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Cyclerion Therapeutics, Inc. (CYCN-NASDAQ)

CYCN: Engineering a Reset; Initiating Coverage of Cyclerion Therapeutics…

Based on our probability adjusted DCF model that takes into account potential future revenues for CYC-126 in TRD, CYCN is valued at $8.00/share. This model is highly dependent upon the clinical success and commercial potential of CYC-126 and will be adjusted accordingly based upon future clinical results.

Current Price (02/02/26)	$1.36
Valuation	**$8.00**

OUTLOOK

We are initiating coverage of Cyclerion Therapeutics, Inc. (CYCN) with a valuation of $8.00. Following a strategic relaunch as a neuropsychiatric therapeutics company, Cyclerion is initially targeting treatment-resistant depression (TRD) through CYC-126, a EEG-guided therapeutic platform designed to address the network-level dysfunction in these patients. A Phase 2 proof-of-concept study is scheduled to launch in the second half of 2026. It is designed to evaluate the safety and performance of the CYC-126 system, the ability to induce and maintain distinct EEG signatures, the antidepressant effects associated with slow-wave activity (SWA)- and burst suppression (BS)-targeted EEG signatures, and to identify the preferred EEG signature for use in future confirmatory randomized, controlled trials. While the TRD treatment landscape is increasingly crowded, Cyclerion is poised to differentiate itself through a novel combination of pharmacology, electrophysiology, and systems neuroscience.

SUMMARY DATA

52-Week High	**$5.32**
52-Week Low	**$1.18**
One-Year Return (%)	**-65.31**
Beta	**0.98**
Average Daily Volume (sh)	**4,505,897**
Shares Outstanding (mil)	**4**
Market Capitalization ($mil)	**$5**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**76**
Insider Ownership (%)	**34**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2026 Estimate	**-0.1**
P/E using 2027 Estimate	**N/A**

Risk Level	**Above Avg.**
Type of Stock	**Small-Value**
Industry	**N/A**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2024	0.0 A	0.0 A	0.2 A	1.8 A	2.0 A
2025	0.1 A	0.1 A	0.9 A	0.1 E	1.1 E
2026					1.0 E
2027					0.0 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2024	-$0.62 A	-$0.53 A	-$0.29 A	$0.22 A	-$1.21 A
2025	-$0.56 A	-$0.11 A	-$0.31 A	-$0.38 E	-$1.34 E
2026					-$0.90 E
2027					-$0.82 E

WHAT'S NEW

Initiating Coverage

We are initiating coverage of Cyclerion Therapeutics, Inc. (CYCN) with a valuation of $8.00. Cyclerion is a clinical-stage biopharmaceutical company that has recently undergone a strategic transformation to focus on the development of novel neuropsychiatric therapies, with an initial emphasis on treatment-resistant depression (TRD). Cyclerion's lead program, CYC-126, is a differentiated, anesthetic-based therapeutic approach designed to induce specific, reproducible brain states associated with rapid and durable antidepressant effects. The company's strategy combines the use of well-characterized and approved pharmacologic agents, propofol and dexmedetomidine, with a proprietary, EEG-guided delivery system intended to consistently, with clinical reliability and at scale, deliver the anesthetic-based therapy.

Major depressive disorder (MDD), and particularly its treatment-resistant forms, remains an area of significant unmet medical need, with a substantial proportion of patients failing to achieve adequate response despite multiple lines of therapy. While recent advances, including esketamine and neuromodulation techniques, have expanded available options for TRD patients, meaningful limitations persist with respect to durability of response, tolerability, access, and cost. Cyclerion is seeking to address these challenges by leveraging decades of clinical experience with anesthetic agents, paired with modern neurophysiologic monitoring and closed-loop control, to deliver a therapy that may offer rapid onset, reproducible efficacy, and a differentiated risk–benefit profile.

Cyclerion plans to advance CYC-126 into a Phase 2 proof-of-concept study in TRD, with the trial expected to be initiated in Australia but also contain U.S. sites and patients. The company has entered into a strategic collaboration with Medsteer, a medical technology company with expertise in anesthetic delivery and neurophysiologic monitoring, to leverage key intellectual property for closed-loop delivery of anesthetics within CYC-126. We view this study as a key inflection point for the company, as positive proof-of-concept data would help validate both the therapeutic hypothesis and the broader platform potential of Cyclerion's anesthetic-based, closed-loop neuropsychiatric approach along with defining the design for confirmatory randomized, controlled trials.

Differentiated Approach to TRD – CYC-126 leverages well-characterized anesthetic agents delivered via a novel, EEG-guided system designed to induce reproducible brain states associated with antidepressant effects, potentially addressing key limitations of existing TRD therapies.

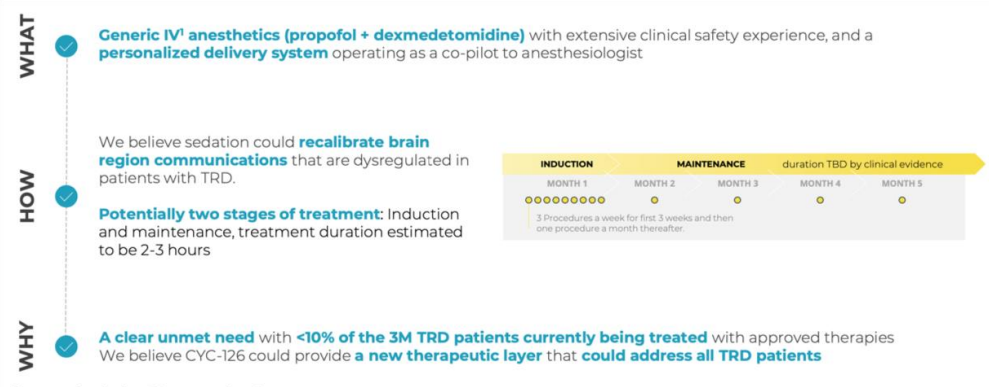
Capital-efficient Clinical Development Strategy – By utilizing approved pharmacologic agents and pursuing an initial multinational Phase 2 proof-of-concept study, in part, under the Australian CTN framework, Cyclerion aims to generate meaningful clinical data while managing development costs and timelines.

Large and Underserved Patient Population – TRD represents a significant subset of the MDD population (3M in the U.S.) with limited effective treatment options, supporting the potential for meaningful clinical and commercial impact if efficacy and durability are demonstrated.

Platform Potential Beyond Depression – While initial development is focused on TRD, management believes its EEG-guided, closed-loop delivery system may have broader applicability across neuropsychiatric and neurologic indications where precise control of brain states is clinically relevant.

INVESTMENT THESIS

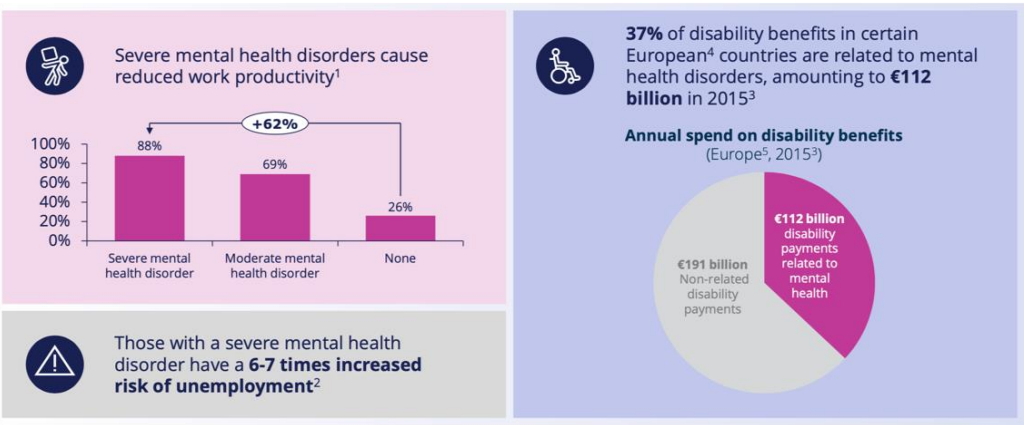
Cyclerion Therapeutics, Inc. (CYCN) is a pharmaceutical company that is pursuing a differentiated therapeutic approach to neuropsychiatric drug development by targeting brain state resynchronization rather than single molecular pathways, with an initial focus on treatment-resistant depression. The company's lead program, CYC-126, combines two well-characterized anesthetic agents, propofol and dexmedetomidine, delivered via a proprietary electroencephalographic (EEG)-guided, closed-loop system designed to reproducibly induce resynchronized neurophysiologic states that have been associated with rapid and durable antidepressant effects. We believe this strategy reflects an effort to address both the biological complexity of depression and the reproducibility challenges that have historically limited anesthetic-based approaches in psychiatry.



Source: Cyclerion Therapeutics, Inc.

Depression and Treatment-Resistant Depression

Major depressive disorder (MDD) is a heterogeneous and multifactorial disease characterized by disturbances in mood, cognition, sleep, and affective processing. In the United States, approximately 8%–9% of adults experience a major depressive episode each year, corresponding to more than 20 million individuals (National Institute of Mental Health). Depression is a leading cause of disability worldwide, with profound functional, economic, and societal costs.

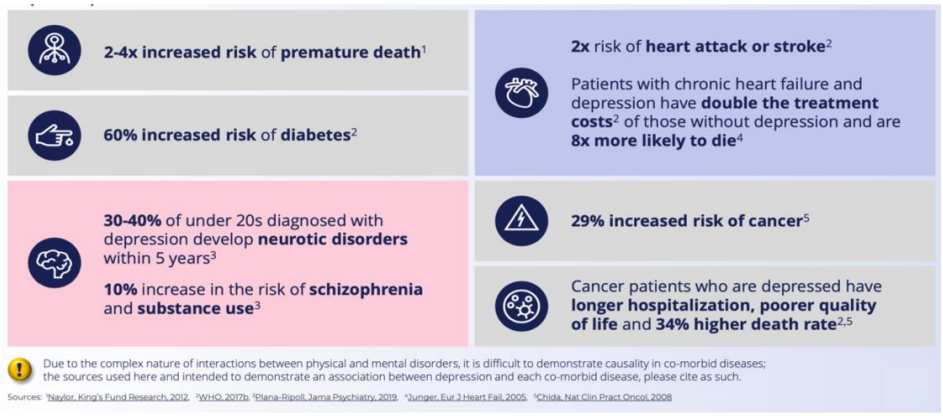


Source: Cyclerion Therapeutics, Inc.

Treatment-resistant depression (TRD) is commonly defined as inadequate response to at least two antidepressants of adequate dose and duration (Han *et al.*, 2020). Estimates suggest that 20%–30% of patients with MDD ultimately develop treatment resistance, a population associated with disproportionately high rates of relapse, suicide attempts, hospitalization, and functional disability (Souery

et al., 2006). Importantly, treatment resistance is not merely a more severe form of depression but may reflect distinct underlying neurobiological features, including altered network connectivity, impaired synaptic plasticity, and dysregulated cortical oscillatory activity.

The STAR*D trial, the largest pragmatic, multistep study of antidepressant treatments, showed that cumulative remission rates decline sharply with sequential treatment failures. By the third or fourth steps of STAR*D, remission rates declined to the teens, indicating diminishing effectiveness of traditional antidepressant strategies (Rush *et al.*, 2006). A large population-based analysis from the Stockholm MDD cohort found patients with TRD had substantially higher risks of intentional self-harm, mortality, and healthcare utilization compared to patients with non-TRD MDD, emphasizing the severity and poorer outcomes in this population (Lundberg *et al.*, 2023). Real-world assessments reveal that many TRD patients live with moderate to severe symptoms for prolonged periods, with significant impacts on quality of life, work productivity, and functioning compared with non-TRD patients (DiBernardo *et al.*, 2018).



Source: Cyclerion Therapeutics, Inc.

Limitations of Current Treatment Options in TRD

Current pharmacologic treatments for depression primarily target monoaminergic systems (serotonin, norepinephrine, dopamine), a strategy that has remained largely unchanged for decades. While effective for some patients, these therapies are associated with delayed onset of action and diminishing returns in treatment-resistant populations. Even recently approved agents such as esketamine, which modulates glutamatergic signaling, highlight both the promise and the limitations of rapid-acting antidepressants.

Esketamine has demonstrated statistically significant improvements in depressive symptoms in TRD; however, real-world use has been constrained by the need for frequent in-clinic administration, dissociative side effects, blood pressure elevations, and questions regarding durability of response following discontinuation (Daly *et al.*, 2018). Ketamine infusions, widely used off-label, yield rapid mood improvement in many cases but are constrained by variability in protocols, short duration of benefit, dissociation, and concerns about long-term safety and addiction potential. Systematic analyses continue to explore the efficacy of ketamine and neurostimulation modalities, emphasizing that a subset of interventions (ECT, TMS, ketamine) show effect over sham/placebo in TRD but with varied effect sizes and patient acceptance (Saelens *et al.*, 2025).

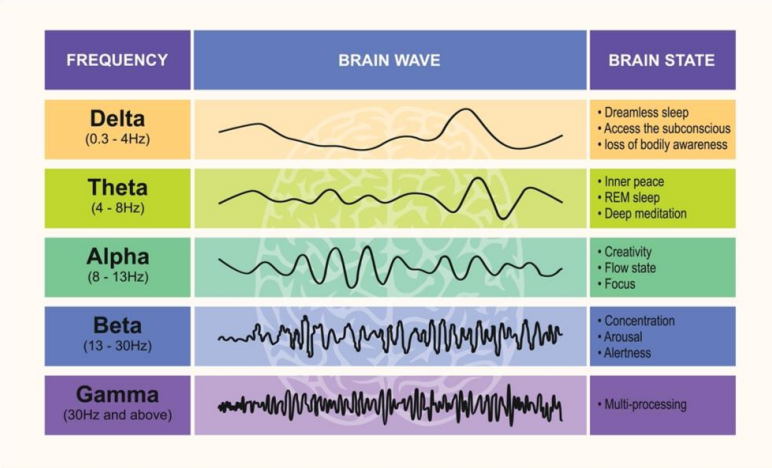
Non-pharmacologic interventions such as electroconvulsive therapy and transcranial magnetic stimulation can provide meaningful benefit but face practical limitations. Electroconvulsive therapy, despite high efficacy rates, is associated with cognitive adverse effects and persistent stigma, while transcranial magnetic stimulation requires weeks of daily treatment and demonstrates variable response rates in highly resistant populations.

These approaches underscore a central challenge in TRD: while rapid symptom relief is achievable, consistent and durable modulation of the underlying disease process remains elusive.

Background on Electroencephalography

Electroencephalography (EEG) is a noninvasive method for measuring cortical electrical activity generated by synchronized neuronal firing, primarily reflecting summed postsynaptic potentials in pyramidal neurons (Schomer et al., 2017). EEG provides millisecond-level temporal resolution, making it well suited for characterizing rapid transitions between brain states and large-scale network dynamics.

EEG activity is commonly characterized into frequency bands associated with distinct neurophysiologic states. Delta activity (approximately 0.5 – 4 Hz) predominates during sleep and deep anesthesia and reflects highly synchronized slow-wave cortical activity. Theta activity (4 – 8 Hz) is associated with drowsiness, limbic engagement, and memory processing, and has been implicated in emotional regulation and depressive symptomology. Alpha activity (8 – 12 Hz) is most prominent during relaxed wakefulness and is thought to reflect inhibitory control and large-scale network coordination, particularly with frontal and posterior cortical regions. Higher-frequency beta (13 – 30 Hz) and gamma (> 30 Hz) activity are associated with alertness, cognition, and local cortical processing.



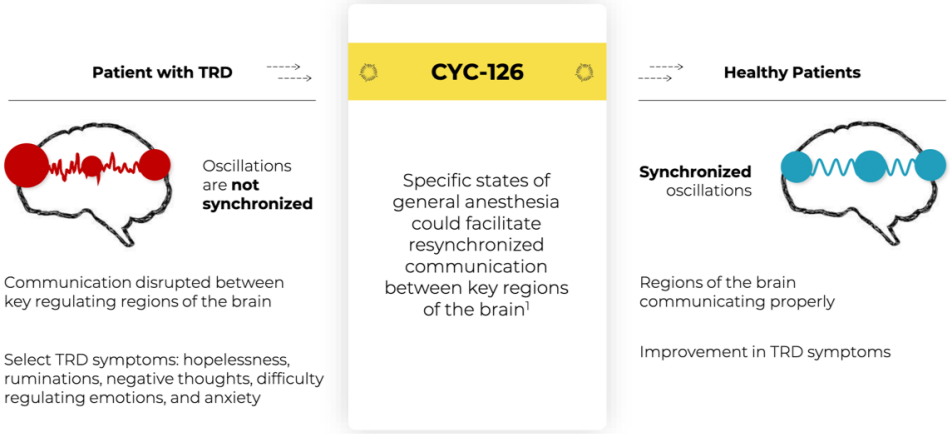
Source: Shutterstock

Beyond spectral power, EEG enables assessment of functional connectivity, coherence, phase coupling, and state transitions over time. Alterations in alpha symmetry, theta-alpha balance, and large-scale coherence have been repeatedly observed in depression (Grin-Yatsenko *et al.*, 2010), supporting the use of EEG as both a mechanistic probe and a pharmacodynamic biomarker. Importantly, EEG signatures induced by anesthetic agents are well characterized and reproducible, allowing objective verification of drug-induced brain states rather than reliance on dose or behavioral surrogates alone (Purdon *et al.*, 2015).

In the therapeutic context, EEG provides a means of defining, monitoring, and controlling brain states. By anchoring intervention to measurable neurophysiologic features, EEG enables a shift from pharmacokinetic-based dosing toward state-based treatment paradigms, a distinction that underpins the rationale for EEG-guided approaches such as CYC-126.

Neural Circuitry, Brain State Dysregulation, and EEG Biomarkers in Depression

MDD is increasingly understood as a disorder of large-scale neural circuitry rather than isolated neurotransmitter deficits. Neurophysiologic and neuroimaging studies indicate that depression is associated with abnormal activity and connectivity across prefrontal, limbic, and default mode networks, which are systems involved in emotional regulation, cognitive control, and self-referential processing. These abnormalities are observable at rest and during activities, suggesting that a persistent dysregulation of baseline brain states is causative rather than context-dependent dysfunction alone.



Source: Cyclerion Therapeutics, Inc.

EEG has played a central role in characterizing these abnormalities by providing a non-invasive, real-time window into brain network dynamics. Resting-state EEG studies have demonstrated that depressed patients exhibit altered hemispheric power distributions, particularly in frontal regions (Quraan *et al.*, 2013). Differences in alpha and theta band activity between hemispheres have been repeatedly observed, reflecting imbalances in prefrontal cortical activity that may underlie affective and cognitive symptoms of depression. A comprehensive review of resting-state EEG in depression documented frontal alpha and theta asymmetries as well as altered inter-hemispheric coherence, supporting the presence of network-level abnormalities rather than concentrated deficits (Olbrich *et al.*, 2013).

Among EEG features, frontal alpha asymmetry has been one of the most extensively studied biomarkers in depression. Increased right-frontal alpha power, which is interpreted as reduced cortical activity, has been associated with negative affect, withdrawal behavior, and vulnerability to depressive symptoms. Meta-analytic evidence suggests that while alpha asymmetry alone has limited diagnostic specificity, it consistently reflects altered prefrontal functional organization and remains relevant for mechanistic and longitudinal studies (van der Vinne *et al.*, 2017). In certain cohorts, frontal alpha symmetry has also demonstrated predictive value for antidepressant treatment response, reinforcing the idea that EEG features can reflect clinically meaningful brain states rather than epiphenomenal findings (Thibodeau *et al.*, 2006).

Frontal theta activity has emerged as a complementary EEG marker of interest. Theta oscillations are implicated in cognitive control, emotional processing, and communication between prefrontal and limbic circuits. Studies comparing depressed individuals to healthy controls have identified differences in frontal theta power and asymmetry, suggesting altered engagement of regulatory networks central to mood regulation (Dharmadhikari *et al.*, 2018). Collectively, these findings support a conceptual framework in which depression involves dysregulated coordination across distributed neural networks rather than isolated regional hypo- or hyperactivity.

Beyond static power measures, composite EEG metrics that integrate absolute and relative power have shown greater relevance to treatment response. Prefrontal theta cordance, which reflects changes in cortical perfusion and neuronal activity, has been associated with early antidepressant treatment effects and has demonstrated predictive value for subsequent clinical response (de la Salle *et al.*, 2020). In longitudinal studies, early shifts in theta cordance preceded symptomatic improvement, supporting the concept that modulation of brain state may be a prerequisite for therapeutic benefit rather than a downstream consequence.

Importantly, EEG abnormalities observed in depression are not fixed traits but dynamic, state-dependent features. Changes in oscillatory activity, hemispheric balance, and network coherence have been observed following antidepressant treatment, electroconvulsive therapy, and rapid-acting agents, reinforcing the concept that EEG markers reflect state-dependent brain function. This state sensitivity

distinguishes EEG from structural or genetic biomarkers and underpins its utility as a real-time pharmacodynamic readout (Leuchter *et al.*, 2012).

In summary, the EEG literature supports a model in which depression is characterized by maladaptive, self-reinforcing brain states defined by aberrant oscillatory dynamics and network organization that are measurable, reproducible, and modifiable. While no single EEG feature serves as a standalone diagnostic biomarker, patterns across frequency bands, hemispheric balance, and composite metrics such as cordance provide reproducible and clinically relevant insight into brain state and treatment response. These properties make EEG particularly well suited for therapeutic strategies that seek to deliberately induce, monitor, and control specific neurophysiologic states, rather than relying solely on fixed-dosing or symptom-based assessments.

Rationale for Anesthetic-Induced Brain State Modulation in Depression

General anesthetic agents provide a unique and well-characterized means of inducing rapid, large-scale alterations in brain activity that are both reproducible and quantifiable using EEG (Purdon *et al.*, 2015). Unlike conventional antidepressants, which exert gradual effects on synaptic signaling over weeks, anesthetics induce abrupt transitions between discrete neurophysiologic states, characterized by suppression of cortical excitability, modulation of synaptic strength, and large-scale reorganization of functional brain networks. EEG patterns such as slow-wave activity and burst suppression are hallmark signatures of deep anesthetic states and are neurophysiologically distinct from natural sleep or light sedation, reflecting profound shifts in cortical connectivity that may transiently disrupt maladaptive network dynamics implicated in TRD.

Propofol, a GABAergic intravenous anesthetic, has been the most extensively studied agent in this context. Propofol reliably induces characteristic EEG signatures including increased delta and slow-wave activity, suppression of higher-frequency oscillations, and alterations in frontal coherence. Comparative human studies demonstrate that propofol produces EEG patterns distinct from other sedative agents, reflecting deeper cortical suppression and altered thalamocortical communication rather than simple sedation (Akeju *et al.*, 2014). Preclinical and translational studies further support the ability of propofol to induce stable, dose-dependent brain states characterized by synchronized slow oscillations, reinforcing the concept that anesthetic-specific brain states can be identified and differentiated electrophysiologically (Obert *et al.*, 2024).

Beyond its effects on global brain state, propofol has been shown to influence neural circuits relevant to mood and emotional processing. In human studies, subanesthetic propofol disrupts hippocampal-mediated emotional memory systems, suggesting direct effects on circuitry implicated in affective regulation (Pryor *et al.*, 2015). In preclinical models of depression, propofol has demonstrated antidepressant-like effects, including enhancement of synaptic plasticity and modulation of glutamate reuptake mechanisms within hippocampal circuits, providing mechanistic plausibility for antidepressant action beyond anesthesia alone (Wang *et al.*, 2025; Breault *et al.*, 2025).

These mechanistic observations are supported by early clinical evidence:

- Mickey *et al.*, 2018: This was the first clinical trial of deep propofol anesthesia in ten subjects with TRD (NCT02935647). Study subjects received ten propofol infusions over three weeks. The results demonstrated significant reductions in Hamilton Depression Rating Scale (HDRS) scores following the treatments, with 60% (6/10) of subjects meeting response criteria (≥50% reduction from baseline on HDRS) and 50% met the definition for remitters (final HDRS ≤10). In addition, 80% (4/5) of remitters sustained remission for ≥3 months, three continued to ~5 months, and two continued to >6 months. Importantly, EEG measures correlated with clinical response, supporting the use of EEG as a pharmacodynamic biomarker of therapeutic engagement.

- Tadler *et al.*, 2023: This was a randomized controlled trial that evaluated low (n=12) versus high (n=12) doses of propofol (3x per week for two weeks) guided by real-time EEG (targeting burst

suppression versus no burst suppression) (NCT03684447). The primary outcome was the 24-item HDRS scale (HDRS-24) and the Patient Health Questionnaire (PHQ-9). The results showed that 50% (6/12) of subjects in the high dose cohort were responders and 42% (5/12) were remitters (same measure of efficacy as the study by Mickey *et al*.). The low dose cohort only had 8% (1/12) responders and 8% (1/12) remitters. A third cross-over cohort evaluated eight patients who moved from low dose to high dose, and the results showed 50% (4/8) responders and 42% (3/8) remitters. These results demonstrated medium-sized effects that suggest propofol may have dose-dependent antidepressant effects that supports future larger studies focusing on dose optimization.

- Rios *et al*., 2024: The SWIPED (Slow Wave Induction by Propofol to Eliminate Depression) Phase 1 trial enrolled a total of 15 geriatric (≥ 60) patients who received two 2-hour propofol infusions 2-6 days apart. The propofol infusions were individually titrated to maximize the expression of EEG slow waves. Results from the study were presented at the Gordon Research Conference on Depression and showed that 67% (10/15) of patients were responders (defined as ≥30% reduction from baseline in MADRS / > 6 change in MADRS at any point). In addition, there was a dose-dependent change in baseline MADRS at 3 weeks that correlated inversely with the average propofol dose administered.

Dexmedetomidine, a selective alpha-2 adrenergic agonist, offers a complementary pharmacologic profile to propofol. Dexmedetomidine induces sedation primarily through inhibition of noradrenergic signaling from the locus coeruleus, resulting in reduced sympathetic tone and cortical arousal via mechanisms distinct from GABAergic anesthetics. EEG studies indicate that dexmedetomidine produces slow-wave and spindle-like activity resembling non-rapid eye movement sleep, while preserving certain aspects of cortical connectivity. Direct comparisons with propofol demonstrate distinct spectral signatures, supporting the view that these agents modulate brain state through complementary neurophysiologic pathways (Akeju et al., 2014).

When used in combination, propofol and dexmedetomidine interact to shape anesthetic EEG expression in a manner that may enhance both tolerability and reproducibility. Clinical studies employing EEG spectrogram guidance during total intravenous anesthesia demonstrate that co-administration of dexmedetomidine alters EEG features and reduces propofol requirements while maintaining targeted anesthetic depth, suggesting that EEG-guided administration can be used to reproducibly achieve specific brain states while minimizing inter-individual variability (Lin et al., 2024). In addition, preclinical studies demonstrate that dexmedetomidine attenuates central neuroinflammation and downregulates pro-inflammatory cytokines and NF-κB pathway activation in rodent models, supporting a role in modulating stress-related circuitry relevant to depression pathophysiology (Zhang *et al*., 2018).

The data on propofol and dexmedetomidine supports the hypothesis that anesthetic agents can be used not just for sedation, but as tools to deliberately induce and control specific neurophysiologic states. By leveraging EEG biomarkers to guide and verify these states, anesthetic-based approaches offer a mechanistically grounded strategy for targeting the network-level dysfunction that characterizes TRD.

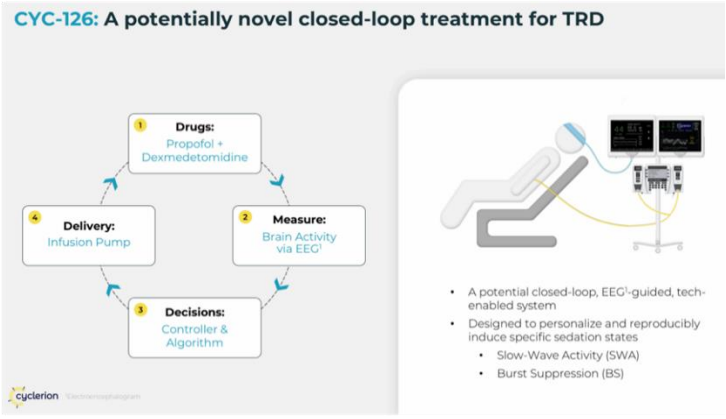
CYC-126

The identification of reproducible EEG abnormalities in depression, combined with evidence that these features are dynamically modifiable, provides a mechanistic foundation for therapeutic strategies that directly target brain state rather than downstream symptoms. Importantly, EEG biomarkers offer real-time, objective measures of neural activity that can be continuously monitored and used to guide intervention, addressing a key limitation of conventional psychiatric treatments that rely on fixed dosing and subjective symptom reporting.

Cyclerion's CYC-126 program is designed to translate this concept into a clinically deployable, EEG-guided therapeutic platform for TRD. Rather than administering anesthetic agents at fixed doses, CYC-126 integrates continuous EEG monitoring with real-time adjustment of drug delivery to reproducibly

induce predefined brain states associated with therapeutic benefit. By anchoring treatment to objective neurophysiologic endpoints, the approach seeks to reduce inter-patient variability, improve reproducibility of response, and mitigate risks associated with under- or over-exposure.

CYC-126 represents a shift from symptom-based pharmacotherapy toward state-based neurotherapeutics, in which treatment success is achieved by engagement of a target brain state combined with structured patient feedback rather than solely by clinical observation. In the context of TRD, where heterogeneity of response and delayed onset remain major challenges, the program leverages continuous EEG monitoring as both pharmacodynamic readouts and control variables, enabling a more precise and mechanistically grounded intervention.



Source: Cyclerion Therapeutics, Inc.

The pharmacologic backbone of CYC-126 consists of propofol and dexmedetomidine, two intravenous agents with complementary and well-understood neurophysiologic effects. Within the CYC-126 framework, these agents are not positioned as standalone antidepressants but as tools to reliably access and shape specific brain states. Propofol enables rapid induction of deep cortical states characterized by large-scale network reorganization, while dexmedetomidine modulates arousal circuitry to stabilize and refine EEG expression and enables the use of less propofol, thus improving recovery and making treatment more desirable for patients. Their combined use allows control over both the depth and qualitative features of the induced brain state.

A defining feature of CYC-126 is its closed-loop architecture. Continuous EEG data are analyzed in real time to assess whether the brain is within the desired neurophysiologic state. Drug infusion rates are adjusted dynamically based on this feedback, rather than relying on weight-based dosing or fixed infusion protocols. This design explicitly accommodates inter-individual variability in pharmacokinetics, baseline brain activity, and anesthetic sensitivity, all factors that have historically limited the reproducibility of anesthetic-based interventions in psychiatric indications.

From a mechanistic standpoint, CYC-126 reframes anesthetic exposure as a means of inducing a controlled network-level “reset.” By disrupting maladaptive oscillatory patterns and altering functional connectivity across prefrontal and limbic circuits, the induced brain state may allow for reorganization of neural activity that persists beyond drug clearance. EEG serves both as the operational control signal for achieving the target state and as a confirmation of engagement of the intended mechanism, positioning CYC-126 as a deliberately engineered brain state intervention rather than an empiric pharmacologic treatment.

Role of Patient Feedback

While EEG provides an objective, real-time measure of neurophysiologic state, Cyclerion’s CYC-126 program incorporates structured patient feedback as a complementary component of treatment optimization. This approach reflects the recognition that TRD is defined not only by measurable

abnormalities in brain activity, but also by dimensions that cannot be fully captured by electrophysiology alone, such as subjective symptom burden, functional impairment, and durability of response.

In the context of CYC-126, patient-reported outcomes and clinician-administered rating scales are integrated with EEG-defined brain states to refine therapeutic targets over time. This distinction is critical: EEG serves as the primary control variable within the closed-loop system, while patient feedback informs higher-level optimization of target state definitions, treatment duration, and session frequency across patients and cohorts.

The incorporation of patient feedback also addresses a key limitation of prior anesthetic-based and neuromodulatory approaches, which have often relied on fixed protocols without systematic linkage between induced brain states and patient experience. By explicitly tying EEG-defined states to clinical outcomes, CYC-126 aims to move beyond proof-of-concept demonstrations toward a reproducible and scalable treatment paradigm.

Standardized depression rating scales, such as the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery *et al*., 1979) and patient-reported symptom inventories, will be used to assess changes in mood, cognition, and functional status following treatment. These measures enable correlation of clinical outcomes with specific EEG features and brain state characteristics achieved during prior sessions. Over time, this structure allows identification of EEG patterns that are most consistently associated with symptomatic improvement, supporting iterative refinement of therapeutic targets.

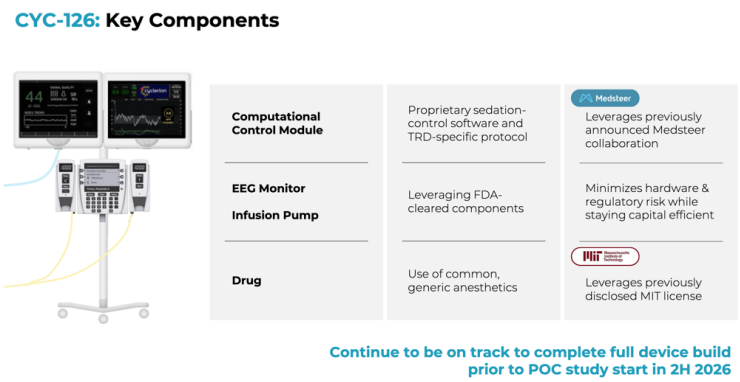
Integration of Key Components

Cyclerion is continuing the integration of key components of CYC-126 in preparation for its clinical trials. To precisely deliver the anesthetics, the CYC-126 program combines a computational control module, continuous EEG monitoring, an infusion delivery system, and the two well-characterized, intravenous anesthetics. Together, these elements are intended to enable reproducible induction and maintenance of predefined neurophysiologic state under controlled clinical conditions.

In January 2026, Cyclerion announced a strategic collaboration with MedSteer, a company specializing in advanced drug delivery and clinical workflow technologies, to support the execution of the CYC-126 clinical program. While detailed technical specifications have not been publicly disclosed, MedSteer's technology is expected to be incorporated into the computational control module to facilitate controlled administration and monitoring during treatment sessions. The collaboration is positioned to enhance operational consistency and data integrity across clinical sites, supporting the reproducibility required for EEG-guided interventions.

From a regulatory and development standpoint, the platform leverages several de-risking features. The EEG monitoring and infusion pump components are based on FDA-approved or widely used clinical devices, reducing device-related regulatory complexity. The pharmacologic agents used in CYC-126 are common, generic anesthetics with well-established safety profiles. CYC-126's therapeutic benefit and IP are enhanced based on the unique closed-loop integrated system, software, and dosing aspects of the delivery mechanism (know-how, data, etc.) as well as regulatory positioning and commercial entrenchment.

The integration of MedSteer's platform is particularly relevant given the complexity of CYC-126's closed-loop architecture, which requires coordination between EEG acquisition, signal interpretation, and drug delivery. By leveraging an external technology partner with experience in regulated clinical environments, Cyclerion aims to reduce execution risk during early-stage trials and ensure that observed outcomes can be attributed to defined neurophysiologic parameters rather than procedural variability.



Source: Cyclerion Therapeutics, Inc.

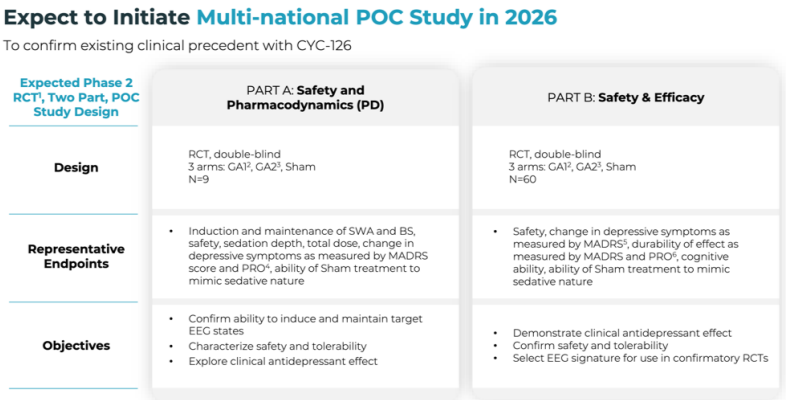
CYC-126 is being advanced toward a Phase 2 proof-of-concept study in TRD. The planned clinical development strategy emphasizes demonstration of feasibility, safety, and reproducible brain state induction, alongside exploratory assessments of antidepressant efficacy and durability of response. By anchoring clinical evaluation to objective EEG brain states, the program aims to generate mechanistic evidence of target engagement alongside traditional clinical outcome measures.

Overall, CYC-126 represents a platform-level approach rather than a single-asset drug program. Its mechanism of action is defined by controlled engagement of neurophysiologic states using established anesthetic agents, guided by real-time EEG feedback. If successful, this strategy could establish a new class of state-based neurotherapeutics with applicability beyond TRD.

Development Strategy and Proof-of-Concept Study Design

Cyclerion's clinical development strategy for CYC-126 is structured to balance mechanistic validation with early signals of clinical efficacy in TRD, while minimizing risk associated with anesthetic-based interventions. Rather than pursuing a conventional dose-escalation paradigm, the program is designed around demonstration of reproducible, EEG-defined brain state induction and its association with symptomatic improvement.

The figure below provides an overview of the planned Phase 2 two-part proof-of-concept study in TRD. The trial is intended to establish three foundational elements: feasibility of EEG-guided closed-loop administration, safety and tolerability of repeated treatments, and evidence of target engagement through the ability to maintain target EEG states. Part A of the study is focused on safety and pharmacodynamics and will enroll nine patients in three arms: general anesthesia state 1 (GA1), GA2, and sham. Part B will expand the cohort sizes to a total of 60 patients and will focus on safety and efficacy. Outcome measures will include change in depressive symptoms as measured by MADRS, durability of effect as measured by MADRS and Patient Reported Outcomes (PRO), cognitive ability, and the ability of sham to mimic sedative nature. Lastly, the EEG signature for use in confirmatory trials will also be established.



Source: Cyclerion Therapeutics, Inc.

Patient selection criteria are expected to focus on individuals with moderate to severe MDD who have failed two or more prior antidepressant therapies (medication or device-based). This population mirrors that enrolled in prior propofol-based depression studies and reflects the clinical setting in which rapid-acting interventions are most relevant. Patients will also need to have a MADRS total score ≥28 at both baseline and screening. Exclusion criteria are designed to mitigate anesthetic risk or neurologic comorbidities that could confound EEG interpretation.

Treatment administration in the Phase 2 study is guided by continuous EEG monitoring, with drug delivery adjusted in real time to achieve predefined brain state targets. These targets are specified in terms of spectral features and state transitions rather than nominal drug doses, an approach intended to reduce inter-subject variability and improve reproducibility across treatment sessions. Propofol and dexmedetomidine are administered intravenously under controlled conditions, with anesthetic depth titrated to remain within a defined therapeutic window rather than deep surgical anesthesia.

The use of EEG-based targets represents a deliberate departure from prior anesthetic depression studies that relied on fixed anesthesiologist-controlled dosing. Historical trials of propofol in treatment-resistant depression demonstrated variability in both EEG expression and clinical response, limiting interpretability despite encouraging signals. By anchoring intervention to objective brain state criteria, CYC-126 aims to address this limitation directly.

Importantly, the study design emphasizes repeated treatment sessions (3x per week for three weeks) rather than a single exposure, reflecting both preclinical evidence and clinical precedent (prior studies showed benefit as early as the second week of treatment) suggesting that durable antidepressant effects may require multiple state-induction events. The initial nine sessions will serve as an induction phase, with maintenance dosing occurring on a once monthly timeframe.

The data generated from the Phase 2 program are intended to inform subsequent trial design. Specifically, Cyclerion plans to use EEG-outcome correlations to refine target state definitions, optimize treatment duration, and identify responder subgroups. This adaptive learning approach is consistent with the platform nature of CYC-126 and reflects an understanding that the optimal therapeutic brain state may not be fully defined at study initiation.

Competitive Landscape and Positioning

The treatment landscape for MDD and TRD encompasses a wide range of pharmacologic and device-based interventions, reflecting both the heterogeneity of the disease and the limited efficacy of any single therapeutic class. While numerous antidepressant drugs are approved and widely prescribed, treatment resistance remains common, with approximately 30–40% of patients failing to achieve adequate response after multiple trials of standard therapies (Rush *et al*., 2006). The following table lists the major classes of therapeutics for MDD and TRD, examples of drugs in those classes, their mechanisms, and limitations in TRD.

Major Therapeutic Classes in Major Depressive Disorder and TRD			
Therapeutic Class	**Examples**	**Mechanism**	**Limitations in TRD**
SSRIs / SNRIs	Fluoxetine, Sertraline, Venlafaxine	Monoamine reuptake inhibition	Delayed onset, low efficacy after multiple failures
TCAs / MAOIs	Amitriptyline, Phenelzine	Broad monoaminergic modulation	Safety, tolerability, limited modern use
Atypical Antidepressants	Bupropion, Mirtazapine	Mixed monoaminergic mechanisms	Modest efficacy in TRD
Augmentation Agents	Aripiprazole, Quetiapine, Lithium	Dopaminergic, serotonergic, intracellular signaling	Metabolic and neurologic side effects
NMDA Antagonists	Ketamine, Esketamine	Glutamatergic modulation, synaptic plasticity	Transient efficacy, dissociation, frequent dosing
NMDA/Sigma-1 Modulators	Dextromethorphan-bupropion	Low-affinity NMDA antagonism, sigma-1 antagonism	Oral dosing, limited TRD data, no biomarker guidance
Neurosteroids	Brexanolone, Zuranolone	GABA-A modulation	Limited TRD data, sedation
Psychedelics	Psilocybin	5-HT2A-mediated network reorganization	Regulatory, durability unknown
Neuromodulation	TMS, ECT, DBS	Electrical or magnetic circuit modulation	Burden, variability, invasiveness
State-Based Therapy	CYC-126	EEG-guided brain state induction	Early-stage clinical validation

Source : Zacks Small Cap Research

Approved pharmacologic treatments for depression are dominated by agents targeting monoaminergic neurotransmission. Selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and atypical agents such as bupropion and mirtazapine form the backbone of first- and second-line therapy. These drugs exert antidepressant effects primarily through chronic modulation of synaptic monoamines and downstream neuroplastic changes. However, onset of clinical benefit is typically delayed by weeks, and efficacy declines substantially in patients with prior treatment failures. Large meta-analyses and real-world studies indicate diminishing response rates with successive antidepressant trials, underscoring the limited utility of monoaminergic agents in established TRD.

Augmentation strategies, including atypical antipsychotics such as aripiprazole, quetiapine, and brexpiprazole, as well as lithium and thyroid hormone, are commonly employed in TRD. While these approaches can improve response rates in some patients, benefits are often modest and accompanied by metabolic, neurologic, or endocrine adverse effects that limit long-term use.

More recently, rapid-acting antidepressant strategies have focused on glutamatergic modulation, particularly NMDA receptor antagonism. Intravenous ketamine has demonstrated rapid antidepressant effects in multiple randomized controlled trials involving patients with TRD, with symptom improvement observed within hours to days. However, these effects are typically transient, with relapse occurring within one to two weeks in the absence of repeated dosing. Spravato® (esketamine), the S-enantiomer of ketamine, was approved by the FDA for TRD based on randomized trials demonstrating superiority over placebo when added to oral antidepressants, though effect sizes are modest, durability requires ongoing, frequent administration, patients are required to have active supervision, and some patients report uncomfortable dissociative effects (Daly *et al.*, 2018; Popova *et al.*, 2019). Spravato is forecast to generate approximately $3.5 billion in revenues in 2030 (EvaluatePharma).

In addition to ketamine-based interventions, the antidepressant landscape has expanded to include oral therapies that partially engage glutamatergic mechanisms. Auvelity®, a fixed-dose combination of dextromethorphan and bupropion, was approved by the FDA in 2022 for the treatment of MDD. Dextromethorphan is a low-affinity, non-competitive NMDA receptor antagonist and sigma-1 receptor agonist, while bupropion serves both as an antidepressant and a CYP2D6 inhibitor that increases dextromethorphan bioavailability.

Clinical trials of Auvelity demonstrated statistically significant improvements in depressive symptoms compared to placebo, with onset of effect reported as early as one week in some patients (Tabuteau *et al.*, 2022; Iosifescu *et al.*, 2022). However, these studies were conducted primarily in patients with MDD rather than rigorously defined TRD populations. While the drug's mechanism implicates glutamatergic modulation, the degree of NMDA antagonism achieved with oral dextromethorphan is substantially lower

than that observed with ketamine or esketamine, and the antidepressant effects appear to rely on chronic dosing rather than acute brain state alteration. Auvelity is forecast to generate approximately $1 billion in revenues in 2030 (EvaluatePharma).

Beyond NMDA antagonists, other novel pharmacologic approaches under investigation include GABA-A receptor modulators (e.g., brexanolone, zuranolone), psychedelic-assisted therapies targeting 5-HT2A receptors (e.g., psilocybin), and agents modulating inflammation, neurosteroids, or neurotrophic signaling. While some of these approaches have shown promise in early trials, none have yet demonstrated consistent efficacy in heavily treatment-resistant populations, and many rely on subjective experience or prolonged psychotherapeutic frameworks.

Device-based neuromodulation therapies represent a mechanistically distinct category. Transcranial magnetic stimulation (TMS) is FDA-approved for TRD and modulates cortical excitability through focal electromagnetic stimulation. While non-invasive, TMS requires daily treatments over several weeks and exhibits variable response rates (Martin *et al*., 2002). Electroconvulsive therapy remains the most effective intervention for severe or refractory depression, but its use is limited by cognitive side effects, stigma, and the need for repeated anesthesia (Porter *et al*., 2020). More invasive approaches such as deep brain stimulation and vagus nerve stimulation have shown mixed results and are generally reserved for extreme refractory cases.

Within this crowded and heterogeneous landscape, CYC-126 is differentiated by its focus on state-based neurophysiology rather than molecular target modulation or fixed anatomic stimulation. Unlike monoaminergic drugs, glutamatergic agents, or neuromodulation devices, CYC-126 is designed to transiently induce and verify specific brain states associated with antidepressant response, using EEG as an objective, real-time biomarker of target engagement. Rather than competing directly with first-line antidepressants, CYC-126 is positioned for TRD patients (e.g., those who have failed multiple pharmacologic and device-based interventions). Its closed-loop architecture and reliance on reproducible EEG-defined states distinguish it from ketamine-based therapies, which rely on pharmacologic exposure without direct control of neural network dynamics, and from neuromodulation approaches that lack real-time physiologic feedback. If successful, CYC-126 would represent a new therapeutic paradigm within TRD, defined not by a novel receptor target, but by controlled engagement of dysfunctional neural circuitry.

Legacy Assets

Cyclerion became an independent public company on April 1, 2019 through a tax-free spin-off from Ironwood Pharmaceuticals, Inc. to focus on the development of soluble guanylate cyclase (sGC) stimulators in both the central nervous system (CNS) and the periphery. The research and development of sGC stimulators has been discontinued and the company is leveraging the legacy sGC assets to generate non-dilutive capital to drive the development of CYC-126.

- In June 2021, Cyclerion entered into a license agreement with Akebia for the rights to praliciguat. Akebia paid a $3.0 million upfront payment upon signing the agreement. In December 2024, the company announced a re-negotiated mutually beneficial amendment to the original license agreement which included a $1.75 million payment from Akebia to Cyclerion, with $1.25 million paid in December 2024 and $0.5 million paid in September 2025. Cyclerion is eligible to receive milestone cash payments of up to approximately $558.5 million in total. Akebia recently announced the initiation of a Phase 2 trial of praliciguat in focal segmental glomerulosclerosis (FSGS) and the first patient dosed, which will trigger a $1 million milestone payment in the near-term.

- In May 2023, Cyclerion entered into an asset purchase agreement with Tisento Therapeutics for zagociguat that included an $8.0 million cash payment at closing along with $2.4 million for reimbursement for certain operating expenses related to the asset, and shares of common stock of Tisento comprising 10% of the then issued and outstanding equity securities of Tisento. In

January 2025, Tisento announced it had initiated the Phase 2b PRIZM trial of zagociguat for the treatment of fatigue, cognitive impairment, and other key aspects of the rare mitochondrial disease MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes).

- In July 2024, Cyclerion entered into an option to license agreement for olinciguat with a third party, which included a $150,000 option fee in August 2024 and subsequent fees totaling $80,000 to extend the term of the option agreement. Cyclerion and the optionee were unable to agree upon terms of a license agreement and in October 2025 the option agreement was terminated.

Intellectual Property and Exclusivity

Cyclerion's intellectual property strategy for CYC-126 reflects the platform nature of the program and the use of established, off-patent pharmacologic agents. Unlike traditional drug development programs centered on novel molecular entities, CYC-126's defensibility is expected to derive primarily from method-of-use claims, system-level protection (the integrated system design and manufacturing), and proprietary know-how related to EEG-guided brain state control.

One component of Cyclerion's intellectual property position is a patent license agreement entered into with the Massachusetts Institute of Technology (MIT) in September 2025. Under this agreement, Cyclerion obtained rights to a portfolio of patents and patent applications originating from academic research conducted at MIT. While the specific patents covered by the license have not been publicly disclosed in detail, the company has indicated that the licensed intellectual property underpins the core concepts of EEG-guided anesthetic brain state modulation for neuropsychiatric indications, including methods of inducing and maintaining defined neurophysiologic states using anesthetic agents for the treatment of depression and other neuropsychiatric conditions.

The pharmacologic components of CYC-126 (propofol and dexmedetomidine) are both widely used, generic anesthetic agents with no remaining composition-of-matter exclusivity. As a result, Cyclerion does not rely on drug substance patents to protect the program. Instead, the company's IP strategy is focused on protecting the specific therapeutic application of these agents in neuropsychiatric disorders, the parameters of administration, the proprietary software elements, the device-based components, and the integration of EEG-based closed-loop control.

Beyond formal patent protection, a significant component of CYC-126's exclusivity is likely to be data- and execution-driven. The identification of therapeutically relevant EEG signatures, the development of algorithms for state detection and control, and the correlation of EEG features with clinical outcomes constitute proprietary know-how that is not readily replicable. As clinical development progresses, these datasets may represent an increasingly important barrier to entry, particularly if specific EEG-defined states emerge as predictive of durable antidepressant response.

The closed-loop system architecture itself may further reinforce practical exclusivity. Integration of EEG acquisition, signal processing, and drug delivery within a controlled clinical framework introduces operational complexity that extends beyond the use of individual off-the-shelf components. The collaboration with MedSteer may enhance this effect by embedding aspects of the therapeutic workflow within specialized delivery and monitoring infrastructure used in regulated clinical environments. Regulatory exclusivity could provide an additional, though time-limited, layer of protection depending on the ultimate development and approval pathway. However, given the use of approved anesthetic agents, such exclusivity is not expected to serve as the primary source of long-term defensibility.

Financials and Capital Structure

On November 12, 2025, Cyclerion filed form 10-Q with financial results for the third quarter of 2025. The company report $800,000 in the third quarter of 2025 compared to $194,000 for the third quarter of 2024. The revenues in the current quarter derived from a purchase agreement with Akebia for the purchase of additional development materials. The revenue from the comparative quarter derived from an option

agreement with an optionee, under which the optionee had the option to enter into an exclusive license to olinciguat for human therapeutics. R&D expense for the third quarter of 2025 were $348,000 compared to $81,000 for the third quarter of 2024. The increase was primarily due to increased license fees, consulting fees, and outside service fees. G&A expenses for the third quarter of 2025 were approximately $1.5 million compared to approximately $1.2 million in the third quarter of 2024. The increase was primarily due to increased consulting, outside service, and corporate legal fees.

Cyclerion exited the third quarter of 2025 with approximately $4.6 million in cash and cash equivalents. We estimate that the company will need approximately $20 million to finance the company through initial data from the Phase 2 study in 2027 and approximately $50 million to get through the full proof-of-concept data in 2028. As of Nov. 10, 2025, Cyclerion had approximately 3.9 million shares outstanding and, when counting stock options, RSUs, and preferred stock, a fully diluted share count of 4.7 million. Importantly, the company has no debt or warrants.

Risks to Consider

In addition to the risks listed below, we encourage investors to read the company's latest 10-K filing that discusses additional risk factors.

Clinical Risk: CYC-126 is in early-stage development, and the planned Phase 2 proof-of-concept study is designed primarily to establish feasibility, safety, and mechanistic engagement rather than definitive efficacy. Although prior studies of propofol in TRD have demonstrated encouraging signals, these studies were small, heterogeneous, and not powered for regulatory endpoints. There is no guarantee that EEG-guided brain state induction will translate into consistent or durable antidepressant effects in a broader patient population. While EEG provides a well-established, objective measure of brain activity, the identification of specific EEG signatures that reliably predict antidepressant response remains an evolving area of research. It is possible that the targeted brain states selected for CYC-126 may not correlate with meaningful or durable clinical benefit, or that inter-patient variability in EEG expression could limit reproducibility despite closed-loop control.

Regulatory Risk: Although the pharmacologic agents used are FDA-approved, the combination of drugs, EEG-guided closed-loop control, and psychiatric indication introduces regulatory complexity. There is uncertainty regarding acceptable endpoints, trial design requirements, and the evidentiary standard required to support approval. Regulatory feedback could necessitate additional studies, extended timelines, or changes in development strategy. Even if CYC-126 is shown to be effective in clinical trials, there is no guarantee that would translate into approval by regulatory agencies.

Financial Risk: As of the most recent reporting period, Cyclerion has limited cash resources and the company will need significant amounts of additional financing in order to continue operations. Advancement of CYC-126 into and through Phase 2 clinical development will require additional capital, and there is no assurance that such funding will be available on favorable terms. Continued reliance on equity financing may result in dilution to existing shareholders.

Commercial Risk: The TRD treatment landscape includes a growing number of pharmacologic and device-based therapies, including approved NMDA antagonists, neuromodulation approaches, and emerging psychedelic-assisted treatments. While CYC-126 is differentiated by its state-based, EEG-guided approach, competing therapies with simpler administration, lower cost, or greater clinical familiarity could limit market adoption even if efficacy is demonstrated. Even if CYC-126 were to gain approval, there is no guarantee that it would be accepted by patients, physicians, or payers as a means to treat TRD.

MANAGEMENT PROFILES

Regina M. Graul, PhD – Chief Executive Officer

Regina M. Graul, Ph.D. has served on Cyclerion's Board of Directors since August 2024, as the President since December 2023 and as the company's President and Chief Executive Officer since August 2024. Before joining Cyclerion as President, Dr. Graul served as vice president, program executive at EQRx Therapeutics, Inc. from February 2021 where she led multiple portfolios and cross-functional research and development teams in oncology. From April 2019 through February 2021, Dr. Graul served as senior director, global development leader at Cyclerion and lead the olinciguat franchise. From 2004 through February 2021, Dr. Graul served in numerous roles of increasing responsibility across the organization at Ironwood Pharmaceuticals, Inc., most recently as the head of internal innovation and senior director of research and development. Dr. Graul did her post-doctoral work at MIT, received her Ph.D. in synthetic organic chemistry from Rice University and a B.A. in chemistry from Saint Anselm College.

Rhonda M. Chicko – Chief Financial Officer

Rhonda M. Chicko, C.P.A. is a consultant to Cyclerion and has served as the company's Chief Financial Officer since January 2024. Ms. Chicko has been consulting as a chief financial officer to various life science companies since October 2019. Ms. Chicko previously served as chief financial officer of Scholar Rock from April 2018 through October 2019 and vice president of finance at Editas Medicine from September 2015 through March 2018. From 2005 to 2015, Ms. Chicko worked at Ironwood Pharmaceuticals, Inc. in financial roles of increasing responsibility, culminating as senior director, finance and tax. Earlier in her career, Ms. Chicko held a range of positions at investment management and accounting firms, including Wellington Management Company, LLP and PricewaterhouseCoopers, LLP. Ms. Chicko holds a M.S.T. from Bentley University and a B.S. in accounting from Le Moyne College.

VALUATION

We are initiating coverage of Cyclerion Therapeutics, Inc. (CYCN) with a valuation of $8.00. Cyclerion is a pharmaceutical company that is pursuing a differentiated approach to neuropsychiatric drug development by targeting brain state resynchronization rather than single molecular pathways, with an initial focus on treatment-resistant depression. The company's lead program, CYC-126, combines two well-characterized anesthetic agents, propofol and dexmedetomidine, delivered via a proprietary electroencephalographic (EEG)-guided, closed-loop system designed to reproducibly induce resynchronized neurophysiologic states that have been associated with rapid and durable antidepressant effects. We believe this strategy reflects an effort to address both the biological complexity of depression and the reproducibility challenges that have historically limited anesthetic-based approaches in psychiatry.

CYC-126

Cyclerion's CYC-126 program is a clinically deployable, EEG-guided therapeutic platform for TRD. Rather than administering anesthetic agents at fixed doses, CYC-126 integrates continuous EEG monitoring with real-time adjustment of drug delivery to reproducibly induce predefined brain states associated with therapeutic benefit. By anchoring treatment to objective neurophysiologic endpoints, the approach seeks to reduce inter-patient variability, improve reproducibility of response, and mitigate risks associated with under- or over-exposure.

CYC-126 represents a shift from symptom-based pharmacotherapy toward state-based neurotherapeutics, in which treatment success is achieved by engagement of a target brain state combined with structured patient feedback rather than solely by clinical observation. In the context of TRD, where heterogeneity of response and delayed onset remain major challenges, the program leverages continuous EEG monitoring as both pharmacodynamic readouts and control variables, enabling a more precise and mechanistically grounded intervention.

The pharmacologic backbone of CYC-126 consists of propofol and dexmedetomidine, two intravenous agents with complementary and well-understood neurophysiologic effects. Within the CYC-126 framework, these agents are not positioned as standalone antidepressants but as tools to reliably access and shape specific brain states. Propofol enables rapid induction of deep cortical states characterized by large-scale network reorganization, while dexmedetomidine modulates arousal circuitry to stabilize and refine EEG expression and enables the use of less propofol, thus improving recovery and making treatment more desirable for patients. Their combined use allows control over both the depth and qualitative features of the induced brain state.

CYC-126 is being advanced toward a Phase 2 proof-of-concept study in TRD. The planned clinical development strategy emphasizes demonstration of feasibility, safety, and reproducible brain state induction, alongside exploratory assessments of antidepressant efficacy and durability of response. By anchoring clinical evaluation to objective EEG endpoints, the program aims to generate mechanistic evidence of target engagement alongside traditional clinical outcome measures.

The data generated from the Phase 2 program are intended to inform subsequent trial design. Specifically, Cyclerion plans to use EEG-outcome correlations to refine target state definitions, optimize treatment duration, and identify responder subgroups. This adaptive learning approach is consistent with the platform nature of CYC-126 and reflects an understanding that the optimal therapeutic brain state may not be fully defined at study initiation.

Valuation

We value Cyclerion using a probability adjusted discounted cash flow model that takes into account potential future revenues of CYC-126 in treating treatment-resistant depression (TRD). While not currently incorporated into the model, the company does have plans to pursue CYC-126 in patients with additional neuropsychiatric conditions and this represents potential upside to the valuation.

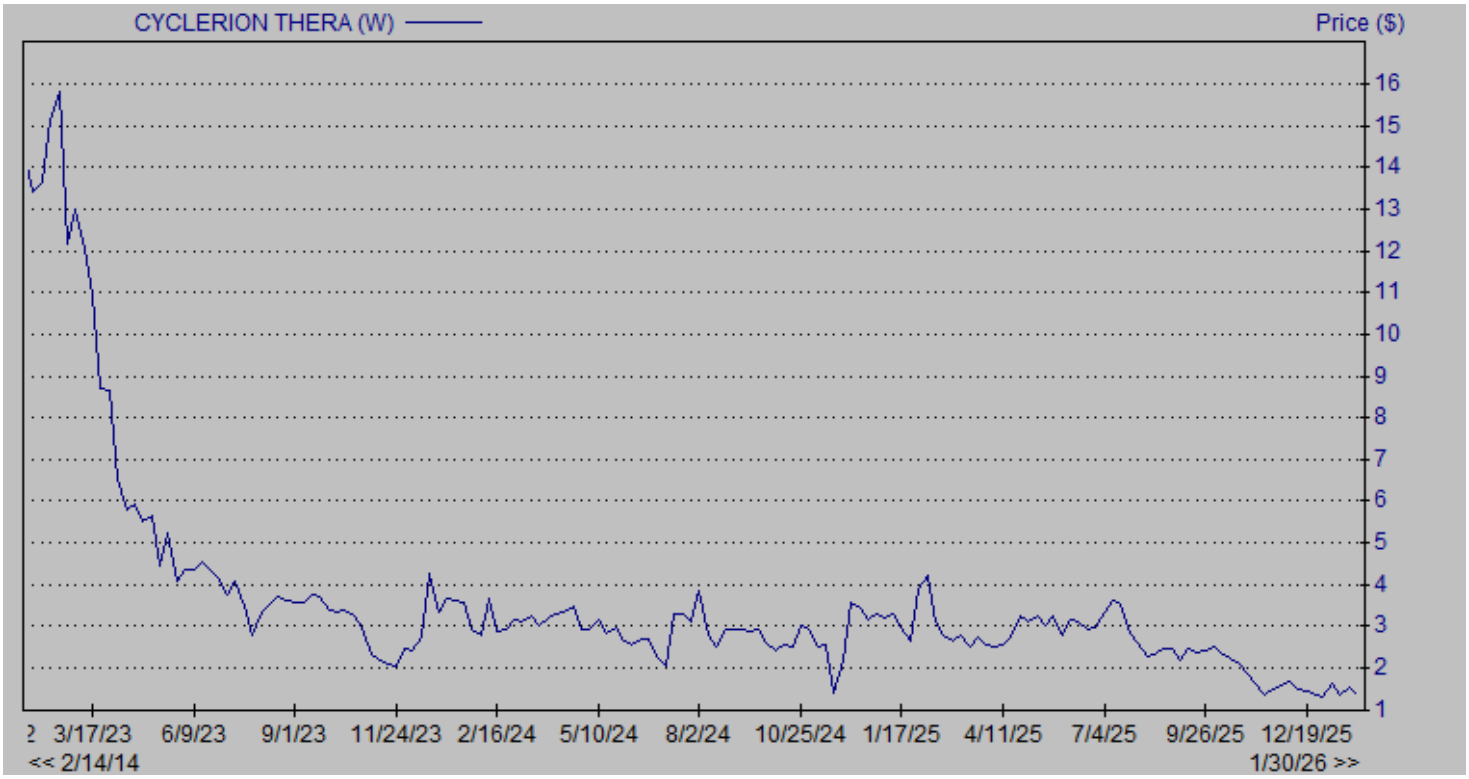
For TRD, we estimate there are approximately three million patients in the U.S. While TRD is defined as depression that does not respond to at least two antidepressants of adequate dose and duration, Cyclerion will be targeting the entire TRD population and not just TRD patients that have already failed other therapies. Following initiation of the Phase 2 proof-of-concept study in the second half of 2026, we anticipate initial data from that study in 2027 and the full dataset to be available in 2028. We estimate that positive results will lead to a Phase 3 program initiating in 2029, topline data reported in 2032, and the potential for approval in 2033. Electroconvulsive therapy (ECT) was used to treat approximately 100,000 patients in 2024, even with the acute and chronic safety concerns associated with the procedure. Since these concerns are not an issue for CYC-126, we believe CYC-126 could be used to treat at least double that number of patients per year. We model for patients to be treated an average of 15 times per year (nine induction treatments and then six maintenance treatments), however there will probably be some variance in that number. Modeling for 200,000 patients treated per year leads to peak sales of approximately $2 billion, which we model as occurring nine years after approval. Prior to commercialization, we model operating expenses on an absolute basis that transitions to revenue-based assumptions post-launch as the business scales. Using a 12% discount rate and a 33% probability of approval leads to a net present value for the TRD indication of $189 million. Combining that with the current cash balance and dividing by the diluted share count plus an additional 20 million shares to account for future dilution leads to a valuation of $8.00 per share.

PROJECTED FINANCIALS

Cyclerion Therapeutics, Inc.	2024 A	Q1 A	Q2 A	Q3 A	Q4 E	2025 E	2026 E	2027 E
CYC-126	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
License and other revenues	$2.0	$0.1	$0.1	$0.9	$0.1	$1.1	$0.0	$0.0
Total Revenues	**$2.0**	**$0.1**	**$0.1**	**$0.9**	**$0.1**	**$1.1**	**$0.0**	**$0.0**
Cost of revenues	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Research & development	$0.3	$0.0	$0.1	$0.3	$0.2	$0.6	$6.0	$8.5
General & administrative	$5.3	$1.5	$1.7	$1.5	$1.5	$6.2	$7.0	$7.3
Operating Income	($3.6)	($1.5)	($1.7)	($1.0)	($1.6)	($5.8)	($13.0)	($15.8)
Non-Operating Expenses (Net)	$0.6	$0.0	$1.3	$0.0	$0.1	$1.5	$1.0	$1.0
Pre-Tax Income	($3.1)	($1.4)	($0.4)	($1.0)	($1.5)	($4.3)	($12.0)	($14.8)
Income Taxes	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Net Income	**($3.1)**	**($1.4)**	**($0.4)**	**($1.0)**	**($1.5)**	**($4.3)**	**($12.0)**	**($14.8)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($1.21)**	**($0.56)**	**($0.11)**	**($0.31)**	**($0.38)**	**($1.34)**	**($1.20)**	**($0.99)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	2.5	2.6	3.1	3.2	3.9	3.2	10.0	15.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

HISTORICAL STOCK PRICE



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