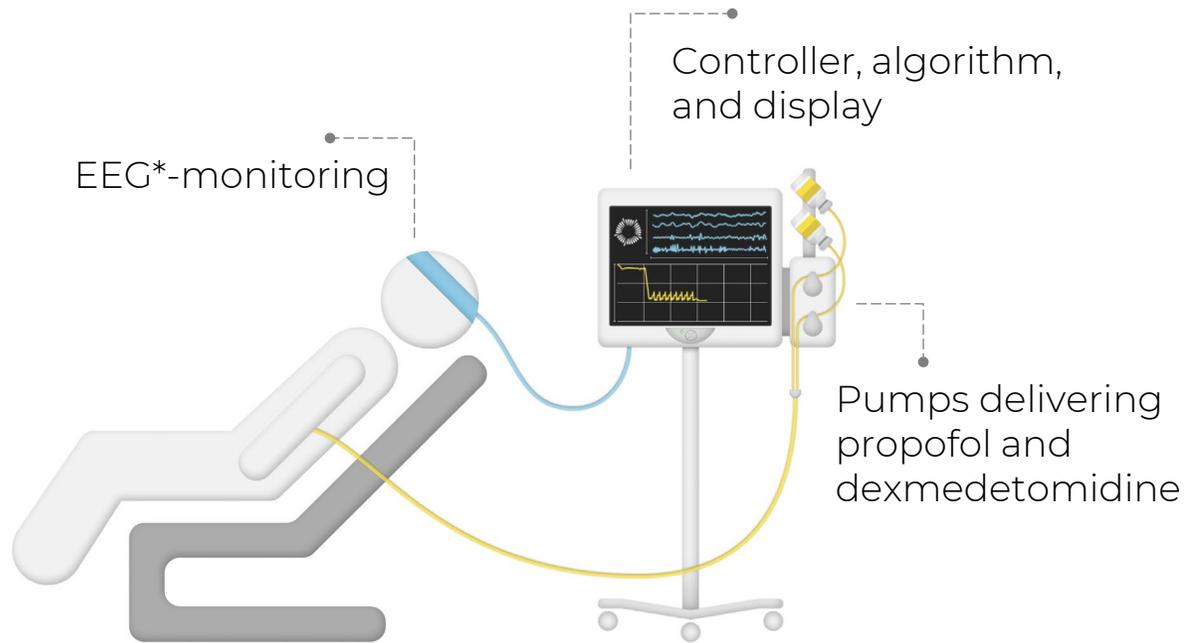
Brain stimulation devices that carry inconsistent effectiveness\*\*\*

### ECT

- Anesthetized patient receiving repeated seizure-inducing treatment at the hospital
- Acute and chronic safety concerns, including memory loss\*\*\*\*

# The Cyclерion Solution: personalized delivery of common anesthetics

Potential **First-in-class option for anesthetic-based therapy**  
to be a: **Improved therapy for TRD patients desperate for new options**



## Potential to be the preferred treatment for TRD

- Tech-driven system may provide precise control anesthetic delivery and desired EEG state
- May enable optimized and individualized patient treatment
- Opportunity to expand access to treatment options for TRD patients

**Licensing agreement with MIT secures critical intellectual property**

# Potential to be the preferred option for patients, providers, and hospitals



## Patient Preference



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Potential for a safe, efficacious, and well-tolerated treatment with a fast time back to normal activities



## Provider Preference



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Potential for lower provider burden to administer treatment; and for limited cognitive side effects, dissociative effects, and stigma



## Hospital Preference



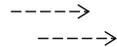
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Potential reimbursement for procedure, device, AND drugs, while still mimicking established procedural framework within PACU setting

# Proven mode of action for use of sedation for TRD

Brain regions communicate with each other via oscillatory brain waves:

## Patient with TRD



Oscillations are **not synchronized**

Communication disrupted between key regulating regions of the brain

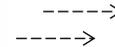
Select: TRD Symptoms: hopelessness, ruminations, negative thoughts, difficulty regulating emotions, and anxiety



## Cycleron Therapy

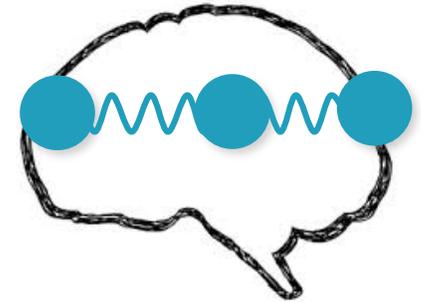


Specific states of general anesthesia could facilitate resynchronized communication between key regions of the brain\*



## Healthy Patients

**Synchronized** oscillations



Regions of the brain communicating properly

Improvement in TRD symptoms

# Compelling Clinical Precedent for such use of anesthetics for TRD

Three early-phase clinical studies support propofol's potential as a rapid-acting antidepressant in TRD

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## Propofol showed consistent signals of efficacy with favorable safety profiles

- Rapid onset of antidepressant effect seen within **1-2 weeks**
  - Durable benefit lasting 3–6 months
  - No major safety signals
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## Anesthesiologist-controlled open loop dosing was central to all propofol studies:

- Burst suppression (RCT\* + Pilot) or slow-wave sleep (SWS) optimization (SWIPED\*\*)
  - Propofol titrated using EEG metrics (e.g., suppression ratio, SWS density)
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# Compelling Clinical Data for such use of propofol for TRD

Clinical Trial > Int J Neuropsychopharmacol. 2018 Dec 1;21(12):1079-1089.  
doi: 10.1093/ijnp/ppy085.

## Propofol for Treatment-Resistant Depression: A Pilot Study

Brian J Mickey<sup>1,2,3</sup>, Andrea T White<sup>1,2</sup>, Anna M Arp<sup>1</sup>, Kolby Leonardi<sup>1</sup>, Marina M Torres<sup>1</sup>, Adam L Larson<sup>2</sup>, David H Odell<sup>1,2</sup>, Sara A Whittingham<sup>2</sup>, Michael M Beck<sup>2</sup>, Jacob E Jessop<sup>2</sup>, Derek J Sakata<sup>2</sup>, Lowry A Bushnell<sup>1</sup>, Matthew D Pierson<sup>1</sup>, Daniela Solzbacher<sup>1</sup>, E Jeremy Kendrick<sup>1</sup>, Howard R Weeks 3rd<sup>1,2</sup>, Alan R Light<sup>2</sup>, Kathleen C Light<sup>2</sup>, Scott C Tadler<sup>1,2</sup>

Affiliations + expand  
PMID: 30260415 PMCID: PMC6276046 DOI: 10.1093/ijnp/ppy085

### Population and Design

- N=10: moderate-to-severe TRD patients
- 10 propofol infusions over 3 weeks

### Results

- 60% (6/10) responders
- 50% (5/10) remitters
- 4/5 remitters sustained remission  $\geq 3$  months; 3 of which continued to  $\sim 5$  months, 2 of which continued to  $> 6$  months

### Additional Details

- Efficacy  $\sim 2$  days after final infusion; HRDS assessments up to 6 months
- Responder =  $\geq 50\%$  reduction from baseline on MADRS
- Remitter = Final HDRS  $\leq 10$

> medRxiv [Preprint]. 2023 Sep 15:2023.09.12.23294678. doi: 10.1101/2023.09.12.23294678.

## Propofol for treatment resistant depression: A randomized controlled trial

Scott C Tadler, Keith G Jones, Carter Lybbert, Jason C Huang, Rana Jawish, Daniela Solzbacher, E Jeremy Kendrick, Matthew D Pierson, Kamile Weischedel, Noreen Rana, Rebecca Jacobs, Lily C Vonesh, Daniel A Feldman, Claire Larson, Nathan Hoffman, Jacob E Jessop, Adam L Larson, Norman E Taylor, David H Odell, Kai Kuck, Brian J Mickey

PMID: 37745479 PMCID: PMC10516089 DOI: 10.1101/2023.09.12.23294678

- N=24: moderate-to-severe TRD patients
  - N=12: high dose to suppress EEG activity
  - N=12: low dose to avoid BS
  - N=8: crossed over from low dose to high dose
- 6 propofol infusions (3x/week for 2 weeks)

### High Dose

- 50% (6/12) responders; 42% (5/12) remitters

### Low Dose

- 8% (1/12) responders; 8% (1/12) remitters

### Crossed Over Low Dose to High Dose

- 50% (4/8) responders; 42% (3/8) remitters

- Efficacy  $\sim 1$  week after final infusion; HRDS assessments up to 2 weeks
- Responder =  $\geq 50\%$  reduction from baseline on MADRS
- Remitter = Final HDRS  $\leq 10$

## Propofol dosing and enhancement of slow wave sleep predict antidepressant response in geriatric patients with treatment-resistant depression [Poster presentation].

Palanca, B. J. A., Ching, S., Farber, N. B., Lin, N., Lucey, B. P., Reynolds, C. F., Lenze, E. J., & SWIPED Study Team. (2025).

Gordon Research Conference on Depression, Ventura, CA.

- N=15 geriatric ( $\geq 60$ ) TRD patients
- 2  $\times$  2-hour infusions, 2–6 days apart
- Manually dosed to avoid burst suppression  $\sim 2$  hr infusion

- 67% (10/15) responders
- Dose-dependent percentage change in baseline MADRS at 3 weeks: correlates inversely with average propofol dose administered

- Responder =  $\geq 30\%$  reduction from baseline MADRS/ $> 6$  change in MADRS at any point

# Expect to initiate **Proof-of-Concept study in 2026**

To confirm existing clinical precedent with Cycleron therapy

## Expected Phase 2 RCT, Two Part, POC Study Design



### Design

#### PART A: **Safety and Pharmacodynamics (PD)**

RCT, double-blind  
3 arms: GA1\*, GA2\*\*, Sham

#### PART B: **Safety & Efficacy**

RCT, double-blind  
3 arms: GA1, GA2, Sham



### # of Participants

9 total  
Treatment arms N=6 (1:1)  
Sham N=3

50 total  
Treatment arms N=40 (1:1)  
Sham N=10

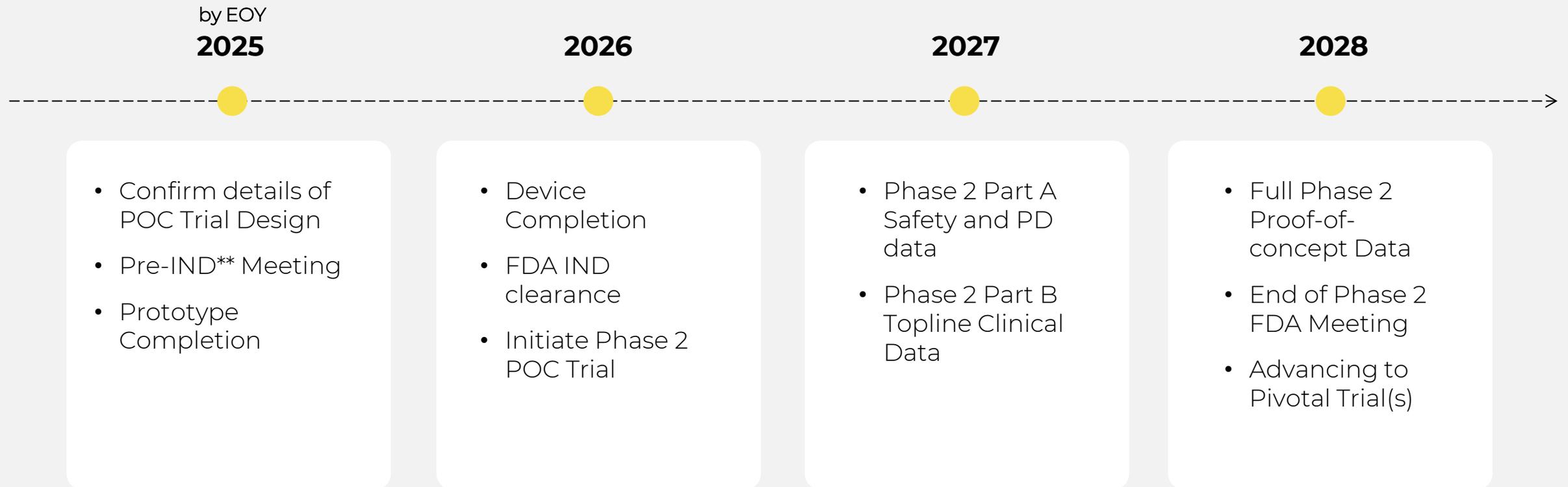


### Length

Treatment: 3x / week for 3 weeks  
Follow up: months 1-6

Treatment: 3x / week for 3 weeks  
Follow up: months 1-6

# Expected Milestones



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- Pipeline Expansion Opportunities
  - Potential non-dilutive capital from historical portfolio
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# Thank You

September 2025

