Cyclerion: Pioneering a New Era in Neuropsychiatric Therapies

Investor Call: January 6th, 2026

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Today's Agenda

1. **Cyclerion and CYC-126 Overview**

2. **CYC-126 in Treatment Resistant Depression (TRD): Unmet Need and Planned Phase 2 Proof-of-Concept (POC) Study**

3. **Provide Updates on Path Toward Initiating CYC-126's Phase 2 Proof-of-Concept Study in 2026**
   - Product development including the recently announced Medsteer collaboration
   - Regulatory
   - Financial

4. **Timelines and Milestones**

Cyclerion and CYC-126 Overview

Cyclerion: a new, pioneering neuropsychiatric-focused company

Platform	• **Lean, nimble team** with **world-class neuropsychiatric, anesthesia, intelligent medical systems and biopharma experience** • Potential **first-in-class platform** for tech-enhanced therapeutics aiming to optimize patient benefit
CYC-126: Initial Therapy	• Potential **first anesthetic-based therapy** in a **patient feedback loop** for **neuropsychiatric indications** • **Differentiated** treatment for **3M+ patients with TRD desperate for new options** • **Known Mode of Action** and **compelling clinical precedent** could help **de-risk** therapeutic use of **propofol for TRD** • Fits **within existing treatment paradigm**, with the **opportunity to be the preferred treatment** for patients, physicians, and hospitals
Milestones	• **Today's announcement**: Medsteer collaboration provides agreement to incorporate key aspects of closed-loop anesthetic delivery for clinical applications within and well beyond neuropsychiatric diseases, such as TRD • **Capital-efficient path** to **initiate POC study in 2H 2026 with initial POC data expected in 2027**, and full POC data expected in 2028

CYC-126: Potential to be the first individualized treatment for TRD

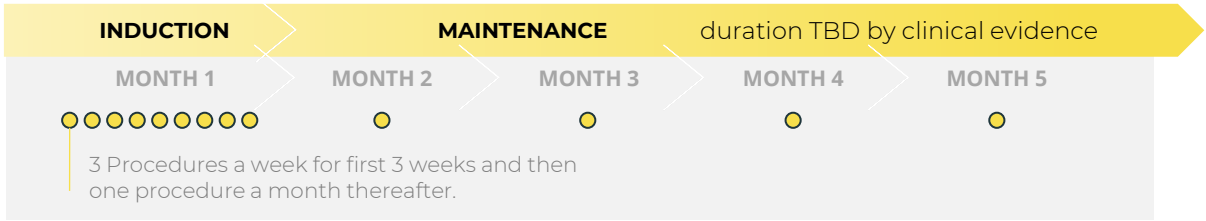
WHAT

Generic IV[1] 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.

Potentially 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**

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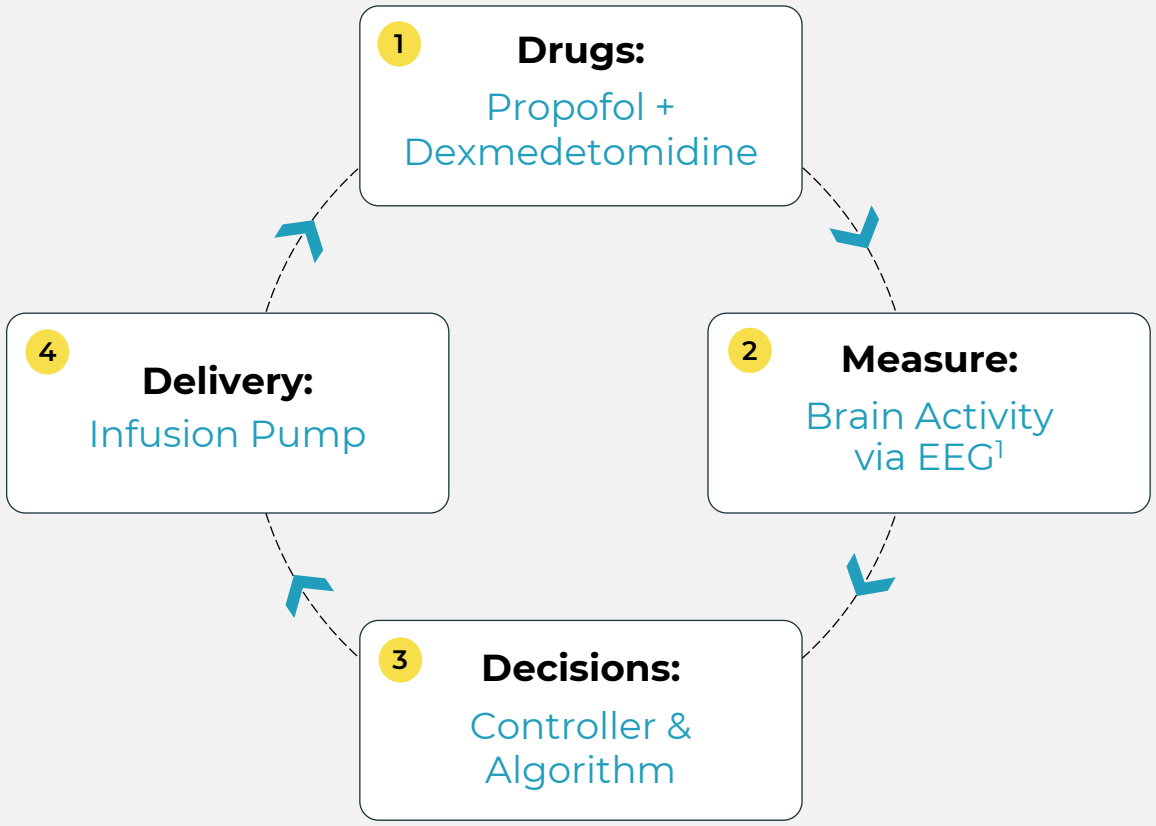
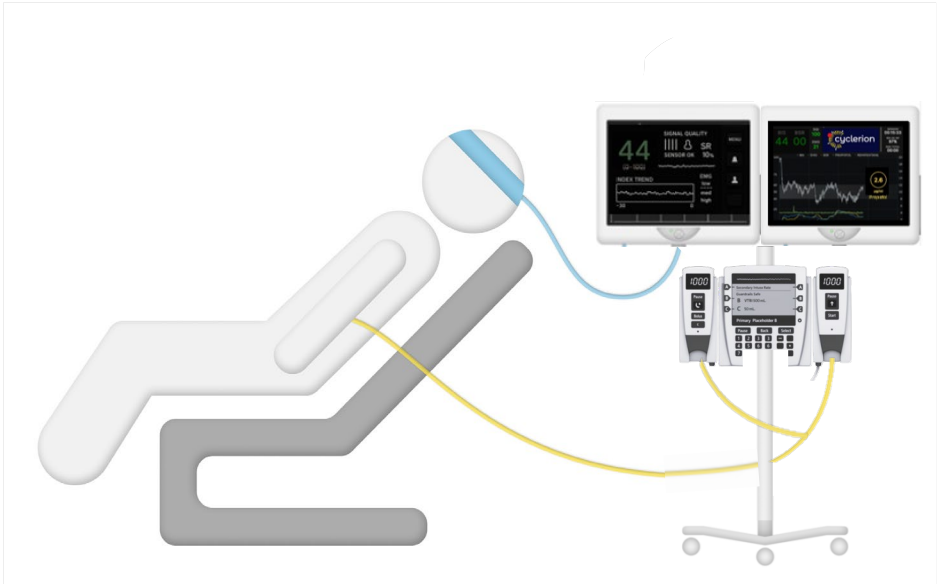
CYC-126: A potentially novel closed-loop treatment for TRD





- A potential closed-loop, EEG[1]-guided, tech-enabled system
- Designed to personalize and reproducibly induce specific sedation states
  - Slow-Wave Activity (SWA)
  - Burst Suppression (BS)

[1]Electroencephalogram

CYC-126 in Treatment Resistant Depression: Unmet Need and Phase 2 Proof-of-Concept Study

Burden of the disease: Unmet need to be addressed by novel therapeutics

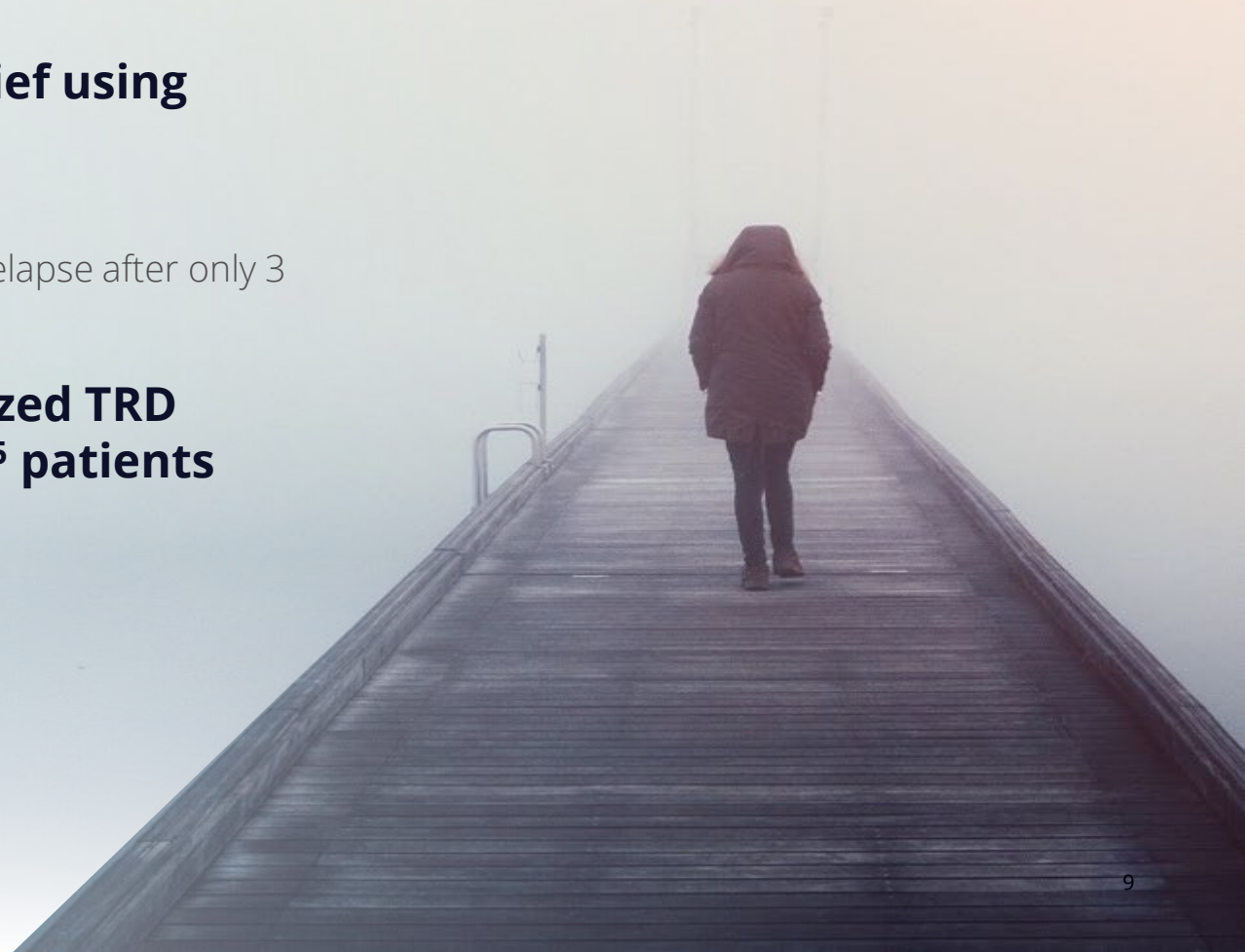
Major depression: #1 cause of disability worldwide[1]

~1 in 3 patients do not achieve adequate relief using current treatments[2]

- ~3+ million US adults with treatment-resistant depression[3]
- Of TRD patients who respond to a current treatment, ~1/2 relapse after only 3 months of maintenance treatment

7x Suicide rate is 7-fold higher among hospitalized TRD patients than in treatment responsive MDD[5] patients

- Current treatments require 3-6 weeks to become effective – too slow to aid acutely suicidal patients[4]



[1]World Health Organization, "Global Burden of Mental Disorders". [2]Cleveland Clinic Journal of Medicine. Volume 75 • Number 1 January 2008. [3]IMS and Truven Health. [4]National Center for Injury Prevention and Control CDC, 2014. [5]Major Depressive Disorder

Depression is linked to a number of co-morbidities and increased risk of other mental and physical illnesses

Depressed patients also have:

2-4x increased risk of **premature death**[1]

60% increased risk of **diabetes**[2]

30-40% of under 20s diagnosed with depression develop **neurotic disorders** within 5 years[3]

10% increase in the risk of **schizophrenia** and **substance use**[3]

2x risk of **heart attack or stroke**[2]

Patients with chronic heart failure and depression have **double the treatment costs**[2] of those without depression and are **8x more likely to die**[4]

29% increased risk of cancer[5]

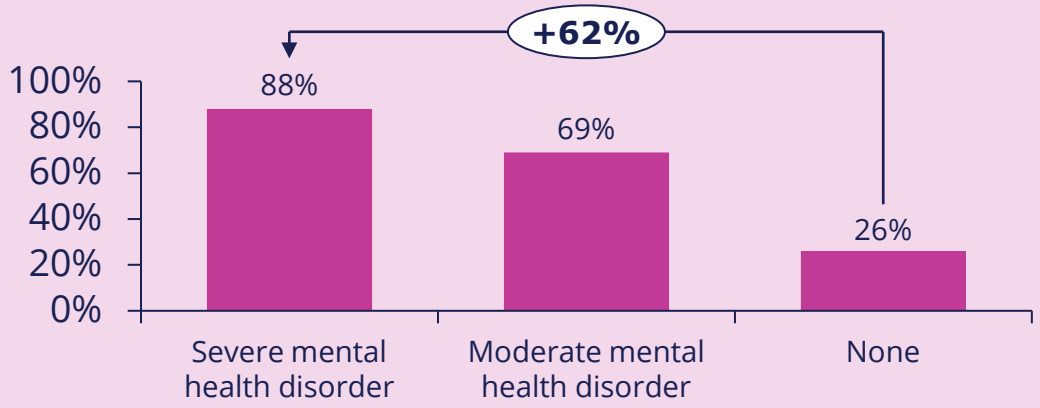
Cancer patients who are depressed have **longer hospitalization, poorer quality of life** and **34% higher death rate**[2,5]

Due to the complex nature of interactions between physical and mental disorders, it is difficult to demonstrate causality in co-morbid diseases; the sources used here and intended to demonstrate an association between depression and each co-morbid disease, please cite as such.

Sources: [1]Naylor, King's Fund Research, 2012, [2]WHO, 2017b, [3]Plana-Ripoll, Jama Psychiatry, 2019, [4]Junger, Eur J Heart Fail, 2005, [5]Chida, Nat Clin Pract Oncol, 2008

Mental health disorders have a significant impact on patient ability to work, leading to increased work absence and disability payments

Severe mental health disorders cause reduced work productivity[1]



Those with a severe mental health disorder have a **6-7 times increased risk of unemployment**[2]

37% of disability benefits in certain European[4] countries are related to mental health disorders, amounting to **€112 billion** in 2015[3]

Annual spend on disability benefits
(Europe[5], 2015[3])

Sources: [1]OECD, 2015, [2]OECD, 2014, [3]OECD Health at a Glance: Europe 2018
[4]Average based on data from Austria, Belgium, Denmark, Netherlands, Sweden and the UK; [5]average based on data from 21 European countries included in the 2010 Eurobarometer

The pressing need for better approved treatment options for the 3+M 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

Spravato[1]: 35K Patients in 2024

Recently approved drug, but carries safety warnings, potential risk for abuse and misuse[2]

rTMS[3]: 44K Patients in 2023

Brain stimulation devices that carry inconsistent effectiveness[4]

ECT[5]: 100K Patients in 2024

- Anesthetized patient receiving repeated seizure-inducing treatment at the hospital
- Acute and chronic safety concerns, including memory loss[6]

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[1]Evaluate Pharma | [2]See Spravato prescribing information for full boxed warning | [3]Repetitive Transcranial Magnetic Stimulation, Neurotech Features | [4]DOI: 10.1002/14651858.CD003493
[5]Johns Hopkins University School of Medicine | [6]DOI: 10.1192/bjo.2020.17

Clinical precedent for use of propofol in TRD

Three early-phase clinical studies[1] support propofol's potential as a rapid-acting antidepressant in TRD

Propofol showed consistent signals of efficacy with favorable safety profiles[1]

- **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 closed-loop dosing

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

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[1]DOI: 10.1136/bmjopen-2024-087516; DOI: 10.1093/ijnp/pyy085; DOI: 10.1101/2023.09.12.23294678

Expect to initiate multi-national POC study in 2026

To confirm existing clinical precedent with CYC-126

Expected Phase 2 RCT[1], Two Part, POC Study Design	PART A: **Safety and Pharmacodynamics (PD)**	PART B: **Safety & Efficacy**
Design	RCT, double-blind 3 arms: GA1[2], GA2[3], Sham N=9	RCT, double-blind 3 arms: GA1[2], GA2[3], 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 PRO[4], ability of Sham treatment to mimic sedative nature	• Safety, change in depressive symptoms as measured by MADRS[5], durability of effect as measured by MADRS and PRO[6], 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

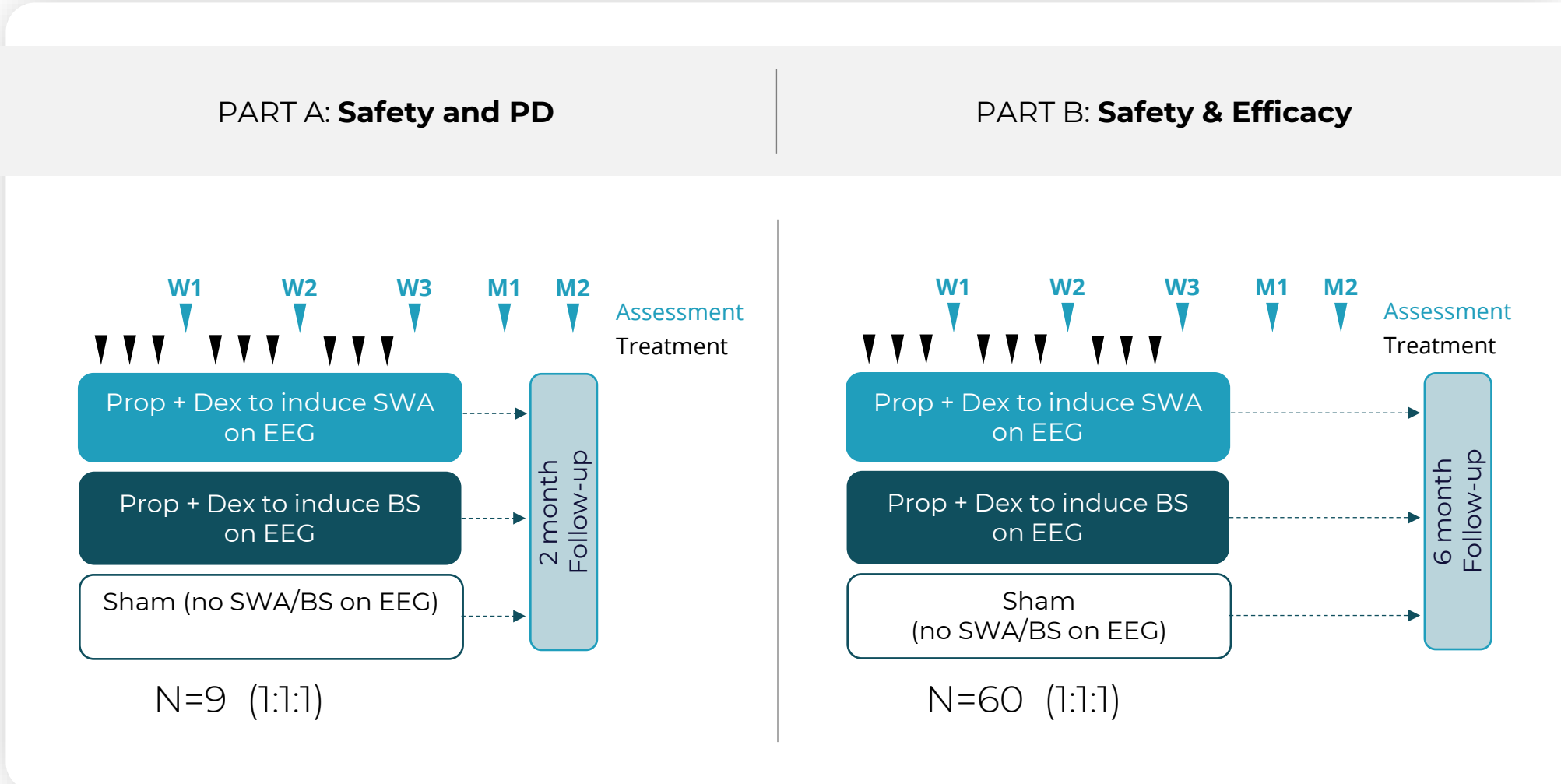
[1]Randomized Controlled Trial | [2]GA1=General Anesthesia State 1 | [3]GA2=General Anesthesia State 2 | [4]MADRS=Montgomery–Åsberg Depression Rating Scale and Patient Reported Outcomes assessed monthly through 2M | [5]Change from baseline in MADRS at Day 29; Response is defined as ≥50% reduction in MADRS total score from baseline to Day 29. Remission is defined as a MADRS total score ≤ 12 on Day 29 | [6]Assessed monthly through 6M by MADRS score and PRO

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/D[1]
- 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-III[2]

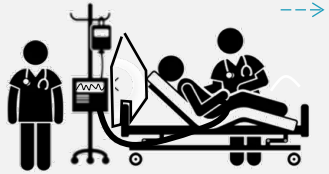


[1]ADM/D = antidepressant medication or device-based treatment [2]American Society of Anesthesiologists Physical Status Scale

Potential efficiency of workflow for patients, providers, and facilities

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

Hospital

Referral	Check-in Consultation	Undergo treatment in PACU[1]/Procedure room	Recovery in PACU	Completed
		 Anesthesiologist + Psychiatrist		
Prescribed CYC-126 from Psychiatrist	**15 - 30 minutes**	**30 – 45 minutes**	**30 – 60 minutes**	**Return to daily activities**

Expected time onsite = 2-3 hours

[1]Post-Anesthesia Care Unit

Working toward a new efficacious Rx being implemented to support an optimal patient and clinical experience

THE JOURNEY

SEEKING BETTER TREATMENT	SCREENING & PLANNING	SITE ADMINISTRATION	ADMINISTRATION	RELEASE & REPEAT	MAINTENANCE
Searching	Initial Consultation	Prior Authorization	Patient Education & Self-Administration	Patient Release / Planning for Next Visit	Self-Administration & HCP Observation
Patient Doctor Discussion	Benefits Investigation & Induction Scheduling	Rx & Product Ordering	HCP Observation	Caregiver / Rideshare Transport Home	Caregiver / Rideshare Transport Home

Early experience is critical; the frequency of sessions accelerates adoption

Supporting fewer sites of care at launch with live and digital support, then move into maintenance

Psychiatrists will need significant clinical & operational support for reimbursement, REMS[1], Ops

Invest in contract fulfillment roles at launch to educate and support reimbursement

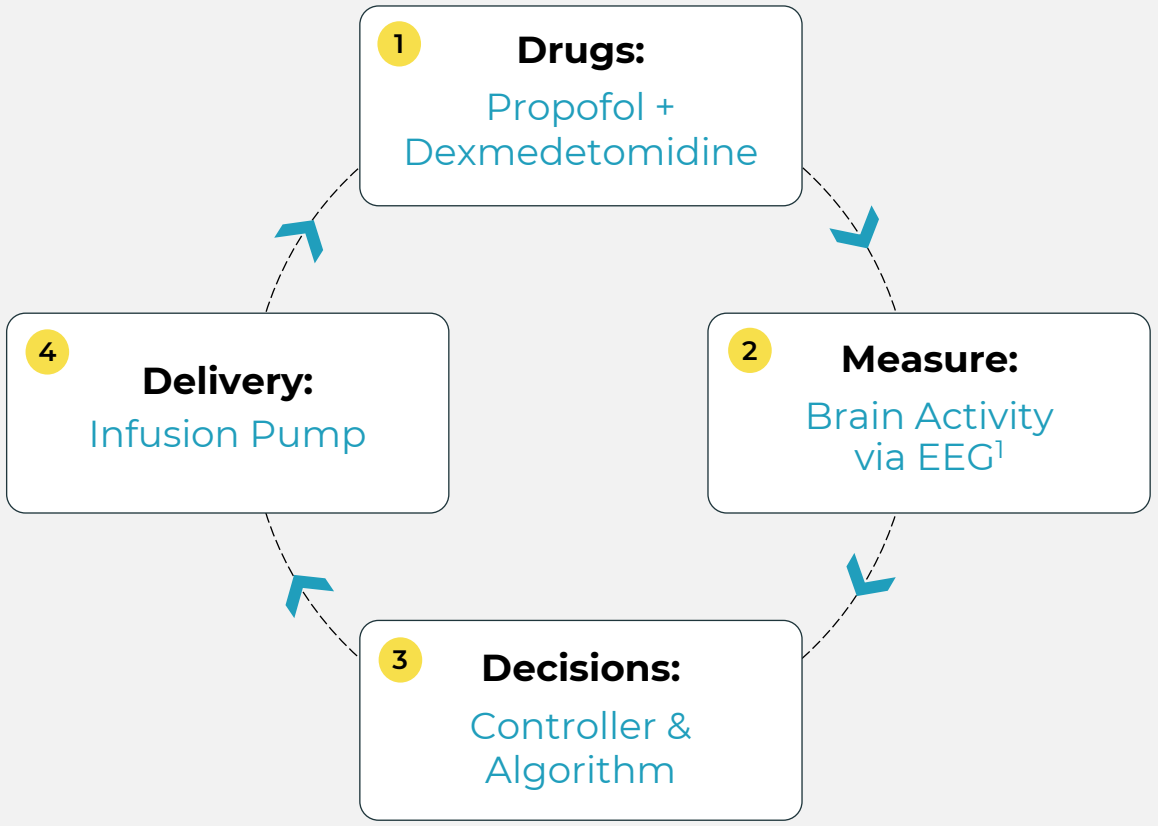
The majority of psychiatrists are unable / unwilling to become sites of care, so they prefer to refer their patients to suitable site

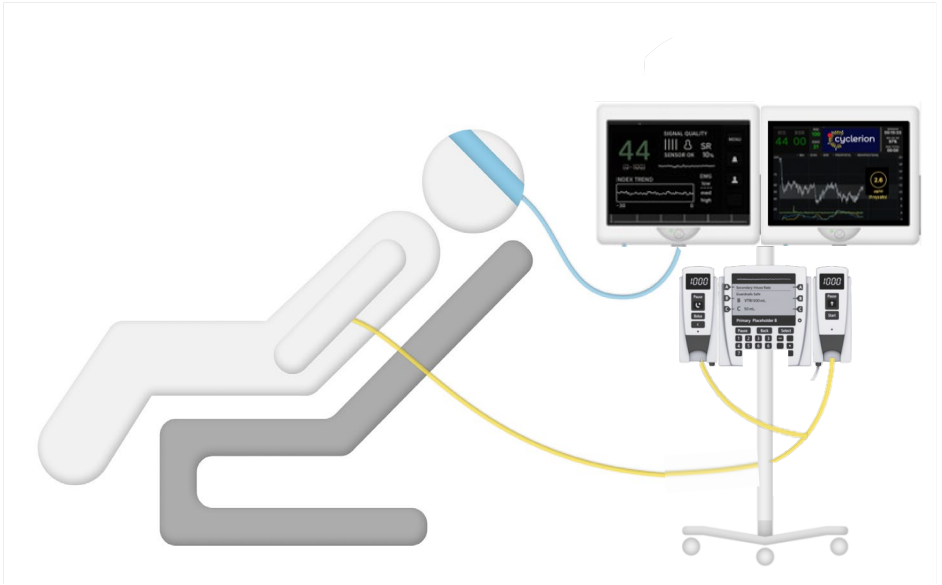
Leveraged a site of care locator and also support the onboarding of sites that want to treat

[1]Risk, Evaluation, Mitigation Strategies

Product Development Update

CYC-126: A potentially novel closed-loop treatment for TRD





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CYC-126: Progress with integrating key components

Key Components

Computational Control Module	Proprietary sedation-control software and TRD-specific protocol	Leverages Medsteer collaboration announced today
EEG Monitor **Infusion Pump**	Leveraging FDA-cleared components	Minimizes hardware & regulatory risk while staying capital efficient
Drug	Use of common, generic anesthetics	Leverages previously disclosed MIT license

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

Medsteer multi-dimensional strategic collaboration

Medsteer 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

Scope of agreement

- 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

Intended to enable faster, lower-risk development of our closed-loop system in neuropsychiatry and other indications

Regulatory Update

Regulatory strategy: Multinational path to Phase 2 POC

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

AUS TGA[1]: enables early FPI[2]

- TGA CTN[3] anticipated, ethics (HREC[4]) lead review
- Enable FPI with commercially sourced drugs
- Expect submission and FPI in 2026

US FDA[5]: ongoing engagement

- Initial feedback from FDA received
- Regulated as Drug-led drug-device combination product
- Pre-IND[6] feedback in Q1 2026

[1]Therapeutic Goods Administration | [2]First Patient In | [3]Clinical Trial Notification | [4]Human Research Ethics Committee | [5]Food and Drug Administration | [6]Investigational New Drug

Financial Update

Financial updates

$4.6M Cash Balance as-of September 30th, 2025

Praliciguat Update

- Akebia Therapeutics announced initiation of Phase 2 in focal segmental glomerulosclerosis (FSGS)
- Expect $1M milestone paid upon first-patient-dosed in 1H 2026

Additional capital needs:

- $50M needed to get through full POC data in 2028
- $20M needed to get through initial data in 2027

Expected Timeline and Milestones

Expected milestones

2025

- ✓ Pre-IND meeting package prepared
- ✓ Finalized details of POC Study Design
- ✓ Prototype components selected

2026

- FDA pre-IND feedback (Q1)
- CTN filing following HREC approval
- Initiate Phase 2 POC Study AUS (2H)

2027

- Phase 2 Part A Safety and PD data

2028

- Full Phase 2 proof-of-concept data
- Preparing for end of Phase 2 meeting
- Planning for pivotal studies(s)

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

Thank You

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