Building for Success
A New
Transformational Opportunity

Updated as of March 2025

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Cyclerion's opportunity to build a new portfolio

Initial Focus

Create an innovative therapeutic option for patients with debilitating depression as **the foundational asset**

Future

Expand to enable individualized treatment of **other neuropsychiatric** conditions and **settings**

No Cyclerion investment in sGC

- All resources directed to build a focused portfolio
- Extensive cost savings-measures to extend use of shareholder capital
- Potential revenue stream from historical portfolio
  - Praliciguat - Licensed to Akebia for kidney disease
  - Olinciguat - Exclusive option agreement complete
  - Tisento Therapeutics - 10% equity ownership

Team built and new product opportunity identified

- Leveraging internal expertise and connections to external world leaders in field
- Committed consultant team of industry veterans uncovering assets & conducting diligence
- Foundational asset in treatment resistant depression (TRD) identified
- Significant market potential in TRD

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Potential to transform care for Treatment Resistant Depression patients

21M diagnosed yearly with Major Depressive Disorder in the US | **3M progress to TRD**

Current

- Standard of care in TRD is electroconvulsive therapy (ECT) despite having significant side effects - most notably, memory loss
- Over 100k ECTs are performed yearly @ ~540 centers
- Patients undergo about 30 invasive ECT treatments a year including induction and maintenance
- Psychiatrists, patients and caregivers want better, safer alternatives

Potential Cyclerion Solution

- **Provide patients with an efficacious, safe alternative prior to ECT**
- **Individualized TRD treatment (drug + device combination) using a feedback-controlled delivery system**
- **Leverages the safety profile of common anesthetics that are being used as intended**
- **Clinical evidence supports our scientific rationale; (2 clinical studies with anesthetics being used for TRD*)**
- **Potential for expedited regulatory path to approval**

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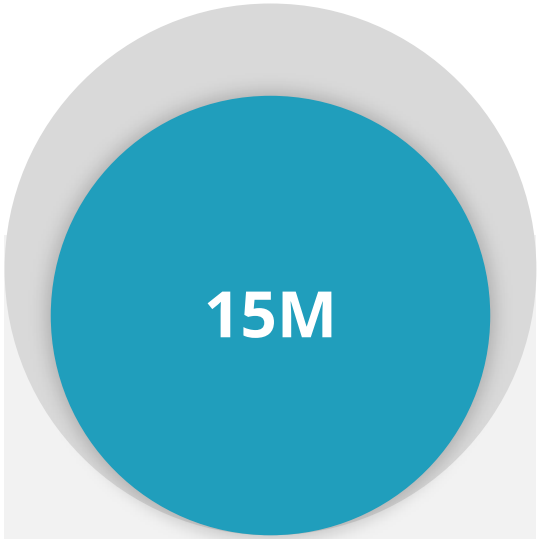
*2018 Dec 1;21(12):1079-1089: doi: 10.1093/ijnp/pyy085; https://doi.org/10.1101/2023.09.12.23294678

Depression is a growing crisis*

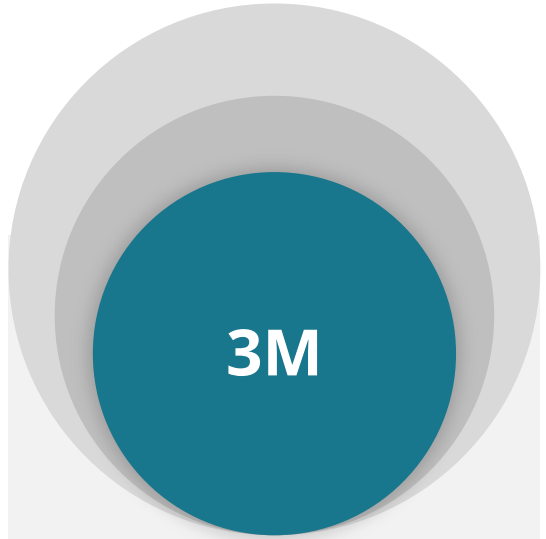
Americans suffer from depression



Americans enter 1st line treatment

50% failure rate in the 1st line

Moderate satisfaction with all available therapies due to limitations and drawbacks



Progress to treatment resistance

Failure to respond to two or more antidepressant regimens despite adequate dose and duration and adherence to treatment

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*Mental Health America/SAMHSA; Clin Psychiatry. 2021 Mar 16;82(2):20m13699

The pressing demand for better treatment options in TRD

~15M
Enter Treatment

~3M Progress to TRD

1st Line	2nd Line	3rd Line	4th Line	5th Line	6th Line +
Monotherapy	Alternative Monotherapy	Combination or Augmentation	Therapies	ECT Introduced	ECT + Invasive Therapies

2nd Gen SSRI or SNRI

Unclear treatment protocols lots of trial-and-error testing:

+ Others (ex BUP and DXM)

In special circumstances
+ Potential Mood Stabilizer
+ Antipsychotic

Cyclerion Product Candidate

Provides psychiatrists and patients alternative prior to escalation to ECT

Ketamine — not approved in TRD

Esketamine: **Spravato** — safety warnings and potential risk for abuse and misuse*

rTMS (transcranial magnetic stimulation) — differing evidence of effectiveness**

ECT — acute & chronic safety concerns***

~100k yearly patients

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*see prescribing information for full boxed warning
**DOI: 10.1002/14651858.CD003493
***DOI: 10.1192/bjo.2020.17

The potentially first individualized treatment for TRD

Being designed to deliver an improved treatment option for patients; using biofeedback for optimal safety and efficacy

WHAT

Generic IV anesthetics with dense safety databases, and a **personalized delivery system** operating as a co-pilot to anesthesiologist

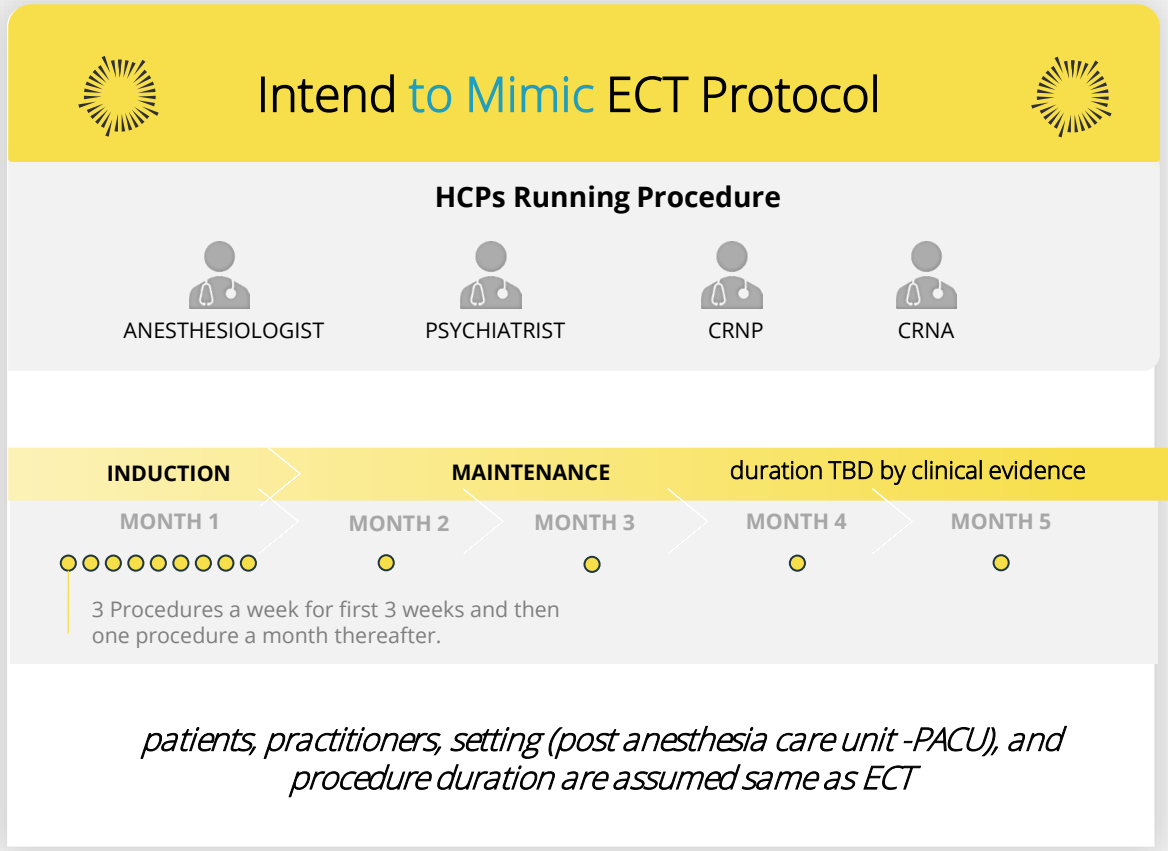
HOW

Sedation could **recalibrate brain region communications (via brainwaves)** that are dysregulated in patients with TRD

Two stages of treatment: Induction and maintenance, treatment duration estimated to be 1.5 hours

WHY

Patients deserve alternative options



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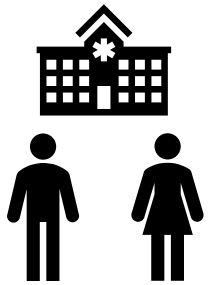
Vision for a "Day in The Life" of Cyclerion TRD TX – Analogous to Current ECT Practice*

~1.5 hours total time investment on day of procedure

Patient arrives at hospital with caregiver



Patient Caregiver

15 minute check-in & pre-procedure consultation

Anesthesiologist

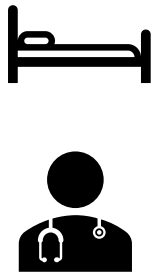
Psychiatrist

30 minute procedure in PACU

Psychiatrist Anesthesiologist

CRNA CRNP

30 minute recovery in PACU



CRNA

Patient leaves facility

Patient Caregiver

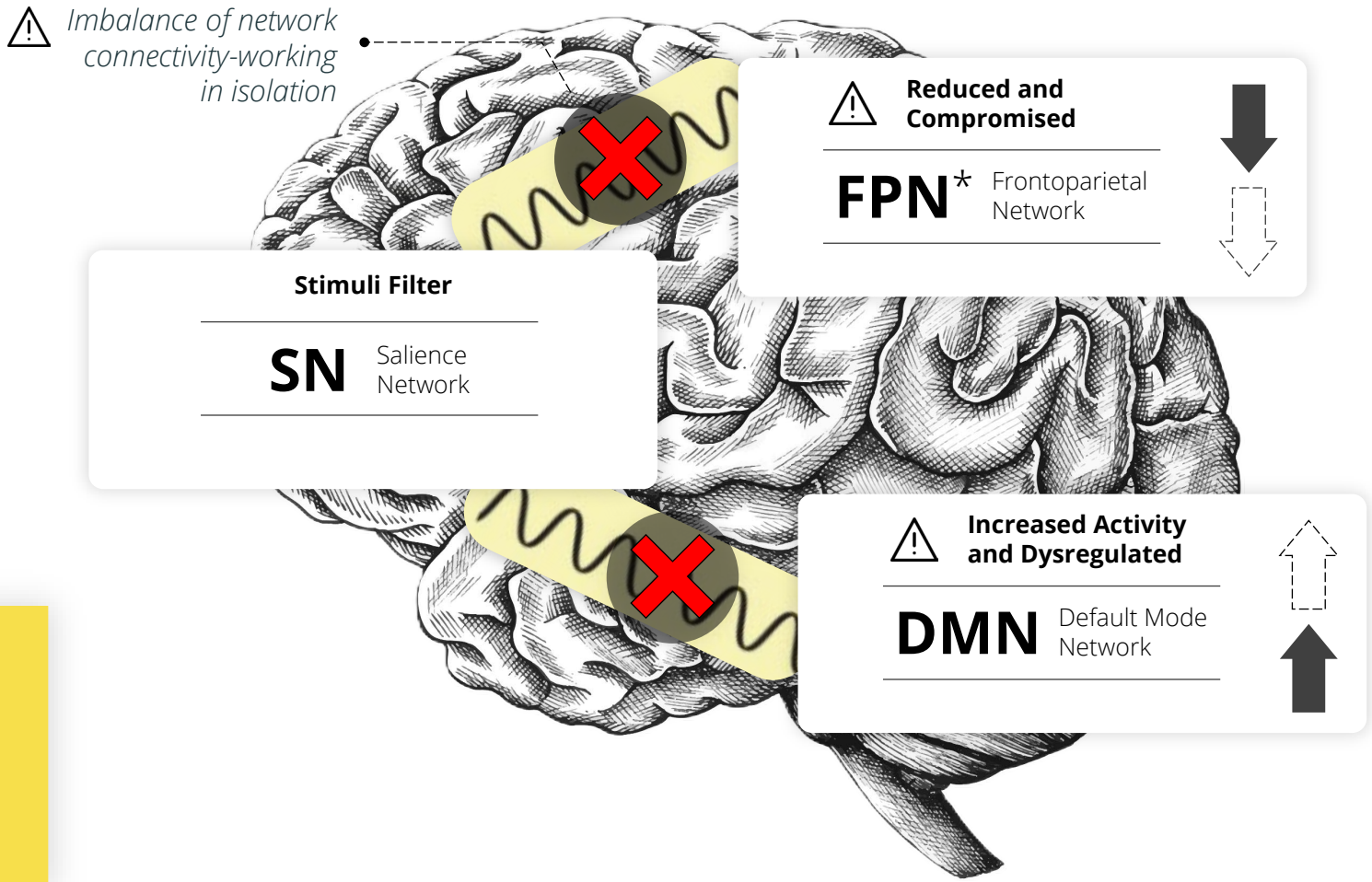
*will consider expansion to infusion centers etc. in the future

Hypothesis of the problem: there is altered brain functional connectivity in TRD

⚠ Key brain regions **communicate** through synchronized patterns of neural activity called **oscillatory brain waves-** ∿∿∿ generated by electrical activity of neurons

⚠ There is discoordination of neural activity in TRD causing an imbalance between inwardly-reflective and outward-reflective states

***SYMPTOMS**: Guilt, Hopelessness, Ruminations, Negative thoughts, Difficulty regulating emotions, Difficulty concentrating, Disruption of goal-directed cognition and working memory, and Anxiety*



*FPN is also CEN- central executive network

Relevant Citations:

Tura, A., Goya-Maldonado, R. Brain connectivity in major depressive disorder: a precision component of treatment modalities?. Transl Psychiatry 13, 196 (2023). https://doi.org/10.1038/s41398-023-02499-y

An, Z., Tang, K., Xie, Y. et al. Aberrant resting-state co-activation network dynamics in major depressive disorder. Transl Psychiatry 14, 1 (2024). https://doi.org/10.1038/s41398-023-02722-w

https://doi.org/10.1016/j.nicl.2021.102731

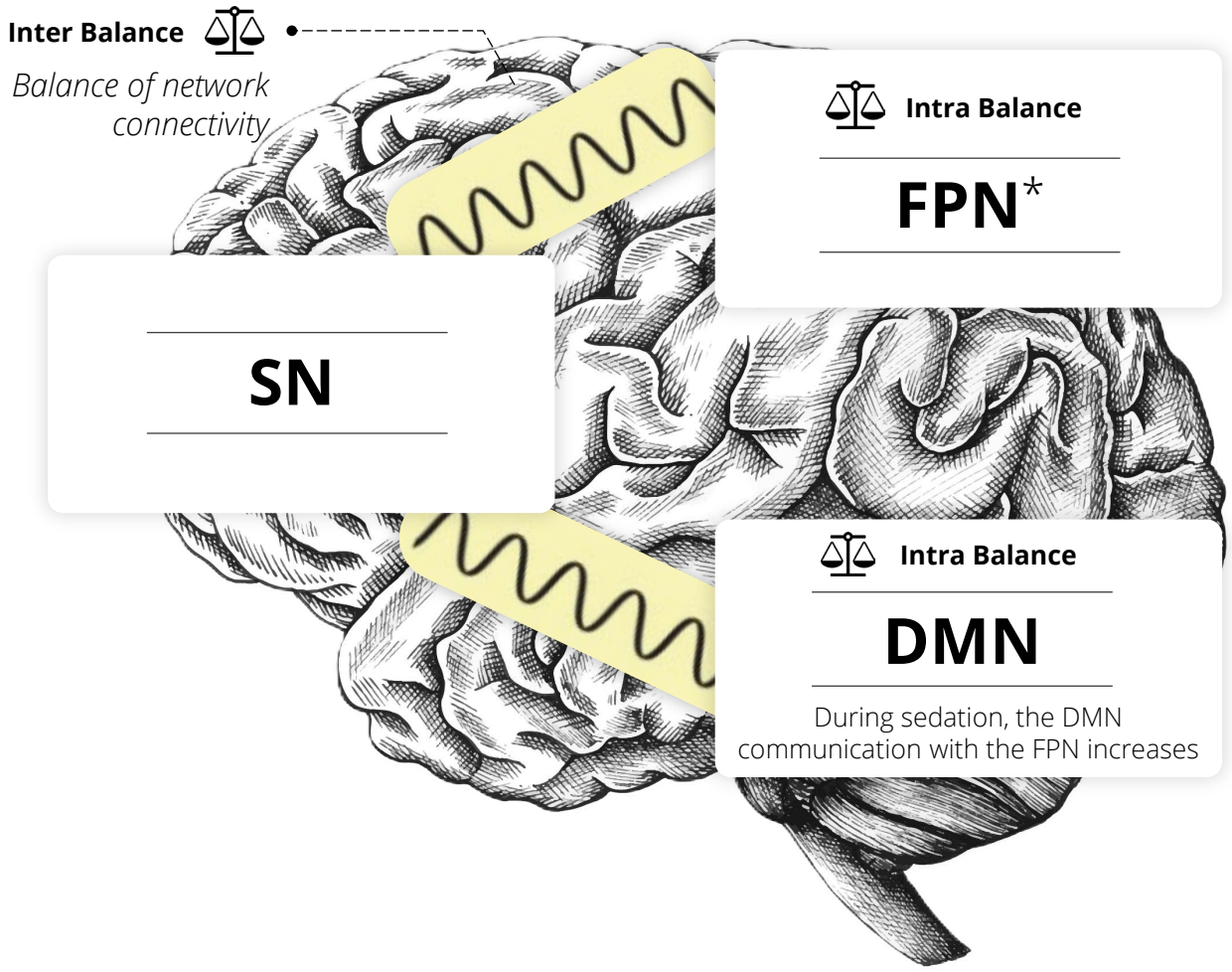
Mechanistic hypotheses are supported by clinical evidence

Sedation could facilitate resynchronization of **brain oscillations** and **communication** of brain regions

Cyclerion Product Candidate

Controlled dosing of **anesthetics** are linked to **synaptic** health and **homeostasis** by preventing synaptic overload and **clearing incorrect communications**

Two clinical studies** suggest that anesthetics could produce robust and durable antidepressant effects



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Positioning Cyclerion for Success

Strategy Established & Ready to Go

- Built a cross-functional internal team, strategically supported by expert advisors from leading CROs
- Executed an option agreement to negotiate access to key intellectual property
- Engaged in advanced diligence and active discussions with device companies
- Initiated regulatory engagement, including early work toward FDA designation
- Ongoing market research and pricing strategy development to inform future commercialization efforts

THANK YOU