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Cybin Inc. (NYSE American:CYBN, US$0.35; CBOE:CYBN, C$0.48)

Initiating Coverage with BUY (Speculative); TP US$3.00. Leading Innovative Psychedelic.

Bloom Burton is initiating research coverage of Cybin Inc. with a BUY rating (Speculative risk). Target price of US$3.00 is based on 6.0x Bloom Burton's peak worldwide sales estimate (US$2.1B in 2032), discounted 8 years (12% rate) and risk adjusted using a 55% probability of success.

Psychedelics are emerging as a new option for depression, a condition suffered by >20 million Americans. Additional mood disorders potentially benefiting from psychedelics include PTSD and anxiety. Markets are large, with antidepressant drug sales in the U.S. reaching $6B in 2023 despite genericization of first line therapies.

Psychedelics (re)establish neural connections lost in depressed patients. Clinical trials demonstrating superior efficacy of psychedelic drugs vs current antidepressants have been reported across multiple psychedelic drug classes including tryptamines, lysergamides and phenethylamines.

Among the numerous psychedelic programs, the furthest advanced are based on unmodified or slightly modified molecules with clinical shortcomings and limited IP potential.

Cybin's CYB003 is the most advanced 'next generation' psychedelic - an active deuterated analogue of tryptamine, psilocybin.

Compared to natural psilocybin, CYB003 has superior PK and because of this, provides a shorter hallucinogenic "trip time" (which improves efficiency of clinics) with signs also of improved safety. Composition of the molecule is protected by a recently issued U.S. patent which provides coverage until at least 2041.

In a 34-patient placebo-controlled phase 2 trial in patients with major depressive disorder (MDD) who were not responding adequately to their current antidepressant medication, a single treatment with CYB003 beat placebo by 13.8 points on MADRS at 3 weeks (SSRIs, on average, beat placebo by approximately 2 points and only after longer treatment periods); 44% of patients treated with CYB003 responded at 3 weeks and 75% of patients were in remission 4 months after receiving two treatments.

A phase 3 MDD program including two clinical trials is expected to begin in mid-2024 with first results expected in mid-2026. Cybin is also developing CYB004, a deuterated dimethyltryptamine in a randomized phase 2 trial (n=36) in patients with general anxiety disorder (top-line results expected in 4Q-2024). The company recently raised US$150M and expects this will fund both the CYB003 phase 3 program, and the CYB004 phase 2.

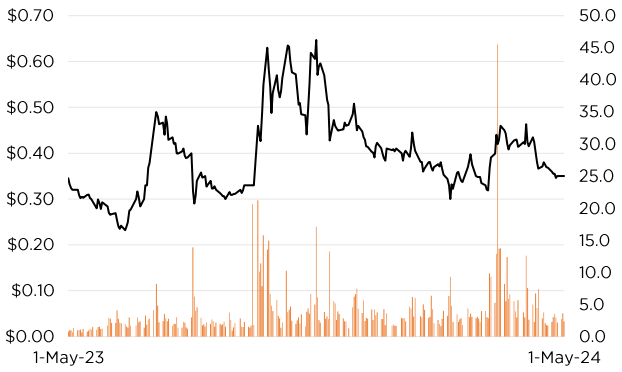
The main risk for CYBN is competition in a busy space, however, CYB003 offers material benefits in a large market, and we believe our estimates are conservative.

Rating:	BUY
Risk:	Speculative
12 Month Price Target:	US$3.00

Price	US$0.35
Implied Return	757.1%
Fiscal Year End	March 31
52 Week Range	US$0.21-US$0.74
Shares Outstanding (M)*	765.0
Market Cap. (M)	US$267.7
Cash**	US$169.5
Avg. Daily Volume (M)	5.52

*Includes Class B shares; **Proforma financing

(C$M, except EPS)	2023A	2024E	2025E	2026E
EPS	($0.26)	($0.24)	($0.11)	($0.12)
Cash (EOP)	$16.6	$217.6	$150.8	$74.5



This report is priced as of prior trading day's close. All values in US$ unless otherwise noted.

Company Overview

Cybin is a clinical stage biopharmaceutical company focused on advancing psychedelic-based compounds, delivery mechanisms, and protocols as a potential treatment for various psychiatric and neurological conditions. Psychedelic-based therapeutics have potential advantages over traditional MDD treatments including rapid and sustained therapeutic effects, as well as efficacy with only 1-2 doses compared to existing chronic daily treatments.

The company is developing preclinical and clinical stage drug candidates as well as drug delivery systems. Their IP portfolio consists of over 50 patents granted with 170 filings pending across 6 patent families spanning 7 research programs. Their lead drug compounds contain structural modifications of known tryptamine and phenethylamine derivatives – the modifications made to improve the pharmacokinetic properties while maintaining pharmacology.

Cybin is evaluating a wide array of novel, synthetic psychedelic active pharmaceutical ingredients intended to be delivered orally or through alternative drug delivery modalities including inhalation, intravenous (IV), intramuscular (IM), or subcutaneous administration.

The company has 3 key clinical programs under development including:

1. Deuterated psilocybin analog (CYB003)
2. Deuterated dimethyltryptamine program (dDMT)/ DMT (CYB004 (lead), SPL028, and SPL026)
3. Phenethylamine derivatives program (CYB005)

CYB003 is an orally delivered deuterated psilocybin analog which has shown several advantages compared to traditional oral psilocybin, including faster onset of action, shorter duration of effect, less variability in plasma levels, and improved brain penetration. It is currently being studied for the treatment of major depressive disorder (MDD) and alcohol use disorder (AUD). Topline phase 2 data for CYB003 in MDD has shown preliminary evidence for significant and durable clinical improvements in depression symptoms. The phase 3 program is anticipated to include 2 studies with a total of 550 patients enrolled. Each study is expected to run for approximately 18-24 months, with first topline results expected in mid-2026. CYB003 for the treatment of AUD is in preclinical stages of development.

The company's DMT program is currently focused on CYB004, a deuterated, IM-administered analogue of DMT. In October 2023, Cybin acquired Small Pharma to consolidate IP related to therapeutic uses of DMT. Small pharma was developing DMT-based drugs, SPL026 and SPL028, with positive phase 1/2 results reported for SPL026 in January 2023. These compounds have since been deprioritized, with CYB004 becoming the lead DMT-based candidate for the company. Cybin initiated a randomized, double-blind phase 2 study of CYB004 for generalized anxiety disorder (GAD) in March 2024. The study aims to recruit approximately 36 participants split into 2 groups, with the treatment group receiving two IM doses of CYB004, three weeks apart, while the second group will receive two low-dose control administrations. The primary endpoint is a change in the Hamilton Anxiety Rating Scale (HAM-A) with the participants followed for a period of 3 months and an optional additional assessment at 6 months. Topline safety and efficacy data are expected in Q4 2024.

The CYB005 program is focused on the development of therapeutic phenethylamine-based drugs such as MDMA derivatives. The company's proprietary approach to phenethylamines modification with novel chemistry, proprietary formulations and directed delivery systems has yielded a number of novel, IP protected leads with therapeutic potential. These compounds are still in the preclinical stage of development, with ongoing *in vitro* and *in vivo* studies being conducted to investigate the effects of phenethylamine derivatives on neuroplasticity, and for the potential treatment of psychiatric disorders, neuroinflammation and other neurological conditions.

Management has extensive experience in the pharmaceutical industry, including medicinal chemistry and drug delivery, as well as leading the clinical development of novel medications for multiple psychiatric indications.

Cybin went public via reverse takeover in November 2020 and recently raised US$150 million via private placement to fund the phase 3 CYB003 MDD and phase 2 CYB004 anxiety trials (proforma cash: approximately US$170M), which should provide a runway into early 2027 allowing for key data readouts. Following the financing, the company has 759.7M common shares, 5.3M Class B shares, 114.7M warrants (C$0.79 weighted average exercise price) and 67.1M options (C$0.94 weighted average exercise price) outstanding which if fully exercised, would result in proceeds of C$153.8M (US$112.2M). Institutional shareholders include Deep Track Capital, RA Capital Management, Point72 Asset Management, Anson Funds Management, Avidity Partners, Acorn Bioventures, Altium Capital, Logos Capital, Octagon Capital, Rosalind Advisors, and Sphera Healthcare among others.

Major Depressive Disorder

MDD is characterized by persistent feelings of sadness and loss of interest which can interfere with work, study, sleep, eating and social activities. Treatments include medication, psychotherapy or both.

People with clinical depression typically have low levels of neurotransmitters: serotonin, dopamine and norepinephrine each of which is released by presynaptic nerves triggered by nerve impulses in different parts of the brain, followed by their biding to postsynaptic receptors which leads to nerve impulses in the postsynaptic neurons. Although the three neurotransmitters regulate different functions in the brain (serotonin - mood, perception, memory; dopamine - reward, movement regulation; norepinephrine - alertness, arousal), the nerve pathways that are affected by each can project to common regions in the brain (eg., prefrontal cerebral cortex, hypothalamus).

Low CNS neurotransmitter levels are often caused by increased levels of monoamine oxidase A (MAO-A), an enzyme that breaks down the neurotransmitters. This can lead to cortical neuron atrophy including neurite retraction, dendritic spine loss, and decreased synaptic density as well as neurotransmitter imbalances.

One or more factors may be causal: physical changes in the brain which may include inflammation, oxygen restriction and shrinkage; altered production of neurotransmitters at the cellular level; hormonal changes which affect neurotransmitter balance which may be related to pregnancy and the postpartum period (rapid changes in estrogen and progesterone), thyroid problems, menopause and other conditions.

As it is more common in people whose relatives also have the condition, depression has also been linked to genes such as SLC6A4 which encodes the serotonin transporter, 5-HTT, TPH2 which encodes tryptophan hydroxylase, the rate limiting enzyme in serotonin synthesis, the gene encoding brain-derived neurotrophic factor (BDNF) which plays a role in the maintenance and survival of neurons and in synaptic plasticity, among others.

Treatment-Resistant Depression (TRD)

Treatment-resistant depression is defined by the FDA and EMA as failure to respond to two or more antidepressant regimens despite adequate dose and duration and adherence to treatment. There are several identifiable reasons that antidepressants may stop working including drug or alcohol use, new stressors causing a mood or hormonal response that overwhelms drug effect, or other medications. Often, however, there seems to be no reason for development of resistance.

Similarly, for many patients who never respond to current antidepressant drugs, reasons appear to be diverse and complex. One group at the Salk Institute recently identified serotonin receptor upregulation (and hyperactive response to serotonin) as cause for SSRI resistance in some patients (link).

In other patients, the same group detected structural differences in neurons, with the neurons of SSRI non-responders having much longer neurites than those of SSRI responders causing disruption of communication in serotonin brain circuits. Genetic analysis also uncovered, in non-responder cells, much weaker expression of the genes *PCDHA6* and *PCDHA8* which have a key role in the growth and formation of nerve cells (link; link). Other

genetic variants have also been shown to alter the effect of SSRIs. MTHFR C677T C/T or T/T variants can lead to decreased synthesis of monoamines, leading to lower neurotransmitter levels even if reuptake is inhibited, and susceptibility to depression (link). Some reuptake transporters bind antidepressants less well, such as SLC6A4 S/S variants (link).

Another group at Northwestern (link) studied the expression of 30,000 genes in animal models of depression and stress, and found very little overlap between the two models. Therefore, while chronic stress may induce depressive behaviour, its molecular underpinnings differ from those of endogenous depression in animals and possibly in humans, suggesting the need for different treatments. Furthermore, the group's work showed that changes in expression of monoaminergic transmission-related genes in both models were not consistently linked to either the depressed or stress states, again speaking to heterogeneity at the causal level, and providing a possible explanation for the differential responsiveness of MDD patients to current neurotransmitter-based therapies. The Northwestern group found signs that early changes in the development of neurons may be causal to depression independent of stress. To our knowledge, however, that group has not elucidated underlying biology of the developmental changes, although there may be some cross-over to the findings of the Salk group.

Overall, depression is a heterogenous disease with multiple etiologies. As more biomarkers are identified, it should become possible to better target therapies to individual patients, but this is still a few years off. In the meantime, psychedelics are attractive despite drawbacks (administration and monitoring requirements; addiction potential) because they appear to be broadly acting even in refractory patients, and because they add more tools to the toolbox.

Prevalence and Market Size

Globally, approximately 300 million people suffer from depression. In the United States, 5% to 9% of the population has at least one episode of Major Depressive Disorder (MDD) each year (link), with approximately 60% seeking treatment (75% of those receive pharmacological treatment), and the yearly economic burden has been estimated at $210 B (link).

With current antidepressant medications, patients require at least a 2-4 week course of treatment before experiencing any beneficial effects (remission, if achieved, after an average 47 days) and up to 40% of patients do not improve at all to their first line drug treatment, and only 40% experience remission (link).

Precedence Research estimates that the U.S. market for antidepressants is currently $6.0 B (link), while Data Bridge Market Research forecasts that the global market for pharmaceutical psychedelics will reach $6.9B by 2027 (link).

Treatment Algorithm

If a primary care doctor has prescribed an SSRI or SNRI and symptoms continue or recur despite treatment, psychotherapy with a psychiatrist and/or switching or combining antidepressants are common next steps. It is believed that switching from one antidepressant to another may result in better outcomes despite the drugs' common goal of modulating monoamine neurotransmitters, due to each drug's slightly different mechanism of action. For example, Zoloft has some DNRI effect, Paxil has some NE effect, while Celexa and Lexapro are the most pure SSRIs. In addition, the way each drug binds to the reuptake transporter can be different.

Should patients continue to relapse, they are considered treatment resistant. The chances of remission after two trials of medication decreases substantially and treatment options become much more complex. Physicians at this point may augment treatment with off-label antianxiety or antipsychotic drugs, transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), electroconvulsive therapy (ECT), IV infusions of ketamine and esketamine. For TRD specifically, there are currently only two pharmacological agents that are approved by the FDA: Symbyax (a combination of olanzapine and fluoxetine; approved in 2009) and Spravato (approved in 2019).

Current Medicines to Treat Depression

Outside of the approval of Spravato (esketamine) and the associated wave of interest in psychedelics, there has been no significant change in the pharmacological treatment of depression since the 1990s when selective serotonin reuptake inhibitors (SSRIs) were introduced. Serotonin is one of three major monoamine neurotransmitters which signal between nerves in the brain (the other main neurotransmitters are dopamine and norepinephrine). In addition to promoting signaling in the brain, over time, SSRIs also induce neuroplastic changes (growth and reorganization of neural networks) which facilitate relearning (link).

SSRIs, serotonin and selective norepinephrine reuptake inhibitors (SNRIs) as well as earlier generation monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants work by increasing levels of serotonin and, in the case of SNRIs, norepinephrine, in the synaptic cleft between neurons in the brain. SSRIs, SNRIs and tricyclics increase neurotransmitter levels by blocking their reabsorption back into the nerve cells that released them; MAOIs prevent their breakdown.

The older MAOIs and tricyclic antidepressants are highly effective, but burdened with numerous side effects (dry mouth, nausea, diarrhea or constipation, drowsiness or insomnia, weight gain, excessive sweating, urinary retention, sexual dysfunction, cardiovascular problems). Many of these side effects are avoided or reduced with SSRIs and SNRIs, and as a result, the newer reuptake inhibitors took over first-line treatment of MDD upon their entry onto the market. Despite the side effects, the older antidepressants are still used as second or third-line options in patients who do not respond to SSRIs and SNRIs, as are atypical antidepressants (eg. mirtazapine - noradrenergic antagonist; trazodone – serotonin antagonist and reuptake inhibitor; bupropion – dopamine reuptake inhibitor). All main classes of legacy antidepressant drugs are now genericized, which will push new (more expensive options) to 2L or later. As discussed above, however, there remain millions of patients who do not respond to current therapies.

In March 2019, Johnson & Johnson's nasal esketamine spray, Spravato, was approved by the FDA in conjunction with an oral antidepressant for treatment of depression in adults with TRD, thus becoming the first N-methyl D-asparate (NMDA) receptor antagonist approved for psychiatric use. Antagonism of the NMDA receptor modulates the balance between two other neurotransmitters: neuroexcitory glutamate and neuroinhibitory GABA. Because of the risk of serious adverse outcomes resulting from sedation and dissociation caused by Spravato, and the potential for abuse and misuse of the drug, it is only available through a restricted distribution system, under a Risk Evaluation and Mitigation Strategy (REMS) and must be administered by a healthcare provider. Despite the restrictions, sales of Spravato were $690M in 2023 (+84% Y/Y), and are expected to grow to >$2B by 2030 (*source: Evaluate Pharma*).

In August 2022, Axsome Therapeutics' (NASDAQ:AXSM; unrated) oral NMDA antagonist, Auvelity, was approved for treatment of MDD including front-line. Auvelity combines dextromethorphan and bupropion. Both drugs increase the availability of norepinephrine by inhibiting its reuptake and also act as alpha-4-beta-2 nicotinic (nACh) antagonists. Bupropion also increases the availability of dopamine by blocking its reuptake. Dextromethorphan acts as NMDA receptor antagonist and increases glutamate levels, it also increases serotonin levels by blocking its reuptake and boosting its action in the dorsal raphe via sigma-1 agonism. Auvelity is differentiated clinically based on its mechanism, and by its ability to work quickly, with symptom improvement seen within 1 week of treatment onset (vs up to 6-8 weeks for legacy antidepressants) and remission seen in some patients by week 2. In a 318 patient phase 3 study, patients treated with Auvelity improved by 15.9 points on MADRS at week 6, bettering the 12.1 point improvement among patients receiving placebo by 3.8 points (link). While dextromethorphan makes bupropion work faster and boosts its antidepressant efficacy, it also adds side effects, particularly drowsiness. However, no cases of psychosis, dissociation, serotonin syndrome, or addictive behaviors were seen with Auvelity.

Both Spravato and Auvelity are fast acting, with Spravato the faster of the two. Because Spravato is a nasal spray, it enters the bloodstream quickly, reaching its plasma highest concentration within 20 to 40 minutes. As a

result, improvement in depression symptoms can occur as quickly as 2-4 hours. With Auvelity, on the other hand, improvements are felt approximately 1 week after starting treatment due that drug's titration schedule.

Exhibit 1 details some of the most widely used antidepressant drugs, noting that some of the drugs included are approved for more than just treatment of depression. For example, Cymbalta (duloxetine) is approved to treat MDD, anxiety, diabetic peripheral neuropathic pain, fibromyalgia and chronic skeletal pain.

Exhibit 1. Major antidepressant medicines

Brand (Generic)	Company	Mechanism	Year Approved	Indication	Peak Sales
Parnate (tranylcypromine)	Smith, Kline and French	MAOI	1961	MDD, GAD , etc.	N/A
Elavil (amitriptyline)	Merck	tricyclic	1961	MDD	N/A
Wellbutrin (buproprion)	GSK	NE and dopamine reuptake inhibitor	1985	MDD	$2.3B
Prozac (fluoxetine)	Eli Lilly	SSRI	1987	MDD, OCD, etc.	$2.8B
Effexor (venlafaxine)	Pfizer	SNRI	1993	MDD, GAD , etc.	$2.7B
Celexa (citalopram)	Forest	SSRI	1998	MDD	$1.1B
Zoloft (sertraline)	Pfizer	SSIR	1999	MDD, OCD, etc.	$3.4B
Paxil CR (paroxetine ER)	GSK	SSRI	2001	MDD, OCD, etc.	$2.7B
Lexapro (escitalopram)	Forest	SSRI	2002	MDD, GAD	$3.0B
Cymbalta (duloxetine)	Eli Lilly	SNRI	2004	MDD, GAD , etc.	$5.0B
					2023 Sales (2030E Sales)
Spravato (esketamine)	Janssen	NMDA receptor antagonist	2019	TRD	$689M ($2.1B)
Zulresso (brexanolone)	Sage	GABA-A agonist	2019	PPD	$10M ($10M)
Auvelity (dextromethorphan HBr + bupropion HCl)	Axsome	NMDA receptor antagonist	2022	MDD	$130M ($1.5B)

Source: STAT+; Symphony Health; Evaluate Pharma; company documents

Recently Approved Antidepressant Drugs

Zurzuvae (zuranolone)

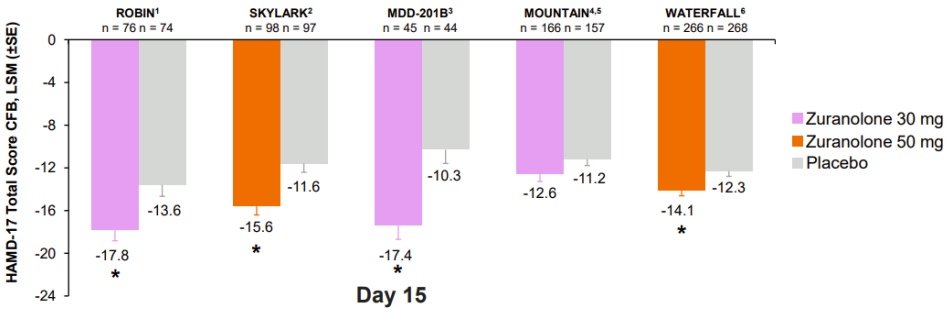
Sage's Zurzuvae was approved in the U.S. in August 2023 – the first oral drug for treatment of women with postpartum depression (the company's iv administered drug, Zulresso, was approved for the indication in 2019). Zurzuvae is partnered with Biogen (NASDAQ;BIIB; unrated) in the U.S. and with Shionogi (TYO:4507; unrated) in Japan, Taiwan and South Korea (Biogen also has an exclusive license to develop and commercialize the drug outside of the U.S. and Shionogi's markets). Biogen paid $1.5B upfront ($875M in cash and $650M equity investment) for rights to Zurzuvae and another drug (SAGE-324 for essential tremor), with an additional $1.6B in development and commercial milestones.

Zuranolone is a neuroactive steroid that binds to both synaptic and extrasynaptic GABA receptors, enabling the differential modulation of GABA signalling, which may play a role in restoring adaptive signalling in the brain. The drug is administered as a once daily oral therapy with a 2-week treatment course.

In PPD, zuranolone was studied in two pivotal phase 3 studies, ROBIN (efficacy and safety of 30 mg zuranolone in women with severe PPD) and SKYLARK (efficacy and safety of 50 mg zuranolone in women with severe PPD), as well as in 3 studies in MDD (217-MDD-201, MOUNTAIN and WATERFALL).

The primary endpoint in the studies was the statistical change in depression symptoms, as measured by the HAM-D scale at day 15. These studies demonstrated statistically significant (except in the MOUNTAIN study) improvements in depression symptoms after the two-week treatment period. However, the treatment effects for zuranolone are relatively modest (-4.2 in ROBIN and -4.0 in SKYLARK, both in PPD), although still clinically meaningful.

Exhibit 2. Summary of phase 3 trials for zuranolone in PPD (ROBIN, SKYLARK) and MDD (217-MDD-201, MOUNTAIN and WATERFALL) demonstrating improvements in depression symptoms.



Source: Sage Therapeutics Investor Presentation

Zuranolone's efficacy in PPD was rapid, demonstrating a -2.7 point HAM-D improvement vs placebo in the ROBIN study at day 3 and a -3.4 point improvement in the SKYLARK study at day 3 - much faster than conventional monoamine-based antidepressants.

The benefit also appears to be sustained, albeit less pronounced than at day 15, with a -2.9 point HAM-D improvement in the SKYLARK study at day 28 and a -3.5 point improvement at day 45.

At the same time that zuranoloe was approved for PPD, FDA refused to approve the drug for MDD, indicating that the application did not provide substantial evidence of effectiveness. In MDD phase 3 trials, zuranolone demonstrated a modest statistically significant 2-point reduction in HAM-D symptom scores at 3 days, but showed only a trend towards improvement over placebo at 15 days and was equivalent to placebo at 42 days (link).

Zuranolone is generally well tolerated, with the most common treatment emergent side effects being somnolence, dizziness, sedation, headache, diarrhea, nausea, and urinary tract infection. No evidence of withdrawal symptoms or increased suicidal ideation or behavior were identified.

Exxua (gepirone)

In September 2023, FDA approved Fabre-Kramer Pharmaceuticals' Exxua, for treating MDD. Gepirone exerts its effects through selective agonist activity at the serotonin 1A receptor. As well as its unique mechanism of action, Exxua is differentiated with a label that's free of warnings or side-effect language related to weight gain or sexual dysfunction.

Previously, the FDA refused to approve the drug in 2002 and 2004, voicing concerns over a number of failed studies that the agency believed outweighed a few positive ones. The company appealed, which led to a advisory committee hearing, and eventually the approval in 2023.

Age of Aquarius Redux – Psychedelic Drugs to Treat Depression

Psychedelic drugs offer a new approach for treating depression, with numerous clinical trials showing robust, rapid and durable benefits for patients resistant to current serotonergic therapies.

Most psychedelic drugs fall into one of the three families of chemical compounds: tryptamines, phenethylamines, or lysergamides . Each act as agonists on serotonin 2A (5-HT_{2A}) receptors - modulating the activity of key circuits in the brain involved with sensory perception and cognition.

The current wave of research into the use of psychedelics began in the mid-2010s, led by academic groups at the University of California, New York University, University of Zurich, Johns Hopkins University and Imperial College London, which showed that psychedelics, particularly psilocybin, could be potential treatments for TRD.

In addition to depression, companies are now actively researching the potential of psychedelics for anxiety, attention deficit hyperactive disorder (ADHD) and addiction disorders. Depression, post-traumatic stress disorder (PTSD) and addiction appear to share common neural pathways (link), tend to have high comorbidity (link) and are each multi-billion dollar drug markets globally. Each one of these indications represents a large market opportunity (Exhibit 3).

Exhibit 3. Global drug market values for indications being pursued by psychedelic drug developing companies.

	Patients	Market Value
Depression	264 MM	$9.6 B
Anxiety disorders	284 MM	$4.7 B
ADHD	212 MM	$9.5 B
Alcohol and Drug Use Disorders	178 MM	$5.8 B

Source: IQVIA Global Sales Report, 2021; Ritchie H, Roser M (2018) - "Mental Health". Published online at OurWorldInData.org

In recent years there has been a dramatic shift in mindset regarding the therapeutic potential of psychedelics in the treatment of mental health issues. This has been crystalized with the FDA awarding breakthrough therapy designations for molecules classified as Schedule I drugs (MDMA for PTSD and psilocybin for TRD), and the agency's March 2019 approval of Spravato (esketamine – also granted breakthrough designation) for treatment of TRD in adults and depressive symptoms in adults with MDD with acute suicidal ideation or behavior.

The new regulatory stance has led to increased interest by both the scientific and investment communities. Post-Spravato approval, more than 80 companies have arisen, devoted to developing or administering psychedelic compounds (link). Numerous studies are underway involving what are called 'classic' psychedelics, consisting of naturally occurring products that have been used in indigenous cultures for thousands of years as well as synthetic molecules such as LSD that were reclassified during the 1970s war on drugs (Exhibit 4). In addition to these molecules, sub anesthetic dosing of ketamine is seeing wider use off-label in depression and assisted psychotherapy, and the more potent (S)-enantiomer of ketamine, esketamine (Spravato) was approved by FDA in March 2019 as mentioned above. The less potent (R)-enantiomer is also being developed (phase 1) as an oral drug to treat depression by ATAI Life Sciences (NASDAQ:ATAI; unrated).

Exhibit 4: Schedule I psychedelic molecules and related studies underway

Molecule	Number of Studies (Clinicaltrials.gov)
Psilocybin	61
MDMA	64
LSD	15
DMT	12

Source: clinicaltrials.gov; Bloom Burton research

Mechanistic Rationale

While both psychedelics and typical antidepressants exert their effects through serotonin receptors, the psychedelics are direct agonists that act immediately and with great effect on the receptors, whereas SSRIs/SNRIs/MAOIs and tricyclics act over time to gradually increase endogenous serotonin levels (hence, the slower onset of antidepressant effects). Additionally, as reuptake inhibitors increase serotonin levels over time, serotonin receptors can become downregulated, giving rise to resistance (link). As a result, patients may need to withdraw in advance from their antidepressant medication to gain the full benefit. Theoretically, with psychedelics, if the serotonin receptors are directly hit hard with infrequent exposures, the effect should be both rapid and long lasting, with less chance of resistance mounting.

This appears to be the case – as well as the early dissociative effects, psychedelics have also been shown to promote the growth of neurons, dendritic spines and synapses (reversing the deleterious structural and functional changes associated with depression), as well as quiet existing negative thought patterns and making patients more receptive to psychotherapy.

Brain scans (measuring blood flow and electrical activity) of humans administered psychedelics show that the drugs quiet the default mode network, a collection of brain areas that together function as the "command-and-control" center of the brain. This allows for normal thought to be temporarily disorganized and for the formation of new connections/patterns, and possibly new thoughts, that would otherwise be prevented by an alert default mode network (link).

In vitro and *in vivo* experiments (conducted in fruit flies) showed that the neural growth is triggered by psychedelic drug stimulation of 5-HT_{2A} and TrkB (receptor for BDNF), which activates mTOR. The structural effect is comparable to, or greater than, ketamine (link), but unlike ketamine, the classic psychedelics are generally considered physiologically safe, with less risk of dependence and addiction (link). And, while the hallucinogenic effects tend to last as long as plasma concentrations of the drugs persist, sustained neural growth continues well beyond the short periods of stimulation (link; link).

The neuroplasticity induced by psychedelic drugs seems to move patients into a state in which ingrained negative neural pathways in the brain can be deprioritized in favor of new pathways formed around feelings of psychological wellbeing. While the biology of the response is not fully elucidated, we gain comfort from the mounting clinical evidence that psychedelic drugs are effective in patients suffering from depression. This includes patients who no longer respond, or never responded, to the classic monoamine neurotransmitter-based drugs which have been the mainstay for MDD for the past 60 years.

Delivering the Benefit

At the same time clinical research is taking place with psychedelic drugs, companies are recognizing that treatment of mental disorders with these drugs will not resemble the traditional care delivery models. Current usage of psychedelics in therapy consists of 'macro-doses' leading to hallucinogenic experiences during which patients are treated or monitored by health professionals. This is creating innovative approaches to treatment delivery, be it with treatment centers or digital toolsets, integrated with therapeutic protocols. Other companies are pursuing novel chemical entities with aim of 1) limiting the dissociative effects (visual and auditory

distortions, feeling of detachment from reality) of the classic compounds and 2) securing patent protected molecules for long term competitive advantage.

The Drugs - Rounds 1 and 2: Ketamine and Esketamine

Ketamine

Ketamine is a Scheduled III controlled substance. Although not a classic psychedelic, the drug does induce psychedelic experiences. Formally approved as an anesthetic agent for diagnostic and surgical procedures, but also used off-label at specialized treatment centers to quickly relieve depression in people who do not respond well to other treatment, ketamine was first synthesized in 1962, at Wayne State University. The drug exerts its effects principally through blocking N-methyl-D-aspartate (NMDA) receptors resulting in the excessive release of excitatory neurotransmitters glutamate and acetylcholine, with additional effects on dopamine and μ-opioid receptors. The drug also does have actions on the 5HT2A receptor but more weakly than tryptamine compounds such as psilocybin and N,N-Dimethyltryptamine (DMT).

At high concentrations, ketamine blocks the flow of ions triggered by the action of glutamate (the major excitatory amino acid in the brain) on the NMDA receptor. In this way, ketamine acts as a sedative (its initially intended use). However, at lower concentrations, ketamine's antagonism of the NMDA receptor leads to a 1-2 hour period of dissociation followed by anti-depressant and anti-suicidal effects which last 3-7 days, brought about by increased glutamate release in the prefrontal cortex (region of the brain responsible for controlling complex behavior, impulse control and emotional reactions; link).

Ketamine also causes neural structural changes. The initial glutamate surge triggers release of BDNF and activation of another major class of receptors, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Activation of AMPA receptors results in an increase in synaptic connections in brain regions known to undergo atrophy in depressed patients and stressed animals. In preclinical studies, a single dose of ketamine rapidly increased the number and function of synapses in excitatory neurons of the prefrontal cortex, as well as increased the amplitude and frequency of postsynaptic currents in pyramidal neurons (link). Additionally, ketamine rapidly reversed the synaptic deficits caused by chronic stress exposure, which correlated with a reduction in behavioral abnormalities, notably anhedonia (the inability to experience pleasure) and helpless behaviors (link).

In a multicenter, double-blind repeat dosing study, adults with TRD were randomized to receive either intravenous ketamine (0.5 mg/kg of body weight) or intravenous placebo either two or three times weekly, for up to 4 weeks. The primary outcome measure was change from baseline to day 15 in total score on the Montgomery-Åsberg Depression Rating Scale (MADRS). In total, 67 randomized patients received treatment. In the twice-weekly dosing groups, the mean change in MADRS score at day 15 was -18.4 (+/- 12.0) for ketamine and -5.7 (+/- 10.2) for placebo; in the three times a week groups, it was -17.7 (+/-7.3) for ketamine and -3.1 (SD+/-5.7) for placebo (link).

Headache, anxiety, nausea, and dizziness were the most common treatment-emergent adverse events and ketamine has a sedation risk along with the transient dissociative effects that require medical monitoring. The drug has also been associated with liver and urinary toxicity.

Most concerning are the long-term effects of ketamine use since tolerance and addiction (potentially related to its action on opioid receptors) can occur when the drug is taken for prolonged periods at high doses. Abuse can cause high blood pressure and dangerously slowed breathing, psychosis (delusions, delirium) similar to the related, but more potent NMDA receptor antagonist, phencyclidine (PCP, angel dust), and combined with alcohol, ketamine can be fatal. Long term, users may become depressed and irritable, and suffer insomnia, ulcers, bladder and kidney problems and stomach pain.

For the roughly 50% of patients who derive rapid benefit from ketamine, in order to prolong the antidepressant effect, ketamine treatment requires repeated clinical visits and once a round of infusion therapy is complete, symptomatic relief lasts only about 5 weeks before another round is needed (link).

Spravato (esketamine)

Isolated from racemic ketamine, the (S)-enantiomer (esketamine) is twice as potent as the mix of (S)- and (R)-enantiomers. This enabled Janssen (NYSE:JNJ; unrated) to develop a drug that could be delivered intranasally, (whereas ketamine is administered by infusion over 40 minutes). Head-to-head trials have not been conducted, however, cross-trial comparisons suggest that intravenous ketamine is moderately more effective than esketamine (link), although the nasal delivery of Spravato is more convenient, and approval of Janssen's product for depression supports reimbursement in some situations.

Spravato, was FDA approved in 2019 based on results of 4 efficacy studies, and one special safety study (link):

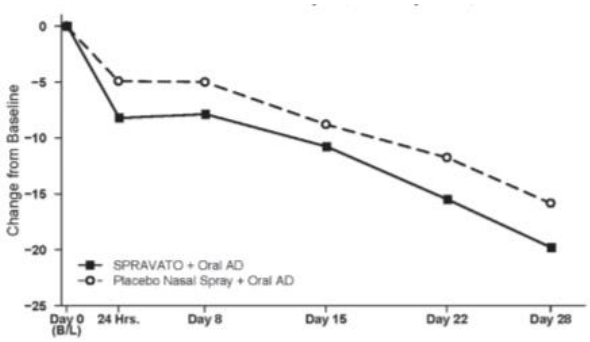
Study 1. Adult patients (n=223) with TRD (who had not responded adequately to at least two different antidepressants) were randomized to receive twice weekly doses of intranasal Spravato (56 mg or 84 mg) or intranasal placebo for four weeks. All patients also received open-label concomitant treatment with an oral antidepressant. The primary efficacy measure was change from baseline in the MADRS total score at the end of the 4-week treatment period. Spravato plus oral antidepressant demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus oral antidepressant (MADRS score benefit: 19.8 +/-1.3 vs 15.8 +/-1.3; LS mean difference (95% CI): -4.0 (-7.3, -0.6). Most of the drug's treatment benefit was observed by 24 hours following treatment.

Study 2. Remitters and responders from previous esketamine trials were assessed for time to relapse. Subjects were randomized separately to continue intranasal treatment with Spravato, or switch to placebo nasal spray, in both cases with continuation of their oral antidepressant, for a period of up to 80 weeks. The primary study endpoint was time to relapse (MADRS total score ≥22 for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse) in the stable remitter group. Patients who continued treatment with Spravato plus oral antidepressant experienced a statistically significantly longer time to relapse than did patients on placebo nasal spray plus an oral antidepressant: HR=0.49 (95% CI: 0.29, 0.84), however, the benefit was greatest early on and by week 38, 40% of patients in the Spravato group had relapsed (vs 43% in placebo). Although not the primary endpoint, time to relapse was also significantly delayed in the stable responder population: HR=0.30 (95% CI: 0.16, 0.55).

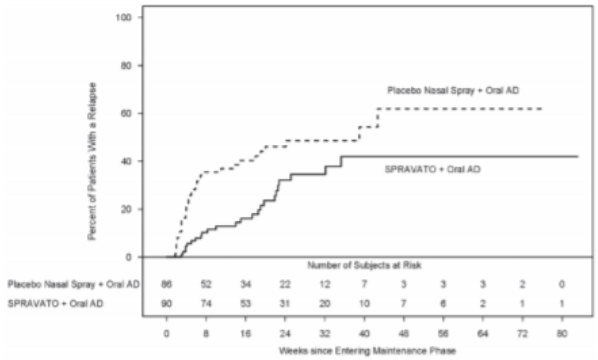
Studies 3 and 4. Spravato was evaluated in two identical phase 3 short-term (4-week) randomized, double-blind, multicenter, placebo-controlled studies in adults with moderate-to-severe MDD (MADRS total score >28) who had active suicidal ideation and intent. In these studies, patients received treatment with Spravato 84 mg or placebo nasal spray twice weekly for 4 weeks. All patients received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant or antidepressant plus augmentation therapy as determined by the investigator. The primary efficacy measure was the change from baseline in the MADRS total score at 24 hours after first dose. In both studies 3 and 4, Spravato plus standard of care demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus standard of care (MADRS score improvements – Study 3: -15.9 vs -12.0; Study 4: -16.0 vs -12.2). In both Study 3 and Study 4, Spravato's treatment difference compared to placebo was observed starting at 4 hours. Between 4 hours and day 25, both the Spravato and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through Day 25.

Exhibit 5. Spavrato clinical trial results. (A) Study 1; (B) Study 2; (C) Study 3.

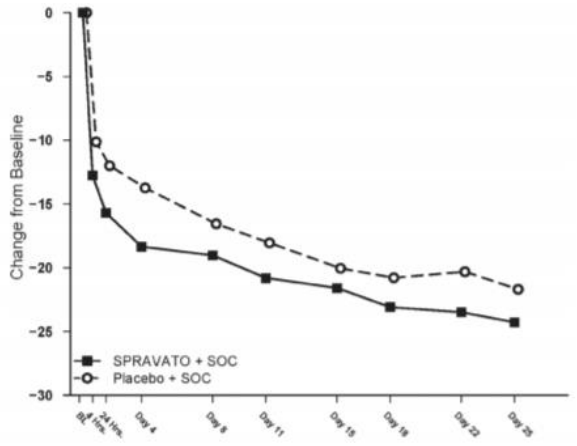
(A) Change from baseline in MADRS total score in patients with TRD (Study 1)



(B) Time to relapse in TRD patients who achieved stable remission previous Spravato studies (Study 2)



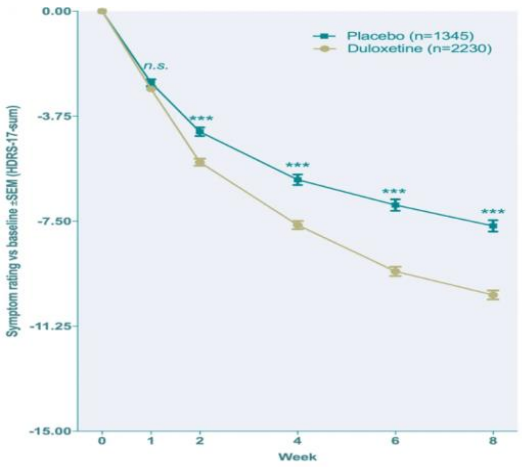
(C) Change from baseline in MADRS total score in patients with MDD with acute suicidal ideation or behaviour (Study 3)



Source: Spravato Prescribing Information

For comparison purposes, Exhibit 6 provides results of a meta-analysis of 15 company-sponsored, placebo-controlled studies assessing the efficacy of SNRI Cymbalta (duloxetine) in the treatment of depression.

Exhibit 6. Meta-analysis (15 studies) of clinical results for Cymbalta in the treat of patients with depression.



Source: Neuropsychopharmacology, 2020

By week-1, there was no separation between patients treated with Cymbalta or placebo (both groups improved by approximately 2.5 points on the 17-item, 52-point HAM-D scale). This is in contrast to the early separation between Spravato and placebo at 4 hours, and the approximate 8-point improvement (about 3.5 points better than placebo) on the 10-item, 60-point MADRS scale achieved with Spravato at week-1 (Figure 5A). By week-4, patients treated with Cymbalta improved approximately 8 points on HAM-D. By week-4, patients treated with Spravato had improved approximately 20 points on MADRS. Acknowledging that it is not ideal to draw conclusions by comparing results across trials, and that the scales used to measure the severity of depression were different for Cymbalta and Spravato, it is also important to note that the Spravato results were achieved in patients who had failed 2 prior antidepressants, presumably including SNRIs and/or SSRIs for most or all patients, and that patients in both arms of the Spravato trial received an oral antidepressant in addition to Spravato or placebo – i.e., the effect of Spravato was on top of standard care.

Along with the benefits, esketamine also shares the same risks as ketamine and as a result, has been approved with black box warnings related to sedation and dissociation (requiring the monitoring of patients for at least 2 hours after administration); abuse and misuse; and suicidal thoughts and behaviours. Based on these risks, Spravato is only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.

Currently, the cost of Spravato ranges from $410 to $475 per 28 mg unit. During induction (weeks 1-4), the starting dose is 56 mg followed by 56 mg or 84 mg doses twice a week. In weeks 5-8, 56 mg or 84 mg doses are administered once per week then after week-8, once every two weeks. Annual cost is approximately $30,000 to $45,000 in the first year, then $24,000 to $36,000 thereafter. In June 2019, the drug received a negative opinion from Institute for Clinical and Economic Review (ICER) due to an unfavorable cost/benefit assessment. According to ICER, the fair value-based price benchmark for Spravato is between $17,700 and $25,200 per year (an equivalent dose of generic ketamine can cost as little as $15.00).

Spravato's pricing, safety risks and mode of delivery have led to a more modest sales ramp than the initially projected blockbuster sales for the drug. Nonetheless, worldwide sales of the product reached $689M in 2023 (↑84% Y/Y; $589M in the U.S.), with sales forecasts climbing to $1.9B by 2028 (source: Evaluate Pharma).

The Drugs - Rounds 3, 4, 5 and…: Classic Psychedelic-based Drugs in Development for Treatment of Depression Including Major Competing Programs

Tryptamines: eg, psilocybin, N,N-Dimethyltryptamine (DMT)
Lysergamides: eg, lysergic acid diethylamide (LSD)
Phenethylamines: eg, 3,4-Methylenedioxymethamphetamine (MDMA)

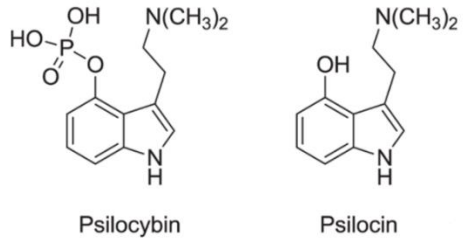
Molecules in each of the three classes are serotonergic, either directly as agonists on the 5-HT_2 receptors or, in the case of MDMA, also indirectly by increasing the amount of serotonin released into the synapse (link; link). 5-HT_{2A} is the main excitatory receptor subtype among the G-protein coupled receptors (GPCRs) which, when activated by psychedelics, increases potassium conductance, thus hyperpolarizing the nerve membrane and reducing the firing rate of serotonergic and pyramidal neurons in the cortex and hippocampus – resulting in the drugs' hallucinogenic/dissociative effects.

Most classic psychedelics have relatively long durations of dissociative effects, which is a burden in clinical practice since patients must be monitored and are limited in their activities: MDMA – 8 or more hours, psilocybin - up to 8 hours; LSD - approximately 10 hours; DMT – approximately 4 hours if swallowed (30-45 minutes if smoked).

Psilocybin

Psilocybin is naturally occurring in mushrooms of the Psilocybe genus. It is an inactive pro-drug that is dephosphorylated in the stomach upon ingestion, and on first pass through the liver. Dephosphorylation produces the active metabolite, psilocin (Exhibit 7), a strong agonist of serotonin 5-HT_{2A} receptors which has been shown to induce antidepressive effects which persist for six or more months following one or two treatments (link). Psilocybin was initially investigated as a potential treatment for mood disorders stretching back to the 1950s. Due to its addition to the list of scheduled substances in the 1970s, however, most research was halted until the recent shift in mindset at the FDA regarding psychedelics (discussed earlier).

Exhibit 7. Molecular structures of psilocybin and psilocin.

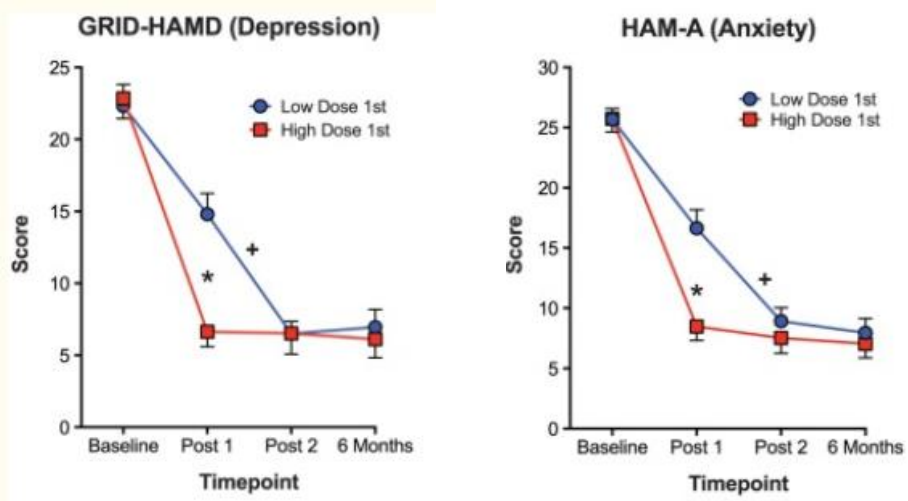


Source: The Journal of Antibiotics, 2020

In an open label proof-of-concept study (link) conducted at Imperial College London, measured on the 16-item, 27-point Quick Inventory of Depressive Symptoms (QIDS) scale, high dose psilocybin (2x 25 mg, 7 days apart) caused a marked and sustained improvement in depressive symptoms 1 week (-11.8) and 3 months (-9.2) after treatment, with no serious or unexpected side effects.

In a Johns Hopkins-run double-blind cross-over study, effects of high (22-30 mg/70 kg) and very low placebo-like (1-3 mg/70 kg) doses of psilocybin on 17 clinician and self-rated measures of depression and anxiety were assessed in terminally ill cancer patients (n=51). High-dose psilocybin produced large and statistically significant improvements in 16 of the outcome measures, including the two primary therapeutic outcome measures GRID-HAMD-17 (depression) and HAM-A assessed with the SIGH-A (anxiety). At 6-month follow-up, these changes were sustained, with 80% of patients continuing to report significant improvements in depression (Exhibit 8).

Exhibit 8. Effects of psilocybin vs baseline GRID-HAMD and HAM-A scores, 5 weeks after sessions 1 and 2, and after 6 months follow-up. Patients who received high dose psilocybin during session 1, switched to low dose for session 2, and vice versa.



Source: Journal of Psychopharmacology, 2016

In another UK study, psilocybin was compared head-to-head against the SSRI, escitaprolam. 59 patients with long-standing moderate-to-severe MDD were assigned in a 1:1 ratio to receive two separate doses of 25 mg of psilocybin 3 weeks apart, plus 6 weeks of daily placebo (psilocybin group), or two separate doses of 1 mg of psilocybin 3 weeks apart, plus 6 weeks of daily oral escitalopram (escitalopram group). All patients also received psychological support. The 16-item QIDS-SR-16 scale was used to assess efficacy, and there were 16 secondary outcomes, including QIDS response (defined as a reduction in score of >50%) and QIDS remission (defined as a score of ≤5) at week 6. The mean changes in the QIDS scores from baseline to week 6 were −8.0±1.0 points in the psilocybin group and −6.0±1.0 in the escitalopram group (95% confidence interval [CI], −5.0 to 0.9). A QIDS-SR-16 response occurred in 70% of the patients in the psilocybin group and 48% in the escitalopram group; QIDS-SR-16 remission occurred in 57% and 28%, respectively. While the result trended in favor of psilocybin, statistical significance was not reached, likely in part due to the small size of the trial. The incidence of adverse events was similar in both trial groups (link).

Following these encouraging small studies, Compass Pathways (NASDAQ:CMPS; unrated), initially founded as a non-profit company, began filing patents for a specific form (Polymorph A) of synthesized psilocybin. During this period, the company also developed and received Breakthrough Therapy Designation for its proprietary polymorphic crystalline oral capsule formulation of psilocybin, COMP360. Beginning in March 2019, COMP360 was tested in a randomized, controlled, double-blind phase 2b trial in 233 patients with TRD (22 sites across Europe and North America; NCT03775200) – becoming the most advanced clinical program testing the effects of psilocybin in depression.

In November 2021, Compass reported topline results for the trial. Patients with TRD went through a 3-6 week washout period for other antidepressants prior to receiving single doses of either 1, 10 or 25 mg of COMP360. Efficacy was robust: on the primary endpoint (3-week change from baseline on the 0-60 point MADRS scale), patients in the 25 mg treatment group improved by 12.0 points vs 7.9 and 5.4 in the 10 mg and 1 mg groups, respectively, and separation of the groups began as early as day 1 (p=0.002). The 25 mg 6.6 point improvement vs the 1 mg dose at 3 weeks was statistically significant, and superior to both conventional antidepressants (typically 2-point MADRS improvements vs placebo in less heavily pretreated patients, often with several weeks before curves begin to separate; link) and Spravato (4 point improvement vs placebo at 24 hours and 4 weeks). The remission rate at 3-weeks in 25 mg group was 29% - also beating 9% and 8% in the 10 mg and 1 mg groups, respectively.

However, when Compass subsequently published full phase 2b results in the NEJM in November 2022, the sustained response rate at 12 weeks was reported at 20% for patients in the 25mg group (link) - the difference apparently due to a switch in how response durability was assessed.

So, while efficacy was robust, it did decline over time following the single treatment. And the revised 12-week response rate reported in NEJM did not help quell questions regarding the durability of the treatment effect. That said, repeat dosing will be tested in phase 3, and it is important to contextualize the clinical benefit realizing that the patients studied had highly refractory TRD with limited options.

COMP360 was generally well tolerated, with more than 90% of treatment-emergent adverse events (TEAEs) being mild or moderate in severity. Four patients treated with 10 and 25 mg doses of COMP360 had suicidal thoughts including 3 with suicidal behaviours. Suicidality is not unexpected in TRD patients (potentially exacerbated by the washout period in the COMP360 trial), and has been linked to other antidepressants (link) which have, nonetheless, remained on the market on the basis of risk/reward.

Based on the phase 2 results, Compass is running a phase 3 program which includes two pivotal trials and one long-term follow-up study as follows:

- Pivotal trial 1 (COMP 005) (n=378): a single dose (25 mg) monotherapy compared with placebo (not the 1 mg dose of COMP360 used in the phase 2b). This trial is designed to replicate the treatment response seen in the company's Phase 2b study and to establish the safety of the drug vs a placebo. Results from this trial are expected by year end 2024;

- Pivotal trial 2 (COMP 006) (n= 568): a fixed repeat dose monotherapy using three dose arms: 25 mg, 10 mg and 1 mg. This trial is principally designed to investigate whether a second dose at 3 weeks can improve the response seen in the company's phase 2b study. Results from this trial are expected in mid-2025;

The primary endpoint in both pivotal trials is the change from baseline in MADRS total score at week 6. Both trials also have long-term follow-up periods that will help determine the durability of the COMP360 therapeutic response.

Compass is also expanding the development of COMP360 into PTSD (phase 2 trial initiated in July 2022) and in anorexia nervosa (phase 2 trial initiated in August 2022).

Compass will rely on patent and regulatory exclusivity for COMP360, with 5 U.S. patents granted (including a pharmaceutical composition comprising of crystalline Polymorph A of psilocybin combined with a pharmaceutically acceptable excipient, as well as additional formulation patents and methods of treating TRD with these formulations), and 5 years of possible data protection in the U.S., if COMP360 is registered as a New Chemical Entity. However, for some time, there has been a debate over the strength of Compass' patents, with detractors arguing that its proprietary Polymorph A is not in fact a unique compound, but rather a mixture of known polymorphs (thus already existing in the public domain and not patentable).

The validity of COMP360 patents was being challenged by a group called Freedom to Operate, which petitioned the Patent Trial and Appeal Board (PTAB) to revoke the COMP360 patents it had previously granted (disputed patents 10,947,257 and 10,954,259, directed to compositions and oral dosage forms containing the Polymorph A of psilocybin). Had PTAB seen some validity to Freedom to Operate's argument, the case would have gone to trial. However, on June 23, 2022, PTAB sided with Compass and its interpretation of the patents (that COMP360 is a unique chemical shape, Polymorph A, as determined by x-ray power diffraction), meaning the case would not proceed, with no right to appeal.

While the patentability of COMP360 seems validated legally for now, other manufacturers of psilocybin-based drugs may develop other polymorphs which may be ANDA eligible. Compass would likely sue for infringement

on the basis of its patents, and other polymorphs would need to have similar PK and stability. Nonetheless, we expect this will be an overhang for Compass, and to a certain extent, psychedelic drug developers more broadly, for the foreseeable future.

Despite the promising clinical proof-of-concept established by COMP360, delivery of the therapy is cost and time intensive. Psilocybin's lengthy 'trip time' of 6-8 hours requires a full day for each medicated session, and this is followed by the patient returning the next day and a week later for psychological support (consolidation) sessions to help patients derive their own insights and solutions from the experience with psilocybin. This leaves room for improvements to ease patient/caregiver burden, which opening the door for shorter acting psychedelics.

Another group looking to advance the benefits of psilocybin: Usona is a medical research organization which collaborates with scientists and clinicians - running clinical trials studying classic psychedelics including psilocybin and 5-MeO-DMT in mental health indications. Usona's randomized phase 2 trial of synthetic psilocybin vs niacin (placebo) in patients with MDD achieved its primary endpoint (MADRS score reduction at day 43; p<0.001) - results were published in August 2023 in JAMA (link; NCT03866174). In March 2024, Usona initiated a randomized phase 3 trial in MDD (NCT06308653). Approximately 240 adults will be enrolled in the trial and will receive either a 25mg dose of psilocybin, 5mg dose of psilocybin or placebo, administered alongside psychosocial support. The initial phase of the trial will span six weeks. Following this treatment period, participants will undergo a one-year follow-up to assess the durability of the treatment and its long-term safety. Primary completion of the study is expected in April 2025.

Reunion Neuroscience (private) is developing RE104, a pro-drug of 4-Hydroxy-N, N-diisopropyltryptamine (4-HO-DiPT), a tryptamine homologue of psilocybin. Previously the company reported phase 1 results which indicated that RE104 produces a psychoactive experience similar to psilocybin but with a reduced duration (three to four hours vs six to eight hours for psilocybin). A phase 2 study evaluating RE104 in moderate and severe PPD patients is planned to begin in mid-2024.

Cybin's CYB003 combines the strongest efficacy reported to-date for a psilocybin-based drug with the most attractive commercial characteristics in the class. It is discussed in depth later in this report.

3,4-Methylenedioxymethamphetamine (MDMA)

MDMA increases the amount of serotonin and dopamine released into the synapse due to its interaction with transporter proteins, SERT and DAT. Among the classic psychedelic drugs, MDMA is furthest along the regulatory path, being studied as a treatment for PTSD in conjunction with psychotherapy by Lykos Therapeutics (previously MAPS PBC). In a 90-patient phase 3 trial in which participants were randomized 1:1 to receive psychotherapy in conjunction with either MDMA or placebo, the mean change in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) scores at 2 months was -24.4 +/-11.6 in the MDMA group and -13.9 +/-11.5 in the placebo group (p<0.0001). Nearly 60% of patients who received MDMA-assisted therapy no longer met the clinical definition of PTSD after 3 sessions. MDMA was safe and well tolerated and was not associated with abuse potential (link). A long-term observational follow-up showed that participants in the phase 3 study had a durable response of at least six months, and in some cases a year or more. In a confirmatory phase 3 trial, MDMA-assisted therapy significantly reduced PTSD symptoms versus placebo with therapy as measured by CAPS-5 reductions at 18-weeks of -23.7 (-26.94, -20.44) for MDMA-assisted therapy versus –14.8 (-18.28, -11.28) for placebo with therapy. Based on the positive results for both phase 3 trials in PTSD, a NDA was submitted to FDA in December 2023 and accepted this February (PDUFA date: August 11).

N,N-Dimethyltryptamine (DMT)

DMT (active component in ayahuasca), like psilocybin, a tryptamine agonist of the 5-HT_{2A} receptor, has not been studied in clinical trials as extensively as psilocybin. However, there is evidence supporting its rapid benefit in TRD. In a randomized clinical trial of 29 patients given a single dose of ayahuasca or placebo, MADRS scores

were significantly lower in the ayahuasca group compared with placebo at days 1 and 2 and remission rate showed a trend toward significance at day 7 (36% v. 7%, p = 0.054; link).

While DMT is a much shorter acting psychedelic than psilocybin (4 hours when oral and 30-45 min when DMT is inhaled vs 8 hours with psilocybin and 4-6 hours expected with CYB003), the psychoactive experience with DMT can be very intense for patients, potentially increasing the risk of exacerbating anxiety. This can be problematic given the MDD/TRD patient population often has comorbid anxiety (link). Ayahuasca is also associated with side effects of nausea, vomiting and diarrhea. Despite the drawbacks, attracted by the short trip time, multiple groups including GH Research (NASDAQ:GHRS; unrated) and Cybin are developing DMT-based therapies as options for patients with TRD.

GH's lead candidate, GH001, is an inhalable formation of 5-MeO-DMT - a naturally occurring methoxylated derivative of DMT. The drug has psychoactive effects with very rapid onset (within seconds) and short duration (5-30 min of hallucinations), with initial treatment requiring a single visit and no accompanying psychotherapy. GH001 has been tested in two phase 1 clinical studies in healthy volunteers and a phase 1/2 trial in patients with TRD. In the phase 2 portion of GH's trial, a single dose of GH001 led to remission in 2/4 (50%) of patients at 12 mg and 1/4 (25%) of patients at 18 mg. Multi-dosing (up to 3 doses of 6, 12 and 18 mg in 3-hour intervals) at 7 days post-treatment, increased remission to 7/8 (88%) of patients with mean MADRS score improving by 24.4 (link). The clinical benefit appears strong (on par with Cybin's CYB003) and the short hallucinogenic period is attractive, however, the maximum benefit required multiple doses at 3-hour intervals and GH's trial was very small and with no control arm. Furthermore, while there were no serious adverse events reported, 1 patient (6%) in the phase 1 single dose part of the trial (n=18) experienced moderate elevation of heart rate and 2 cases (25%) of moderate nausea and 2 cases (25%) of anxiety occurred in the phase 2 multi-dose part of the trial (n=8). In May 2023, GH initiated a European phase 2b trial in TRD which randomizes 80 patients 1:1 to receive either multidose GH001 or multidose placebo using externally-sourced inhalation devices. Primary endpoint is change in MADRS at day 7. Top-line results are expected in 3Q or 4Q-2024. FDA has put a clinical hold on the GH001 program in the U.S. due to insufficient information to assess risks to human subjects related to a proprietary aerosol delivery device GH intends to use in U.S. trials. GH is working to respond to the agency's requests, and will provide an update regarding its IND response submission and a planned phase 1 healthy volunteer PK trial in the second quarter of 2024. The company is also running European GH001 phase 2a trials in PPD (top-line data expected in 3Q-2024) and bipolar II disorder (time to completion not disclosed), and is developing an i.v. version of 5-MeO-DMT (GH002, phase 1) and a nasal version (GH003, preclinical).

As mentioned, Cybin is also developing a DMT product, CYB004 (deuterated dimethyltryptamine). CYB004 is discussed in more detail, below.

Also in the DMT mix, ATAI is developing VLS-01, an oral transmucosal administration of DMT. A phase 1 study of VLS-01 was completed in October 2023, and the company now plans further optimization of the formulation in a forthcoming Phase 1b prior to initiating a Phase 2 study in TRD.

Lysergic acid diethylamide (LSD)

LSD, one of the longest acting and most potent hallucinogens, binds the 5-HT_{2A} receptor as a partial agonist and 5-HT_{1A} as an agonist. Prior to its prohibition in the U.S. in 1967, LSD was marketed by Sandoz (SWX: NOVN; unrated) under the brand name, Delysid, and was used to induce behavioural and personality changes, as well as remission of psychiatric symptoms in various disorders. The drug remains one of the most stigmatized and legally restricted agents among psychoactive substances. A number of academic groups have investigated microdosing of LSD to determine whether therapeutic benefits can be achieved without hallucinogenic effects, with Mind Medicine (NEO:MMED, NASDAQ:MNMD, Unrated) and Eleusis Therapeutics (private) sponsoring formal clinical trials with the drug.

Mind Medicine's MM-120 (LSD D-tartrate) has been studied in phase 2 for generalized anxiety disorder and ADHD. In the company's phase 2b generalized anxiety trial (n=198), a single 100ug MM-120 oral administration resulted a HAM-A reduction of 21.3 points (vs 13.7 for placebo; p=0.0004); 78% HAM-A response and 50%

remission rates at 4 weeks. The rates declined only slightly between weeks 4 and 12 to 65% (response) and 48% (remission). The company plans to hold an End-of-Phase 2 meeting with the FDA in the first half of 2024 and initiate a Phase 3 clinical program in the second half of 2024. The company's phase 2a proof-of-concept trial in adults with ADHD failed to meet the primary endpoint of the study, and the program was discontinued in January 2024.

Eleusis' trial tested low dose LSD in healthy volunteers – trial ended in 2017; no results have been posted and the program appears no longer to be active (link).

Non-Hallucinogenic Neuroplastogens

Delix Therapeutics (private), Transcend Therapeutics (private) and BetterLife Pharma (CN:BETR; unrated) are developing neuroplastogens with dialed-out hallucinogenic effects. Delix is completing a phase 1 with DLX-001 which it intends to develop for treatment of MDD; is at the IND stage with DLX-007 which it plans to develop for substance abuse disorders, and has several additional preclinical programs running. In December 2023, Transcend Therapeutics, with its methylone-based candidate, TSND-201, reported a strong 36.2 point decrease in CAPS-5 in PTSD patients, bettering the Lykos results in two phase 3 trials (-24.4 and -23.7), but the Transcend results were in a small 14-patient, open-label part of a phase 2 (trial has now advanced to a randomized, placebo-controlled phase). TSND-201 is in phase 2 in PTSD. BetterLife's BETR-001 (2-bromo-LSD), a partial agonist on serotonin 5-HT2A receptors, is at the IND stage, and the company currently has plans to develop the drug in MDD and anxiety disorder.

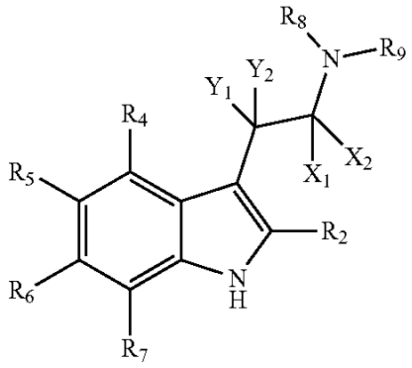
This strategy is worth monitoring from a competitive standpoint, however, clinical efficacy trials will be necessary to determine whether compounds in this class are able provide therapeutic benefits at the level of their hallucinogenic cousins, or more similar to traditional antidepressants which have milder effects on the same neurotransmitter receptors.

Cybin: Second Generation Improved and Patentable Psychedelic Therapies

CYB003

CYB003 is a synthetic analogue of psilocybin (Exhibit 9). It is deuterated to protect it from degradation during absorption, but upon entering the blood stream, CYB003 is already in an active form. Psilocybin, on the other hand, must be dephosphorylated before it becomes psychoactive – this takes time and results in PK and PD variability.

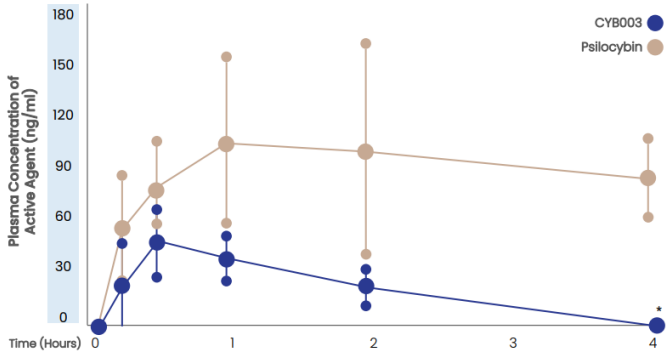
Exhibit 9. Molecular structure of compounds disclosed in Cybin U.S. patent 11,958,807 B2 (for some embodiments, X1, X2, Y1 and Y2 are deuterium. Unlike psilocybin, compounds described and tested in Cybin's '807 patent lack the de-activating phosphate group at position R4).



Source: USPTO

Because CYB003 is active from the outset, there is tighter correlation (lower variability) between drug dose and active drug concentration in the plasma (Exhibit 10), and clearance of active drug begins more uniformly, shortly after ingestion. This is in contrast to psilocybin, which is dephosphorylated over time, delaying the onset of activity and more importantly, extending and adding variability to the time it takes to clear the active metabolite, psilocin.

Exhibit 10. PK curves for CYB003 and psilocybin in rat.

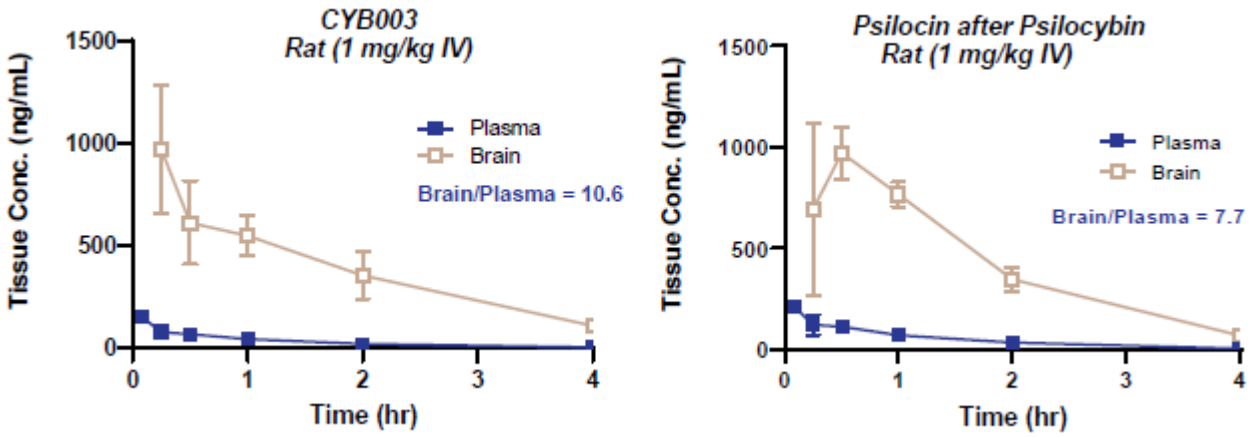


Source: Cybin

As a result, with CYB003, the psychoactive period can be more precisely controlled by dosing. In the clinic, this should translate into shorter treatment/monitoring sessions – Cybin indicates that patient sessions typically last 4-6 hours vs 6-8 hours standard for psilocybin (source: link; link). This, in turn, has the potential to increase productivity and throughput in the clinics that will administer these products.

Another advantage related to CYB003's narrower, less variable psychoactive window, is that less drug can be used to achieve similar peak levels of activity. Cybin has reported that the brain to plasma ratio with CYB003 is 42% higher with CYB003 vs psilocybin in rats (Exhibit 11). Together, these characteristics should reduce patients' exposure to the drug outside of the CNS, and reduce the risk of non-CNS deleterious effects (including cardiotoxicity and GI nausea/vomiting).

Exhibit 11. Brain to plasma ratio (CYB003 vs psilocybin).



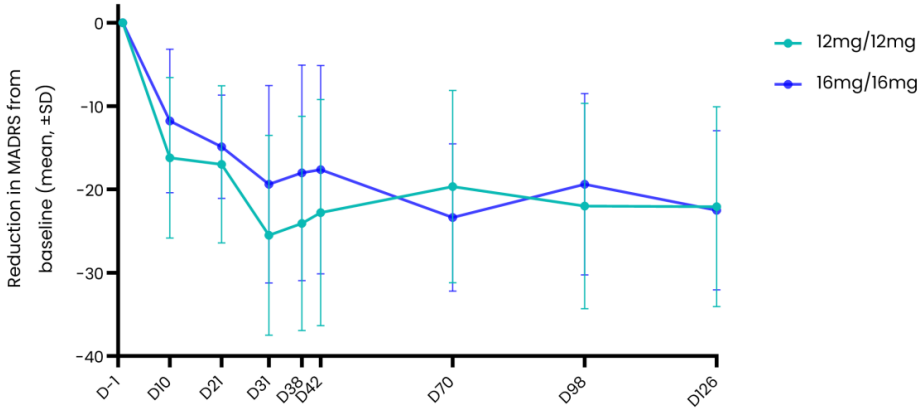
Source: Cybin

Ideal in theory, but a key question remained – would shortening the hallucinogenic period with CYB003 reduce/negate its therapeutic benefit in mood disorders.

This question was, for the most part, put to bed on November 30, 2023 when Cybin reported results for its placebo-controlled phase 2 CYB003 trial in MDD patients. In fact, while the study was small (n=33), there were strong signals that CYB003 potentially has sector-leading efficacy on multiple measures (along with the commercially and medically attractive attributes, discussed above).

Thirty-three patients with MDD were treated either with CYB003 12 mg (n=15), CYB003 16 mg (n=9) or placebo (n=9). Three weeks following the dosing, mean MADRS scores decreased from baseline by 17 points (12 mg dose; p=0.0001), 15 points (16 mg dose; p=0.008) and 3 points (placebo). MADRS scores after a second treatment with CYB003 improved further to -23 (12 mg) and -18 points (16 mg). Four months following treatment, improvements on the MADRS remained stable for patients treated at the 12 mg dose (-22) and increased moderately at the 16 mg dose (-23) (Exhibit 12).

Exhibit 12. MADRS 4 months after CYB003 therapy (2 Treatments Q3W).



Source: Cybin

Remission rates after 4 months were 60% (12 mg) and 75% (16 mg).

In comparison to other notable psychedelic studies, CYB003 looks highly competitive. The 12.0 (16 mg) and 14.1 (12 mg) MADRS improvements vs placebo at 3 weeks, beat the 6.6 point improvement over placebo reported by Compass for the 25 mg dose in its phase 2b TRD study of COMP360. The absolute MADRS improvements with CYB003 at 3 weeks (12mg dose: -17; 16 mg dose: -14.9) also surpassed Compass (-12.0 at 3 weeks). It should be noted, however, that the Cybin trial treated patients with CYB003 as an adjunct to SSRI/SNRIs, whereas patients in the Compass phase 2b were washed out of prior meds which does not necessarily favor CYB003 in a comparison (especially when adjusting for placebo effect).

GH Research reported a very high 24.4 point MADRS improvement 7 days after multi-dosing DMT product GH001 in a phase 1/2 trial TRD trial, however, the result was based on only 8 patients, and there was no placebo control. Remission rates at day 7 for single doses of GH001 were 50% (12 mg) and 25 mg (18 mg), and this increased to 87.5% when the drug was dosed multiple times at 3-hour intervals. Remission rates for CYB003 approached this level, but only after 6 weeks: 79% remission (12 mg); 50% remission (16 mg) – the remission rate for the 16 mg dose increased to 75% by 4 months.

While comparisons across trials are not ideal, results to-date suggest that CYB003 has an attractive product profile. To put this in context, Exhibit 13 highlights results of notable studies of psychedelic drugs used in the treatment of mood disorders.

Exhibit 13. Table highlighting results of key psychedelic drug studies

Product	Company/Organization	Indication	Stage	N	Clinical Data		
					Endpoint	Arm	Result
Psilocybin							
CYB003	Cybin	MDD	Phase 2	33	Change in MADRS (3 weeks)	CYB003 (12 mg)	-17.0
						CYB003 (16 mg)	-14.9
						Placebo	-2.9
					Change in MADRS (6 weeks)	CYB003 (12 mg)	-22.8
						CYB003 (16 mg)	-17.6
					Change in MADRS (4 months)	CYB003 (12 mg)	-22.0
						CYB003 (16 mg)	-22.5
					Response (3 weeks)	CYB003 (12 mg)	53%
						CYB003 (16 mg)	44%
						Placebo	0%
					Response (6 weeks)	CYB003 (12 mg)	79%
						CYB003 (16 mg)	75%
					Remission (3 weeks)	CYB003 (12 mg)	20%
						CYB003 (16 mg)	22%
						Placebo	0%
					Remission (6 weeks)	CYB003 (12 mg)	79%
						CYB003 (16 mg)	50%
					Remission (4 months)	CYB003 (12 mg)	60%
						CYB003 (16 mg)	75%
COMP360	Compass Pathways	TRD	Phase 2b	233	Change in MADRS (3 weeks)	COMP360 (1 mg)	-5.4
						COMP360 (10 mg)	-7.9
						COMP360 (25mg)	-12.0
						Delta (25mg vs 1mg	6.6
					Remission (3 weeks)	COMP360 (1 mg)	8%
						COMP360 (10 mg)	9%
						COMP360 (25mg)	29%
					Response (3 weeks)	COMP360 (1 mg)	18%
						COMP360 (10 mg)	19%
						COMP360 (25mg)	37%
					Sustained response (12 weeks)	COMP360 (1 mg)	10%
						COMP360 (10 mg)	5%
						COMP360 (25mg)	20%
Synthetic psilocybin	Usona	MDD	Phase 2	104	Change in MADRS (day 15)	Psilocybin	-18.0
						Placebo	-6.9
					Change in MADRS (day 29)	Psilocybin	-19.2
						Placebo	-5.5
					Change in MADRS (day 43)	Psilocybin	-14.2
						Placebo	-6.8
					Remission (days 8-43)	Psilocybin	25.0%
						Placebo	9.1%
					Response (days 8-43)	Psilocybin	41.7%
						Placebo	11.1%

Note: MADRS response - score decrease ≥50%; Remission - score ≤10

Exhibit 13. Table highlighting results of key psychedelic drug studies (continued)

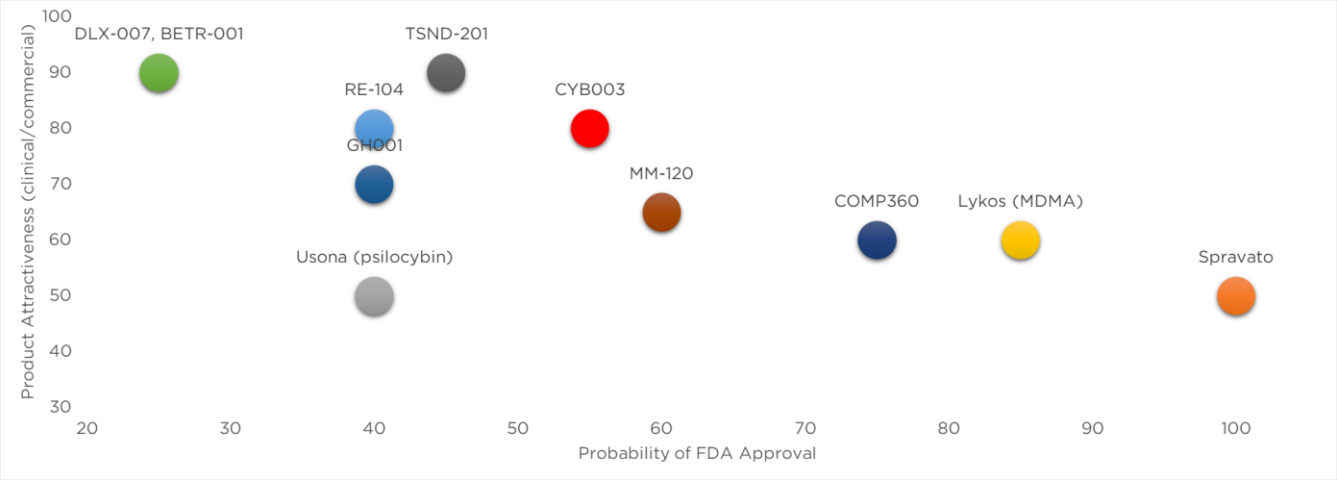
Product	Company/Organization	Indication	Stage	N	Clinical Data		
					Endpoint	Arm	Result
Esketamine							
Spravato	Johnson & Johnson	TRD	Phase 3	223	Change in MADRS (4 weeks)	Spravato	-19.8
						Placebo	-15.8
Spravato	Johnson & Johnson	TRD (phase 3 responders)	Extensior	176	Relapse (38 weeks)	Continue Spravato	40%
						Switch to Placebo	43%
						Placebo	-12.0
Spravato	Johnson & Johnson	MDD and suicidal ideation	Phase 3	273	Change in MADRS (24 hours)	Spravato	-16.0
						Placebo	-12.3
3,4-Methylenedioxymethamphetamine (MDMA)							
MDMA capsules	Lykos Therapeutics (previously MAPS)	PTSD	Phase 3	90	Change in CAPS-5 (2 months)	MDMA	-24.4
						Placebo	-13.9
						Delta	10.5
MDMA capsules	Lykos Therapeutics (previously MAPS)	PTSD	Phase 3	121	Change in CAPS-5 (18 weeks)	MDMA	-23.7
						Placebo	-14.8
N,N-Dimethyltryptamine (DMT)							
Ayahuasca extract	Onofre Lopes University Hospital (Brazil)	TRD	IST	29	Change in MADRS (day 1)	ayahuasca	-24
						placebo	-8
					Change in MADRS (day 2)	ayahuasca	-25.5
						placebo	-10.5
					Remission (day 7)	ayahuasca	36%
						placebo	7%
GH001	GH Research	TRD	Phase 1/2	8	Remission (day 7)	GH001 (12 mg SD)	50%
						GH001 (18 mg SD)	25%
					Remission (day 7)	GH001 (multidose)	87.5%
					Change in MADRS (day 7)	GH001 (multidose)	-24.4
SPL026	Small Pharma	MDD	Phase 1/2	34	Change in MADRS (2 weeks)	SPL026 (21.5 mg)	-11.0
						placebo	-3.6
					Remission (12 weeks)	SPL026	57%
Lysergic acid diethylamide (LSD)							
MM-120	Mind Medicine	Generalized Anxiety Disorder	Phase 2b	198	Change in HAM-A (4 weeks)	MM-120 (100 ug)	-21.3
						placebo	-13.7
					HAM-A response (4 weeks)	MM-120 (100 ug)	78%
					HAM-A response (12 weeks)	MM-120 (100 ug)	65%
					HAM-A remission (4 weeks)	MM-120 (100 ug)	50%
					HAM-A remission (12 weeks)	MM-120 (100 ug)	48%
Other							
TSND-201	Transcend Threrapeutics	PTSD	Phase 2	14	Change in CAPS-5 (10 weeks)	TSND-201	-36.2

Note: MADRS response - score decrease ≥50%; Remission - score ≤10

Source: Company Documents

Exhibit 14 positions CYB003 in a 2-way competitive grid of select psychedelic products on the market (Spravato) or in development for treating MDD, TRD, PTSD or anxiety. For each of the products, based on quality of data reported to-date (drug-placebo delta, size of trial), FDA interactions, biological rationale, and funding source, we estimated probability of FDA approval (x-axis). Based on clinical efficacy, adverse events (reported as well as potential based on mechanism) and trip time, we estimated product attractiveness. From this analysis, we view CYB003 as more attractive than programs that are further advanced (Spravato, Lykos MDMA and COMP360) as well as MM-120 which, although having a larger phase 2 than Cybin, had a smaller drug-placebo delta and few patients in remission at long term follow-up (noting however, that indications and endpoints were different). Also of note, Compass' phase 2 trial was substantially larger than Cybin's phase 2, hence the higher probability of approval assigned to COMP360 in our analysis. The non-hallucinogenic neuroplastinogens (DLX-007, BETR-001 and TSND-201) rank highly on potential attractiveness, but lower on probability of success as there has been very little clinical data reported to date for these compounds, and where there is clinical data, it is from a very small, uncontrolled trial.

Exhibit 14. Competitive positioning of CYB003.



Source: Company documents, Bloom Burton estimates

CYB003 was well tolerated at both doses in Cybin's phase 2, with no SAEs (including no suicidal ideation). Most common AEs were nausea, elevated blood pressure and headache – all were mild or moderate in intensity, and blood pressure and heart rate changes were transient and resolved without intervention. There were no clinically relevant changes in chemistry, hematology or ECG parameters. All drug-related adverse event are listed in Exhibit 15.

Exhibit 15. CYB003 phase 2 drug-related adverse events.

	CYB003 n (%)	Placebo n (%)
At least one AE	21 (60.0)	8 (61.5)
Nausea	6 (17.1)	3 (23.1)
Blood pressure increased	5 (14.3)	3 (23.1)
Headache	3 (8.6)	0
Vomiting	2 (5.7)	1 (7.7)
Eructation	1 (2.9)	0
Dizziness	1 (2.9)	0
Affect lability	1 (2.9)	0
Anxiety	2 (5.7)	1 (7.7)
Panic Attack	1 (2.9)	0
Confusional state	1 (2.9)	0
Nasal congestion	1 (2.9)	0
Tachycardia	1 (2.9)	0

Source: Cybin

The phase 3 program for CYB003 is anticipated to initiate in mid-2024 and will include 2 studies with a total of 550 patients. Fifteen U.S. study sites have been targeted, all of which have experience running psychedelic clinical trials. The Company intends to add approximately 8 additional sites in Europe. Each study is expected to run for approximately 18-24 months, with topline results for the first trial expected in mid-2026. The primary endpoint of both studies is the change in MADRS total score from baseline at Week 6, with a secondary endpoint at Week 12, each compared to placebo. Details below:

- CYB003-002 (n=220): Fixed repeat dose study of 16mg CYB003, with two doses 3 weeks apart compared to two doses of placebo. The trial is designed to replicate the treatment response seen in the Company's Phase 2 study.
- CYB003-003 (n=330): Three-arm fixed repeat dose study of CYB003 (16mg or 8mg), with two doses 3 weeks apart. Each active arm will be compared to two doses of placebo.
- Patients from each of these Phase 3 trials will enroll in a one-year extension study, during which time non-responders and relapsing patients will receive one full cycle of CYB003 16mg (two doses, three weeks apart).
- Moderate to severe MDD patients enrolled in both studies (MADRS >/=24) will be on stable doses of background antidepressant medication, positioning CYB003 as a convenient, adjunctive treatment option.
- CYB003-002 is anticipated to begin around mid-year 2024, with CYB003-003 anticipated to initiate a few months later. Each study is expected to run for approximately 18-24 months.

Patient recruitment for the Phase 3 program will include a broad MDD population including only patients that are currently on antidepressants with no washout period (i.e., CYB003 will be assessed as an adjuvant to patients' current meds). This aligns with the phase 2 trial and should reduce some of the inherent recruitment challenges seen in other depression studies.

On March 13, 2024, Cybin announced that the FDA had granted Breakthrough Therapy Designation to CYB003.

CYB004

Cybin's lead DMT product, CYB004 (deuterated dimethyltryptamine) is currently in a randomized phase 2 trial (n=36) as an adjunct to SOC anxiolytics and antidepressants to treat patients with general anxiety disorder (top-line results expected in 4Q-2024). In the trial, two doses of CYB004 or control are administered IM to patients 3 weeks apart. Participants will be followed for a period of three months, with an optional additional assessment at

six months. The primary endpoint is a change in the Hamilton Anxiety Rating Scale ("HAM-A") score from baseline at six weeks following the second dose.

Intellectual Property

Cybin has over 50 patents granted with 170 filings pending across 6 patent families spanning 7 research programs. The company's filings cover a wide range of novel compounds from different psychedelic classes, including claims to targeted structural modifications to improve the drug pharmacokinetic characteristics and safety profiles without altering their receptor binding.

On April 16, 2024, Cybin announced the USPTO granting of U.S. patent 11,958,807 protecting the composition and methods of using CYB003. The '807 patent is expected to provide exclusivity until at least 2041.

The company has also holds a U.S. composition of matter patent for CYB004 which similarly, is expected to provide protection until at least 2041.

The World Intellectual Property Organization (WIPO) has published an international patent application for Cybin covering inhalation delivery methods for multiple psychedelic molecules that are currently being researched and developed by Cybin as well as other psychedelic molecules that may be developed in the future.

Other Notable Competitors

In addition to companies and organizations mentioned earlier in this report (J&J, Compass, Lykos/MAPS, Usona, GH Research, Mind Medicine, Delix and BetterLife), at least 80 additional companies are exploring psychedelics for mental health. Some have focused on providing ketamine therapy at clinics; others are leveraging expertise in growing mushrooms for the retail and natural health market. Below, we highlight three notable companies which are involved in developing novel or classic molecules that will follow conventional clinical trial pathway, and be subject to regulatory oversight.

ATAI Life Sciences (NASDAQ:ATAI)
ATAI is an incubator that is assembling one of the largest portfolios of psychedelic compounds in the industry (includes a 14% ownership stake in Compass Pathways). The Peter Thiel-backed company's strategy is to provide capital and operational support to other developers in exchange for a majority stake in their drug programs.

Gilgamesh Pharmaceuticals (private)
Gilgamesh is seeking to create completely novel psychedelics via machine learning, with a specific view to overcoming the limitations of the classic molecules due to administration and duration of dissociative effects. The company's oral NMDAR antagonist (GM-1020) and 5-HT2A agonist/5-HT releaser (GM-2505) are both currently in phase 2.

Beckley Psytech (private)
Beckley is focused on developing novel formulations of first-generation psychedelics, as well as second- and third-generation versions. Its lead product, BPL-003 (intra-nasal 5-MeO-DMT) is currently in phase 2 in TRD and alcohol use disorder. In January 2024, ATAI invested $50M in Beckley.

CYB003 Forecasts

We forecast $2.1B of WW peak sales of CYB003 in 2032 based on the following assumptions: NIH estimates that approximately 8% of the U.S adult population (21M individuals) has a major depressive episode each year. Approximately 60% seek treatment (link) and of those, about 75% are treated with an antidepressant (link; link). Approximately 50% of patients fail to respond adequately to first line treatment (link) and about 20% are prescribed an add-on (adjunctive) drug (link) with most others switching to another drug.

For our base case, we assume that CYB003 will launch in the U.S. in 2H-2027 and will achieve 5% peak market share as an adjunctive therapy by 2032. Based on these assumptions, we forecast that 97,000 patients will be treated with CYB003 in the U.S. in 2032, and assuming net annual pricing at $19,144 ($15,000 in first year of launch, increasing 5% per year), our peak U.S. sales estimate in 2032 is $1.9B. We forecast 2032 ROW sales of CYB003 at $277.8M (13% of WW sales) based on regional trends for Spravato. Exhibit 16 shows our base case forecasts for worldwide sales of CYB003.

Exhibit 16. Bloom Burton's forecasts for worldwide sales of CYB003.

	2027E	2028E	2029E	2030E	2031E	2032E
US population	339,036,101	340,392,246	341,753,815	343,120,830	344,493,313	345,871,287
US population >18	263,431,051	264,484,775	265,542,714	266,604,885	267,671,305	268,741,990
MDD episode occurance	21,074,484	21,158,782	21,243,417	21,328,391	21,413,704	21,499,359
Patients seeking treatment	12,644,690	12,695,269	12,746,050	12,797,034	12,848,223	12,899,616
Patients prescribed 1L antidepressants	9,483,518	9,521,452	9,559,538	9,597,776	9,636,167	9,674,712
Patients failing to respond adequately	4,741,759	4,760,726	4,779,769	4,798,888	4,818,083	4,837,356
Patients receiving adjunctive therapy	1,896,704	1,904,290	1,911,908	1,919,555	1,927,233	1,934,942
CYB003 market share	0.05%	0.5%	1.5%	3.0%	4.5%	5.0%
Patients Treated with CYB003	948	9,521	28,679	57,587	86,726	96,747
Cost Per treatment	$ 15,000	$ 15,750	$ 16,538	$ 17,364	$ 18,233	$ 19,144
U.S. CYB003 net sales	$ 14,225,277	$ 149,962,867	$ 474,272,565	$ 999,956,275	$ 1,581,230,858	$ 1,852,148,411
ROW sales		$ 22,494,430	$ 71,140,885	$ 149,993,441	$ 237,184,629	$ 277,822,262
WW sales	$ 14,225,277	$ 172,457,298	$ 545,413,449	$ 1,149,949,716	$ 1,818,415,487	$ 2,129,970,673

Source: Bloom Burton estimates

Valuation

Bloom Burton's target price for Cybin is US$3.00 per share based on 6.0x Bloom Burton's worldwide peak sales estimate (US$2.1B in 2032), discounted 8 years (12% rate) and risk adjusted using a 55% probability of success.

Exhibit 17 shows valuations based on different discounted multiple of peaks sales scenarios with sensitivities including CYB003 annual cost of therapy ($5,000 – approximate annual cost of Auvelity, to $30,000 – approximate annual cost of Spravato) and peak market share (1% to 20%).

Exhibit 17. Risk-adjusted multiple of peak sales valuation sensitivities.

Annual Cost of Tx \ Peak Market share	1.0%	2.5%	5.0%	10.0%	20.0%
$5,000	$0.32	$0.62	$1.12	$2.12	$4.12
$10,000	$0.52	$1.12	$2.12	$4.12	$8.11
$15,000	$0.72	$1.62	$3.12	$6.12	$12.11
$20,000	$0.92	$2.12	$4.12	$8.11	$16.11
$30,000	$1.32	$3.12	$6.12	$12.11	$24.11

Source: Bloom Burton estimates

Key Risks

Commercial Risk (Competition)

Although depression and related mood disorders are rampant, and markets very large, the biggest risk facing Cybin (and other companies in the psychedelic therapeutic space) is commercial due in large part to the numerous players in the space, and the ability to source potent psychoactive drugs from multiple natural

sources. As a result, future competition may come not only from other products with strong patent protection, but also from unpatented products, at least one of which is being developed by a non-profit organization (Usona), as well as from potential generics of weakly or completely unprotected products. We do believe that funding for late-stage clinical development and commercialization of psychedelic therapies may be difficult for non-profit organizations, however, as discussed above, Usona has started a phase 3 psilocybin trial (although we are not certain whether this trial is fully funded, or whether a second trial will be required).

Partially mitigating this risk for the for-profit companies, are the benefits provided by second and third generation psychedelics – for some programs, the shorter trip time, and in the case of CYB003, the addition of potential safety benefits.

Despite the mitigating factors, to account for this risk in our modeling, while Spravato currently costs about $30,000 per year in the U.S., we have set our US$3.00 valuation for CYBN stock based on a CYB003 treatment cost of $15,000 annually (assuming 5% peak market share of patients receiving an adjuvant therapy following inadequate response to first line SSRI/SNRIs).

Even if we assume a worst case scenario of $1,000 per year for CYB003 (slightly above the current cost of generic SSRI/SNRIs) but at a higher 20% peak market share of MDD first line adjunctive market, we still come out to a valuation of US$0.90 per CYBN share, approximately 2.6X the current price of CYBN stock. Our model currently does not include CYB004 which could add upside if that program succeeds in the current phase 2 trial (initial results are expected later this year).

Clinical/Regulatory Risk

Unlike most biotech companies following successful but small phase 2 trials, we believe the clinical and regulatory risk for Cybin is comparatively low. On the clinical side, this is due to the wealth of PD and clinical outcome data supporting strong mental benefits when patients with mood disorders are treated with psychedelic drugs including psilocybin (upon which CYB003 is based), as well as the wide drug-placebo delta reported by Cybin in its CYB003 phase 2 trial (albeit in relatively few patients). On the regulatory side, FDA appears to have embraced psychedelics with its approval of the mildly psychedelic (but addictive) drug, Spravato, and its awarding of Breakthrough Therapy Designation to a number of psychedelic drugs, including CYB003.

Valuations of Other Advanced Psychedelic Drug Developers and Neurology Companies

We have excluded a comparable companies analysis in our valuation of Cybin since other advanced psychedelic drug developers are pursuing different indications with differing levels of efficacy, safety and IP protection. That said, Cybin's enterprise value is substantially discounted vs the group, and discounted vs other phase 3 neurology companies (Exhibit 18).

Exhibit 18. Enterprise values of advanced psychedelic drug developers and phase 3 neurology companies.

Company	Ticker	Price	Shares	Mkt Cap	Cash	Debt	EV (US$)	Lead Indication, Stage
Advanced Psychedlic Drug Developers								
Mind Medicine	MNMD	US $ 9.43	70.5	$ 664.8	$ 99.7	$ 14.10	$ 579.2	GAD, phase 3 (2H-2024)
GH Research	GHRS	US $ 11.95	52.0	$ 621.7	$ 106.0	$ -	$ 515.8	TRD, phase 2b (EU)
Compass Pathways	CMPS	US $ 8.48	68.3	$ 579.5	$ 220.6	$ 58.80	$ 417.7	TRD, phase 3
Average							*$ 504.2*	
Phase 3 Neurology Companies								
Xenon Pharmaceuticals	XENE	US $42.49	75.4	$ 3,205.1	$ 638.1	$ -	$ 2,567.0	epilepsy, phase 3
Neumora Therapeuctics	NMRA	US $ 9.10	159.5	$ 1,451.0	$ 454.0	$ -	$ 997.0	MDD, phase 3
Average							*$ 1,782.0*	
Cybin*	CYBN	US $ 0.35	765.0	$ 267.7	$ 169.5	$ -	$ 98.3	MDD, phase 3 (mid-2024)

*proforma financing

Source: FactSet, company documents

Exhibit 19. Actual and Bloom Burton Forecasted Income Statement for Cybin.

Income Statement (C$000's)	2023A	1QA	2QA	3QA	4QE	2024E	2025E	2026E	2027E
OPERATING EXPENSES									
Share-Based Compensation	$ 4,686	$ 1,275	$ 1,414	$ 9,928	$ 4,206	$ 16,823	$ 17,327	$ 17,847	$ 18,383
General and administrative	$ 21,341	$ 5,048	$ 5,800	$ 9,657	$ 6,835	$ 27,340	$ 28,707	$ 30,142	$ 31,649
R&D	$ 25,491	$ 6,384	$ 6,696	$ 7,439	$ 6,840	$ 27,359	$ 38,302	$ 47,878	$ 43,090
Total operating expenses	$ 51,518	$ 12,707	$ 13,910	$ 27,024	$ 17,880	$ 71,521	$ 84,336	$ 95,867	$ 93,122
Other Income (expenses)									
Interest Income	$ 603	$ 84	$ 52	$ 141	$ 92	$ 369	$ 369	$ 369	$ 369
Impairment	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Change in fair value	$ (589)	$ -	$ -	$ -	$ -	$ -	$ -		
Foreign currency translation gain (loss)	$ 4,027	$ (1,891)	$ 1,968	$ (3,447)	$ (1,123)	$ (4,493)	$ -		
Other	$ (13)	$ -	$ -	$ -	$ -	$ -	$ -		
Net income (loss) before taxes	$ (47,490)	$ (14,514)	$ (11,890)	$ (30,330)	$ (18,911)	$ (75,645)	$ (83,967)	$ (95,498)	$ (92,753)
Income Tax	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Net Loss	$ (47,490)	$ (14,514)	$ (11,890)	$ (30,330)	$ (18,911)	$ (75,645)	$ (83,967)	$ (95,498)	$ (92,753)
Other Comprehensive Income									
Foreign Currency translation	$ (1,669)	$ 1,177	$ (1,216)	$ 1,636	$ -	$ 1,597	$ -	$ -	$ -
Net and Comprehensive (Loss)	$ (49,159)	$ (13,337)	$ (13,106)	$ (28,694)	$ (18,911)	$ (74,048)	$ (83,967)	$ (95,498)	$ (92,753)
EPS (basic)	$ (0.26)	$ (0.07)	$ (0.05)	$ (0.09)	$ (0.03)	$ (0.24)	$ (0.11)	$ (0.12)	$ (0.12)
EPS (fully diluted)	$ (0.26)	$ (0.07)	$ (0.05)	$ (0.09)	$ (0.03)	$ (0.24)	$ (0.11)	$ (0.12)	$ (0.12)

Source: FactSet, Bloom Burton estimates

Exhibit 20. Actual and Bloom Burton Forecasted Balance Sheet for Cybin.

Balance Sheet (C$000's)	2023A	1QA	2QA	3QA	4QE	2024E	2025E	2026E	2027E
ASSETS									
Cash	$ 16,633	$ 9,349	$ 18,118	$ 38,999	$ 217,557	$ 217,557	$ 150,799	$ 74,529	$ 1,540
Accounts Receivable	$ 3,050	$ 3,211	$ 3,682	$ 4,256	$ 4,256	$ 4,256	$ 4,256	$ 4,256	$ 4,256
Prepaid expenses	$ 1,733	$ 1,300	$ 3,065	$ 3,312	$ 3,312	$ 3,312	$ 3,312	$ 3,312	$ 3,312
Other Assets	$ 1,769	$ 1,787	$ 1,874	$ 2,152	$ 2,152	$ 2,152	$ 2,152	$ 2,152	$ 2,152
Total Current Assets	**$ 23,185**	**$ 15,647**	**$ 26,739**	**$ 48,719**	**$ 227,277**	**$ 227,277**	**$ 160,519**	**$ 84,249**	**$ 11,260**
Investments	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Property Plant & Equipment	$ 450	$ 388	$ 340	$ 300	$ 291	$ 291	$ 266	$ 241	$ 217
Intagible and right of use assets	$ 5,470	$ 5,401	$ 5,780	$ 44,603	$ 44,518	$ 44,518	$ 44,662	$ 44,806	$ 44,949
Goodwill	$ 24,792	$ 24,255	$ 24,768	$ 36,102	$ 36,102	$ 36,102	$ 36,102	$ 36,102	$ 36,102
Total Non Current Assets	**$ 30,712**	**$ 30,044**	**$ 30,888**	**$ 81,005**	**$ 80,911**	**$ 80,911**	**$ 81,030**	**$ 81,149**	**$ 81,268**
TOTAL ASSETS	**$ 53,897**	**$ 45,691**	**$ 57,627**	**$ 129,724**	**$ 308,188**	**$ 308,188**	**$ 241,549**	**$ 165,398**	**$ 92,528**
LIABILITIES									
Accounts Payable & Accrued Liabilities	$ 5,663	$ 5,999	$ 9,243	$ 8,137	$ 8,137	$ 8,137	$ 8,137	$ 8,137	$ 8,137
Current portion of contingent liabilities	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Other	$ -	$ -	$ -	$ 324	$ 324	$ 324	$ 324	$ 324	$ 324
TOTAL CURRENT LIABILITES	**$ 5,663**	**$ 5,999**	**$ 9,243**	**$ 8,461**	**$ 8,461**	**$ 8,461**	**$ 8,461**	**$ 8,461**	**$ 8,461**
Non-Current Liabilities	$ -	$ -	$ -	$ 42	$ 42	$ 42	$ 42	$ 42	$ 42
TOTAL LIABILITES	**$ 5,663**	**$ 5,999**	**$ 9,243**	**$ 8,503**	**$ 8,503**	**$ 8,503**	**$ 8,503**	**$ 8,503**	**$ 8,503**
EQUITY									
Share capital	$ 158,162	$ 161,682	$ 177,467	$ 251,247	$ 444,417	$ 444,417	$ 444,417	$ 444,417	$ 444,417
Contributed surplus	$ 2,102	$ 2,277	$ 3,725	$ 4,236	$ 4,236	$ 4,236	$ 4,236	$ 5,736	$ 7,236
Options reserve	$ 27,283	$ 28,383	$ 29,505	$ 38,922	$ 43,128	$ 43,128	$ 60,455	$ 78,302	$ 96,685
Warrants reserve	$ 10,873	$ 10,873	$ 14,316	$ 32,139	$ 32,139	$ 32,139	$ 32,139	$ 32,139	$ 32,139
Accumulated OCI	$ (2,035)	$ (858)	$ (2,074)	$ (438)	$ (438)	$ (438)	$ (438)	$ (438)	$ (438)
Deficit	$ (148,151)	$ (162,665)	$ (174,555)	$ (204,885)	$ (223,796)	$ (223,796)	$ (307,763)	$ (403,261)	$ (496,014)
TOTAL EQUITY	**$ 48,234**	**$ 39,692**	**$ 48,384**	**$ 121,221**	**$ 299,685**	**$ 299,685**	**$ 233,046**	**$ 156,895**	**$ 84,025**
TOTAL LIABILITIES AND EQUITY	**$ 53,897**	**$ 45,691**	**$ 57,627**	**$ 129,724**	**$ 308,188**	**$ 308,188**	**$ 241,549**	**$ 165,398**	**$ 92,528**

Source: FactSet, Bloom Burton estimates

Exhibit 21. Actual and Bloom Burton Forecasted Cash Flow Statement for Cybin.

Statement of Cash Flows (C000's)	2023A	1QA	2QA	3QA	4QE	2024E	2025E	2026E	2027E
OPERATING ACTIVITES									
Net Loss	$ (47,490)	$ (14,514)	$ (11,890)	$ (30,330)	$ (18,911)	$ (75,645)	$ (83,967)	$ (95,498)	$ (92,753)
Depreciation and Amortization	$ 251	$ 69	$ 71	$ 142	$ 94	$ 376	$ 376	$ 376	$ 376
Share based compensation	$ 4,686	$ 1,275	$ 1,414	$ 9,928	$ 4,206	$ 16,823	$ 17,327	$ 17,847	$ 18,383
Interest income	$ (18)	$ -	$ -	$ -	$ -	$ -	$ -	$ 1,500	$ 1,500
Options issuance	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Accretion of convertible debt/contingent liability	$ 13	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Change in fair value	$ 589	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Impairment	$ -	$ -	$ -	$ 18	$ -	$ 18	$ -	$ -	$ -
Unrealized foreign exchange loss	$ (4,025)	$ 1,883	$ (1,978)	$ 2,578	$ -	$ 2,483	$ -		
Other	$ -	$ -	$ -	$ 4	$ -	$ 4	$ -	$ -	$ -
Net Change in non-cash working capital	$ (1,437)	$ 590	$ 921	$ (8,382)	$ -	$ (6,871)	$ -	$ -	$ -
CASH USED IN OPERATING ACTIVITIES	$ (47,431)	$ (10,697)	$ (11,462)	$ (26,042)	$ (14,612)	$ (62,813)	$ (66,264)	$ (75,775)	$ (72,494)
INVESTING ACTIVITES									
Purchase of Investments	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Purchase of PP&E	$ (142)	$ -	$ -	$ (13)	$ -	$ (13)	$ (13)	$ (13)	$ (13)
Purchase of intagible assets	$ (3,167)	$ (65)	$ (258)	$ (159)	$ -	$ (482)	$ (482)	$ (482)	$ (482)
Other	$ -	$ -	$ -	$ 7,632	$ -	$ 7,632	$ -	$ -	$ -
CASH FROM INVESTING ACTIVITIES	$ (3,309)	$ (65)	$ (258)	$ 7,460	$ -	$ 7,137	$ (495)	$ (495)	$ (495)
FINANCING ACTIVITIES									
Proceeds from issuance of common shares	$ 13,202	$ 3,520	$ 20,384	$ 39,742	$ 193,170	$ 256,816	$ -	$ -	$ -
Proceeds from Warrants	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Warrant/Option exercise	$ 362	$ -	$ -	$ 56	$ -	$ 56	$ -	$ -	$ -
Other	$ -	$ -	$ -	$ (56)	$ -	$ (56)	$ -	$ -	$ -
CASH PROVIDED BY FINANCING	$ 13,564	$ 3,520	$ 20,384	$ 39,742	$ 193,170	$ 256,816	$ -	$ -	$ -
Net Change in cash	$ (37,176)	$ (7,242)	$ 8,664	$ 21,160	$ 178,558	$ 201,140	$ (66,759)	$ (76,270)	$ (72,989)
Exchange Rate	$ 168	$ (42)	$ 105	$ (279)	$ -	$ (216)	$ -	$ -	$ -
Cash at beginning of period	$ 53,641	$ 16,633	$ 9,349	$ 18,118	$ 38,999	$ 16,633	$ 217,557	$ 150,799	$ 74,529
CASH AT END OF PERIOD	$ 16,633	$ 9,349	$ 18,118	$ 38,999	$ 217,557	$ 217,557	$ 150,799	$ 74,529	$ 1,540

Source: FactSet, Bloom Burton estimates

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