

Cyclerion: Pioneering a New Era in Neuropsychiatric Therapies

January 2026



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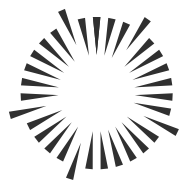
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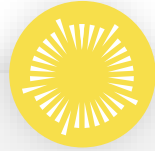
Cyclerion Therapeutics:

A Pioneering Neuropsychiatric-focused Company



- ✓ A foundational platform for anesthetic-based therapeutic innovation in neuropsychiatry
- ✓ First asset, CYC-126, a potentially first-in-class, anesthetic-based, drug-device, closed-loop therapy for Treatment Resistant Depression (TRD)
- ✓ Potentially de-risked mode of action with clinical precedent in TRD
- ✓ Potentially capital efficient path to generating clinical Proof-of-Concept (POC) data
- ✓ Expect to initiate Phase 2 POC study in 2H 2026; initial data in 2027, full POC data in 2028
- ✓ Experienced team, advisors, and Board of Directors with strong execution track record

Cyclerion's Neuropsychiatric Expertise and Agility in Action



Key Management and Clinical Advisors



Regina Graul, PhD; Chief Executive Officer

- Experienced biopharma executive with significant clinical-stage expertise



Rhonda Chicko; Chief Financial Officer

- Experienced public company CFO



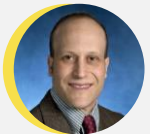
Husseini Manji, MD, FRCPC; Neuroscience and Neuropsychiatry

- Globally recognized leader in neuroscience and mental health innovation



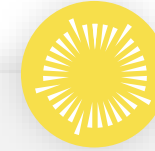
Linda Carpenter, MD; Clinical Advisor, Neuropsychiatry

- Leader in Neuropsychiatry



Laeben Lester, MD; Clinical Advisor, Anesthesiology

- Anesthesiology Leader



Board of Directors



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Regina Graul, PhD

EQRx, Ironwood,
Cyclerion



Dina Katabi, PhD

MIT, Emerald
Innovations,
MacArthur Fellow

Building a Pipeline of Innovative Therapies **Focused on Neuropsychiatric Disorders**

Our Pipeline



Foundational Product: CYC-126 for TRD

- Potentially first-in-class, anesthetic-based, drug-device, closed-loop therapy; using propofol & dexmedetomidine



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

- Potential non-dilutive capital to drive pipeline development¹

Significant Recent Progress for CYC-126

- ✓ **Unmet need:** a new treatment layer for the 3M TRD patients in the US² desperate for new treatment options
- ✓ **Intellectual Property:** license agreement with MIT³ and collaboration with Medsteer to incorporate key aspects into CYC-126
- ✓ **Clinical:** Phase 2 POC Trial design finalized; on track to initiate in 2H 2026
- ✓ **Regulatory:** ongoing engagement with US FDA⁴ and AUS TGA⁵ indicates multinational path to Phase 2 POC
- ✓ **Product Development:** Continue to be on track to complete full device build prior to POC study start

CYC-126: Potential to be the First Individualized Treatment for TRD

WHAT



Generic IV¹ anesthetics (propofol + dexmedetomidine) with extensive clinical safety experience, and a **personalized delivery system** operating as a co-pilot to anesthesiologist

HOW



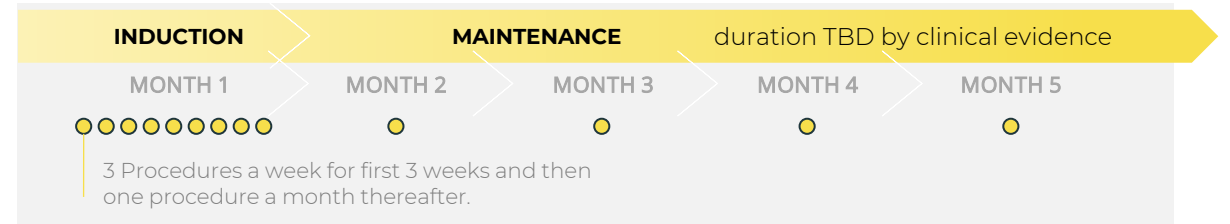
We believe sedation could **recalibrate brain region communications** that are dysregulated in patients with TRD

Two stages of treatment: Induction and maintenance, treatment duration estimated to be 2-3 hours

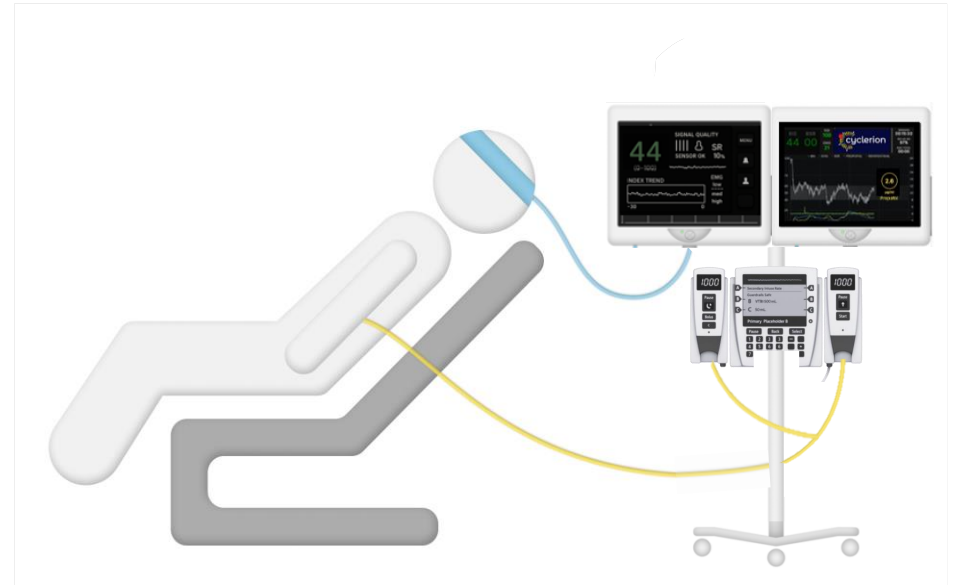
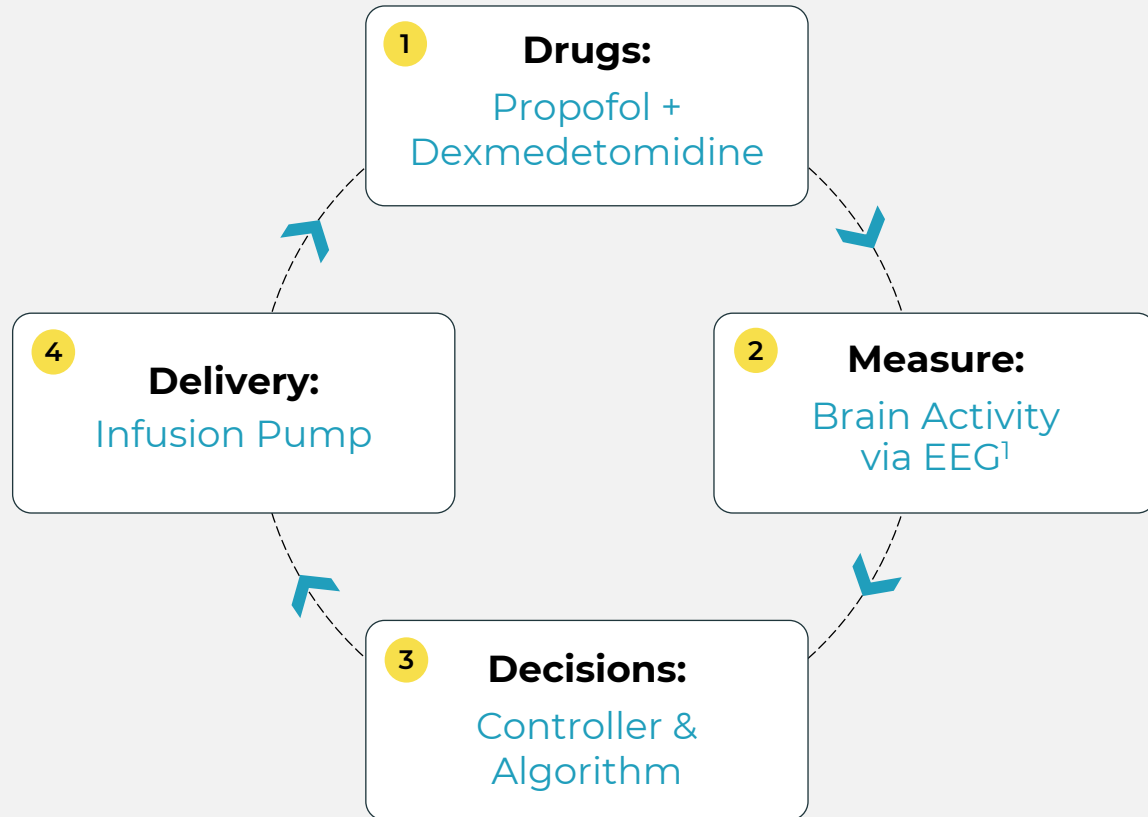
WHY



A clear unmet need with **<10% of the 3M TRD patients currently being treated** with approved therapies
We believe CYC-126 could provide **a new therapeutic layer** that **could address all TRD patients**



CYC-126: A Potentially Novel Closed-Loop Treatment for TRD



- A potential closed-loop, EEG¹-guided, tech-enabled system
- Designed to personalize and reproducibly induce specific sedation states
 - Slow-Wave Activity (SWA)
 - Burst Suppression (BS)

CYC-126: Key Components



Computational Control Module

Proprietary sedation-control software and TRD-specific protocol



Leverages previously announced Medsteer collaboration

EEG Monitor

Leveraging FDA-cleared components

Minimizes hardware & regulatory risk while staying capital efficient

Infusion Pump

Use of common, generic anesthetics



Leverages previously disclosed MIT license

Drug

Continue to be on track to complete full device build prior to POC study start in 2H 2026

Treatment-Resistant Depression is a Growing Crisis¹

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% of patients that progress to TRD represent 50% of the \$40B yearly cost associated with MDD.

¹Mental Health America/SAMHSA; Clin Psychiatry. 2021 Mar 16;82(2):20m13699
www.psychiatrytimes.com/view/managing-suicidal-thoughts-behaviors-and-risk-in-treatment-resistant-depression
www.jamanetwork.com/journals/jamapsychiatry/fullarticle/2799488
www.psychiatrist.com/jcp/prevalence-national-burden-treatment-resistant-depression-major-depressive-disorder-in-us/

The Pressing Need for Better Approved Treatment Options for the 3M+ U.S. Patients that Progress to TRD

3M TRD Patients that Progress through Therapy

Cyclerion Product: Potentially Applicable to All TRD Patients

Potentially safe and effective treatment through personalized delivery of common anesthetics

Spravato¹:
35K Patients in 2024

Recently approved drug, but carries safety warnings, potential risk for abuse and misuse²

rTMS³:
44K Patients in 2023

Brain stimulation devices that carry inconsistent effectiveness⁴

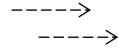
ECT⁵: 100K Patients in 2024

- Anesthetized patient receiving repeated seizure-inducing treatment at the hospital
- Acute and chronic safety concerns, including memory loss⁶

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

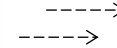
Select TRD symptoms: hopelessness, ruminations, negative thoughts, difficulty regulating emotions, and anxiety



CYC-126

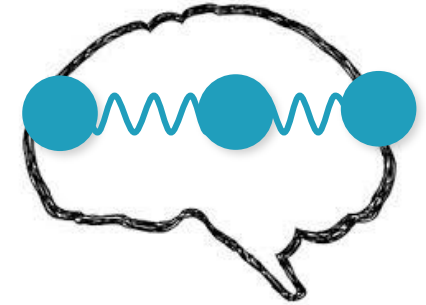


Specific states of general anesthesia could facilitate resynchronized communication between key regions of the brain¹



Healthy Patients

Synchronized oscillations



Regions of the brain communicating properly

Improvement in TRD symptoms

Clinical Precedent for Use of Propofol in TRD

Three early-phase clinical studies¹ support propofol's potential as a rapid-acting antidepressant in TRD

Propofol showed consistent signals of efficacy with favorable safety profiles¹

- **Rapid onset** of antidepressant effect seen within **1-2 weeks**
- **Durable benefit lasting 3–6 months**
- No major safety signals
- Achieving specific EEG state is critical for clinical efficacy

Difficult to achieve and maintain specific EEG state (BS or SWA) with Anesthesiologist-controlled dosing



CYC-126 is intended to provide proprietary, tech-enabled, closed-loop delivery of anesthetics to precisely achieve and maintain specific EEG state

Expect to Initiate Multi-national POC Study in 2026

To confirm existing clinical precedent with CYC-126

Expected Phase 2 RCT¹, Two Part, POC Study Design

Design

PART A: Safety and Pharmacodynamics (PD)

RCT, double-blind
3 arms: GA1², GA2³, Sham
N=9

PART B: Safety & Efficacy

RCT, double-blind
3 arms: GA1², GA2³, Sham
N=60

Representative Endpoints

- Induction and maintenance of SWA and BS, safety, sedation depth, total dose, change in depressive symptoms as measured by MADRS score and PRO⁴, ability of Sham treatment to mimic sedative nature

- Safety, change in depressive symptoms as measured by MADRS⁵, durability of effect as measured by MADRS and PRO⁶, cognitive ability, ability of Sham treatment to mimic sedative nature

Objectives

- Confirm ability to induce and maintain target EEG states
- Characterize safety and tolerability
- Explore clinical antidepressant effect

- Demonstrate clinical antidepressant effect
- Confirm safety and tolerability
- Select EEG signature for use in confirmatory RCTs

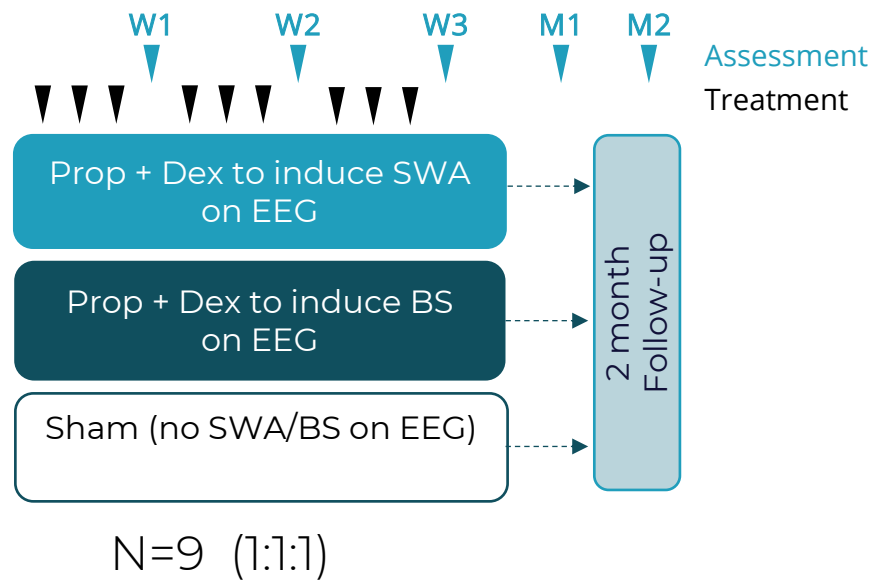
Proof-of-Concept Study Design: Expect Initial POC Data in 2027

Expected Phase 2 RCT, Two Part, POC Study Design

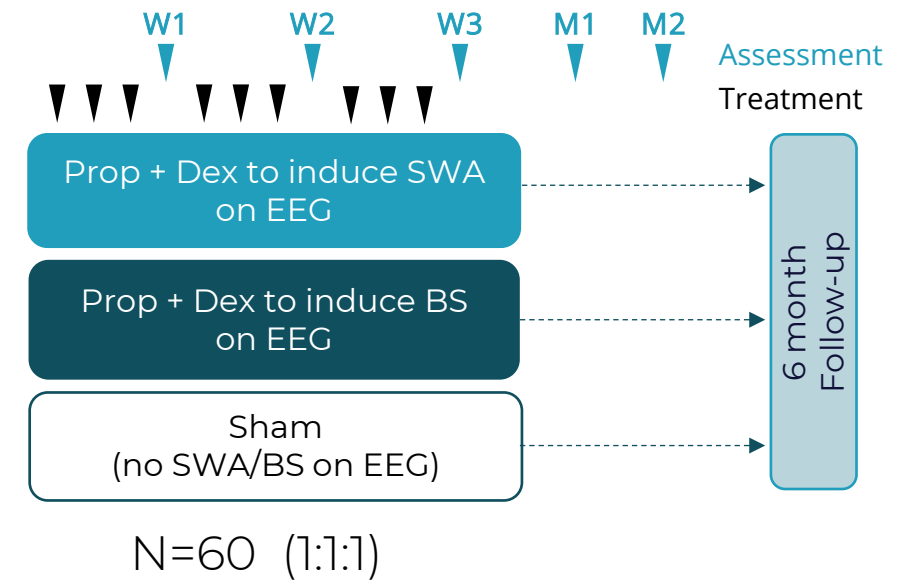
Patient Population Key Criteria

- 18-65 yrs
- TRD; Failed 2+ ADM/D¹
- MADRS total score ≥ 28 at both baseline and screening
- No active suicidal ideation
- No contraindication to anesthesia
- No diagnosed bipolar or schizophrenia
- ASA Class I-III²

PART A: Safety and PD

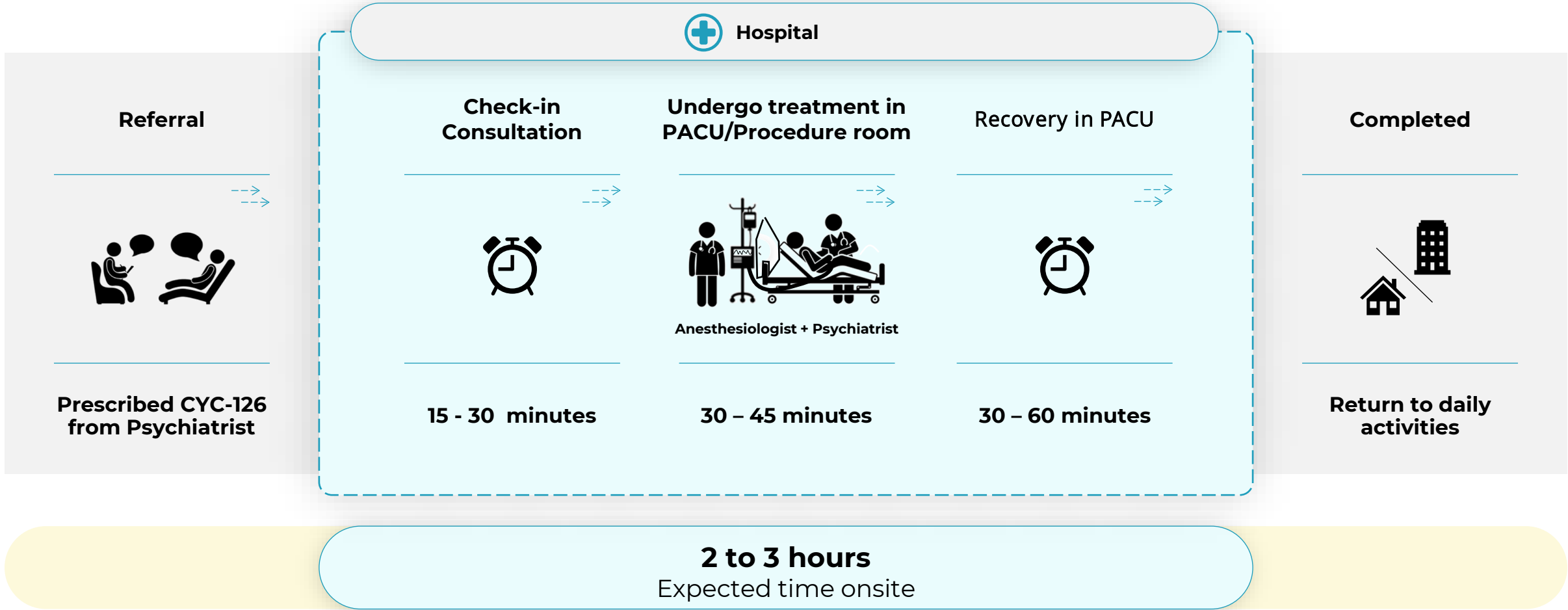


PART B: Safety & Efficacy



Potential Efficiency of Workflow for Patients, Providers, and Facilities

Opportunity for physicians and centers to provide effective & safe care, at scale, to people living with TRD



Potential to be the Preferred Option for Patients, Providers, and Hospitals



Patient Preference



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



Provider Preference



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

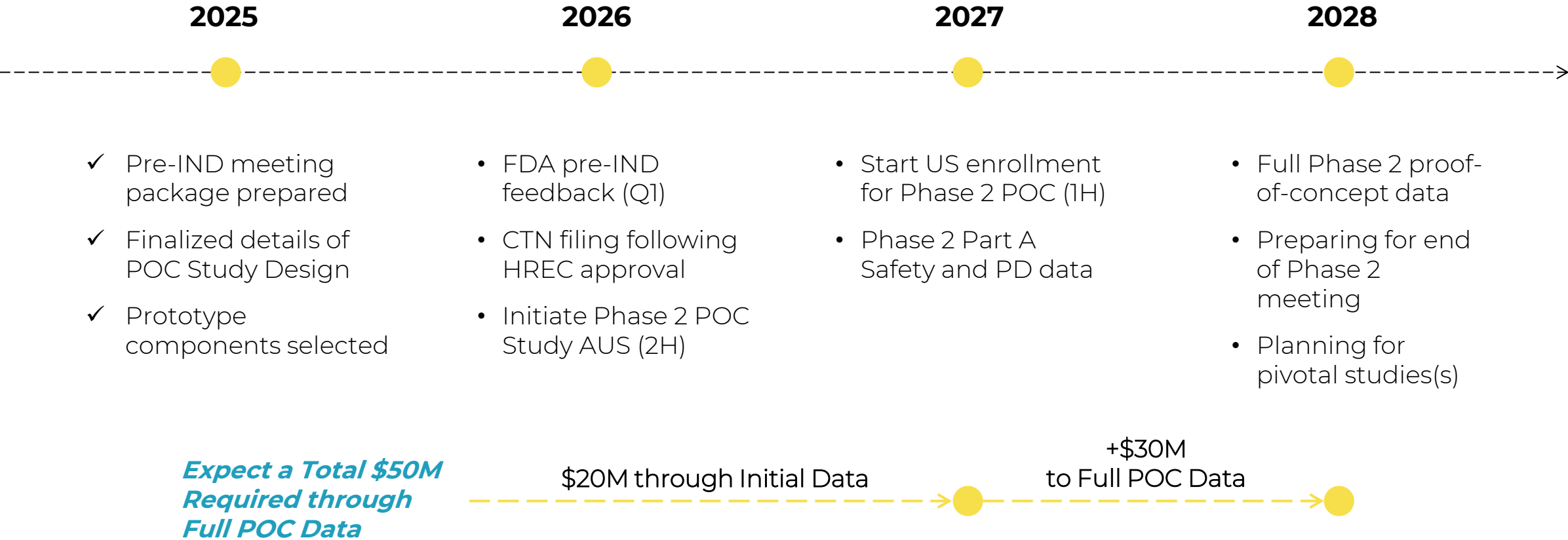


Hospital Preference



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

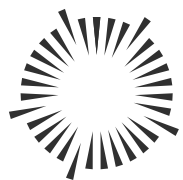
Expected Milestones and Capital Requirements



- Pipeline expansion opportunities
- Potential non-dilutive capital from historical portfolio

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Appendix

We believe recent collaborations enable faster, lower-risk development of our closed-loop system with common anesthetics



Closed-loop delivery

Has significant expertise in closed-loop anesthesia delivery

- Using EEG signal inputs & proprietary algorithms to administer a precise rate of drug to achieve a specific sedation state
- Backed by 25 clinical trials, more than 9,000 patients and broad research use in the hospital setting, deep translational expertise

Strategic Collaboration Framework

- Development Agreement: Integrate Medsteer's proprietary technology and know-how into CYC-126
- Option to License (exclusive, worldwide): Patent rights, know-how, and software to enable CYC-126 and beyond

Strategic Collaboration Framework

- Cyclerion's field extends within and beyond neuropsychiatric diseases such as TRD; and includes all uses other than major surgery, general or multi-bed intensive care units, and medical transport



*Foundational
Method-of-Use IP*

Combinations of Anesthetics for TRD

- Covers single-agent and combination use

PCT filed Oct 15, 2025; patent life expected to 2045



Regulatory strategy: Multinational path to Phase 2 POC

Single Australia (AUS) and United States (US) study for Cycleron drug-device combination product



AUS TGA¹: enables early FPI²

- TGA CTN³ anticipated, ethics (HREC⁴) lead review
- Enable FPI with commercially sourced drugs
- Expect submission and FPI in 2026



US FDA⁵: ongoing engagement

- Initial feedback from FDA received
- Regulated as Drug-led drug-device combination product
- Pre-IND⁶ feedback in Q1 2026

Compelling Clinical Data for use of propofol for TRD

Clinical Trial > Int J Neuropsychopharmacol. 2018 Dec 1;21(12):1079-1089.
doi: 10.1093/ijnp/pyy085.

Propofol for Treatment-Resistant Depression: A Pilot Study

Brian J Mickey^{1,2,3}, Andrea T White^{1,2}, Anna M Arp¹, Kolby Leonardi¹, Marina M Torres¹, Adam L Larson², David H Odell^{1,2}, Sara A Whittingham², Michael M Beck², Jacob E Jessop², Derek J Sakata², Lowry A Bushnell¹, Matthew D Pierson¹, Daniela Solzbacher¹, E Jeremy Kendrick¹, Howard R Weeks 3rd^{1,2}, Alan R Light², Kathleen C Light², Scott C Tadler^{1,2}

Affiliations + expand
PMID: 30260415 PMCID: PMC6276046 DOI: 10.1093/ijnp/pyy085

Population and Design

- N=10: moderate-to-severe TRD patients
- Dosed to suppress EEG activity
10 propofol infusions over 3 weeks

Results

- 60% (6/10) responders
- 50% (5/10) remitters
- 5/6 responders sustained remission to at least 5 months

Additional Details

- Efficacy ~2 days after final infusion; HRDS assessments up to 6 months
- Responder = ≥50% improvement HRDS
- Remitter = Final HRDS ≤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, Kamille 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=7: low dose non-responders crossed over to receive open label high dose
6 propofol infusions (3x/week for 2 weeks)

High Dose

- 25% (3/12) responders; 17% (2/12) remitters
- HDRS-24 decreased 9.3 pts (33%) in high-dose vs 5.3 pts (17%) in low-dose

Low Dose

- 17% (2/12) responders; 8% (1/12) remitters

Crossed Over Low Dose to High Dose

- Mean change in HDRS-24 score from Wk 2 to Wk 4 was -12.5 points [-19.2, -5.8], or 49% improvement

- Efficacy ~1 week after final infusion; HRDS assessments up to 2 weeks
- Responder = ≥50% improvement HRDS
- Remitter = Final HRDS ≤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 (≥ 60 yr) TRD patients
- Manually dosed to avoid burst suppression
2 × 2-hour infusions, 2–6 days apart

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

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