Mindset Pharma Inc. (MSSTF)
Rating: Buy

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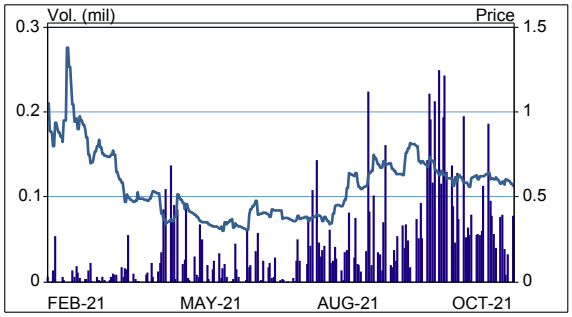
Pioneering Next Generation Psychedelic-Enhanced Therapies; Initiating With a Buy and $5 Price Target

Stock Data	11/02/2021
Price	$0.62
Exchange	OTC
Price Target	$5.00
52-Week High	$2.00
52-Week Low	$0.30
Market Cap (M)	$52
Shares Outstanding (M)	83.8
3 Month Avg Volume	82,782
Balance Sheet Metrics	
Cash (M)	C$6.60
Total Debt (M)	C$0.00
Total Cash/Share	C$0.08
Book Value/Share	C$0.12

EPS (C$) Diluted			
Full Year - Jun	2020A	2021A	2022E
1Q	--	(0.12)	(0.05)
2Q	0.00	(0.03)	(0.04)
3Q	(0.02)	(0.02)	(0.04)
4Q	(0.01)	(0.06)	(0.04)
FY	(0.03)	(0.20)	(0.16)

Revenue (C$M)			
Full Year - Jun	2020A	2021A	2022E
1Q	0.0	0.0	0.0
2Q	0.0	0.0	0.0
3Q	0.0	0.0	0.0
4Q	0.0	0.0	0.0
FY	0.0	0.0	0.0



Differentiated platform focused on next-generation psychedelics. Mindset Pharma, founded in 2019, is a neuro-focused biotech that seeks to advance medicines based on psychedelic substances through rigorous scientific and clinical trials. Mindset identified more than 100 New Chemical Entities (NCEs) across four "families", which are in preclinical development, leading to a pipeline that includes diverse patent-pending psilocybin and DMT and 5-MeO-DMT-inspired drug candidates. We focus on lead candidate MSP-1014, which could have improved pharmacology compared to psilocybin, a classic psychedelic that has shown potential in a psychedelic-assisted psychotherapy (PAP) framework to be safe and effective across a variety of mood disorders (see Appendices A and B). Mindset has filed eight provisional patent applications to-date including four final PCT applications, which cover a broad range of novel, next generation drugs inspired by the aforementioned psychedelics, and a novel psilocybin synthesis and manufacturing method. Importantly, we believe Phase 2b trial data from COMPASS Pathways on COMP360, an oral form of psilocybin, could be a key near-term catalyst for Mindset, particularly as investors may then evaluate Mindset's IP positioning and pipeline, which is on track to generate initial platform-validating data in 2H22. For these reasons, we initiate coverage on Mindset Pharma with a Buy and $5 price target.

MSP-1014 could be a differentiated psilocybin-based analog. Discovery of MSP-1014 came from the first family of Mindset compounds, which are prodrugs, conjugates, and deuterated analogs of psilocybin. These prodrugs and conjugates have shown rapid metabolism into active metabolites with verified efficacy in both *in vitro* and *in vivo* though also with superior effects on behaviors associated with 5-HT2A agonism compared to psilocybin *in vivo* and improved safety signals according to Mindset. MSP-1014 in particular incorporates a conjugated amplifier into a psilocybin-like structure to create a more potent and effective compound. In preclinical studies, MSP-1014 has demonstrated stronger 5-HT2A activity than psilocybin and attenuated reduction in locomotor activity, and has also demonstrated consistent body temperature at higher doses, which could indicate a potential safety advantage according to Mindset. We note that MSP-1014 is nearing the start of Investigational New Drug (IND)-enabling studies and is to be evaluated in treatment-resistant depression (TRD) and end of life cancer angst. Broadly, we have a favorable view of psilocybin in treatment of depression primarily based on the outcomes from modern exploratory studies, notably Davis, Barrett, et al., 2020, and Carhart-Harris, Giribaldi, et al., 2021, among others. We believe these studies demonstrate psilocybin's potential to demonstrate positive efficacy, an acceptable safety profile, and improved tolerability in difficult-to-treat depression patients. Phase 1 data for MSP-1014 should be reported in 2H22, followed by Phase 2 trials that could further de-risk the compound. Not risk-adjusted, we estimate MSP-1014 could generate peak revenues of more than C $3B. For additional details on the psychedelics space, refer to our July 1 primer entitled *The Doors of Perception: Psychedelic Renaissance Could End With Multiple Breakthrough Therapies in Psychiatry and Beyond*.

MSP-1014 could be disruptive as treatment for end of life cancer angst, a potential blockbuster indication. Mindset has not yet indicated when a Phase 2 trial in cancer patients suffering from end of life cancer angst could start, though we think the study could start in 2H22 with initial data is possible in 2023. This timing could position Mindset among the first psychedelics companies to generate clinical data in this important indication, in our view. Recall that cancer patients often develop a chronic, clinically significant syndrome of psychosocial distress having depressed mood, anxiety, and reduced quality of life as core features, with up to 40% of cancer patients meeting criteria for a mood disorder according to Griffiths et al., 2016. In cancer patients, depression and anxiety have been associated with decreased treatment adherence, prolonged hospitalization, decreased quality of life, and increased suicidality. Antidepressants and, less frequently, benzodiazepines are used to treat depressed mood and anxiety in cancer patients, although evidence suggesting efficacy is limited and conflicting, and benzodiazepines are generally only recommended for short-term use because of side effects and withdrawal. Two double-blind, placebo-controlled studies with the classic psychedelics psilocybin (Grob et al., 2011) and LSD (Gasser et al., 2014) examined effects in 12 patients with life-threatening illness, including cancer. Both studies showed promising trends toward decreased psychological distress. Moreover, Griffiths et al. 2016 provided a rigorous evaluation of the efficacy of a classic psychedelic for treatment of depressed mood and anxiety in psychologically distressed cancer patients. The study evaluated a range of clinically relevant measures using a double-blind cross-over design to compare a very low psilocybin dose (intended as a placebo) to a moderately high psilocybin dose in 51 patients under conditions that minimized expectancy effects. No serious adverse events attributed to psilocybin administration occurred; a number of adverse events occurred during psilocybin sessions, none of which were deemed to be serious. Psilocybin produced large and sustained effects on the two primary clinician-rated therapeutically relevant outcome measures as well as most of the secondary measures assessed at Baseline, 5 weeks after each session, and at 6-month follow-up. Of the 17 measures assessed, 16 showed significant effects (i.e. a between-group difference at the Post-session 1 assessment and/or a difference between Post-session 1 and Post-session 2 assessments in the Low-Dose-1st Group). (Refer to page 36 of this report for additional details on Griffiths et al.). More recently, an open-label study of COMP360 conducted by Maryland Oncology at the Aquilino Cancer Center in Rockville, Maryland demonstrated remission of major depression symptoms for 50% of participants. Thus, we view the potential of classic psychedelics and analogs of these psychedelics as having strong potential in end of life cancer angst, an indication we estimate could generate annual revenues of $1B-plus globally, and we believe MSP-1014 is well-positioned as a potential next generation psychedelic therapy in this area.

Next generation DMT and 5-MeO-DMT inspired drug candidates represent next potential wave of upside. In September 2021, Mindset identified three pipeline opportunities from its DMT and 5-MeO-DMT-inspired novel drug candidates, MSP-4018, MSP-4019 and MSP-4020. In preclinical studies, MSP-4018, MSP-4019 and MSP-4020 demonstrated a significant decrease in signs of serotonergic toxicity, which is a considerable health risk associated with the first-generation psychedelic, 5-MeO-DMT, according to Mindset. Broadly, we view shorter-acting tryptamines as being potentially disruptive in the psychedelics space and with Mindset developing a next generation form of these compounds, Mindset could be ideally positioned to benefit from potential superior pharmacology compared to longer acting tryptamines such as psilocybin and LSD.

Additional NCEs could soon enter the pipeline with potential to improve on existing psychedelic pharmacology. Mindset's second family compounds demonstrate increased potency and efficacy compared to psilocin and psilocybin based on both *in vitro* and *in vivo* data, respectively. Certain compounds also show oral bioavailability and are brain penetrant with *in vivo* pharmacokinetic evidence of shorter duration than psilocybin in rodents. This profile positions the second family of compounds as so-called third generation in-clinic candidates to support PAP applications and protocols. Separately, the third family of compounds has demonstrated unique and promising *in vitro* profiles, in particular, showing similar binding profile to the human 5-HT2A receptor comparable to that of psilocin's though with a smaller effect size and much longer duration of action based on human liver microsome stability data according to Mindset. This profile positions the third family of compounds for potential in so-called microdosing or subperceptual applications such as specialized populations and indications including pediatric attention deficit hyperactivity disorder (ADHD) and Alzheimer's disease. We anticipate a further buildout of the pipeline could generate additional enthusiasm around Mindset's platform, which is emerging as a potential leader in the psychedelics space, in our view.

Valuation and risks. We value Mindset Pharma using a discounted cash flow (DCF)-based methodology. We assume a probability of success of 25% for MSP-1014 in TRD and end of life cancer angst. We model equity raises of C$20-100M annually from F2022 to F2028 to fund clinical development and the potential therapy launch, which could dilute existing shareholders. We employ a 12% discount rate and a terminal multiple of 6.0x. We note that Mindset Pharma trades on the U.S. OTC, which could bring with it increased risk of investment including though not limited to liquidity risk and regulatory disclosure risk. Additional risks include though are not limited to: (1) clinical development risk tied to lead program MSP-1014 and the next generation programs to follow; (2) competitor risk in relevant therapeutic areas; (3) government regulatory risk, such as in the need to re-schedule psychedelics, which are often classified as illegal substances in countries around the world; (4) capital market and dilution risk; (5) commercialization risk, and in particular the build out of a therapist network to deliver psychedelic-assisted therapy in accordance with a potential FDA label; (6) reimbursement risk; (7) pricing risk; (8) business development risk; and (9) risk from COVID-19 should a renewed wave lead to re-enactment of broad lock-downs globally.

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I. Company Overview

- **Mindset Pharma founding.** Mindset is a neuro-pharmaceutical drug development company that seeks to advance medicines based on psychedelic substances through rigorous scientific and clinical trials performed by contract research organizations (CROs). Mindset's mission is to discover, develop, and deploy psychedelic inspired medicines that alleviate suffering and improve health, as well as to prove the safety and efficacy of psychedelic-based substances as disruptive technologies and solutions for a plethora of mental illnesses and other significant unmet medical needs. Mindset is assembling a portfolio of intellectual property related to the synthesis, production, and manufacturing of psychedelic inspired medicines for use as prescription medications primarily based on psilocybin though also on DMT. Through its platform, Mindset designs novel compounds and utilizes a preclinical screening cascade incorporating both *in vitro* and *in vivo* assays to select promising new drug candidates that demonstrate potential to treat a plethora of mental health problems that have proven resistant to traditional drug therapies. Mindset's platform strategy is currently focused on the discovery and preclinical development of psychedelic substances though is expected to ultimately focus on commercializing its psychedelic-inspired medicines in the future via pre-commercialization licensing arrangements with clinical-stage pharmaceutical companies or through development partnerships that include milestone-based payments and royalties. Mindset was founded in 2019; on September 11, 2020, "Original" Mindset completed a business combination with North Sur Resources and began trading publicly in Canada (MSET). Mindset is also listed on the OTCBB (MSSTF).

- **Mindset new drug program.** Mindset has developed a leading pipeline of diverse patent-pending preclinical psilocybin-inspired drug candidates. Mindset identified more than 100 NCEs across four so-called families, which are presently in the preclinical stage of development. We outline the four families in greater detail later on in this report.

- **IP portfolio.** Mindset has filed eight provisional patent applications to-date. Mindset also has filed four final PCT applications, which cover a broad range of novel, next generation drugs inspired by psilocybin, DMT, & 5-MeO-DMT and a novel psilocybin synthesis and manufacturing method.

- **Selected lead candidate.** In September, Mindset selected its first lead clinical candidate, MSP-1014, a potentially differentiated psilocybin-based analog, to move forward into investigational new drug (IND)-enabling studies.

- **Developed first-in-class benchmarking.** Under the Cooperative Psychedelics Evaluation Platform (COPE) program, Mindset and its partner, InterVivo Solutions, continue to develop first-in-class benchmarking data across first-generation psychedelic drugs.

Source: Company filings, H.C. Wainwright & Co.

Company Pipeline

C$ in millions, unless noted

				HCW Peak Estimates		
Program	**Indication**	**Status**	**Rights**	**Risk-Adjusted**	**Not Risk-Adjusted**	**Year**
MSP-1014	Treatment-Resistant Depression (TRD)	Preclinical		658.7	2,634.7	F2040E
	End of Life Cancer Angst	Preclinical		284.8	1,139.2	F2040E
Second Family	TBA	Preclinical	Worldwide			
Third Family	TBA	Preclinical				
Fourth Family	TBA	Preclinical				
Mindset peak pipeline revenues				**943.5**	**3,773.9**	

Source: Company filings, H.C. Wainwright & Co.

II. Catalyst Calendar

Program	Indication	Milestone	Sponsor	Timing	Comments	Impact
COMP360	TRD	Phase 2 dose-ranging study (COMP001) top-line data	COMPASS Pathways	2H21	• Highly anticipated psilocybin study outcome that could have potentially significant positive implications across the psychedelics space.	• High
MSP-1014	TRD End of Life Cancer Angst	Start Phase 1 data readout	Mindset Pharma	2H22	• Though early stage, the Phase 1 data should further elucidate the potentially differentiated pharmacologic profile of MSP-1014.	• Medium
Selection of Second Lead Compound	TBA	TBA	Mindset Pharma	TBA	• Presumably the second lead compound could be a short-acting tryptamine that could further differentiate Mindset's pipeline.	• Medium

Source: Company filings, H.C. Wainwright & Co.

Public companies mentioned above: COMPASS Pathways; CMPS; Buy.

III. Investment Thesis

Key Investment Points

Mindset's platform and robust intellectual property positioning.

- Mindset is applying typical drug development steps to "classic" psychedelic drugs in order to develop new medicines for complex neuropsychiatric indications that have high prevalence rates and unmet medical needs. The focus is on four "families" of compounds, which we outline in greater detail in the sections that follow in this report. Importantly, we note that Mindset has filed eight provisional patent applications to-date.

MSP-1014, next generation psilocybin, could be disruptive in TRD and end of life cancer angst.

- MSP-1014 is a potential NCE that incorporates a conjugated amplifier into a psilocybin-like structure to create a more potent and effective compound. In particular, in preclinical studies, MSP-1014 has demonstrated stronger 5-HT2A activity than psilocybin and attenuated reduction in locomotor activity, and has also demonstrated consistent body temperature at higher doses, which could indicate a potential safety advantage vs. psilocybin. Initially, Mindset intends to explore the potential for MSP-1014 in TRD and end of life cancer angst, indications with high unmet medical need and which could combined generate peak annual revenues of more than C$3.5B, by our estimates.

MSP-4018, MSP-4019, MSP-4020, next generation DMT and 5-MeO-DMT inspired drug candidates represent next potential wave of upside.

- In September 2021, Mindset identified three pipeline opportunities from its DMT and 5-MeO-DMT-inspired novel drug candidates, MSP-4018, MSP-4019 and MSP-4020. In preclinical studies, MSP-4018, MSP-4019 and MSP-4020 demonstrated a significant decrease in signs of serotonergic toxicity, which is a considerable health risk associated with the first-generation psychedelic, 5-MeO-DMT, according to Mindset.

Additional NCEs could soon enter the pipeline with potential to improve on existing psychedelic pharmacology.

- The second family compounds demonstrate increased potency and efficacy compared to psilocin and psilocybin based on both *in vitro* and *in vivo* data, respectively. Certain compounds also show oral bioavailability and are brain penetrant with *in vivo* pharmacokinetic evidence of shorter duration than psilocybin in rodents. This profile positions the second family of compounds as so-called third generation in-clinic candidates to support psychedelic-assisted psychotherapy (PAP) applications and protocols. Separately, the third family of compounds has demonstrated unique and promising *in vitro* profiles, in particular, showing similar binding profile to the human 5-HT2A receptor comparable to that of psilocin's though with a smaller effect size and much longer duration of action based on human liver microsome stability data according to Mindset. This profile positions the third family of compounds for potential in so-called microdosing or subperceptual applications such as specialized populations and indications including pediatric attention deficit hyperactivity disorder (ADHD) and Alzheimer's disease.

Source: Company filings, H.C. Wainwright & Co.

IV. Mindset's Platform and Robust Intellectual Property Positioning

"Normally, there is nothing of which we are more certain than the feeling of our self, of our own ego." (Freud, 1930)

Mindset's Drug Development Approach and Intellectual Property Status

- Mindset is applying typical drug development steps to "classic" psychedelic drugs in order to develop new medicines for complex neuropsychiatric indications that have high prevalence rates and unmet medical needs.

- On February 4, 2020, Mindset filed two provisional patent applications with the U.S. Patent and Trademark Office (USPTO) covering two novel diverse chemical scaffolds protecting the discovery and development of NCEs to treat various mental health disorders. Mindset continues to synthesize a number of compounds and advance them through a range of human serotonin subtype receptor assays (i.e., *in vitro* testing). These assays indicate that a number of Mindset's compounds display an effect at the key 5HT-2A receptor similar to, and in some cases superior to, psilocin, the active metabolite of psilocybin. Mindset is now advancing its proprietary compounds through an *in vivo* program to further elucidate their pharmacokinetic properties, safety profile, and efficacy, with a goal of selecting one or more lead drug candidates to advance to human clinical trials.

- The data from *in vivo* studies demonstrate that compounds that showed 5HT-2A activity are also showing *in vivo* behavioral evidence of 5HT-2A activity that can be blocked with pre-treatment of a full antagonist to the 5-HT-2A receptor. Moreover, the compounds are showing oral activity and promising durations of action in murine and rodent pharmacokinetics studies.

- On the basis of these preliminary results, Mindset filed a provisional USPTO patent application for a third class of compounds in December 2020 and a provisional USPTO patent application covering DMT and 5-MeO DMT analogs in March 2021. In addition, in February 2021, Mindset filed three final PCT patents for psilocybin-based prodrugs, deuterated compounds and side-chain restricted analogs. Preliminary opinions received from the Canadian patent office suggest that the Mindset NCEs identified in the final PCT patent applications demonstrate both novelty and patentability; the applications were published in August 2021.

Filing Jurisdiction	Application Number	Priority / Filing Date	Status	Compound Family
PCT	PCT / CA2021 / 050125	Priority: 2020-02-04 Filed: 2021-02-04	Patent Pending Priority date assumed from 62/969934	One
PCT	PCT / CA2021 / 050123	Priority: 2020-02-04 Filed: 2021-02-04	Patent Pending Priority date assumed from 62/969934	One
PCT	PCT / CA2021 / 050122	Priority: 2020-02-04 Filed: 2021-02-04	Patent Pending Priority date assumed from 62/969894	Two
U.S.	63/056058	24-Jul-20	Patent pending	Mindset Synthesis Process
U.S.	63/122181	7-Dec-20	Patent pending	Three
U.S.	63/155634	2-Mar-21	Patent pending	Four
U.S.	63/202081	26-May-21	Patent pending	Combination NCEs
U.S.	62/969934	4-Feb-20	Expired, priority date claimed and incorporated by reference for PCT/CA2021/050125 and PCT/CA2021/050123	One
U.S.	62/969894	4-Feb-20	Expired, priority date claimed and incorporated by reference for PCT/CA2021/050122	Two

Source: Company filings, H.C. Wainwright & Co.

V. MSP-1014: Mindset's Next Generation Psilocybin Could Be Disruptive

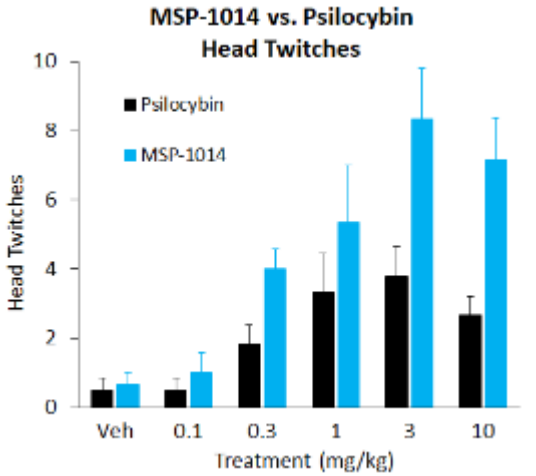
"It does not seem to be an exaggeration to say that psychedelics, used responsibly and with proper caution, would be for psychiatry what the microscope is for biology and medicine or the telescope is for astronomy. These tools make it possible to study important processes that under normal circumstances are not available for direct observation." (Grof, 1980)

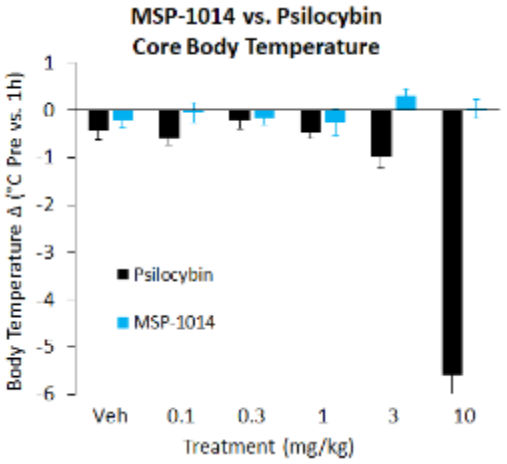
MSP-1014: Mindset's First Lead Candidate

- **First family—prodrugs, conjugates, and deuterated analogs of psilocybin.** The prodrugs and conjugates show rapid metabolism into active metabolites with verified efficacy in both *in vitro* and *in vivo* though also with superior effects on behaviors associated with 5-HT2A agonism compared to psilocybin *in vivo* and improved safety signals according to Mindset. The deuterated analogs have shown similar effects as psilocin on receptor binding and function assays and *in vivo* data indicate similar or greater efficacy to psilocybin with oral bioavailability and central nervous system penetration. This profile positions the first family of compounds as potentially patentable psilocybin-like compounds with potential superior activity compared to psilocybin, implying these compounds could demonstrate dose-related safety and pharmacodynamic advantages compared to psilocybin.

- **MSP-1014 is in preclinical development for TRD and end of life cancer angst.** MSP-1014 is a potential NCE that incorporates a conjugated amplifier into a psilocybin-like structure to create a more potent and effective compound. In particular, in preclinical studies, MSP-1014 has demonstrated stronger 5-HT2A activity than psilocybin and attenuated reduction in locomotor activity, and has also demonstrated consistent body temperature at higher doses, which could indicate a potential safety advantage vs. psilocybin according to Mindset.

- **Phase 1 study start expected around mid-2022.** Mindset has indicated that MSP-1014 could begin its Phase 1 program in 2Q22 or 3Q22.





Source: Company filings, H.C. Wainwright & Co.

VI. Depression Background and the Potential for MSP-1014 to Become a Multi-Blockbuster TRD Therapy

"If, as Freud said, dreams are the royal road to the unconscious, is it possible that psychedelic drugs are a superhighway to the unconscious?" (Holden, 1980)

Brief Background on Major Depressive Disorder (MDD)

- **Background.** MDD, which affects more than 350M people according to the World Health Organization (WHO), is a multifaceted condition characterized by episodes of mood disturbances alongside other symptoms such as anhedonia, psychomotor complaints, feelings of guilt and suicidal tendencies, all of which range in severity.

- **Treatment.** The discovery of mainstream antidepressants (i.e., SSRIs, SNRIs) has largely revolutionized management of depression; however, up to 60% of patients remain inadequately treated. Often this owes to the drugs' delayed therapeutic effect, side effects leading to non-compliance, or inherent non-responsiveness to them.

In the U.S., MDD has a:
- 12-month prevalence of approximately 10%.
- Lifetime prevalence of approximately 21%.

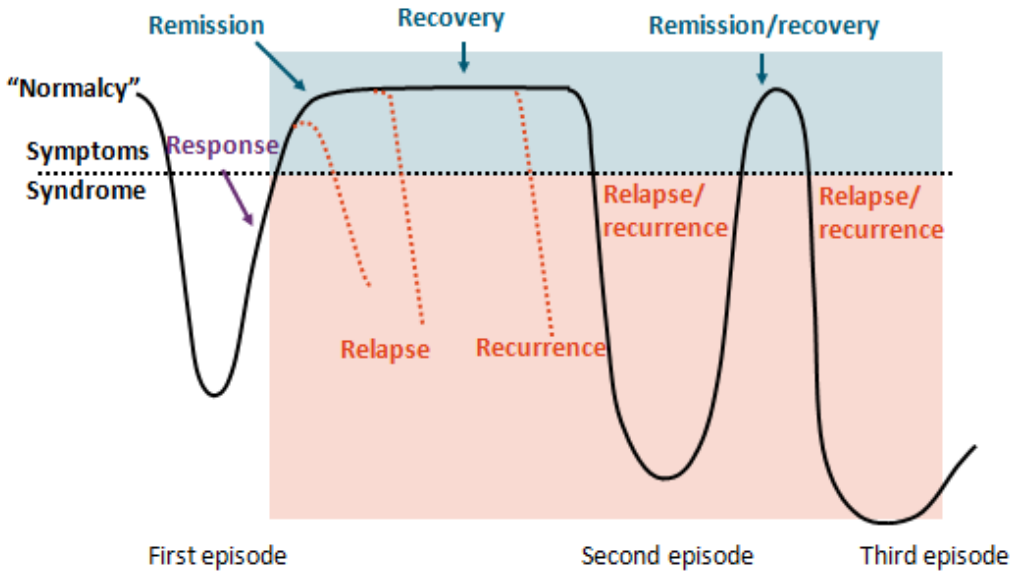
Direct and indirect costs:
- Estimated at $210.5B annually.

Worldwide, MDD is a leading cause of disability

MDD predicts decreases in social functioning:
- Low earnings.
- Poor work performance.
- Difficulties in marital relationships.

MDD is associated with various comorbidities:
- Cardiovascular disease, stroke.
- Chronic fatigue syndrome.
- Fibromyalgia.
- IBS.

Source: Clinicaloptions.com.



Source: Clinicaloptions.com.

Source: Hasin, Sarvet, et al., 2018, Rush, Trivedi, et al., 2006, Guidelines Overview: Augmentation Therapies in Major Depressive Disorder, and Recent Evidence for Treatment Augmentation With Second-Generation Antipsychotics in MDD. Available at clinicaloptions.com. Clinical Care Options, LLC; Reston, VA, USA. H.C. Wainwright & Co.

MDD Assessment Tools and Potential Treatment Algorithm

Nonresponse
- No response despite adequate dose and duration of antidepressant.

Partial Response (or Response)
- Improvement of symptoms.
- ≥ 50% decrease in HAM-D or MADRS.

Remission
- Return to "wellness" or disappearance of symptoms.
- Most frequently measured as HAM-D ≤ 7 or MADRS ≤ 10.

Source: McIntyre RS, et al., 2004.

Validated MDD Assessment Tools	Measurement	Type
Patient Health Questionnaire (PHQ-9)	Symptoms	Self-rated
Beck Depression Inventory (BDI)		Self-rated
Geriatric Depression Scale (GDS)		Self-rated
Quick Inventory for Depressive Symptomatology (QIDS)		Self-rated
Hamilton Depression Rating Scale (HAM-D)		Clinician-rated
Montgomery-Asberg Depression Rating Scale (MADRS)		Clinician-rated
THINC-it	Cognitive impairment	Self-rated
Sheehan Disability Scale (SDS)	Functioning	Self-rated
Multidimensional Scale of Independent Functioning (MSIF)		Clinician-rated
Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)	Side effects	Self-rated

Source: Guidelines Overview: Augmentation Therapies in Major Depressive Disorder. Available at clinicaloptions.com. Clinical Care Options, LLC; Reston, VA, USA.

Selected MDD Guidelines:	Last Updated:
• American Psychiatric Association	2010
• Canadian Network for Mood and Anxiety Treatments (CANMAT)	2013
• Institute for Clinical Systems Impvroement (ICSI)	2013
• Florida Best Practices Psychotherapeutic Medication Guidelines for Adults	2019-2020

Florida Best Practice Psychotherapeutic Medication Guidelines

Level 1 Monotherapy	Level 2 Add:	Level 3 SSRI or SNRI plus:	Level 4 Consider:
• SSRI	• Evidence-based psychotherapy	• Lithium	• MAOI augmentation
• SNRI	• Second-generation antipsychotic FDA-approved	• T3	• FL-methylfolate triple drug combinations*:
• Vortioxetine	• Intranasal esketamine or IV racemic ketamine	• L-methylfolate	SSRI/SNRI + mirtazapine + bupropion
• Buproprion	• Another antidepressent (do not combine SSRI and SNRI)	• S-adenosylmethionine	SSRI/SNRI + mirtazapine + lithium
• Mirtazapine		• Quetiapine (tolerability concerns)	SSRI/SNRI + mirtazapine + second-gen antipsychotic

*Little evidence to support or refute this approach.

Source: Clinical Care Options, H.C. Wainwright & Co.

Additional Details on Selected Depression Scales

- **Hamilton Rating Scale for Depression (HRSD or HAM-D).** The HAM-D, developed around 60 years ago, is the oldest and most widely used instrument to rate the severity of symptoms in depression. It has been criticized in how it rates the various depressive symptoms particularly as it attributes greater weight to items of neurovegetative signs such as sleep and eating. The original 17-item questionnaire was later supplemented with 4 additional items that are generally not included in calculating a total score. The first 17 items are typically included in a total score which ranges from 0 to 52 with 9 items rated in intensity or severity from 0 to 4 (0 = none/absent) and 8 symptom items rated from 0 to 2 (0 = none/absent). Complete remission is generally considered to be a score of less than 7-10. It was designed to be administered by clinicians after a patient interview (either structured or unstructured). In addition, shorter and longer versions of the scale have been developed.

- **Montgomery-Åsberg Depression Rating Scale (MADRS).** The MADRS was developed to address some of the perceived shortcomings of the HAM-D in that it: (1) provides a unidimensional assessment of the symptoms of depression with each symptom weighted similarly; and (2) was derived from a 67-item scale and includes 10 items that showed response to treatment and correlated with the total score change. Individual items are rated in terms of severity from 0 to 6 (0 = no abnormality to 6 = severe), and complete remission is generally considered to be a score of less than 10-12.

- **Beck Depression Inventory (BDI).** The Beck Depression Inventory (BDI) is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression. The BDI has been developed in different forms, including several computerized forms, a card form, the 13-item short form and the more recent BDI-II. The BDI takes approximately 10 minutes to complete, although clients require a fifth to sixth grade reading level to adequately understand the questions. Internal consistency for the BDI ranges from 0.73 to 0.92 with a mean of 0.86. Similar reliabilities have been found for the 13-item short form. The BDI demonstrates high internal consistency, with alpha coefficients of 0.86 and 0.81 for psychiatric and non-psychiatric populations respectively.

- **Quick Inventory of Depressive Symptomatology (QIDS-SR).** The 16-item QIDS-SR is a brief self-report rating scale developed from the 30-item Inventory of Depressive Symptomatology. Selected for the QIDS-SR and its equivalent clinician-rated scale, the QIDS-C are items that evaluate the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) (DSM-IV-TR) depression criterion symptom domains (i.e., sad mood, concentration, self-criticism, suicidal ideation, interest, energy or fatigue, sleep disturbance, appetite or weight change, and psychomotor agitation or retardation). The QIDS-SR rates symptom domains during the prior seven days. Each item is scored on a scale from 0 to 3 points. Total scores range from 0 to 27. Studies of the QIDS-SR in patients with MDD and bipolar disorder have shown good psychometric properties, including strong internal consistency, concurrent validity, sensitivity to symptom change, and ability to distinguish response and remission. Thus, the QIDS-SR is the only brief self-report instrument that assesses all of the clinical domains used in making a diagnosis of MDD based on DSM-IV-TR criteria.

Source: Brown, Murray, et al., 2008, ICER, American Psychology Association, H.C. Wainwright & Co.

Primary Nonresponders Are at Risk of Developing TRD

Predictive Value of Early Antidepressant Response

Metaanalysis

- Twenty-eight randomized controlled trials of SSRIs vs. placebo (n=5,872).
- Treatment with SSRIs is associated with symptomatic improvement by the end of the first week of use.
- Improvement continues at a decreasing rate for at least six weeks.

VAST-D subanalysis

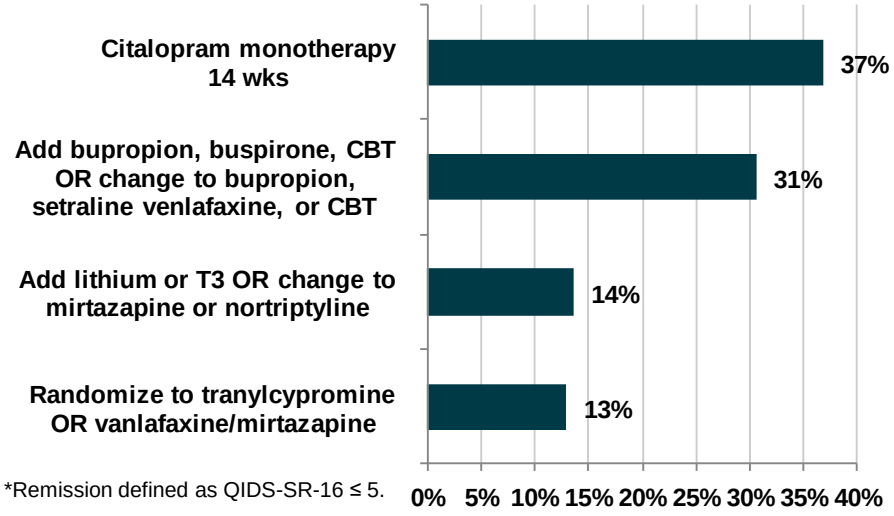
- Odds of achieving response and remission at week 12 are greater among individuals who exhibit improvement by the end of week 2 of initial antidepressant treatment (OR 7.7 and 3.5, respectively).

Source: Taylor et al., 2006.

When MDD treatment fails, leading to TRD.

- In 30-45% of patients, remission is not achieved with a single antidepressant, even at adequate dosage and period.
  - Antidepressant efficacy decreases with successive trials.
  - More than two failed trials: Treatment-resistant depression (TRD).

STAR*D report on acute and long-term depression outcomes points to reduced efficacy with successive acute treatments



*Remission defined as QIDS-SR-16 ≤ 5.

Source: Rush et al., 2006.

Guidelines: When MDD treatment fails

Guideline	Recommendations
APA	• Consider change in treatment if patient has not fully responded to acute phase treatment over 4-8 weeks.
CANMAT	• If no early improvement after 2-4 weeks, consider switching or adding adjunctive treatments. • If early improvement, continue treatment for 6-8 weeks; if remission not attained, consider switching or treatment augmentation.
Florida Best Practice Guideline	• If initial treatment is ineffective or not tolerated, evaluate adherence, optimize dose. • If response is still insufficient, switch to different therapy or augment with psychotherapy, atypical antipsychotic FDA approved for MDD, another antidepressant (do not combine SSRI with SNRI) intranasal esketamine or intravenous racemic ketamine.

Source: Lam et al., 2016, McIntyre et al., 2017.

Source: Hasin, Sarvet, et al., 2018, Rush, Trivedi, et al., 2006, Guidelines Overview: Augmentation Therapies in Major Depressive Disorder. Available at clinicaloptions.com. Clinical Care Options, LLC; Reston, VA, USA. H.C. Wainwright & Co.

Therapies for Treatment-Resistant Depression (TRD) Are Limited

- SPRAVATO (esketamine), a ketamine isomer, is the newest FDA-approved (2019) treatment option for TRD and is indicated in conjunction with an oral antidepressant. The intranasal formulation allows it to bypass the oral-bioavailability issues seen with ketamine and enables it to reach the brain faster, resulting in a quicker onset of antidepressant effects. We discuss esketamine in greater detail later on in this report. SYMBYAX (olanzapine-fluoxetine) is the only other FDA-approved (2003) pharmacotherapy option for TRD; generics are available.

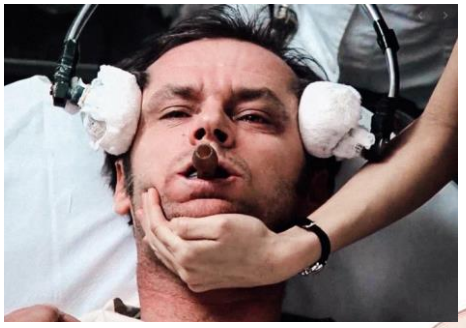
- Electroconvulsive therapy (ECT) is a nonpharmacologic option. All the guidelines advise ECT be reserved for use after a patient has an inadequate response (or intolerance) to several trials of antidepressant classes. The APA suggests ECT as a first-line option for patients who prefer it or those with psychotic symptoms or a positive response to psychotherapy in the past. Despite the stigma we found some clinicians very positive on ECT, framing it as a quick procedure to "re-boot" the system.

- Transcranial magnetic stimulation (TMS), the only FDA-approved somatic therapy, is suggested in all guidelines (except the Canadian guidelines) as a viable treatment option for TRD if pharmacotherapy trials fail. Vagus nerve stimulation (VNS) is suggested as a last-line option. (It is advised against in the Veteran's Affairs (Department of Defense, (VA/DoD) guidelines).

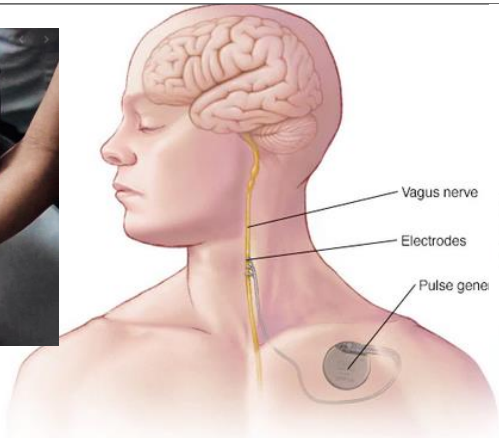
- According to the FDA, some of these treatments are associated with significant adverse reactions and interventional concerns such as use of general anesthesia, seizure induction, and memory loss with ECT; or surgical intervention and infection risk with VNS implantation. Other issues include inconvenient daily office visits such as with TMS.

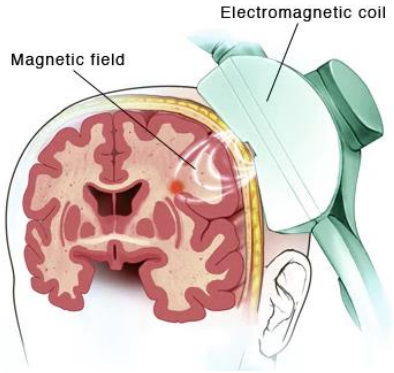
Source: Texas medical center.

Source: DailyMed.



Source: Slate.com.





Source: Mayo Clinic.

Source: Mithawala and Davis, 2020, FDA, H.C. Wainwright & Co.

Summary of FDA-Approved Products for Treatment of TRD

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Notable Safety and Tolerability	Regulatory Authority
SPRAVATO (esketamine)	TRD	1970 (ketamine) 2019 (esketamine)	Intranasally, supervised Induction phase (weeks 1 to 4, 2Qw) Maintenance phase (weeks 5 to 8, Q1w; weeks 9 and after, Q2w or Q1w)	Short-term study: MADRS total score change from baseline of -20 and placebo -16 Long-term study: relapses in stable remission group of 27% and placebo 45%; relapses in stable response group of 26% vs. 58% placebo	Dysgeusia (27% vs. 7% placebo), vertigo (25% vs. 5.5% placebo), somnolence (21% vs. 2% placebo), dizziness (20% vs. 5% placebo), headache (18% vs. 10% placebo), nausea (16% vs. 1% placebo)	CDER
SYMBYAX (fluoxetine plus olanzapine)	TRD	2003	Oral daily	MADRS total score change from baseline of -16 vs. olanzapine -12 and placebo -10 in Study 1; -18 vs. -14 and -9 in Study 2	Olanzapine is an antipsychotic associated with weight gain, hyperglycemia, and extrapyramidal symptoms including akathisia	CDER
ECT	TRD associated with either MDD or bipolar disorder	1976 Most recent update 2018	Bitemporal or unilateral temporal; up to 3 times a week for 6 to 10 treatments initially	Not available; approval based on various studies from research literature	Memory concerns, use of general anethesia	CDRH
TMS	TRD patients who railed only one anti-depressant	2008	Transcranial; up to daily for 4 to 6 weeks initially (20 to 30 sessions)	MADRS total score change from baseline of -6 at week 4 and week 6 active TMS vs. -4 at week 4 and week 6 sham TMS; approval based on post-hoc analysis and responder / remission rates	No major safety issues, limited long-term safety data	CDRH
VNS	TRD	2005	Once (surgical implant)	12-week sham placebo-controlled study not statistically significant; approval was based on long-term open-label HAM-D responder data (30% response in 1 year vs. 13% treatment as usual); 12-week open-label pilot study showed 34% MADRS responders	Surgical intervention risks (allergies, infection, etc.)	CDRH

*Note: SYMBYAX generics entered the market in 2012.

Source: FDA, H.C. Wainwright & Co.

Benchmarking the Competition: Selected MDD and TRD Compounds

We highlight SPRAVATO (esketamine), the S-enantiomer of ketamine (approved in 1970 for anesthesia). Esketamine is an N-methyl-D-asparate (NMDA) receptor antagonist (non-competitive). Prior to its FDA approval, esketamine was approved in Europe and Latin America for an anesthesia indication (IV and/or IM use).

SPRAVATO, administered intranasally (IN), was approved by the FDA on March 5, 2019 after an advisory committee voted overwhelmingly for approval (14 yes votes, two no votes, one abstain). SPRAVATO was also approved on August 3, 2020, to treat depressive symptoms in adults with MDD with acute suicidal ideation or behavior within 24 hours.

Esketamine in TRD differs from anesthesia use; lower dose, chronic administration; administration at supervised settings only, with REMS certified clinician.

For now, we view SPRAVATO as psilocybin's primary competitor in the TRD and MDD with suicidal ideation areas.

In the pages that follow, we include selected psychedelics being evaluated in TRD because if they are successful in TRD, it is possible they could also be assessed in MDD.

Indication	Antidepressant	MADRS LS Mean CFB at Primary Endpoint Range	MADRS LS Mean CFB Difference from Placebo or Active Control	Baseline MADRS Score
MDD	Vortioxetine	-13 to -20	-2.8 to -7.1	31 to 34
	Vilazodone	-9.7 to -13	-2.5 to -3.2	31 to 32
	Levomilnacipran	-14 to -17	-1.3 to -4.9	30 to 36
Adjunctive MDD	Aripiprazole	-8.5 to -8.8	-2.8 to -3.0	31 to 32
	Brexpiprazole	-7.7 to -8.5	-1.3 to -3.1	33 to 35
	Quetiapine XR	-14 to -17	-1.6 to -4.1	38 to 32
TRD	Olanzapine + fluoxetine (fixed-dose combination)	-8.6 to -14	N/A	23 to 30
	Fluoxetine (vs. olanzapine + fluoxetine)	-1.2 to -11	-1.4 to -12	23 to 30
	Olanzapine (vs. olanzapine + fluoxetine)	-2.8 to -10	-0.8 to -11	23 to 30
	Esketamine	-10.1 to -20.8	-3.2 to -4.1	37 to 38 adult, 35 geriatric

Source: FDA Briefing Document (FBD), 2019, H.C. Wainwright & Co.

Benchmarking the Competition: SPRAVATO (Esketamine)

Proposed advantages of SPRAVATO (esketamine) over existing TRD treatments.

(1) Potentially faster onset of action.
(2) Intranasal dosing (less invasive than IV or IM).
(3) Different mechanism of action and AE profile from existing antidepressants (ADs).
(4) Fewer drug-drug interactions than existing ADs.
(5) Less frequent dosing regimen.
(6) No need for general anesthesia, surgical intervention or exogenous electrical exposure (as with ECT, TMS, VNS).

Phase 3 Trial	Design	Arms	Dosing	Duration	Primary Endpoint	Patients Enrolled	Population
TRD3001 TRANSFORM-1	Parallel-Group	Fixed-dose esketamine (56 or 84 mg) vs. pbo + oral AD all arms	Twice weekly IN (oral AD daily)	4-week treatment phase, 24-week follow-up or TRD3003	Change from baseline (CFB) in MADRS total score at week 4	344 total (115 on ESK 56 mg + oral AD; 116 on ESK 84 mg + oral AD; 113 on placebo + oral AD	Adults (18 to 64 years) with TRD
TRD3002 TRANSFORM-2	Parallel-Group	Flexible-dose esketamine (56 or 84 mg) vs. pbo + oral AD both arms	Twice weekly IN (oral AD daily)	4-week treatment phase, 24 week follow-up or TRD3003	Change from baseline (CFB) in MADRS total score at week 4	224 total (114 on ESK + oral AD; 110 on placebo + oral AD)	Adults (18 to 64 years) with TRD
TRD3005 TRANSFORM-3	Parallel-Group	Flexible-dose esketamine (28 or 56 or 84 mg) vs. pbo + oral AD both arms	Twice weekly IN (oral AD daily)	4-week treatment phase, 24-week follow-up or TRD3004 (long-term safety study)	Change from baseline (CFB) in MADRS total score at week 4	137 total (72 on ESK + oral AD; 65 on placebo + oral AD)	Geriatric (65 years and older) with TRD
TRD3003 SUSTAIN-1	Randomized Withdrawal	Flexible or fixed-dose esketamine (56 or 84 mg) vs. pbo + oral AD all arms	Twice weekly IN during 4-week phase, then weekly for next 4 weeks, then weekly or every other week per response (Oral AD Daily)	4-week treatment initiated during open-label direct-entry phase or during 3001 or 3002; then 12-week open-label optimization phase; then ongoing maintenance phase post-randomization	Time to relapse during maintenance phase for stable remitters	705 (437 direct entry + 268 from 3001 or 3002); 176 during maintenance phase (90 on ESK + oral AD; 86 on placebo + oral AD	Adults (18 to 64 years) with TRD

Source: FDA Briefing Document (FBD), 2019, H.C. Wainwright & Co.

SPRAVATO's TRD Data Package Included Two Unremarkable Ph. 3 Trials

- SPRAVATO's FDA label includes the short-term TRANSFORM-2 trial data as it met statistical significance albeit with a modest improvement from baseline, as well as long-term data from SUSTAIN-1, which also met statistical significance.
- However, according to the FDA briefing document, Study 3001 (TRANSFORM-1) did not confirm the dose-response relationship observed in the Phase 2 study (2003), while Study 3005 (TRANSFORM-3) does not appear to be supportive of an esketamine effect.

	Studies	2-Sided P-Value <.05
Phase 3	TRANSFORM-2 (Pivotal)	p = 0.02
	SUSTAIN-1 (Pivotal)	p = 0.003
Phase 2	TRD2001	p ≤ .003
	TRD2002	p <.001
	SYNAPSE (TRD)	p = 0.043 (28 mg) p = 0.002 (56 mg) p < 0.001 (84 mg)
	PERSEVERE (Related population with major depression)	p = 0.015
Phase 3	TRANSFORM-1	p = 0.088
	TRANSFORM-3	p = 0.059

	Treatment Arm	N	Baseline MADRS Total Score (SD)	LS Mean Change from Baseline at Week 4*	LS Mean Difference from Placebo at Week 4*	1-Sided P-Value <0.025
TRANSFORM-1 (Study 3001)	Esketamine 56 mg + oral AD	115	37.4 (4.8)	-18.9 (-21.4 to -16.4)	-4.1 (-7.7 to -0.5)	0.013
	Esketamine 84 mg + oral AD	114	37.8 (5.6)	-18.2 (-20.9 to -15.6)	-3.2 (-6.9 to +0.5)	0.044
	Placebo + oral AD	113	37.5 (6.2)	-14.9 (-17.4 to -12.4)		
TRANSFORM-2 (Study 3002)	Esketamine + oral AD	114	37.0 (5.7)	-19.8 (1.3)	-4.0 (1.7)	0.01
	Placebo + oral	109	37.3 (5.7)	-15.8 (1.2)		
TRANSFORM-3 (Study 3005)	Esketamine + oral AD	72	35.5 (5.9)	-10.1 (-13.1 to -7.1)	-3.6 (-7.2 to 0.07)	0.029
	Placebo + oral AD	65	34.8 (6.4)	-6.5 (-9.4 to -3.6)		

Source: FDA Briefing Document (FBD), 2019, Sponsor Presentation.

Two Phase 3 trials were not significant as shown by 1-sided and 2-sided p-values.

		Treatment Arm	N	Number Censored No Relapse	Number of Relapses	25% Percentile (95% CI)	Median (95% CI)	Hazard Ratio (HR) (95% CI)	1-Sided P-Value <0.025
SUSTAIN-1 (Study 3003)	Time to Relapse (Days) Stable Remitters	Esketamine + oral AD	90	66 (73%)	24 (27%)	153 (105 to 225)	Not estimable (NE)	.49 (0.3 to 0.8)	0.003
		Placebo + oral AD	86	47 (55%)	39 (45%)	33 (22 to 48)	273 (97 to NE)		
	Time to Relapse (Days) Stable Responders	Esketamine + oral AD	62	46 (74%)	16 (26%)	217 (56 to 635)	635 (264 to 635)	0.3 (0.16 to 0.55)	<.001
		Placebo + oral AD	59	25 (42%)	34 (58%)	24 (17 to 46)	88 (46 to 196)		

*95% confidence interval (CI) reflected in TRANSFORM-1 and -3; standard error (SE) reflected in TRANSFORM-2.

Source: FDA Briefing Document (FBD), 2019, H.C. Wainwright & Co.

SPRAVATO: Safety and Tolerability Summary From Ph. 3 Trials

Most frequent long-term AEs were dizziness, dissociation, headache and nausea.

Blood pressure did tend to increase, though transiently (see next page). The FDA label for SPRAVATO does include some warnings around blood pressure.

Few deaths were reported in the trials.

Data from the placebo controlled trials and the long-term, open-label study did not show an increased risk of interstitial cystitis, liver injury, or impaired cognitive function in esketamine-treated patients, all of which are commonly-reported complications associated with repeated use of ketamine, according to the FDA.

Trial	TRANSFORM-1			TRANSFORM-2		TRANSFORM 1 and 2		TRANSFORM-3		SUSTAIN-1		SUSTAIN-2		
Week	4			4		4		4		≥48		4	≥48	≥52
Arm	ESK 56 mg +AD	ESK 86 mg + AD	PBO + AD	ESK + AD	PBO + AD	ESK + AD	PBO + AD	ESK + AD	PBO + AD	ESK + AD	PBO + AD	IND Phase: ESK + AD	OP/MAINT Phase: ESK + AD	Both Phases: ESK + AD
N	115	116	113	115	109	346	222	72	65	152	145	779	603	802
Any TEAE	87	88.8	68.1	85.2	60.6	87	64.4	70.8	60	82.2	45.5	83.8	85.6	90.1
Serious TEAE	1.7	0	0	0.9	0.9	0.9	0.5	4.2	3.1	2.6	0.7	2.2	6.3	6.9
D/C due to TEAE	0.9	6	N/A	7	N/A	4.6	1.4	5.6	3.1	2.6	2.1	6.8	3.8	9.5
Dizziness	27.8	22.4	8.8	20.9	4.6	23.7	6.8	22.2	7.7	20.4	4.8	29.3	22.4	32.9
Dissociation	26.1	27.6	3.5	26.1	3.7	26.6	3.6	12.5	1.5	23	0	23.4	18.7	27.6
Headache	20	20.7	16.8	20	17.4	20.2	17.1	12.5	3.1	17.8	9.7	17.6	19.1	25.1
Nausea	27	31.9	10.6	26.1	6.4	28.3	8.6	18.1	4.6	16.4	0.7	20.2	13.9	25.1
Somnolence	20.9	18.1	11.5	13	6.4	17.3	9	N/A	N/A	21.1	2.1	12.1	14.1	16.7
Dysgeusia	14.8	17.2	15	24.3	11.9	18.8	13.5	5.6	4.6	27	6.9	9.9	9	11.8
Hypoesthesia	12.2	13.8	1.8	7	0.9	11	1.4	5.6	1.5	5.9	0	10.1	6.6	11.8
Vertigo	20.9	20.7	1.8	26.1	2.8	22.5	2.3	11.1	3.1	25	5.5	0.7	7.1	11
Vomiting	6.1	12.1	1.8	9.6	1.8	9.2	1.8	6.9	1.5	6.6	0.7	7.2	7.5	10.8
BP increase	7.8	9.5	4.4	9.6	0	9	2.3	12.5	4.6	6.6	3.4	6.8	7.8	9.5
Hypoesthesia oral	13.9	10.3	1.8	7.8	0.9	10.7	1.4	6.9	0	13.2	0	8.1	N/A	9.1
Anxiety	8.7	7.8	6.2	10.4	4.6	9	5.4	2.8	7.7	7.9	4.1	6.5	N/A	9
Sedation	5.2	6.9	0.9	4.3	0.9	5.5	0.9	0	0	6.6	0.7	6.5	N/A	8.9
Dizziness postural	6.1	6	0	7	0.9	6.4	0.5	N/A	N/A	6.6	2.1	6.9	6.8	8.4
Insomnia	8.7	6.9	9.7	9.6	4.6	8.4	7.2	5.6	4.6	N/A	N/A	5.3	5.8	8.1
Fatigue	10.4	6.9	4.4	4.3	5.5	7.2	5	12.5	7.7	N/A	N/A	5.1	N/A	7.9
Vision blurred	7	7.8	0	12.2	2.8	9	1.4	N/A	N/A	15.8	0.7	6.3	N/A	7.5
Diarrhea	7	4.3	2.7	8.7	9.5	6.6	5.9	N/A	N/A	N/A	N/A	N/A	6.5	7.5
Parasthesia	16.5	9.5	2.7	11.3	0.9	12.4	1.8	5.6	3.1	7.2	0	5.9	N/A	7.2
Death	0	0	0	0.9	0	0.3	0	0	0	0	0	0	0.3	0.2

Note: Data in the above Exhibit expressed as %, unless noted.

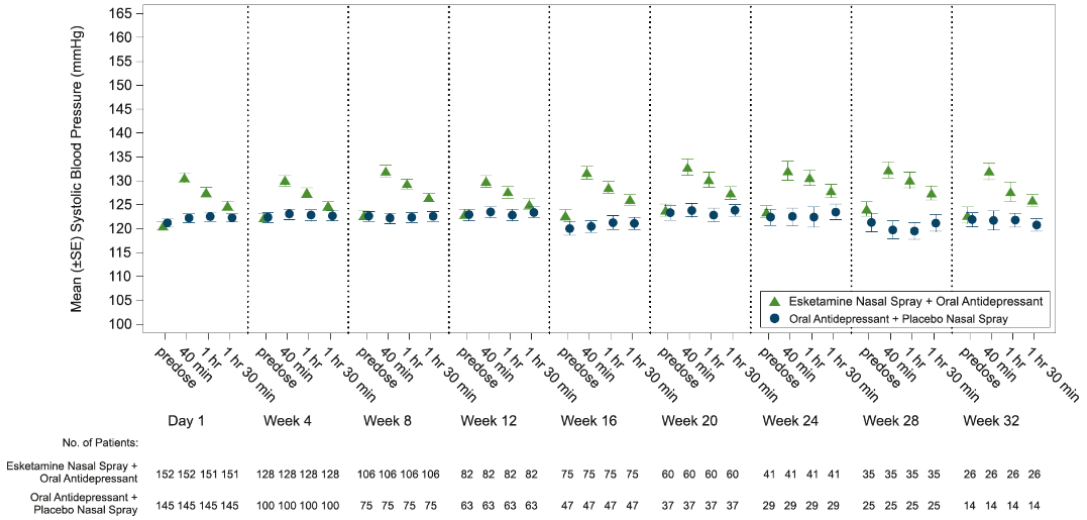
Source: Daly, Trivedi, et al., 2019, Popova, Daly, et al., 2019, Janssen R&D, Advisory Committee Briefing Document, H.C. Wainwright & Co

SPRAVATO: Blood Pressure Tends to Increase Transiently

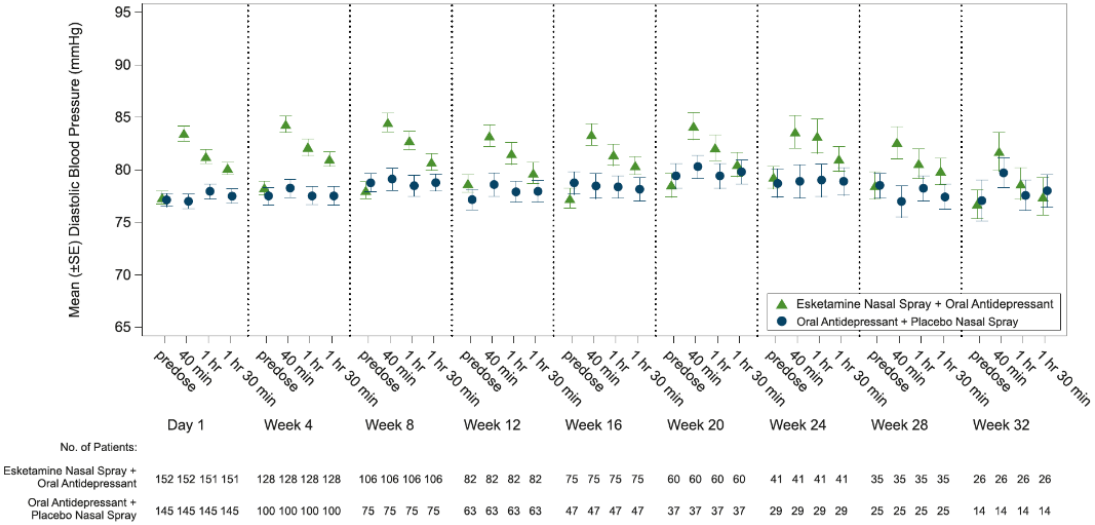
Systolic blood pressure; mean blood pressure over time in the maintenance phase for stable remitters and stable responders

In the Phase 3 trial (SUSTAIN-1) conducted from 2015 to 2018 evaluating esketamine, transient blood pressure increases were observed with esketamine on treatment days; the maximum value was reached at 40 minutes after the start of administration in most cases and typically returned to the predose range by 1.5 hours after administration.

Few patients experienced treatment-emergent transient hypertension, defined as a systolic blood pressure of 180 mmHg or higher and/or a diastolic blood pressure of 110 mmHg or higher (i.e., systolic hypertension: 1 [0.7%] esketamine-treated patient and 0 antidepressant- and placebo-treated patients; diastolic hypertension: 2 [1.3%] esketamine-treated patients and 0 antidepressant-and placebo-treated patients) during the maintenance phase. No clinically significant change in electrocardiographic findings was observed during the study.



Diastolic blood pressure; mean blood pressure over time in the maintenance phase for stable remitters and stable responders



Source: Daly, Trivedi, et al., 2019, H.C. Wainwright & Co.

SPRAVATO: Valid Concerns Raised By Former FDA Official

Learning from esketamine program. A former Medical Officer for the FDA published seven concerns about the efficacy and FDA approval of esketamine that we believe (1) provide lessons for clinical development for psychedelics; and (2) provide an opening for first generation and next generation psychedelics to demonstrate a differentiated efficacy and safety profile from key competitor SPRAVATO in TRD.

Concern #1. Clinical trials used an arguably lax regulatory definition of TRD, specifically "failure of treatment of … any two antidepressants," enabling inclusion of patients in whom only selective serotonin reuptake inhibitors had failed. For instance, among the 702 patients who entered the three short-term Phase 3 trials, 22% had treatment failure with just one class of antidepressants, 60% had treatment failure with two classes of antidepressants, and 18% had treatment failure with three or four classes. Moreover, trial patients were not required to have undergone psychotherapy unsuccessfully.

Concern #2. One of the two non-significant trials (not published) involved older patients, 65 years or older, study 3005 (NCT02422186), p=.06, raising the question of esketamine's efficacy within the geriatric demographic.

Concern #3. In the sole positive short-term Phase 3 trial (3002), the mean decrease from baseline in the MADRS was 20.8 vs. 16.8 for placebo. To the medical officer, this differential is unremarkable.

Concern #4. Participation in the randomized withdrawal trial (3003) was restricted to patients who had been previously randomly assigned to esketamine (not placebo) in a short-term trial and achieved stable remission, which resulted in an enriched population statistically more likely to respond to the drug.

Concern #5. Perhaps most concerning is the idea that an outlier site in Poland disproportionately drove the efficacy overall in study 3003 (see next page).

Concern #6. Meta-analysis of three studies (3001, 3002, 3005) yields a standardized mean difference of 0.28 (0.04-0.45), which is similar to that of olanzapine-fluoxetine (only other drug approved for TRD) and less than other compounds approved as adjunctive therapy for treatment of depression, aripiprazole (0.35, 0.23-0.48) and quetiapine (0.40, 0.26-0.53).

Concern #7. Rapid onset of response was not formally demonstrated.

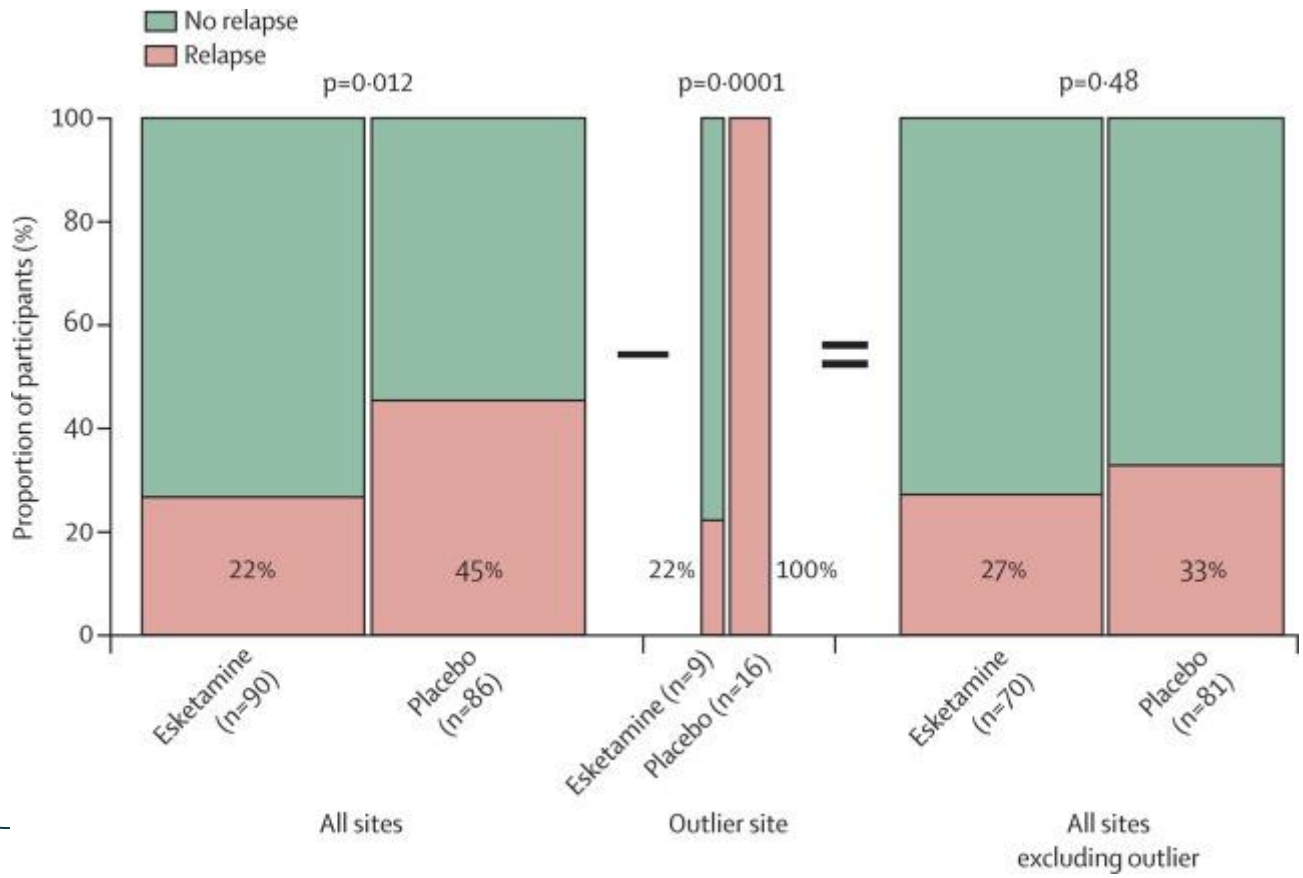
Source: Turner, 2019, H.C. Wainwright & Co.

SPRAVATO: Removal of Outlier Site Eliminates Significance in TRD

Inconsistent with the FDA requirement for "substantial evidence of effectiveness", the results of study 3003 are not robust according to *The Lancet.* "One concern in this study was that one site in Poland drives the overall study result due to a 100% rate of placebo arm relapses."

Although the FDA reassured its Advisory Committee that it had inspected this site and "didn't find any reason to question the data integrity", the issue arose only following a question by a committee member and was not presented in the slides.

Without access to patient-level data, one cannot recalculate time to relapse and the hazard ratio, but one can do a sensitivity analysis using the relapse data provided (FBD p 25). Removing the outlier site changes the results from significant (Fisher's exact test p=.012) to non-significant (p=.48).



Source: Turner, 2019, H.C. Wainwright & Co.

Benchmarking the Competition: COMP360 (Oral Psilocybin)

- **COMPASS Pathways snapshot.** COMPASS is a mental healthcare company pioneering the development of a new model of psilocybin therapy in which psilocybin is administered in conjunction with psychological support. The initial focus is on TRD, a subset of MDD, comprising patients who are inadequately served by the current treatment paradigm. COMPASS developed a proprietary, high-purity polymorphic crystalline formulation of psilocybin, COMP360.

- **Evidence of potential efficacy of psilocybin in depressive and anxiety conditions.** The therapeutic potential of psilocybin in depressive and anxiety conditions has been demonstrated in a number of academic-sponsored studies over the last decade. In these studies, psilocybin, when administered in conjunction with psychological support, provided rapid reductions in depression symptoms after a single high dose, with antidepressant and anxiolytic effects occurring on the day of administration and lasting up to the six-month follow-up period for a number of participants. These studies used a range of widely used and validated scales to assess symptoms related to depression and anxiety. Some of these scales are self-reported and others are rated by clinicians. Relevant studies include: Grob et al., 2011, Ross et al., 2016, Griffiths et al., 2016, Carhart-Harris et al., 2016, 2018, 2021, Davis et al., 2020.

- **Phase 2b trial evaluating COMP360 in TRD.** COMPASS is conducting a randomized controlled Phase 2b trial in approximately 216 patients suffering from TRD at 20 sites across North America and Europe. This dose-finding trial is investigating the safety and efficacy of COMP360 combined with psychological support, for the treatment of TRD, and aims to determine the optimal dose of COMP360, with three doses (1 mg, 10 mg, 25 mg) being explored. Per the trial protocol, the primary endpoint is to evaluate the efficacy of COMP360 as assessed by the change in the Montgomery-Åsberg depression rating scale (MADRS). This trial has been designed to capture a statistically significant reduction in MADRS. COMPASS is to potentially report data from this trial in late 2021 and with it being the largest controlled study conducted to-date evaluating a psychedelic, we believe the outcome from the trial is to be one of the most widely anticipated events in the psychedelics space ever.

COMP360 is considered the leading psilocybin treatment in advanced development for depression; the Phase 2b trial readout could have a positive read through to the entire psychedelics space, in our view.

Phase 2b Clinical Trial: COMP360 Psilocybin Therapy for TRD

Target enrollment of 216 patients

Randomization 1:1:1, 1 mg psilocybin (n=72), 10 mg psilocybin (n=72), 25 mg psilocybin (n=72)

Primary endpoint: reduction of symptoms of depression as measured by MADRS from baseline to three weeks.

Secondary endpoint: proportion of responders who maintained ≥ 50% improvement in MADRS up to week 12.

3-6 weeks	Day 0	Day 1	Week 1	Week 2	Week 3	Week 6	Week 9	Week 12
Screening (V1)	Psilosybin session	V4	V5	V6	V7	Remote visit	Remote visit	End of study
Baseline (V2)	V3					V8	V9	V10
Includes weekly visits								

Source: COMPASS filings and presentations, H.C. Wainwright & Co.

Benchmarking the Competition: PCN-101 (Arketamine)

- **atai Life Sciences snapshot.** Founded in 2018, atai, which operates a decentralized model, has built a pipeline of 10 development programs and six enabling technologies that atai has either acquired a controlling or significant interest in or created de novo.

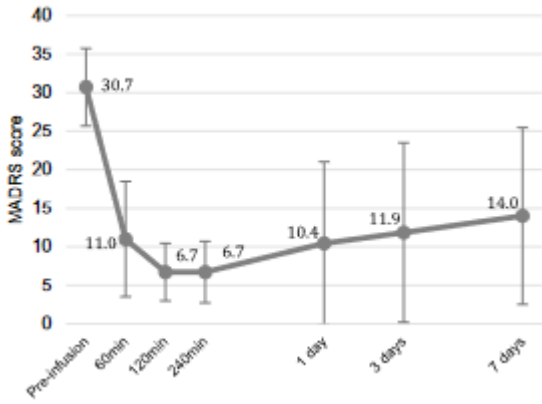
- **R-ketamine (arketamine).** Arketamine and esketamine are the R(-) and S(+) enantiomers of ketamine, a compound that has been used for everything from anesthesia and sedation to chronic pain and depression. Recently, esketamine as a nasal spray (SPRAVATO) made history as the first psychedelic-type substance approved by the FDA for TRD. However, ketamine's often overlooked R(-) enantiomer may be both a more potent antidepressant and effect fewer perceptual disturbances than esketamine.

- **PCN-101 for TRD.** Perception Neuroscience, an atai company, is advancing PCN-101, a subcutaneous formulation of R-ketamine (arketamine) as a rapid-acting antidepressant, with the potential to be an at-home nondissociative alternative to S-ketamine (SPRAVATO). On September 14, atai announced that Perception initiated a Phase 2a trial to evaluate PCN-101 in TRD. The Phase 2a trial is a double blind, placebo-controlled study in patients with TRD. Each of the three parallel arms are expected to enroll 31 patients at multiple locations. Patients are expected to receive either placebo, a 30 mg dose, or a 60 mg dose of R-ketamine intravenously. The trial will aim to enroll approximately 93 patients in total (approximately 31 per cohort). In-clinic treatment will be preceded by a screening period and followed by two follow-up periods where clinical parameters will be assessed. Patients are to be assessed for depressive symptomology over the subsequent 14 days using the MADRS scale; safety assessment measures will include Modified Observer's Assessment of Alertness/Sedation Scale, Brief Psychiatric Rating Scale Positive Symptoms Subscale and CADSS. Top-line data is expected to be reported at the end of 2022.

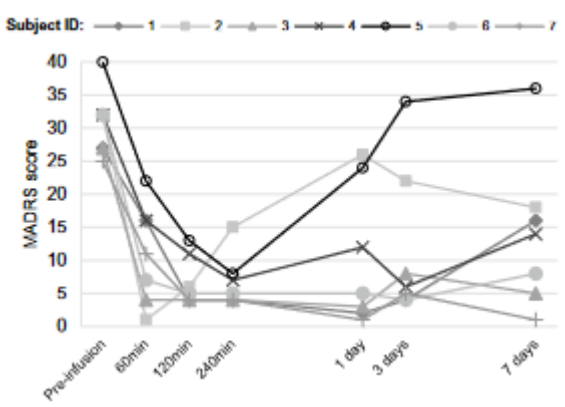
Source: atai Life Sciences filings, H.C. Wainwright & Co.

Open-label study (not conducted by atai) demonstrated potential of arketamine in TRD; mean MADRS score of 30.7 prior to infusion dropped to 10.4 after one day (-66%) on average in seven patients.

Mean MADRS scores through time



Individual MADRS scores through time



Source: Leal, Bandeira, et al., 2021.

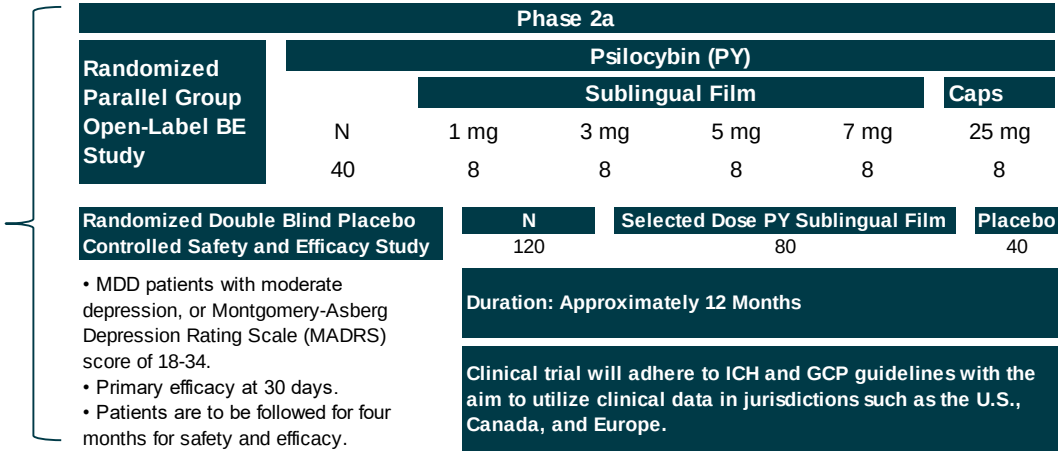
Benchmarking the Competition: CYB001 (Sublingual Psilocybin)

- **Cybin snapshot.** Cybin is an emerging psychedelics leader whose lead candidate, CYB001, is a sublingual film formulation of psilocybin. A provisional patent has been filed covering the sublingual delivery of psilocybin. Cybin has contracted with IntelgenX to undertake the development of a sublingual film formulation of psilocybin. To date, an array of drug formulation candidates have been created and Cybin continues to pursue the optimization of certain characteristics of these formulations including, but not limited to, composition, membrane permeation and stability. Potential benefits of delivering psilocybin sublingually rather than as an oral solid dose: (1) potential faster onset of action; and (2) potential shorter duration of action.

- **The Phase 2a program remains on track to generate initial data by the end of 2021.** Cybin was granted Institutional Review Board (IRB) and Ethics Committee of the Ministry of Health in Jamaica approval for Phase 2 trials evaluating sublingual psilocybin to research the potential treatment of MDD. The purpose of the planned Phase 2a trial is to determine the sublingual film formulation deemed equivalent to a 25 mg capsule of psilocybin administered orally. We note that the study start timing of 4Q21 is slightly delayed from the prior 2Q21 expectation owing to the COVID-19 pandemic, which delayed approval by the IRB in Jamaica; the initial pharmacokinetic data readout should still be ready in 4Q21, and this data should help support an Investigational New Drug (IND) application with the FDA once a final formulation of sublingual film psilocybin has been optimized.

- **Phase 2b trial on track to start in 1H22.** Following completion of the Phase 2a trial, assuming Cybin identifies an appropriate sublingual film dose, Cybin intends to begin a Phase 2b trial with 120 patients in MDD. On July 6, Cybin announced an exclusive agreement with TMS NeuroHealth Centers, a subsidiary of Greenbrook TMS, which operates 129 outpatient mental health service centers in the U.S. We believe the partnership should provide Cybin with ample access to treatment centers to enroll patients in the Phase 2b MDD trial, as well as other psychedelic-based research studies to follow.

Cybin's sublingual film psilocybin could emerge as one of the leading psychedelic programs in depression, with Phase 2b data potentially on track to be reported in 2022 that could validate the program.



Source: atai filings, H.C. Wainwright & Co.

Benchmarking the Competition: Generic Oral Psilocybin

- **Usona Institute snapshot.** Usona is a 501(c)(3) non-profit medical research organization founded in 2014 by Bill Linton, CEO and Founder of the international life sciences company Promega Corporation and Malynn Utzinger, M.D., Director of Integrative Practices at Promega Corporation. Usona conducts and supports biochemical and clinical research to further the understanding of the therapeutic effects of psilocybin and other consciousness-expanding medicines.

- **PSIL201 trial and design.** Usona has developed oral psilocybin (25 mg, single-dose) in conjunction with a supportive set and setting protocol for MDD. Usona is conducting a Phase 2 trial (PSIL201) evaluating a single-dose psilocybin treatment in subjects with MDD. Usona intends to enroll 80 patients aged 21 to 65 who meet the DSM-5 criteria for MDD. Patients are expected to be stratified by study site and randomized (1:1) under double-blind conditions to receive either a single 25 mg oral dose of psilocybin or a single 100 mg oral dose of niacin. Niacin is serving as the active placebo. To enhance participant safety, a Set and Setting (SaS) protocol is expected to be utilized similar to the protocol that has been used in all modern studies of psilocybin. The SaS protocol for this study includes: (1) a period of preparation with session facilitators prior to dosing; (2) administration of study medications in an aesthetically pleasing room under the supervision of two facilitators who are present throughout the session; and (3) three post-dose integration sessions during which participants are encouraged to discuss their intervention experience with the facilitators. The SaS protocol will be identical for those randomized to psilocybin or active placebo.

- **Efficacy objective.** The primary endpoint is the change MADRS total score from baseline to post-dose day eight. Secondary endpoints include sustained depressive symptom response defined as a ≤50% reduction from baseline MADRS score at all post-dose assessments (i.e., day eight, 15, 29, and 43 post-dose) as well as sustained depressive system remission defined as a MADRS score ≤10 at all post-dose assessments, among others.

- **Top-line data report to-be-announced.** Although the primary completion date listed on Clinicaltrials.gov is February 2021, we believe the study enrollment was delayed by the COVID-19 pandemic and possibly a lack of funding, which makes it challenging to know when top-line data is expected.

Usona's PSIL201 Phase 2 trial design

Planned Enrollment	Design	Dosing	Population	FSFV	Subject Exposure per Treatment Arm (M/F)
n = 80	Randomized, double-blind, active placebo-controlled safety and efficacy	Single dose, oral 25 mg psilocybin	Adults (age 21-65) with MDD	19-Dec-19	Planned: 40:40, (20 male and 20 female per arm)

Note: F: Female; FSFV: First subject first visit; M: Male; MDD: Major Depressive Disorder. FSFV date is considered the first date on which a subject signed the informed consent form.

Source: Usona Institute, H.C.W. research.

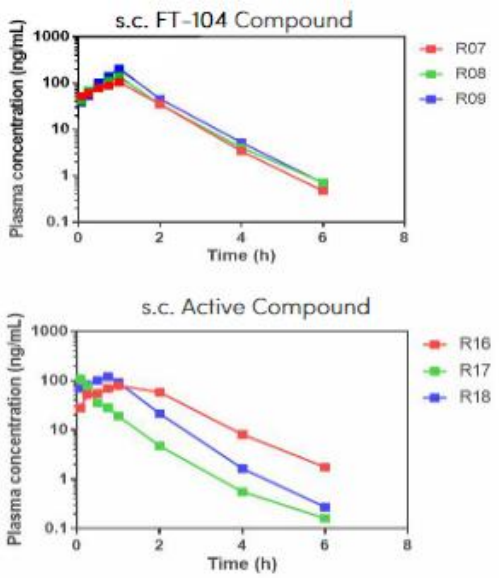
FT-104 (Psilocybin-Like) Nearing Phase 1 Development

- **Field Trip snapshot.** The drug discovery arm of Field Trip, Field Trip Discovery, is focused on creating optimized psychedelic substances that could be differentiated from classic psychedelics.

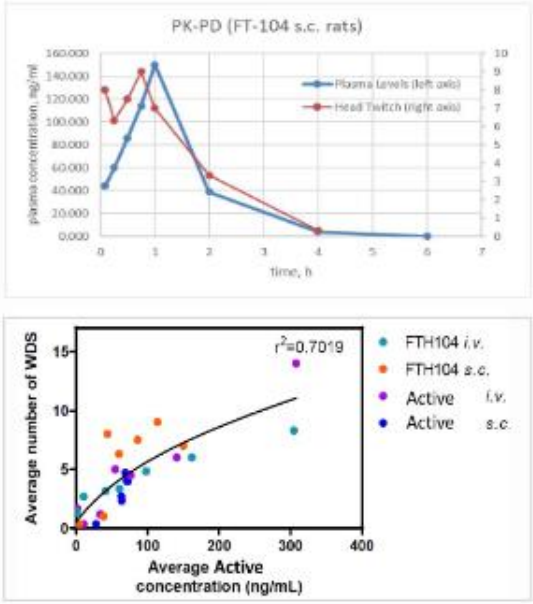
- **FT-104.** Field Trip has noted there is a unique opportunity to optimize psychedelic molecules. The idea is to create a psilocybin-like pharmacological profile to recapitulate documented safety and efficacy and minimize development risk. Moreover, a short-duration psychedelic experience could make for a more practical and safer psychedelic therapy program. A thorough optimization process ended with FT-104, a novel prodrug, as Field Trip's lead candidate, which: (1) is a serotonin-2A agonist; (2) has a potency and pharmacology profile similar to psilocybin; and (3) could be differentiated based on the simple prodrug concept, good drug qualities, short psychedelic trip time, and patent protection (June 2020).

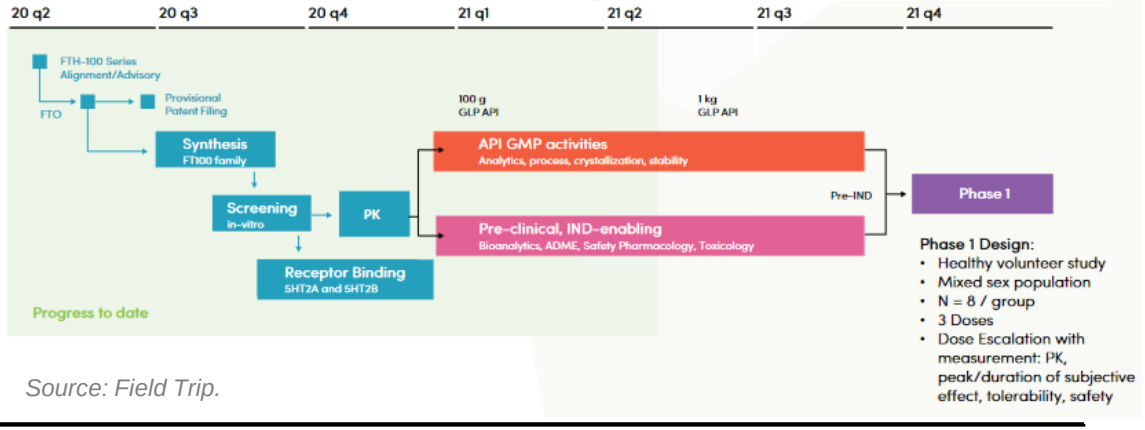
- **Preliminary assessment.** FT-104 highlights: (1) optimized scalable synthetic route to the active substance; (2) prodrug moiety is a natural product (no toxicity); (3) prodrug addition occurs with precipitation as formed, making it simple to isolate and purify FT104. Regarding FT-104's drug characteristics: (1) preliminary solid-state and solution stabilities are acceptable, according to Field Trip; (2) solubility of prodrug greatly improved relative to active species; >20x to >100 mg/mL; (3) enzymatic cleavage is rapid; 100% in <30 min in human plasma.

FT-104 preclinical PK confirms anecdotes, duration < 4 hours.



FT-104 preclinical PK-PD demonstrates CNS uptake and 5HT2A binding.





Source: Field Trip.

Source: Field Trip, H.C. Wainwright & Co.

Modeling Assumptions: MSP-1014 in TRD

- **Addressable patients.** We start with a prevalence of 8% in the U.S. in the adult population, or around 23M people in 2026, which is the potential year of initial launch. We assume a third are non-responders, of which 50% could be treated for TRD, of which 75% could be eligible for treatment. The implication is that the addressable population could exceed 2.5M people in the U.S.
- **Penetration rate.** We assume a psychedelic-assisted psychotherapy penetration of 1% that expands to 10% over time, of which we estimate MSP-1014 could capture around 12.5% of share over time.
- **Probability of success (PoS).** We assume 25% given the favorable comparisons demonstrated preclinically to psilocybin though offset by the early stage of development.
- **Pricing.** We assume a gross cost per treatment of C$20,000 that after a 15% gross-to-net reduction equates to a net cost of C$34,000 per year that increases in-line with inflation annually.
- **Loss of exclusivity (LOE).** We model an LOE in F2040.
- **Peak revenues.** Based on the above considerations, not risk-adjusted, we model peak annual revenues of more than C$2.5B where ROW markets represent 50% of the U.S. Risk-adjusted, our model includes peak annual revenues of more than C$0.5B for TRD.

Source: H.C. Wainwright & Co.

Modeling Assumptions: TRD

C$ in millions, unless noted

MSP-1014	F2026E	F2027E	F2028E	F2029E	F2030E	F2031E	F2032E	F2033E	F2034E	F2035E	F2036E	F2037E	F2038E	F2039E	F2040E	F2041E
TRD U.S. MARKET																
Major depressive disorder (MDD) prevalence	22,964,881	23,424,178	23,892,662	24,370,515	24,857,925	25,355,084	25,862,186	26,379,429	26,907,018	27,445,158	27,994,061	28,553,943	29,125,022	29,707,522	30,301,672	30,907,706
Treatment non-responders	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%	33.0%
TRD patient population	7,578,411	7,729,979	7,884,578	8,042,270	8,203,115	8,367,178	8,534,521	8,705,212	8,879,316	9,056,902	9,238,040	9,422,801	9,611,257	9,803,482	9,999,552	10,199,543
% Treated	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
% Eligible	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%
Eligible patients	2,841,904	2,898,742	2,956,717	3,015,851	3,076,168	3,137,692	3,200,445	3,264,454	3,329,743	3,396,338	3,464,265	3,533,550	3,604,221	3,676,306	3,749,832	3,824,829
% of TRD market treated with psychedelics	1.0%	2.0%	3.0%	4.0%	5.0%	6.0%	7.0%	8.0%	9.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%
TRD patients treated with psychedelics	28,419	57,975	88,702	120,634	153,808	188,261	224,031	261,156	299,677	339,634	346,427	353,355	360,422	367,631	374,983	382,483
Therapy sessions per year	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Total potential psychedelic-based treatments per year	**56,838**	**115,950**	**177,403**	**241,268**	**307,617**	**376,523**	**448,062**	**522,313**	**599,354**	**679,268**	**692,853**	**706,710**	**720,844**	**735,261**	**749,966**	**764,966**
% Penetration rate	2.0%	6.0%	9.0%	11.0%	11.5%	12.0%	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%	12.5%	2.5%
Total therapy sessions with MSP-1014	**1,137**	**6,957**	**15,966**	**26,539**	**35,376**	**45,183**	**56,008**	**65,289**	**74,919**	**84,908**	**86,607**	**88,339**	**90,106**	**91,908**	**93,746**	**19,124**
Gross pricing	20,000	20,400	20,808	21,224	21,649	22,082	22,523	22,974	23,433	23,902	24,380	24,867	25,365	25,872	26,390	26,917
% chg		2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%
Gross-to-net	15.0%	16.0%	17.0%	18.0%	19.0%	20.0%	21.0%	22.0%	23.0%	24.0%	25.0%	26.0%	27.0%	28.0%	29.0%	30.0%
Net pricing per treatment	17,000	17,136	17,271	17,404	17,535	17,665	17,793	17,919	18,044	18,165	18,285	18,402	18,516	18,628	18,737	18,842
Annual cost per year	34,000	34,272	34,541	34,808	35,071	35,331	35,587	35,839	36,087	36,331	36,570	36,804	37,033	37,256	37,473	37,684
Revenues (millions) not risk-adjusted	**19**	**119**	**276**	**462**	**620**	**798**	**997**	**1,170**	**1,352**	**1,542**	**1,584**	**1,626**	**1,668**	**1,712**	**1,756**	**360**
Approval probability (%)	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%
Revenue (millions) risk-adjusted	**5**	**30**	**69**	**115**	**155**	**200**	**249**	**292**	**338**	**386**	**396**	**406**	**417**	**428**	**439**	**90**
% chg		517%	131%	68%	34%	29%	25%	17%	16%	14%	3%	3%	3%	3%	3%	-79%
TRD ROW MARKET																
ROW revenues (millions) not risk-adjusted		**60**	**138**	**231**	**310**	**399**	**498**	**585**	**676**	**771**	**792**	**813**	**834**	**856**	**878**	**180**
% of U.S.		50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
ROW revenues (millions) risk-adjusted		**15**	**34**	**58**	**78**	**100**	**125**	**146**	**169**	**193**	**198**	**203**	**209**	**214**	**220**	**45**
% chg			131%	68%	34%	29%	25%	17%	16%	14%	3%	3%	3%	3%	3%	-79%

Source: H.C. Wainwright & Co.

VII. MSP-1014 Also Has Blockbuster Potential in End-of-Life Cancer Angst

"If we consider contemporary accounts of the mystical consciousness, we can see that the individuality, the "I," disappears and is in a sense "annihilated." (Stace, 1961)

End-of-Life Cancer Angst

- **Background.** Cancer patients often develop a chronic, clinically significant syndrome of psychosocial distress having depressed mood, anxiety, and reduced quality of life as core features, with up to 40% of cancer patients meeting criteria for a mood disorder according to Griffiths et al., 2016. In cancer patients, depression and anxiety have been associated with decreased treatment adherence, prolonged hospitalization, decreased quality of life, and increased suicidality.

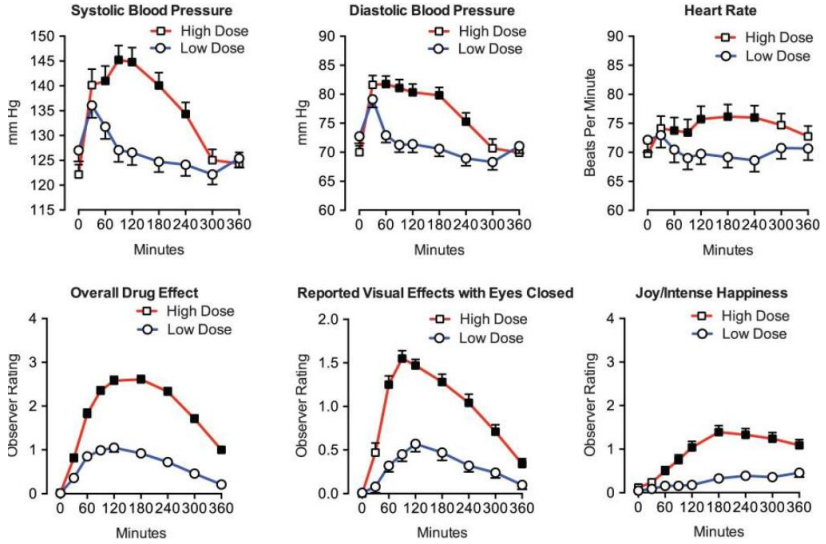
- **Current treatments are inadequate.** Depression is an independent risk factor of early death in cancer patients. Antidepressants and, less frequently, benzodiazepines are used to treat depressed mood and anxiety in cancer patients, although evidence suggesting efficacy is limited and conflicting, and benzodiazepines are generally only recommended for short-term use because of side effects and withdrawal. Although psychological approaches have shown only small to medium effects in treating emotional distress and quality of life, with low quality of reporting in many trials, there are several promising interventions utilizing existential orientations to psychotherapy.

- **Literature and recent study points to potential for psychedelic-enhanced therapy.** Two double-blind, placebo-controlled studies with the classic psychedelics psilocybin (Grob et al., 2011) and LSD (Gasser et al., 2014) examined effects in 12 patients with life-threatening illness, including cancer. Both studies showed promising trends toward decreased psychological distress. In particular, Grob and colleagues showed that a low-moderate dose of psilocybin (14 mg/70 kg) decreased a measure of trait anxiety at 1 and 3 months and depressed mood at 6-month follow-up. Also relevant, an open-label pilot study in 12 patients with treatment-resistant depression showed marked reductions in depressive symptoms 1 week and 3 months after administration of 10 and 25 mg of psilocybin in two sessions separated by 7 days (Carhart-Harris et al., 2016). Moreover, Griffiths et al. 2016 provided a rigorous evaluation of the efficacy of a classic psychedelic for treatment of depressed mood and anxiety in psychologically distressed cancer patients. The study evaluated a range of clinically relevant measures using a double-blind cross-over design to compare a very low psilocybin dose (intended as a placebo) to a moderately high psilocybin dose in 51 patients under conditions that minimized expectancy effects. No serious adverse events attributed to psilocybin administration occurred. A number of adverse events occurred during psilocybin sessions, none of which were deemed to be serious. Psilocybin produced large and sustained effects on the two primary clinician-rated therapeutically relevant outcome measures as well as most of the secondary measures assessed at Baseline, 5 weeks after each session, and at 6-month follow-up. Of the 17 measures assessed, 16 showed significant effects (i.e. a between-group difference at the Post-session 1 assessment and/or a difference between Post-session 1 and Post-session 2 assessments in the Low-Dose-1st Group). (See the next page in this report for additional details on Griffiths et al.). More recently, an open-label study of COMP360 conducted by Maryland Oncology at the Aquilino Cancer Center in Rockville, Maryland demonstrated remission of major depression symptoms for 50% of participants.

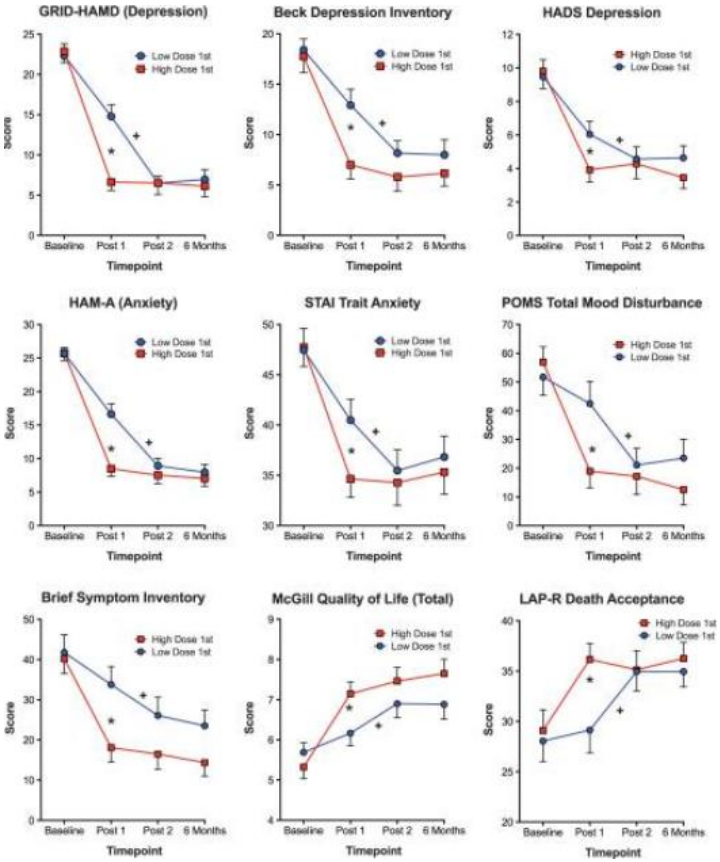
Source: Griffiths, Johnson, et al., 2016, COMPASS Pathways press release, H.C. Wainwright & Co.

Psilocybin Has Demonstrated Potential in End-of-Life Cancer Angst

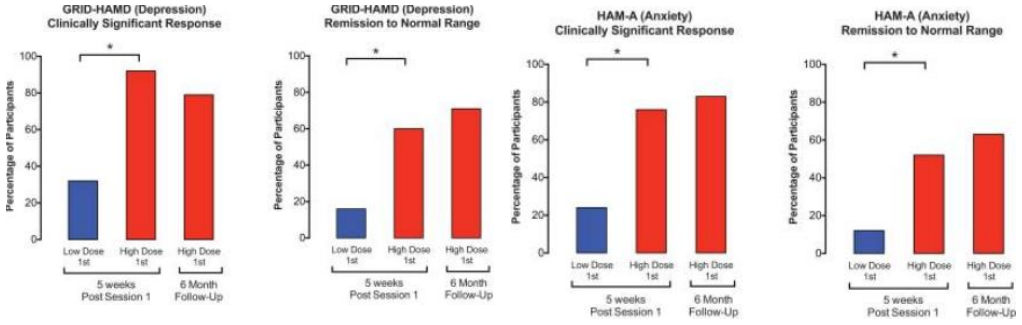
Within-session time-course of psilocybin effects on cardiovascular and observer-rated measures.



Effects of psilocybin on selected outcome measures that were assessed at Baseline, Post-session 1 (5 weeks after Session 1), Post-session 2 (5 weeks after Session 2), and 6-month follow-up.



Effects of psilocybin on clinically significant response rate and symptom remission rate as assessed with clinician-rated measures of depression and anxiety.



Source: Griffiths, Johnson, et al., 2016, H.C. Wainwright & Co.

Modeling Assumptions: MSP-1014 in End-of-Life Cancer Angst

- **Addressable patients.** We estimate a total population suffering from cancer by taking the prevalence of 3-3.5% and adding the incidence of 0.5-1% and subtracting the annual deaths at a rate of around 7%, which implies a total potential population suffering from cancer of nearly 11M in 2026, the first potential year of launch. From here, we assume 10% of patients have end of life angst, which is less than the 40% of cancer patients Griffiths et al. estimated have mood disorders, and that 50% are treated with 75% eligible for treatment, implying a potential addressable patient population of more than 400,000.

- **Penetration rate.** We assume psychedelic enhanced therapy could penetrate more than 5% of these patients, of which we model MSP-1014 capturing a 50% share at peak.

- **Probability of success (PoS).** We assume 25% given the favorable comparisons demonstrated preclinically to psilocybin though offset by the early stage of development.

- **Pricing.** We assume a gross cost per treatment of C$20,000 that after a 15% gross-to-net reduction equates to a net cost of C$34,000 per year that increases in-line with inflation annually.

- **Loss of exclusivity (LOE).** We model an LOE in F2040.

- **Peak revenues.** Based on the above considerations, not risk-adjusted, we model peak annual revenues of more than C$1B where ROW markets represent 50% of the U.S. Risk-adjusted, our model includes peak annual revenues of more than C$0.2B for end of life cancer angst.

Source: H.C. Wainwright & Co.

Modeling Assumptions: End-of-Life Cancer Angst

C$ in millions, unless noted

MSP-1014	F2026E	F2027E	F2028E	F2029E	F2030E	F2031E	F2032E	F2033E	F2034E	F2035E	F2036E	F2037E	F2038E	F2039E	F2040E	F2041E
END OF LIFE ANGST (CANCER) U.S. MARKET																
Prevalence of Cancer cases (5 yr)	9,496,858	9,686,795	9,880,531	10,078,142	10,279,704	10,485,298	10,695,004	10,908,905	11,127,083	11,349,624	11,576,617	11,808,149	12,044,312	12,285,198	12,530,902	12,781,520
% Prevalence rate	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%	3.3%
Incidence of Cancer cases (new cases)	2,097,754	2,139,709	2,182,503	2,226,153	2,270,676	2,316,089	2,362,411	2,409,659	2,457,853	2,507,010	2,557,150	2,608,293	2,660,459	2,713,668	2,767,941	2,823,300
% Incidence rate	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%
Deaths in Cancer cases	671,910	685,349	699,056	713,037	727,297	741,843	756,680	771,814	787,250	802,995	819,055	835,436	852,145	869,188	886,572	904,303
% Death rate	7.1%	7.1%	7.1%	7.1%	7.1%	7.1%	7.1%	7.1%	7.1%	7.1%	7.1%	7.1%	7.1%	7.1%	7.1%	7.1%
Total population suffering from cancer	10,922,701	11,141,155	11,363,978	11,591,258	11,823,083	12,059,544	12,300,735	12,546,750	12,797,685	13,053,639	13,314,711	13,581,006	13,852,626	14,129,678	14,412,272	14,700,517
% Growth	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%
% Cancer patients with end of life angst	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%
Cancer patients with end of life angst	1,092,270	1,114,115	1,136,398	1,159,126	1,182,308	1,205,954	1,230,074	1,254,675	1,279,769	1,305,364	1,331,471	1,358,101	1,385,263	1,412,968	1,441,227	1,470,052
% Treated	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
% Eligible	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%
Eligible patients with end of life angst (cancer)	409,601	417,793	426,149	434,672	443,366	452,233	461,278	470,503	479,913	489,511	499,302	509,288	519,473	529,863	540,460	551,269
% of end of life angst (cancer) market treated with psychedelics	0.5%	1.0%	1.5%	2.0%	2.5%	3.0%	3.5%	4.0%	4.5%	5.0%	5.5%	6.0%	6.5%	7.0%	7.5%	8.0%
End of life angst (cancer) patients treated with psychedelics	2,048	4,178	6,392	8,693	11,084	13,567	16,145	18,820	21,596	24,476	27,462	30,557	33,766	37,090	40,535	44,102
Therapy sessions per year	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Total potential psychedelic-based treatments per year	**4,096**	**8,356**	**12,784**	**17,387**	**22,168**	**27,134**	**32,289**	**37,640**	**43,192**	**48,951**	**54,923**	**61,115**	**67,532**	**74,181**	**81,069**	**88,203**
% Penetration rate	10.0%	15.0%	20.0%	25.0%	30.0%	35.0%	40.0%	45.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	10.0%
Total therapy sessions with MSP-1014	**410**	**1,253**	**2,557**	**4,347**	**6,650**	**9,497**	**12,916**	**16,938**	**21,596**	**24,476**	**27,462**	**30,557**	**33,766**	**37,090**	**40,535**	**8,820**
Gross pricing	20,000	20,400	20,808	21,224	21,649	22,082	22,523	22,974	23,433	23,902	24,380	24,867	25,365	25,872	26,390	26,917
% chg		2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%
Gross-to-net	15.0%	16.0%	17.0%	18.0%	19.0%	20.0%	21.0%	22.0%	23.0%	24.0%	25.0%	26.0%	27.0%	28.0%	29.0%	30.0%
Net pricing per treatment	17,000	17,136	17,271	17,404	17,535	17,665	17,793	17,919	18,044	18,165	18,285	18,402	18,516	18,628	18,737	18,842
Annual cost per year	34,000	34,272	34,541	34,808	35,071	35,331	35,587	35,839	36,087	36,331	36,570	36,804	37,033	37,256	37,473	37,684
Revenues (millions) not risk-adjusted	**7**	**21**	**44**	**76**	**117**	**168**	**230**	**304**	**390**	**445**	**502**	**562**	**625**	**691**	**759**	**166**
Approval probability (%)	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%	25.0%
Revenue (millions) risk-adjusted	**2**	**5**	**11**	**19**	**29**	**42**	**57**	**76**	**97**	**111**	**126**	**141**	**156**	**173**	**190**	**42**
% chg		208%	106%	71%	54%	44%	37%	32%	28%	14%	13%	12%	11%	11%	10%	-78%
END OF LIFE ANGST (CANCER) ROW MARKET																
ROW revenues (millions) not risk-adjusted		**11**	**22**	**38**	**58**	**84**	**115**	**152**	**195**	**222**	**251**	**281**	**313**	**345**	**380**	**83**
% of U.S.		50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
ROW revenues (millions) risk-adjusted		**3**	**6**	**9**	**15**	**21**	**29**	**38**	**49**	**56**	**63**	**70**	**78**	**86**	**95**	**21**
% chg			106%	71%	54%	44%	37%	32%	28%	14%	13%	12%	11%	11%	10%	-78%

Source: H.C. Wainwright & Co.

VIII. MSP-4018, MSP-4019, MSP-4020: Next Generation DMT and 5-MeO-DMT Inspired Drug Candidates Represent Next Potential Wave of Upside

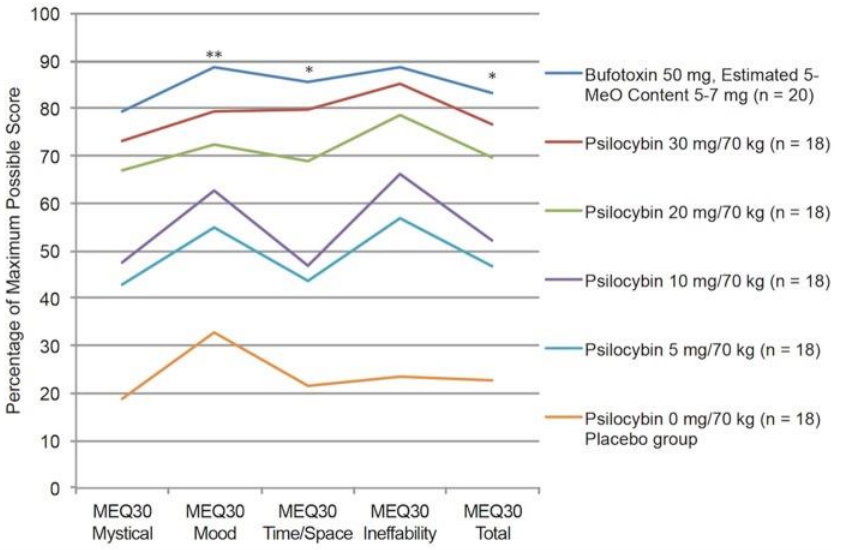
"It's a very salutary thing to realize that the rather dull universe in which most of us spend most of our time is not the only universe there is. I think it's healthy that people should have this experience." (Huxley, Moksha: Writings on psychedelics and the visionary experience, 1977)

Brief Background on DMT and 5-MeO-DMT

- **Background.** Ayahuasca is a hallucinogen brew traditionally used for ritual and therapeutic purposes in Northwestern Amazon. It is rich in the tryptamine hallucinogens N,N-dimethyltryptamine (DMT), which acts as a serotonin 5-HT2A agonist. This mechanism of action is similar to other classic psychedelic compounds such as LSD and psilocybin. Increasing evidence suggests that endogenous DMT plays important roles for a number of processes in the periphery and central nervous system, and may act as a neurotransmitter. Separately, 5-Methoxy-N,N-Dimethyltryptamine (5-MeO-DMT) appears similar to DMT on a macro and micro level with a few extra atoms attached, though the slight change leads to a significant difference. Similar to DMT, 5-MeO-DMT also appears in many plants and animals, including the venom of a particular toad, though unlike DMT has not been found in humans. Although the DMT experience tends to be highly visual, 5-MeO-DMT is more like a perspective shift according to *Psychedelic Times*, which some have described as something akin to a near-death experience.

- **Mystical experience with 5-MeO-DMT comparable to psilocybin.** Several investigators have suggested that mystical-type experiences that could accompany treatment with psychedelics predicts lasting psychiatric and behavioral changes and treatment efficacy. Thus, Barsuglia et al. aimed to examine the intensity of mystical experiences following administration of 5-MeO-DMT to participants as part of a residential psychospiritual retreat, and to compare the intensity of mystical experiences occasioned by 5-MeO-DMT with those recorded in a prior laboratory-based psilocybin study. Participants in the retreat program rated the intensity of mystical effects occasioned by 5-MeO-DMT as moderate-to-strong, similar to prior findings in samples of 5-MeO-DMT users.

Comparison of psilocybin and 5-MeO-DMT groups on the Mystical Experiences Questionnaire (MEQ30); 5-MeO-DMT results from current study and psilocybin ratings from the Griffiths et al., 2011 dose-related effects study; no significant differences are observed between the 5-MeO-DMT and 30 mg/70 kg Psilocybin group; significant differences are observed between the 5-MeO-DMT and 20 mg/70 kg group.



Note: The 10 mg/70 kg, 5 mg/70 kg, and 0 mg placebo groups from Griffiths et al. (2011) are plotted for visual reference and were not statistically compared.. $*p < 0.05$, $**p < 0.01$

Source: Barsuglia, Davis, et al., 2018.

Source: G. dos Santos, Carlos Bouso, et al., 2017, Carbonaro and Gatch, 2016, Psychedelic Times, Barsuglia, Davis, et al., 2018, H.C. Wainwright & Co.

Rapid Antidepressant Effects of the Psychedelic Ayahuasca in TRD

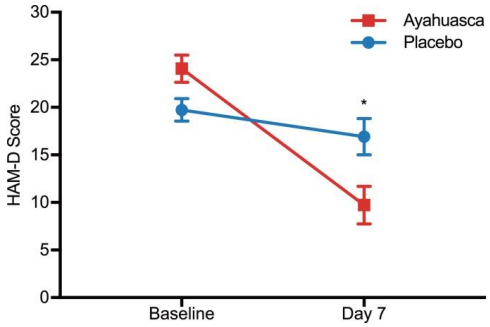
- **Trial design.** Palhano-Fontes et al. conducted a parallel-arm double-blind randomized placebo-controlled trial in 29 patients with treatment-resistant depression (TRD). Patients received a single dose of either ayahuasca or placebo. Changes in depression severity were assessed via the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating scale at baseline, and at 1 (D1), 2 (D2), and 7 (D7) days after dosing.

- **Randomization and masking.** Patients were randomly assigned (1:1) to receive ayahuasca or placebo using permuted blocks of size 10. All investigators and patients were blind to intervention assignment, which was kept only in the database and with the pharmacy administrators. Masking was further achieved by ensuring that all patients were naïve to ayahuasca, and by randomly assigning, for each patient, different psychiatrists for the dosing session and for the follow-up assessments.

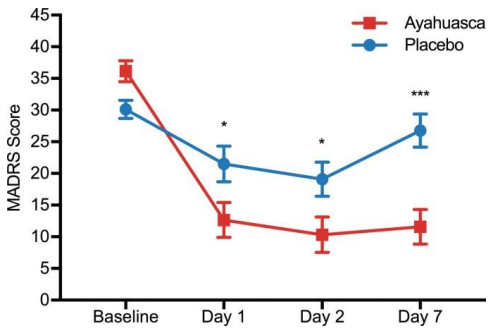
- **Baseline characteristics.** From January 2014 to June 2016, out of 218 patients assessed, 35 met criteria for the trial. On average, patients met criteria for moderate-to-severe depression (mean ± s.d.): HAM-D = 21.83 ± 5.35; MADRS = 33.03 ± 6.49. They had been experiencing depressive symptoms for 11.03 ± 9.70 years and had tried 3.86 ± 1.66 different previous unsuccessful antidepressants. Two patients had a previous history of electroconvulsive therapy (ECT).

- **Positive results.** MADRS scores were significantly lower in the ayahuasca group compared with placebo at D1 and D2 ($p = 0.04$), and at D7 ($p < 0.0001$). Between-group effect sizes increased from D1 to D7 (D1: Cohen's d = 0.84; D2: Cohen's d = 0.84; D7: Cohen's d = 1.49). Response rates were high for both groups at D1 and D2, and significantly higher in the ayahuasca group at D7 (64% v. 27%; $p = 0.04$). Remission rate showed a trend toward significance at D7 (36% v. 7%, $p = 0.054$).

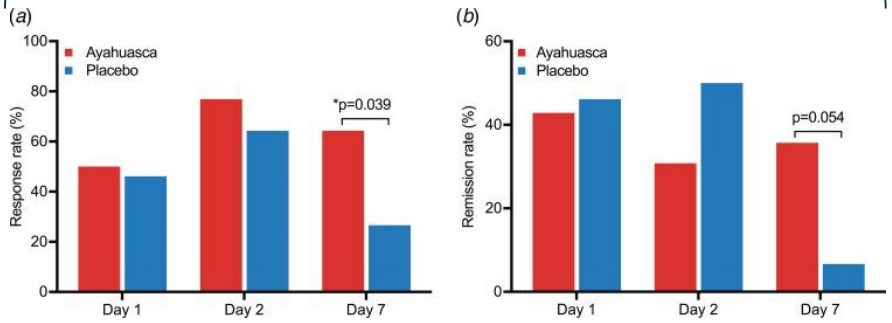
HAM-D scores at baseline and seven days after dosing; significant difference between ayahuasca (squares) and placebo (circles) seven days after dosing ($p = 0.019$) with a robust between-group effect size (Cohen's d = 0.98).



MADRS scores as a function of time; significant differences between ayahuasca (squares) and placebo (circles) at D1 ($p = 0.04$), D2 ($p = 0.04$) and D7 ($p < 0.0001$); between groups effect sizes are high at all time points after dosing: D1 (Cohen's d = 0.84), D2 (Cohen's d = 0.84), and D7 (Cohen's d = 1.49).



Response (a) and remission (b) rates were high for both groups at D1 and D2; at D7, response rate was significantly higher for ayahuasca while remission rate showed a trend toward significance.

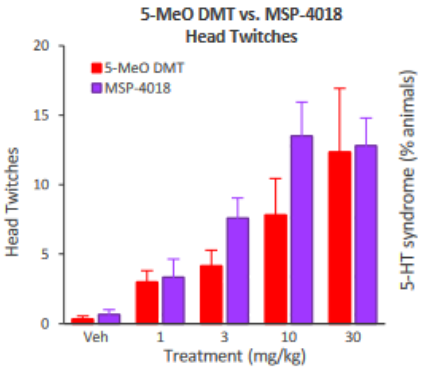


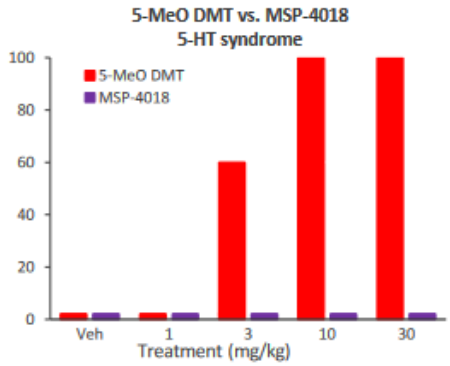
Source: Palhano-Fontes, Barreto, et al., 2019, H.C. Wainwright & Co.

Family Four: Highly Potent and Safer Next Generation 5-MeO-DMT

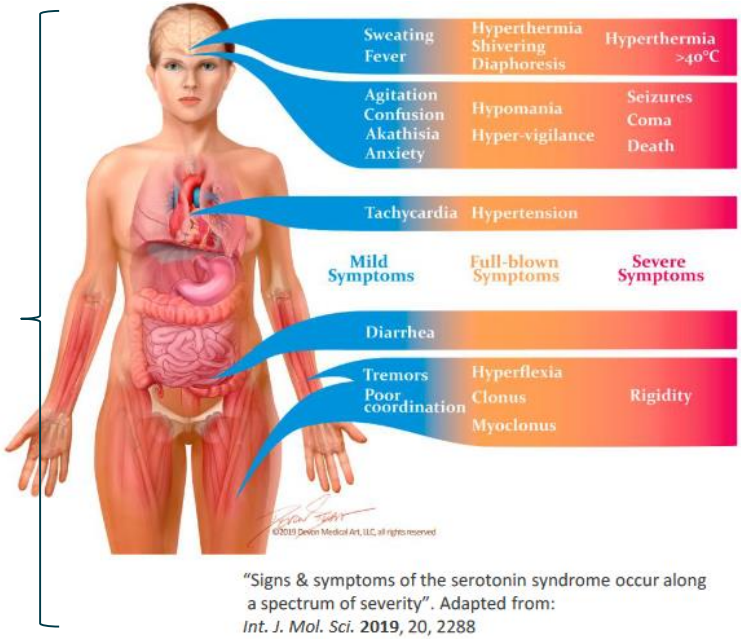
- **Fourth family—analogs of DMT and 5-MeO-DMT.** More than 14 compounds have been synthesized at the sub to multi-gram scale and demonstrate unique and promising *in vitro* profiles. Specifically, these compounds demonstrate a similar binding profile to the human 5-HT2A receptor to that of the reference compounds though with a larger effect size and shorter duration of action compared to psilocin. In addition, these compounds show activity at both 5-HT1A and 5-HT2C receptors, which have been implicated in depression and substance abuse. This profile positions the fourth family of compounds for potential macrodosing applications that could be differentiated from compounds in the second family based on receptor activity signatures. Moreover, recent *in vivo* data suggests that compounds from this class could show a superior safety profile to 5-MeO-DMT, which elicits serotonin syndrome signs in mice.

- **Start of clinical studies targeted for 2023.** Mindset has noted that the lead candidate compounds from family four could enter Phase 1 development in 1Q23.





Ideally an improved form of 5-MeO-DMT would avoid potential safety and tolerability signals such as serotonin syndrome.



"Signs & symptoms of the serotonin syndrome occur along a spectrum of severity". Adapted from: *Int. J. Mol. Sci.* **2019**, 20, 2288

Source: Company filings and presentations, H.C. Wainwright & Co.

IX. Additional NCEs Could Soon Enter the Pipeline With Potential to Improve on Existing Psychedelic Pharmacology

"Taking LSD was a profound experience, one of the most important things in my life. LSD shows you that there's another side to the coin, and you can't remember it when it wears off, but you know it. It reinforced my sense of what was important — creating great things instead of making money, putting things back into the stream of history and of human consciousness as much as I could." (Jobs, 2011)

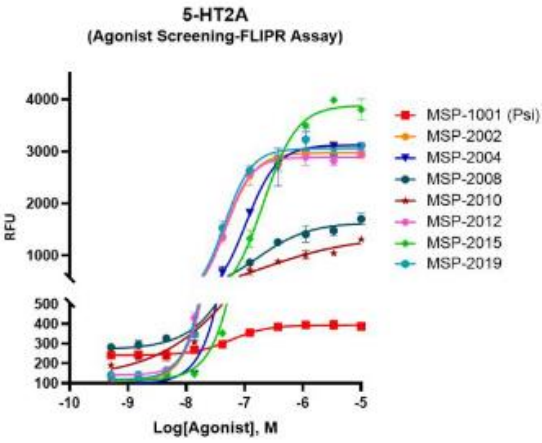
Family Two: Potent, Rapid-Acting "Third Generation" Psilocybin

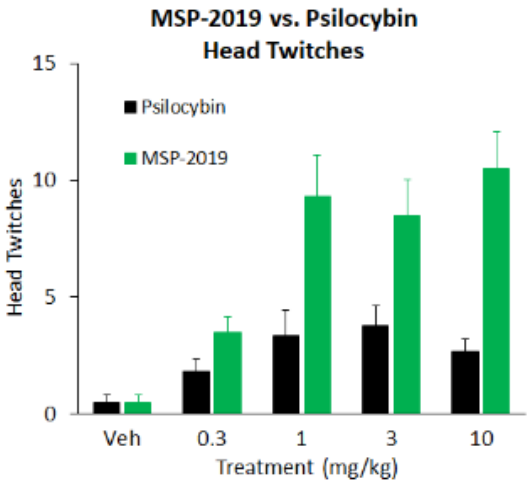
- **Second family—restricted side-chain analogs of psilocybin.** The second family compounds demonstrate increased potency and efficacy compared to psilocin and psilocybin based on both *in vitro* and *in vivo* data, respectively. Certain compounds also show oral bioavailability and are brain penetrant with *in vivo* pharmacokinetic evidence of shorter duration than psilocybin in rodents. This profile positions the second family of compounds as so-called third generation in-clinic candidates to support psychedelic-assisted psychotherapy (PAP) applications and protocols.

- **Start of clinical studies anticipated around mid-2022.** Mindset has noted that the lead candidate compounds from family two could enter Phase 1 development in 2Q22 or 3Q22.

Family two compounds have potential to demonstrate superiority in-clinic macrodose profile to psilocybin according to Mindset.

Parameters	MSP-2019	Psilocybin	
		Psilocybin	Psilocin
Dose IV (mg/kg)	0.3	0.3	n/a
Apparent $t_{1/2}$ (h)	0.43 ± 0.03	n/a	0.98 ± 0.39





Source: Company filings, H.C. Wainwright & Co.

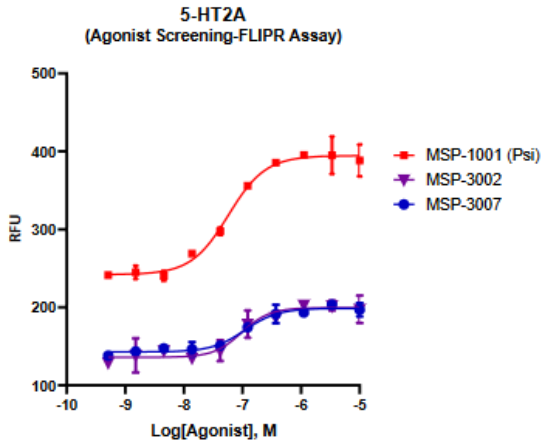
Family Three: Novel Psychedelic Positioned for Subperceptual Dosing

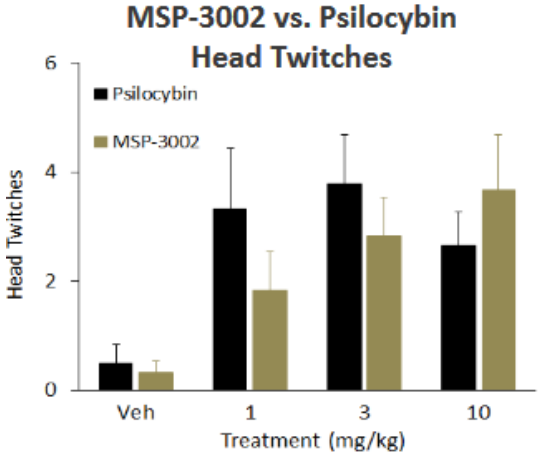
- **Third family—similar though differentiated profile comparable to psilocin.** The third family has demonstrated unique and promising *in vitro* profiles, in particular, showing similar binding profile to the human 5-HT2A receptor comparable to that of psilocin's though with a smaller effect size and much longer duration of action based on human liver microsome stability data. This profile positions the third family of compounds for potential in so-called microdosing or subperceptual applications such as specialized populations and indications including pediatric attention deficit hyperactivity disorder (ADHD) and Alzheimer's disease.

- **Start of clinical studies anticipated in 2023.** Mindset has noted that the lead candidate compounds from family three could enter Phase 1 development in 1Q23.

Family three compounds could have an ideal once-a-day "microdosing" or subperceptual profile according to Mindset.

Compound ID#	Half-life ($t_{1/2}$, min)		
	Human	*Rat*	*Mouse*
Psi Reference	117	89	142
MSP-3002	1317	119	∞





Source: Company filings, H.C. Wainwright & Co.

X. Financial Condition, Sales Estimates, and Valuation

Financials Overview

- Broadly, our near-term assumptions reflect significant R&D investment to support the build out of Mindset's pipeline. Beginning in F2026, our estimate reflect the potential for launches in TRD and end of life cancer angst. We note that there are not enough estimates for Mindset to reflect a true consensus at this time.

C$ in millions, unless noted

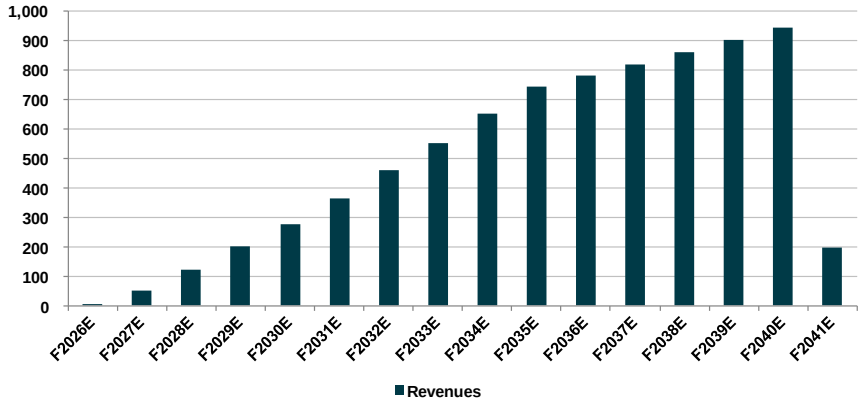
Revenue	F1Q22E	F2Q22E	F3Q22E	F4Q22E	F2022E	F2023E	F2024E	F2025E	F2026E
HCW new estimates	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	6.6

GAAP EPS	F1Q22E	F2Q22E	F3Q22E	F4Q22E	F2022E	F2023E	F2024E	F2025E	F2026E
HCW new estimates	($0.05)	($0.04)	($0.04)	($0.04)	($0.16)	($0.18)	($0.17)	($0.16)	($0.14)

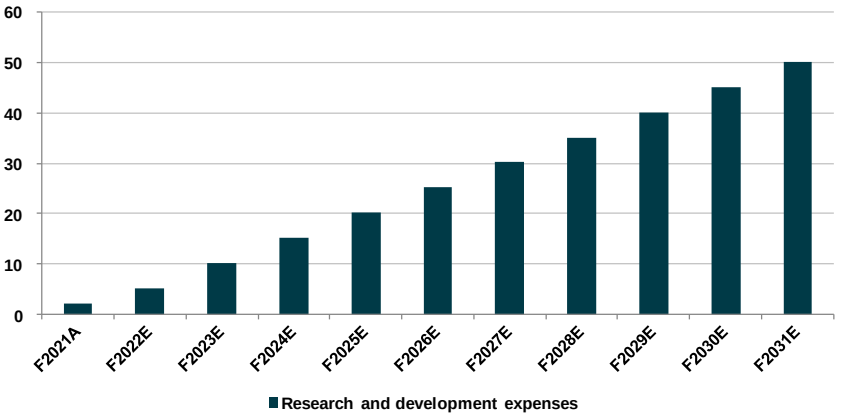
Source: H.C. Wainwright & Co.

Financial Estimates

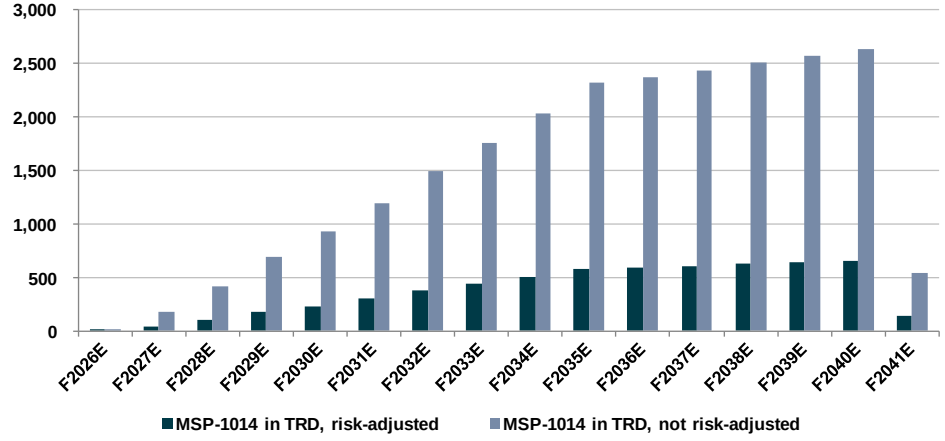
C$ in millions



C$ in millions



C$ in millions



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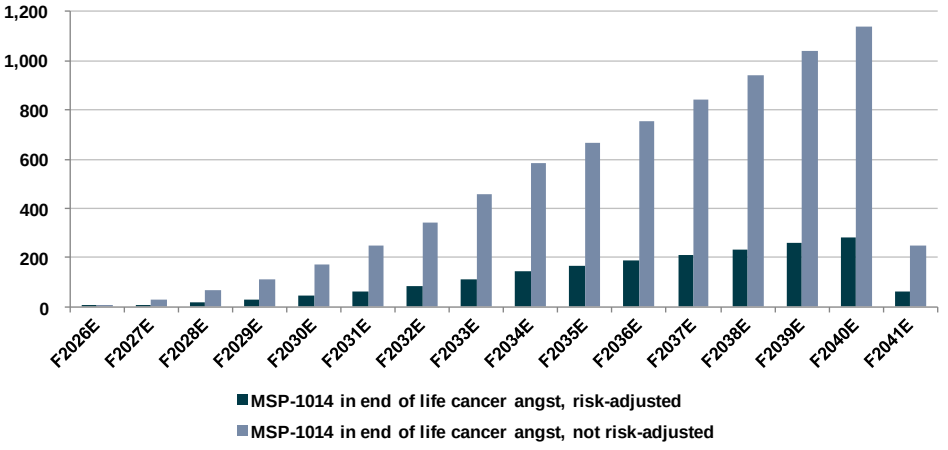
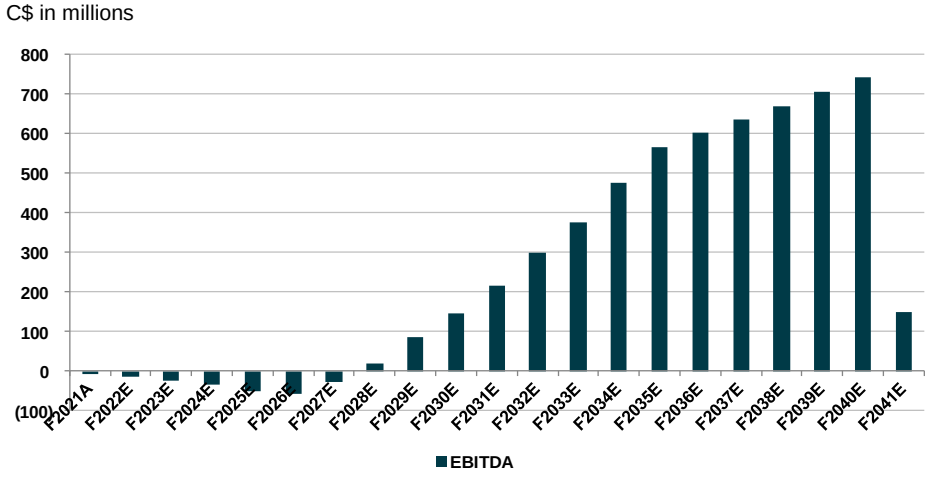


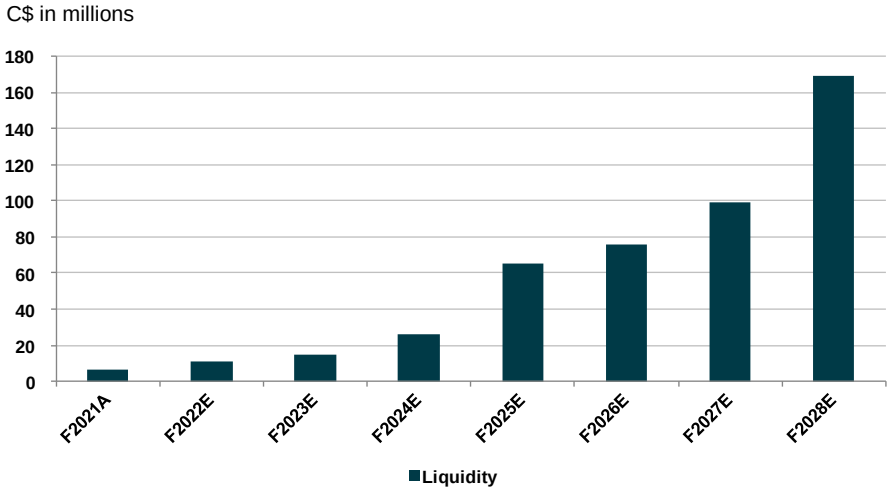
Source: H.C. Wainwright & Co.

EBITDA, Taxes, Interest Expense, Liquidity, and Shares Outstanding

- Our EBITDA modeling assumptions assume Mindset generates losses through 2027E before turning profitable in 2028E. For the foreseeable future our model includes a steady ramp up in R&D and SG&A.
- We model Mindset to begin paying taxes in F2031 at a rate of 20%.
- We model no change to the debt capital or interest expense going forward. We model equity raises of C$20-100M each year from F2022 to F2028. We model an increase in shares outstanding from 81.7M in F4Q21 to 115.5M in F4Q22 reflecting potential equity raises and stock option compensation.



Source: Company filings, FactSet, H.C. Wainwright & Co.



*Liquidity = cash, cash equivalents, and investments.

Source: Company filings, FactSet, H.C. Wainwright & Co.

Valuation

- We value Mindset relying on a discounted cash flow (DCF) model based on net income per asset and free cash flow to the firm (FCFF), respectively. The discount rate of 12% in the SOTP and DCF is comparable to clinical stage companies we cover.

- In our DCF, we start with IFRS net income and then add back selected non-cash items to arrive at FCFF for F2022 to F2041. We think this timeframe extends long enough to capture the value from Mindset's pipeline and to reflect competitive dynamics we anticipate over time. These cash flows are discounted back to approximately one year from now, as is the present value of the terminal value, which is based on EBITDA in 2040 and a terminal multiple of 6.0x. This compares to the long-term SMID biopharmaceutical average of approximately 10.5x and the 6.0x we are assuming for other biopharmaceutical companies in our coverage.

- After adding back cash and securities of approximately C$6.6M at the end of F2021 we arrive at an implied equity value of nearly C$700M. We then adjust the value for the CAD to USD exchange rate at approximately 0.8, leading to an approximate $550M valuation. On diluted shares of approximately 115.5M, Mindset's implied value is approximately $5/share, or more than 700% higher than current levels.

- Hence, we initiate coverage on MSSTF with a Buy recommendation and price target of $5.

- Email us for a copy of our DCF model.

Source: Company filings, H.C. Wainwright & Co.

DCF Model

C$ in millions, unless noted

Discount Rate	12.0%
Terminal Value EV/EBITDA Multiple	6.0x

	F2018A	F2019A	F2020A	F2021A	F2022E	F2023E	F2024E	F2025E	F2026E	F2027E	F2028E	F2029E	F2030E	F2031E	F2032E	F2033E	F2034E	F2035E	F2036E	F2037E	F2038E	F2039E	F2040E	F2041E
GAAP Net Income (Loss)	0.0	0.0	(0.5)	(11.7)	(15.6)	(24.2)	(33.6)	(50.6)	(59.2)	(31.9)	15.0	78.8	137.1	165.1	230.1	292.0	369.7	442.7	470.5	496.3	523.0	550.7	579.3	104.3
Plus: D&A	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.7	1.7	2.9	4.4	5.9	7.2	8.5	9.8	11.0	12.2	13.4	14.4	15.2	15.9	16.6	17.1	17.5
Less: Investment in Working Capital	0.0	0.0	0.1	(1.9)	0.8	0.8	1.0	1.0	(16.7)	(30.0)	(30.0)	(15.0)	(15.0)	(15.0)	(10.0)	(15.0)	(15.0)	(15.0)	(15.0)	(15.0)	(15.0)	45.0	30.0	30.0
Less: Investment in Fixed Capital	0.0	0.0	0.0	0.0	0.0	(1.0)	(4.0)	(7.0)	(10.0)	(13.0)	(14.0)	(15.0)	(16.0)	(17.0)	(18.0)	(19.0)	(20.0)	(20.0)	(20.0)	(20.0)	(20.0)	(20.0)	(20.0)	(20.0)
Free Cash Flow to the Firm (FCFF)	**0.0**	**0.0**	**(0.4)**	**(13.6)**	**(14.8)**	**(24.3)**	**(36.5)**	**(55.9)**	**(84.3)**	**(72.0)**	**(24.5)**	**54.7**	**113.3**	**141.7**	**211.9**	**269.0**	**346.9**	**421.1**	**449.9**	**476.5**	**504.0**	**592.2**	**606.4**	**131.8**

Cumulative FCF	4,007.1
EBITDA (2041)	147.8
Terminal Value	887.0
PV of Free Cash Flow	**582.1**
PV of Terminal Value	103.0
Implied Enterprise Value	685.1
Plus: Cash and Securities	6.6
Less: Total Debt	0.7
Implied Value of Equity	691.0
CAD USD Exchange Rate	0.8
Implied Value of Equity (USD)	552.8
Diluted Shares Outstanding	115.5
Implied Value per Share (USD)	**$5**

					(14.8)	(24.3)	(36.5)	(55.9)	(84.3)	(72.0)	(24.5)	24.7	45.8	51.1	68.2	77.3	89.0	96.5	92.1	87.1	82.2	86.3	78.9	15.3

Implied Equity Value Sensitivity Table

Discount	Terminal Value EV/EBITDA Multiple			
	$5	5.5x	6.0x	6.5x
11.5%	$5	$5	$5	$5
12.0%	$5	$5	$5	$5
12.5%	$4	$4	$4	$4

Source: Company filings, H.C. Wainwright & Co.

Reasoning for Our DCF Methodology

- When valuing small and mid-cap (SMID) biopharmaceutical companies, we prefer to estimate equity value by discounting cash flows for an entire firm and all of its cash flows (FCFF), with the relevant discount rate being close or equal to the weighted average cost of capital (WACC) because this discount rate reflects all the firm's sources of capital. We then subtract the value of the firm's debt to calculate the equity value. The reason we prefer this methodology, rather than discounting free cash flow to equity (FCFE), is that often, particularly for earlier stage pharmaceutical companies, FCFE is negative. In other cases, even for mature pharmaceutical companies, the firm's capital structure (mix of debt and equity financing) is unstable.

- Biopharmaceutical companies engaged in clinical research and/or business development typically turn to public and private investors for capital, which can alter the capital structure over time. When the firm's capital structure is unstable, the required return on equity used in the FCFE approach may be more volatile when the firm's financial leverage (use of debt) is unstable. Similarly, when using historical data to estimate free cash flow growth, FCFF growth might reflect the firm's fundamentals better than FCFE growth, which would fluctuate as debt fluctuates.

- Note that the cash flow from operations as reported in the firm's financial statements is not the same as free cash flow. Similarly, unadjusted financial income measures such as EBITDA do not provide an accurate description of the free cash flow available to the firm's capital providers, in our view. For example, EBITDA and net income do not account for the investment in assets needed to sustain the firm's productive capacity. Although commonly used in valuation, EBITDA is a poor substitute for FCFF and FCFE because it does not account for depreciation, fixed capital investment (FCInv), and working capital investment (WCInv). Likewise, net income is a poor substitute for FCFE because it does not account for depreciation, FCInv, WCInv, and net borrowings.

Source: CFA Institute, H.C. Wainwright & Co.

XI. Investment Risks

Company Risks

- Clinical development risk is primarily owed to lead development MSP-1014, among others.
- Commercialization risk is tied to Mindset (or potential partners) effectively marketing and distributing approved compounds. If this effort is lackluster or disappoints, this presents risk to our sales and cash flow estimates.
- Reimbursement risk entails obtaining proper positioning with payors for approved compounds, which could negatively affect our sales and cash flow estimates.
- Pricing risk is related to rebates and discounts owed to payors, as well as any other payments necessary to secure reimbursement for approved compounds that could be higher than we have estimated in our modeling assumptions, which could negatively affect our sales and cash flow estimates.
- Capital market and dilution risk entails potential challenges in obtaining capital and/or diluting existing shareholder ownership following potential successful capital raises.
- Business development risk entails Mindset executing on the build out of the pipeline as well as partnering existing pipeline compounds should Mindset decide not to commercialize internally developed treatments on its own. A deal that reflects worse economics than we have estimated could adversely impact our sales and cash flow estimates.
- COVID-19 represents unique risk that we believe for Mindset could primarily manifest in the form of delaying or otherwise leading to the halting of ongoing or soon to be started clinical trials.

Source: Company filings, H.C. Wainwright & Co.

Appendix A. Psychedelics: Disruptive Psychopharmacology

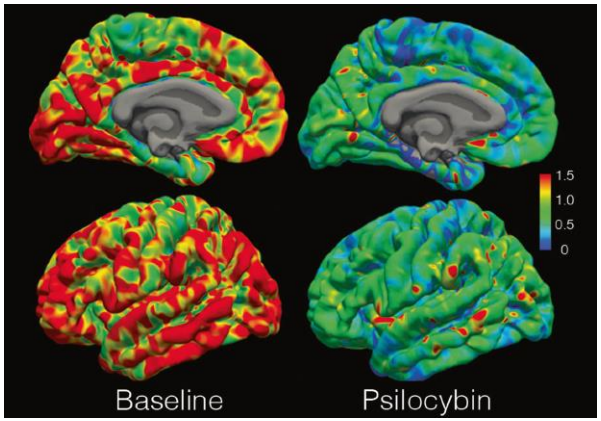
Brief Background on Psychedelics

- **Psychedelics.** Classic psychedelics (or classic hallucinogens) are psychoactive compounds that exert effects through agonist (including partial agonist) activity at the serotonin 2A receptor (5-HT2AR). Substantial evidence suggests that the 5-HT2AR, which is a G-protein-coupled receptor (GCPR), is the most important receptor underlying classic psychedelic effects. Other receptor-level mechanisms contributing to classic psychedelic effects include 5-HT1AR and 5-HT2CR; non-5-HT2ARs are probably also involved.

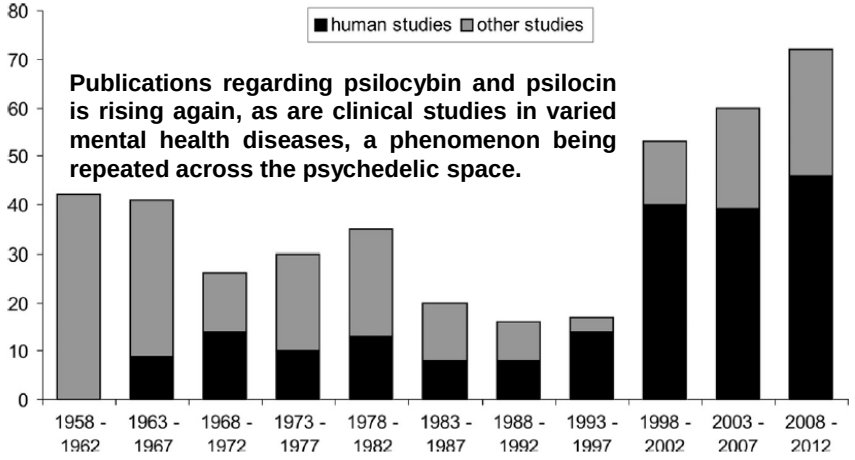
- **Categories.** Classical psychedelics have been categorized into three groups: (1) tryptamines such as psilocin, the psychoactive metabolite of psilocybin, and N, N-dimethyltryptamine (DMT); (2) lysergamines, a group of tryptamines, prominently lysergic acid diethylamide (LSD); and (3) phenethylamines such as mescaline. Entactogens such as MDMA produce psychedeliclike effects with virtually no hallucinations and structurally are closely related to both serotonergic hallucinogens (mescaline) and classic stimulants (amphetamines). Ketamine affects a wide range of cellular processes including blockade of NMDA channels; the role of dissociation in ketamine's antidepressant effects is thoroughly reviewed by Ballard, Zarate, 2020.

- **Mushrooms.** History of the ritual use of hallucinogenic mushrooms dates back 3,000 years in Mexico and regionally its use is still conventional practice today. Western science was introduced to these mushrooms in 1957 by Robert G. Wasson and they were systematically ranked by Roger Heim. In the 1960s, psilocybin was widely used in the experimental research of mental disorders and even in psychotherapy. Psilocybin-containing mushrooms became popular recreationally and consequently psilocybin (and psilocin) was classed a Schedule I illegal drug in the U.S. in 1970. All human experimentation was discontinued. However, since the late 1990s, interest in human experimental research into psilocybin and other psychedelics revived.

Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels



Source: Madsen and Fisher et al., 2019.



Source: Tylš et al.

Source: Johnson and Hendricks et al., 2019, Mahapatra and Gupta, 2017, Tylš and Páleníček , et al., 2013, H.C. Wainwright & Co.

Serotonin and Psychedelic Mechanisms

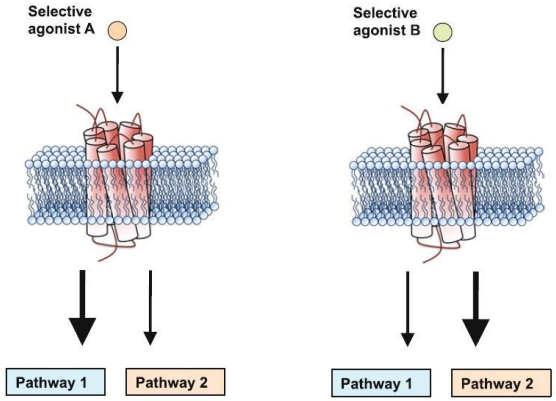
- **Serotonin.** The discovery of serotonin (5-hydroxytryptamine, 5-HT) dates back to the middle of the nineteenth century when early experimenters recognized that a substance contained in serum was capable of inducing the contraction of smooth muscle. 5-HT performs its physiological functions by binding to specific cell membrane receptors. Currently, 14 different serotonin receptors, classified into 7 subfamilies according to their primary structure and functional properties, have been described. Excluding 5-HT3, which belongs to the ion channel receptor superfamily, the remainder of the 5-HT receptors are G-protein coupled receptors (GPCRs).

- **Interaction with 5-HT2AR.** The major physiological effects induced by hallucinogens, in particular when evaluated in human subjects, are related to altered states of consciousness, including changes in cognition, mood, and perception. It is widely accepted at the present time that these effects are generated mostly by the interaction of hallucinogens with 5-HT2A receptors as agonists.

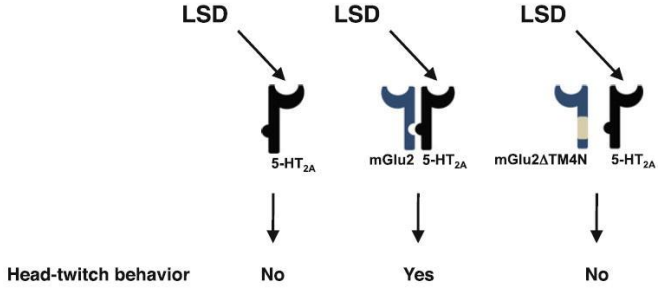
- **Biased agonism.** Interestingly, from a basic pharmacological perspective, whereas all hallucinogens such as LSD, mescaline, and psilocin bind with high affinity and activate the serotonin 5-HT2A receptor, certain closely related 5-HT2A receptor agonists, such as lisuride and ergotamine, do not behave as hallucinogens in humans. The phenomenon of “biased agonism” explains how agonists acting at the same receptor target can elicit different patterns of cellular signaling responses. Individual GPCRs can couple to multiple signal transduction pathways; agonists can stabilize distinct active conformational receptor states. These active states can differ in their propensity to activate the various signaling proteins coupled to the receptor.

- **Downstream signaling.** Recent findings have elucidated additional neuronal signaling pathways downstream from the 5-HT2A receptor that is potentially involved in the unique behavioral effects induced by hallucinogens (Halberstadt 2015; Hanks and Gonzalez-Maeso 2013). For instance, the role of mGlu2 in the psychoactive effects induced by hallucinogens is supported by the impaired ability of the hallucinogens DOI and LSD to induce head-twitch behavior in mGlu2 knockout mice compared to wild-type littermates (Moreno et al. 2011).

Selective agonists stabilize a subset of receptor conformations that selectively activates some but not all signaling pathways; recent findings suggest that biased agonism is involved in the psychoactive differences between hallucinogen and closely related non-hallucinogen 5-HT2A receptor agonists.



Model of the mechanism underlying hallucinogen-induced head-twitch behavioral response.

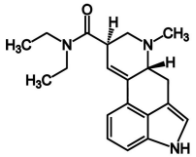


Source: Juan F. López-Giménez and Javier González-Maeso, 2018.

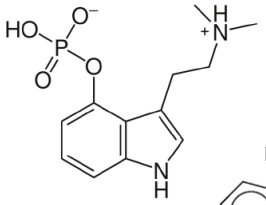
Source: Juan F. López-Giménez and Javier González-Maeso, 2018.

Psychedelics Volatile Early History in Western Medicine

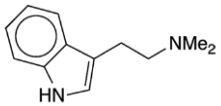
LSD molecule



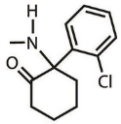
Psilocybin molecule



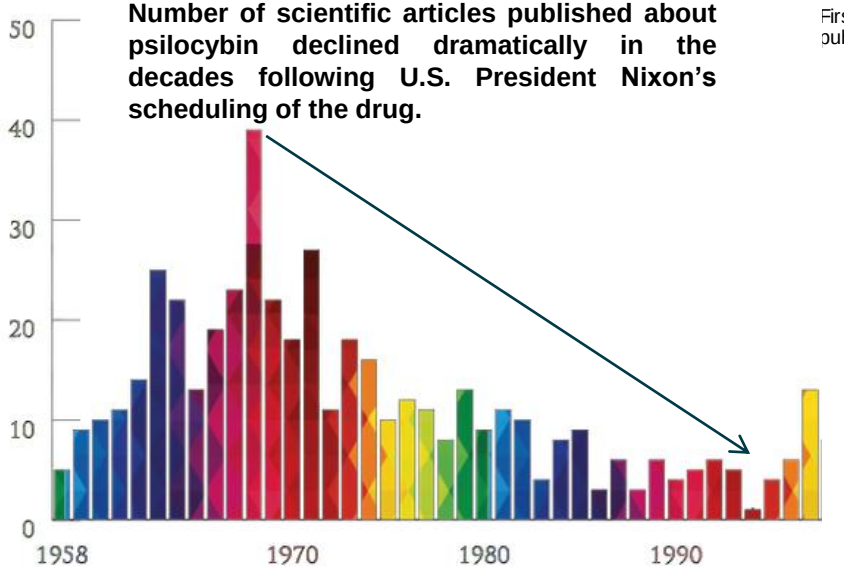
DMT molecule



Ketamine molecule



Number of scientific articles published about psilocybin declined dramatically in the decades following U.S. President Nixon's scheduling of the drug.



Source: Beckley Foundation.

1943 LSD's psychoactive effects discovered by Albert Hofmann.

1947 Werner Stoll publishes first paper on psychological effects of LSD in humans.

1950 First English language publication on LSD.

1953 ACNP Founding president Joel Elkes publishes on LSD after openly self-experimenting with it.

1954 Aldous Huxley's *The Doors of Perception* published: documents mescaline self-experiment.

1956 Term "psychedelic" coined by Humphrey Osmond in communication with Aldous Huxley.

1957 Term "magic mushrooms" coined by LIFE magazine.

1958 Identification of psilocybin in magic mushrooms by Albert Hofmann.

1959 Closed conference held in Princeton on "the use of LSD in psychotherapy, Jonathan Cole attends, an early ACNP president.

1960 First major European conference on psychedelics; Sidney Cohen publishes positive meta-analysis on LSD safety.

1961 Jonathan Cole (ACNP president 1965-66) expresses "very mixed feelings on psychedelic research" as critical commentaries emerge.

1962 The Marsh Chapel or "Good Friday" experiment conducted at Harvard under Timothy Leary's supervision but without institutional approval.

1963 Leary dismissed from Harvard; Aldous Huxley and JFK die (both on November 22).

1964 Cole takes "sober look" at psychedelics in JAMA; discussions on LSD take center stage at 1964 APA meeting; Ken Kesey travels across U.S. taking LSD with "Merry Pranksters".

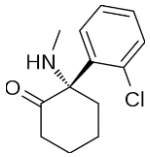
1965 Sandoz stop manufacture of LSD and psilocybin.

1966 Prohibition of psychedelics and curtailment of research begins in U.S.; Senator Robert Kennedy formally questions this move.

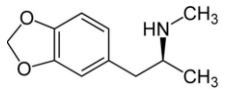
1967 Timothy Leary declares "turn on, tune in and drop out" at festival in Golden Gate Park.

1970 President Nixon signs Controlled Substances Act, LSD and psilocybin made Schedule 1.

Esketamine molecule

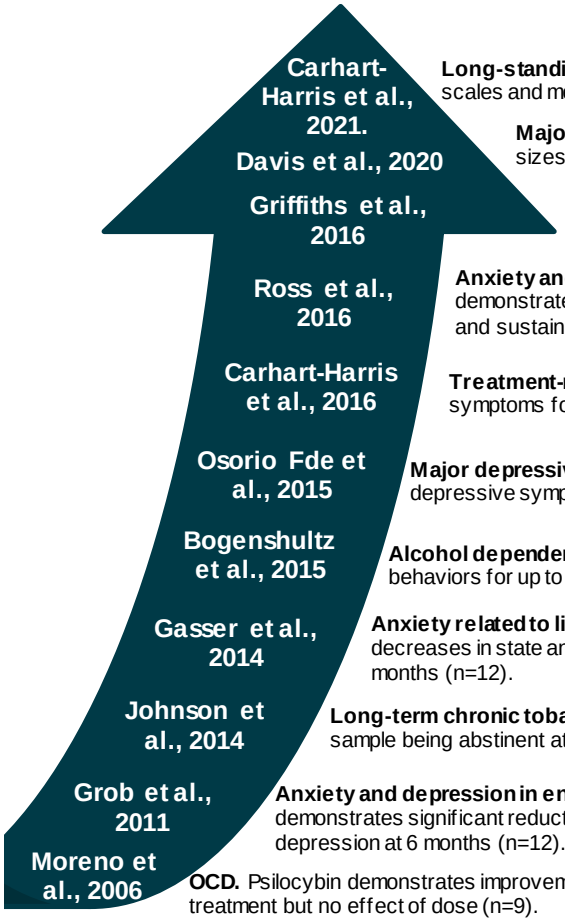


MDMA molecule



Source: Carhart-Harris and Goodwin, 2017, Beckley Foundation, H.C. Wainwright & Co.

New Millennium Renaissance Points to Potential Utility in Psychiatry



Long-standing moderate-to-severe MDD. Psilocybin demonstrates impressive improvements on clinician-rated depression scales and measures of well-being as compared to standard-of-care (escitalopram) (n=59).

Major depressive disorder (MDD). Psilocybin demonstrates significant decrease in depression with effect sizes at week 5 of 2.5 and week 8 of 2.6. (p<.001) (n=27).

Anxiety and depression related to life-threatening cancer. Psilocybin demonstrates significant decrease in anxiety and depression vs. very low dose (VLD) at 5 weeks; effects sustained for 6 months (n=51).

Anxiety and depression related to life-threatening cancer. Psilocybin demonstrates significant decrease in anxeity and depression vs. niacin at 7 weeks and sustained for 6.5 months (n=29).

Treatment-resistant MDD. Psilocybin demonstrates significant decreases in depressive symptoms for up to 6 months (n=12).

Major depressive disorder (MDD). Ayahuasca demonstrates significant decreases in depressive symptoms for up to 21 days (n=17).

Alcohol dependence. Psilocybin demonstrates significant decrease in drinking behaviors for up to 9 months (n=10).

Anxiety related to life-threatening disease. LSD demonstrates significant decreases in state and trait anxiety vs. VLD at 2 months and sustained for 12 months (n=12).

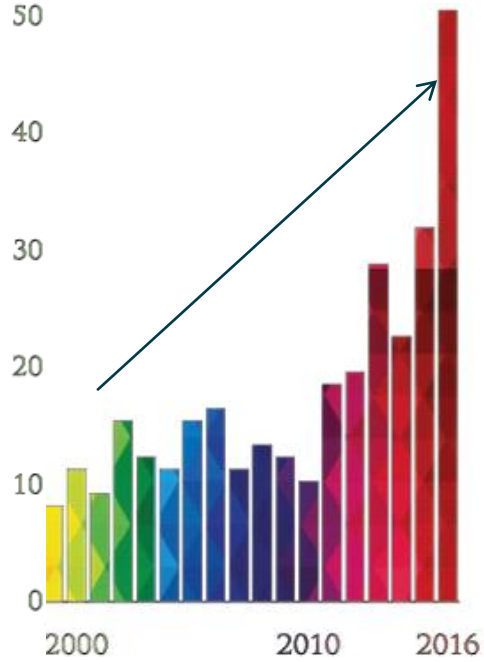
Long-term chronic tobacco smoking. Psilocybin treatment led to 80% of sample being abstinent at 6 months follow-up (n=15).

Anxiety and depression in end-stage cancer. Psilocybin demonstrates significant reductions in trait anxiety at 3 months and depression at 6 months (n=12).

OCD. Psilocybin demonstrates improvements within 24 h of a treatment but no effect of dose (n=9).

Note: Effect size is usually measured by regulators as the difference between the drug and placebo mean change from baseline using a standard measure. An FDA rule of thumb is that an effect is deemed large if it is >0.8, small if it is <0.5, and moderate if it falls between those values.

Number of scientific articles published about psilocybin have seen a renaissance in the new millennium



Source: Beckley Foundation.

Source: Carhart-Harris and Goodwin, 2017, Beckley Foundation, H.C. Wainwright & Co.

Selected Phase 2 Trials Evaluating Psychedelics in Psychiatric Patients

- Robust effect sizes demonstrated by psychedelics in Phase 2 trials supports further evaluation in relevant indications, in our view.

Compound	Route	Therapy Sessions	Indication	N	Masking	Controls	Effect Size (min, max)	Published References
Ketamine	0.5-1.0 mg/kg oral 0.2-0.5 mg/kg intranasal 0.1-1.0 mg/kg IV	1-12	Depression	504	Open label, single-blind, double blind	Placebo, lithium, saline, diphenhydramine, nitroprusside, midazolam, minocyclin, ECT	0.99 - 1.67	Fond et al., 2014; Coyle and Laws, 2015; Lee et al., 2015; McGirr et al., 2015; Parsaik et al., 2015; Romeo et al., 2015; Wan et al., 2015; Kishimoto et al., 2016; Xu et al., 2016
			OCD	35	Open label, double-blilnd	Placebo, saline, midazolam	0.8	Bloch et al., 2012; Rodriguez et al., 2013, 2016
			PTSD	41	Double-blind	Placebo, midazolam	N/A	Feder et al., 2014
			Suicide	12	Open label, double-blind	Saline, midazolam	0.67 - 0.84	Ballard et al., 2014; Price et al., 2014; Murrough et al., 2015
			Cocaine use disorder	8	Double-blind	Lorazepam	N/A	Dakwar et al., 2014, 2016
MDMA	62.5-187.5 mg oral	2-3	PTSD	108	Open label, double-blind	Lactose, 25 mg MDMA, 30 mg MDMA	1.17 - 1.24	Bouso et al., 2008; Mithoefer et al., 2011, 2013, 2018; Oehen et al., 2013; Yazar-Klosinski and Mithoefer, 2017
Psilocybin	10-40 mg oral	1-3	Depression	12	Open label, double blind	Diphenhydramine	2.0 - 3.1	Carhart-Harris et al., 2016, 2017c
			Existential anxiety	80	Double-blind	Placebo, 4 mg psilocybin	0.82 - 1.63	Grob et al., 2011; Griffiths et al., 2016; Ross et al., 2016
			Alcohol dependence	10	Open-label, double blind	Diphenhydramine	1.19 - 1.39	Bogenschutz et al., 2015
			Cigarette dependence	15	Open-label	Transdermal nicotine patch	N/A	Johnson et al., 2014, 2017b; Garcia-Romeu et al., 2015
LSD	200 µm oral	2	Existential anxiety	12	Double blind	Mannitol, 20 mg LSD	1.1 / 1.2	Gasser et al., 2014

Note: Effect size is usually measured by regulators as the difference between the drug and placebo mean change from baseline using a standard measure. An FDA rule of thumb is that an effect is deemed large if it is >0.8, small if it is <0.5, and moderate if it falls between those values.

Source: Schenberg, 2018, Keefe, Kraemer, et al., 2013, H.C. Wainwright & Co.

Rethinking Use of Psychedelics in Mental Health Disorders

- **Back to the future: increased interest in psychedelics.** The paucity of medications with novel mechanisms for the treatment of mental illnesses combined with the delayed response to currently available medications has led to increased enthusiasm regarding the potential therapeutic utility of previously stigmatized medicines such as psilocybin, as well as 3,4-methylenedioxymethamphetamine (MDMA) and ketamine.

- **SPRAVATO approval, breakthrough designations, signal regulatory openness to alternative approaches.** Since 2017, the U.S. Food and Drug Administration (FDA) has approved SPRAVATO (esketamine) for treatment-resistant depression (TRD) while MDMA and psilocybin have received breakthrough therapy designation. If MDMA and psilocybin are approved for post-traumatic stress disorder (PTSD) and TRD, respectively, an updated mental health care infrastructure capable of administering powerful psychoactive substances while simultaneously incorporating psychotherapeutic support is needed, in our view.

- **Broad therapeutic potential of psychedelics and unique considerations.** Although ketamine, MDMA, and psilocybin are pharmacologically distinct, they share the ability to induce an acutely altered state of consciousness, which in the appropriate therapeutic context could lead to rapid therapeutic onset and durable treatment effect. These substances are orally active but have different mechanisms of action. Psilocybin's effects depend on 5-HT2A agonism; MDMA inhibits monoamine transporters, especially for serotonin; ketamine is an NMDA antagonist. The broad indication potential for ketamine, MDMA, and psilocybin, including for depression, eating disorders, addiction, and posttraumatic stress disorder (PTSD), among other ailments could mean that clinicians could have to consider safety issues such as appropriate patient selection, substance abuse potential, and emergent psychiatric and medical crises.

- **Therapeutic set and setting could be crucial.** Great attention is being paid to the therapeutic setting itself in designing trials evaluating MDMA and psilocybin primarily as efficacy could depend on both the drug and the therapeutic environment in which it is administered. For instance, the vivid experiences during a psilocybin session revisited in subsequent therapy sessions could be central to its potential therapeutic action in addressing existential issues and sources of depression and anxiety.

- **Placebo control.** Regarding the challenges of conducting a placebo-controlled trial, the use of dissociative compounds (i.e., dextromethorphan) as comparators for psilocybin or psychostimulants (i.e., methamphetamine) for MDMA could be beneficial.

Source: Heifets and Malenka, 2019, Schenberg, 2018, H.C. Wainwright & Co.

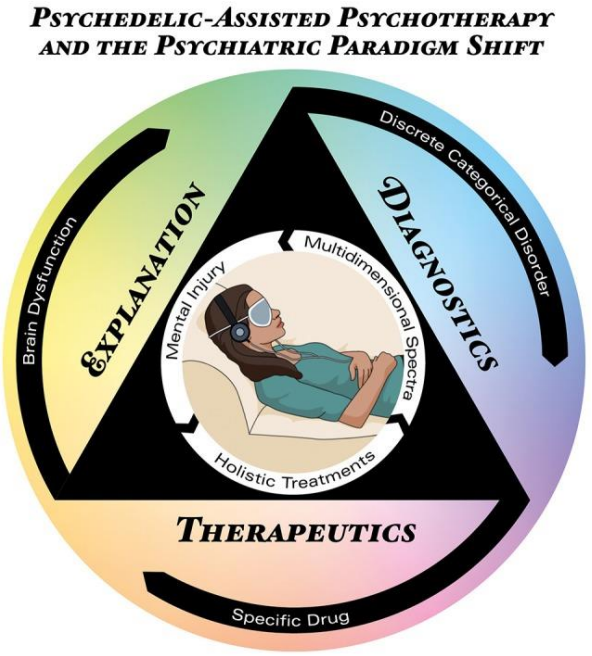
Could Psychedelics Drive a Global Mental Healthcare Revolution?

- **Significant global burden.** Mental health disorders increasingly contribute to global burden of disease with significant socio-economic costs. The "Lancet Commission" report by 28 global specialists in psychiatry, public health and neuroscience, as well as mental health patients and advocacy groups estimated the economic impact from mental health disorders at a staggering $16T by 2030 – and this was estimated prior to the COVID-19 pandemic, which we think will only exacerbate the global mental health dilemma. The commission did not break down the potential $16T costs though we believe it comprises a combination of direct costs of treatment as well as lost opportunity costs to society.

- **New drug approvals have been scarce.** For instance, approval of new molecular entities (NMEs) for psychiatric conditions by the FDA declined from 13 in 1996 to one in 2016 with 49 approved between 1996-2006 declining to 22 from 2007-2016.

- **Psychedelic assisted treatment could provide a solution, in our view.** For instance, psychedelic-assisted psychotherapy (PAP) incorporates the use of a potent psychoactive substance in a few sessions. These are generally accompanied by drug-free sessions before and/or after drug sessions. These are called preparatory and integrative psychotherapy, respectively. The degree of engagement with the therapist could depend on the drug and the indication, with a more thorough engagement likely necessary with MDMA in PTSD and with less engagement possible with psilocybin in depression.

- **Historical success with psychedelic assisted treatment.** With ketamine, positive results were obtained with one to 12 administrations; with MDMA, just three; and with psilocybin and LSD, only two. During drug effects, patients are continuously monitored and supported by trained mental health professionals following available guidelines. Generally patients listen to instrumental evocative music and are encouraged to stay introspective (with eyeshades) and open to feelings, attentive to thoughts and memories, being free to engage in psychotherapy at any time.



Note: The above Exhibit represents Psychedelic-Assisted Psychotherapy (PAP) mapped onto the triple-axis psychiatric crisis. The icon in the center represents the PAP model, located inside the triangle projecting the three axes of the current psychiatric crisis: therapeutics (bottom), diagnosis (right), and explanation (left). The outermost black circle represents the main conceptual formulation for each axis in current psychiatric theory, i.e., brain dysfunctions diagnosed as discrete categorical disorders treated with specific drugs. The innermost white circle represents the concepts supported by PAP: mental injuries diagnosed as a multidimensional spectra treated holistically.

Source: Schenberg, 2018.

Source: Patel, Saxena, et al., 2018, Shenberg 2018, H.C. Wainwright & Co.

Appendix B. Deeper Dive on Psilocybin (Magic Mushrooms)

Brief Background on Psilocybin

- **Background in Western medicine.** Psilocybin was first isolated by Albert Hofmann in 1957 from the Central American mushroom Psilocybe mexicana. The first synthetic psilocybin product was created shortly thereafter in 1958 and continues to be widely used today, both recreationally and in spiritual or religious rituals.

- **Mechanism of action.** Psilocybin, a classic tryptamine hallucinogen, has similar properties to lysergic acid diethylamide (LSD) and mescaline with a slightly different chemical structure. Cross-tolerance between the different psychedelics has been demonstrated, and research shows a common mechanism of action through serotonergic (5-HT) pathways. Psilocybin is a strong agonist at 5-HT2A as well as a moderate agonist at 5-HT1A and 5-HT2C. 5-HT2A receptors are located within the thalamus and cortex of the brain. Activation of 5-HT2A receptors in the thalamus, the area of the brain responsible for sensory input, appears to decrease thalamic activity, thus leading to sensory alterations commonly referred to as hallucinations.

- **Historical research.** Following passage of the Controlled Substance Act (CSA) of 1970, clinical studies using hallucinogens and psychedelics ceased. Much of the research completed on these agents in the 1950s and 1960s was not taken seriously due to the small nature of the studies or methodology inconsistent with current research standards. However, interest in understanding the neuropsychiatric effects of these agents and their potential role in medical therapy persisted.

- **Modern exploratory studies demonstrate potential.** With all caveats of conducting small mostly uncontrolled trials, we note that modern studies show potentially positive benefits with minimal safety concerns for psilocybin use in suicidality, anxiety disorders, OCD, alcohol use disorder, and tobacco use disorder with improvement in target symptoms.

Source: Daniel and Haberman., 2017, H.C. Wainwright & Co.

Psilocybin: basic pharmacokinetics.

Typical dose	Min to achieve effect: 4-10 mg, (0.05-0.3 mg/kg) Recreational use: 10-50 mg • 10-50 g of fresh mushrooms • 1-5 g of dried mushrooms
Onset	10 - 40 min after PO ingestion
Peak	75 - 120 min after PO ingestion
Duration of psychoactive effect	2 - 6 hrs
Half-life	163 ∓64 minutes (~3 hours) oral
Human metabolism	• Hepatic, undergoes a first-pass effect, converts to psilocin • Psilocin is broken down by MAO • Glucuronidated by UGT1A9, UGT1A10 • Excretion: 65% in urine, 20% feces

Psilocybin in psychiatry: potential efficacy in depression and anxiety demonstrated in historical exploratory trials.

Dosage(s)	Study type	Measure(s)	Effect size(s)	Authors
Depression (10 studies)				
0.3 mg/kg	RCT	BDI; HADS-D	Cohen's d = 1.27–1.97	Agin-Liebes et al.
25 mg/70 kg	Open-label	POMS	η_p^2 = 0.32	Barrett et al.
10, 25 mg	Open-label	BDI; HAM-D; QIDS	Hedges' g = 2.0–3.2	Carhart-Harris et al.
10, 25 mg	Open-label	QIDS-SR16	Cohen's d = 2.3	Carhart-Harris et al.
10, 25 mg	Open-label	BDI; HAM-D; QIDS	Cohen's d = 1.52–2.3	Carhart-Harris et al.
1 or 3 mg/70 kg, 22 or 30 mg/70 kg	RCT	BDI; HADS; HAM-D	Cohen's d = 1.55	Griffiths et al.
10, 25 mg	Open-label	HAM-D; QIDS	Hedges' g = 0.7	Lyons and Carhart-Harris
10, 25 mg	Open-label	HAM-D; QIDS	Cohen's d = 1.55	Roseman et al.
0.3 mg/kg	RCT	BDI; HADS	Cohen's d = 0.82–1.32	Ross et al.
10, 25 mg	Open-label	QIDS	η_p^2 = 0.67–0.70	Stroud et al.
Anxiety (5 studies)				
0.3 mg/kg	RCT	HADS-A; STAI	Cohen's d = 0.86–2.67	Agin-Liebes et al.
25 mg/70 kg	Open-label	STAI	η_p^2 = 0.27–0.28	Barrett et al.
10, 25 mg	Open-label	STAI-T	Hedges' g = 2.0–3.2	Carhart-Harris et al.
10, 25 mg	Open-label	STAI	Cohen's d = 1.2–2.2	Carhart-Harris et al.
0.3 mg/kg	RCT	HADS-A; STAI	Cohen's d = 0.8–1.49	Ross et al.

Source: OHSU, The Role of Psychedelics in Modern Psychiatry, 2019, Aday, Davoli, and Bloesch, 2020.

Deeper Dive on the Mechanism Underpinning Classic Psychedelics

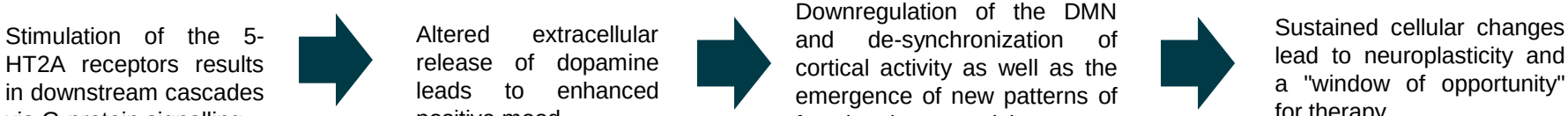
- Most human functional neuroimaging studies of psychedelics have focused on their acute effects with the aim of elucidating the neural correlates of the psychedelic state. Psychedelics appear to dysregulate cortical activity, producing an entropic brain state characterized by compromised modular but enhanced global connectivity referred to previously as network disintegration and desegregation. These effects have been found to correlate with important aspects of the psychedelic experience, including ego-dissolution, and were predictive of post-acute changes in the personality domain openness.

- In a study enrolling 19 patients with treatment-resistant depression (TRD) who completed pre-treatment and one-day post-treatment fMRI scanning, psilocybin therapy produced rapid and sustained antidepressant effects. The mean depression score (QIDS-SR16) for the week prior to the pre-treatment scan was 16.9 ± 5.1, and for the day of the post-treatment scan, it was 8.8 ± 6.2 (change = −8.1 ± 6, t = −5.2, p<.001). The mean QIDS-SR16 score at baseline (screening) was 18.9 ± 3, and for 5-weeks post-treatment, it was 10.9 ± 4.8 (change = −8 ± 5.1, t = −6.3, p<.001).

- For the first time, changes in resting-state brain blood flow and functional connectivity post-treatment with psilocybin for TRD was evaluated. Decreased blood flow was found to correlate (in the amygdala) with reductions in depressive mood. Increased within-default mode network (DMN) resting-state functional connectivity (RSFC) was observed post-treatment, using both seed and network-based analyses, and specific increases in RSFC between the ventromedial prefrontal cortex (vmPFC) and bilateral inferior-lateral parietal cortex (ilPC) nodes of the DMN were greatest in individuals who maintained treatment-response at five weeks.

- Moreover, decreased PH-PFC RSFC was observed post-treatment and this was also predictive of treatment-response at five weeks. An exploratory post-hoc analysis revealed that acute “peak” or “mystical” experience during the high-dose psilocybin session was predictive of these changes in PH RSFC.

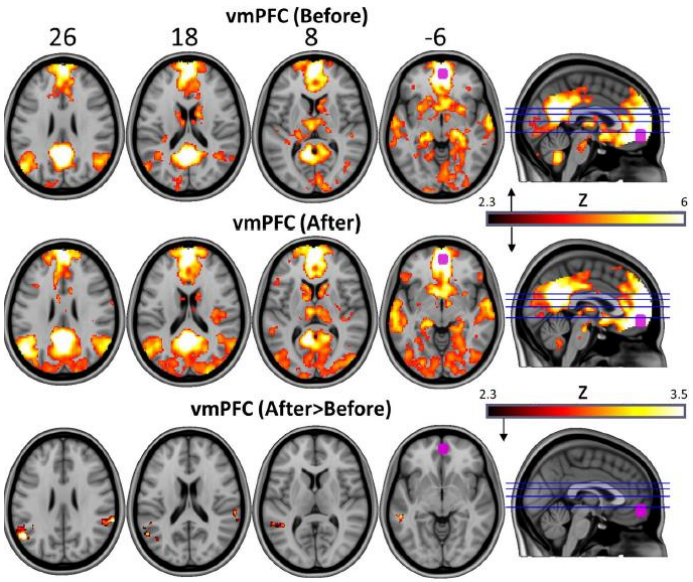
Modulation of Cortical and Limbic Systems via 5-HT2A Receptors



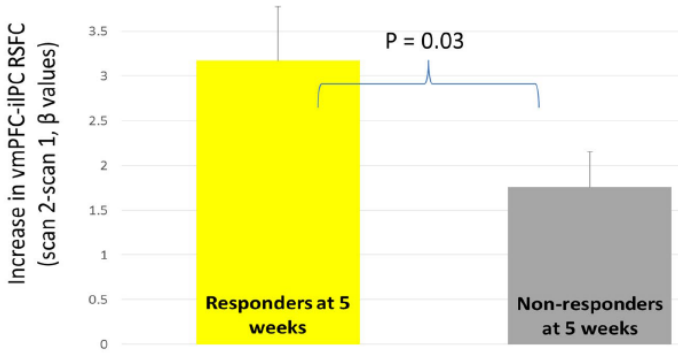
Source: Carhart-Harris, Roseman, et al., 2017, H.C. Wainwright & Co.

Source: Halberstadt et al., 2011, Lpez-Gimenez et al., 2018, Vollenweider et al., 1999, Sakashita et al., 2015, Carhart-Harris et al., 2012a.

Psilocybin for TRD: fMRI-Measured Brain Mechanisms



Increased vmPFC-ilPC RSFC predicts better long-term prognosis



The top two rows are vmPFC (purple) RSFC before and after psilocybin treatment; (hot colors = regions of significantly positive coupling).

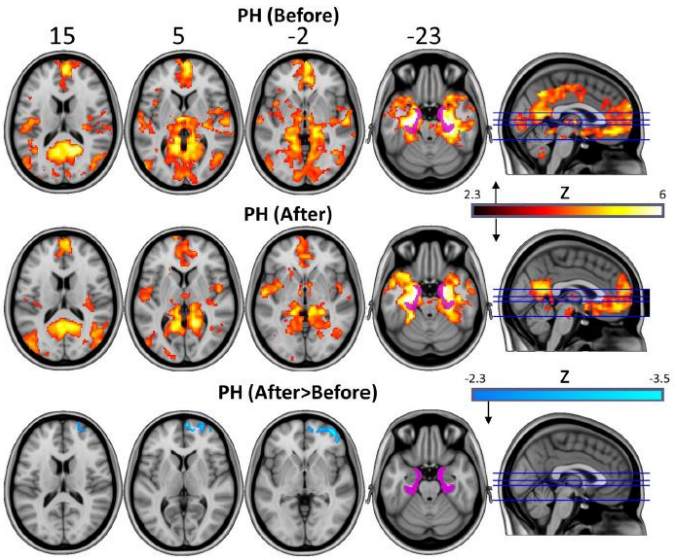
Bottom row reveals regions where there was a significant increase in vmPFC RSFC post-treatment (hot colors). All maps are cluster-corrected, p<.05, Z>2.3.

Increased coupling between the vmPFC and the displayed regions (bottom row) was predictive of clinical response at 5-weeks posttreatment.

Top two rows are bilateral PH (purple) RSFC before and after psilocybin treatment (hot colors = regions of significantly positive coupling).

Bottom row reveals regions where there was a significant decrease in PH RSFC post-treatment (cold colors). All maps are cluster-corrected, p<0.05, Z>2.3.

Decreased coupling between the PH and the displayed regions (bottom row) was predictive of clinical response at 5-weeks post-treatment (t = −1.9, p = 0.04).



Decreased PH-PFC RSFC predicts better long-term prognosis

Source: Carhart-Harris, Roseman, et al., 2017.

Additional Details on the Default Mode Network (DMN)

- The DMN has largely been a cortically defined set of network nodes. Consisting of distinct regions and nodes distributed across the ventromedial and lateral prefrontal, posteromedial and inferior parietal, as well as the lateral and medial temporal cortex, the DMN is considered a backbone of cortical integration. Altered connectivity in the DMN has been observed in a large variety of brain diseases, including Alzheimer's disease, Parkinson's disease, schizophrenia, depression, temporal lobe epilepsy, attention deficit and hyperactivity disorder, and drug addiction, among others.

- *Alves et al.* provided a more comprehensive neurobiological model of the DMN that bridges the gap between local differences in subcortical structures and global differences in the DMN reported in clinical studies. In particular, resting activity of the thalamus could predict response to anti-depressant medication, while the nucleus accumbens mediates response to stress and to anti-depressant medication.

- Broadly, the scientific literature suggests that increased DMN activity may interfere with cognitive performance, and decreased DMN activity is associated with improved performance. Likewise, increased DMN activity has been associated with depression, anxiety, and addiction, among other disorders. Moreover, *Garrison et al.* demonstrate that meditation is associated with relatively lower activity in regions of the DMN in meditators compared to controls during meditation compared to another active cognitive task; mindfulness training has shown utility for addiction, pain, anxiety, and depression. The implication is that a neural mechanism by which meditation results in clinical benefits may be via reducing DMN activity.

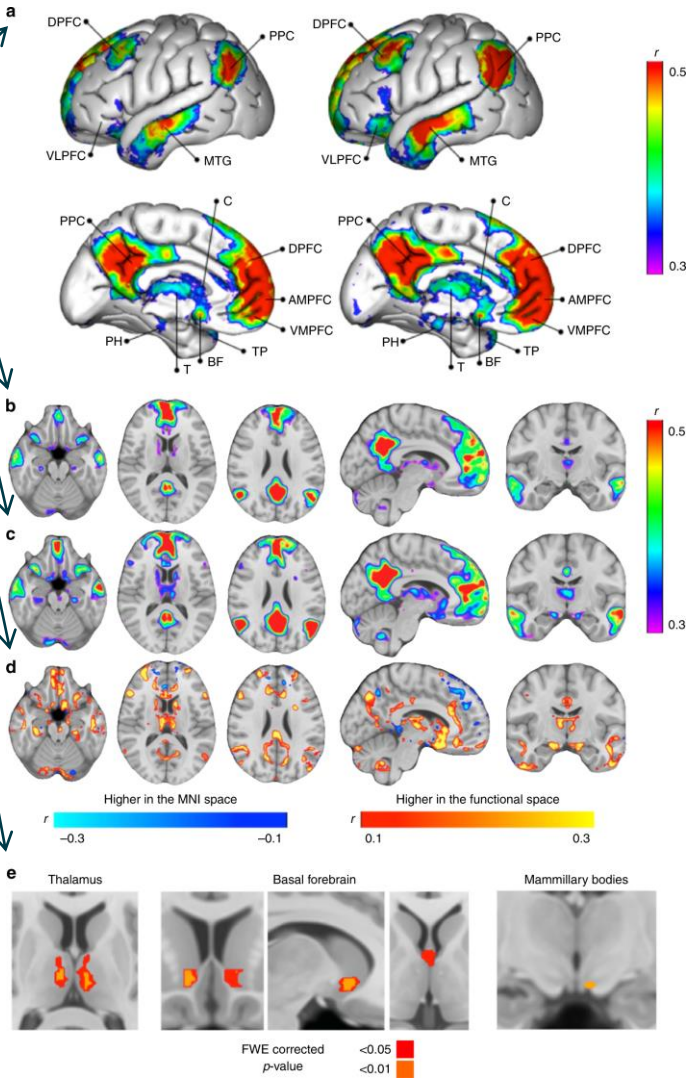
3D view of the two DMN left panel corresponds to the structural space alignment, right panel to the functional space alignment.

Brain sections of the structurally aligned DMN.

Brain sections of the functionally aligned DMN.

Subtraction of the structurally and the functionally aligned DMN maps.

Statistical comparison (paired t test) between the two methods of alignment —structurally and functionally aligned DMN—in the three hypothesized regions, with colors indicating statistically significant differences at two levels of significance: <0.05 and <0.01, family-wise error (FWE) corrected p-values (higher in the functional space).



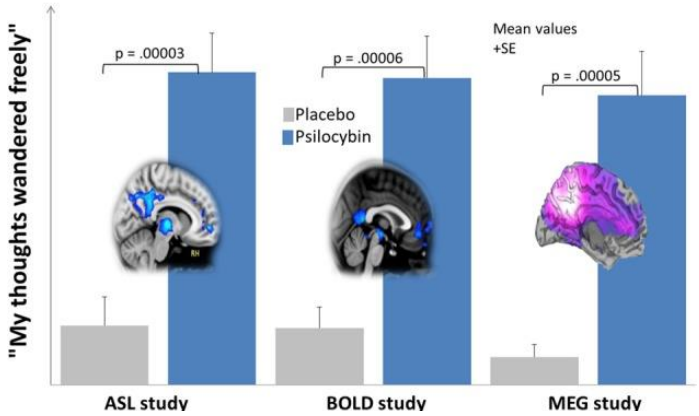
Note: DPFC, dorsal prefrontal cortex, PPC, posterior parietal cortex, VLPFC, ventrolateral prefrontal cortex, MTG, middle temporal gyrus, PCC, posterior cingulate cortex, C, caudate, DPFC, dorsal prefrontal cortex, AMPFC, antero-median prefrontal cortex, VMPFC, ventro-median prefrontal cortex, TP, temporal pole, BF, basal forebrain, T, thalamus, PH, parahippocampal.

Source: Company filings, Anticevic et al., 2012, Sheline et al., 2009, Zhao et al., 2007, Garavan et al., 2000, Alves, Foulon et al., 2019, Garrison, Zeffiro et al., 2015.

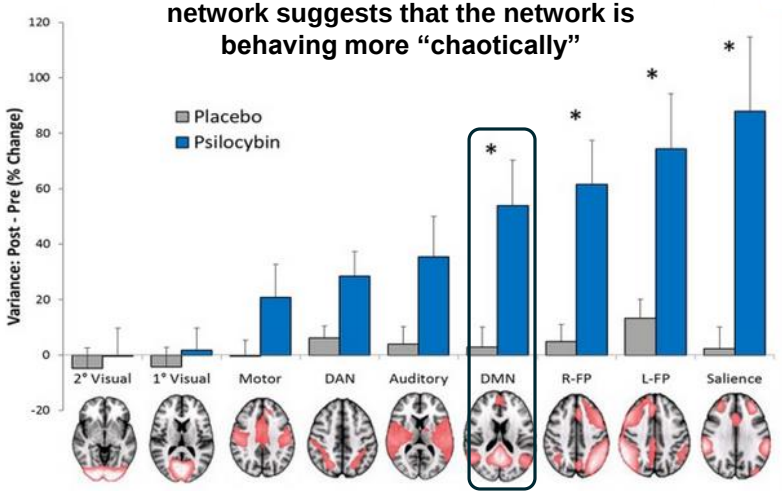
Psilocybin's Impact on Neural Networks

- At the systemic level, psilocybin has been shown to alter the synchronicity of neuronal activation within and between different brain networks, during the psychedelic experience and afterwards.
- During the acute experience, psilocybin appears to temporarily reduce synchronicity of areas within the DMN, whereas connectivity between other brain areas and networks is substantially increased.
- On the day after these acute effects, individuals administered with psilocybin may exhibit increased synchronicity within the DMN, as well as changes between areas of the DMN and other brain regions.
- These brain network alterations may indicate the emergence of novel patterns of connectivity upon decoupling of the DMN and could lead to longer-term changes, such as altered emotional processing, that may ultimately affect behavior according to COMPASS Pathways.

Psilocybin promotes unconstrained thinking and decreases blood flow, venous oxygenation and oscillatory power in the DMN



An increase in metastability for a specific network suggests that the network is behaving more "chaotically"



Note: the significant networks are labeled with an asterisk.

Source: CMPS Company filings, H.C. Wainwright & Co.

Source: Carhart-Harris, Leech, et al., 2014.

Psilocybin Demonstrates Linear PK, Low Abuse Potential in Prior Studies

Study	Trial Design	Dose	N	Population	Outcome	Notable Safety	Investigator	Source
Determine PK of an oral formulation of psilocybin in normal healthy adults	Open-label, dose-escalating	0.3, 0.45, 0.6 mg/kg (oral, dose escalating every four weeks)	12	Healthy adults	Psilocybin, as its active metabolite psilocin, demonstrated linear pharmacokinetics over the dose range tested, as indicated by the noncompartmental evaluation of dose-normalized area under the curve and Cmax. The mean maximal concentration of psilocin increased in a dose proportional manner from 0.3 mg/kg psilocybin (16 µg/L), to 0.45 mg/kg (26 µg/L), to 0.6 mg/kg (37.6 µg/L).	The most frequently occurring AEs related to IP were mild hypertension (N = 22, 83% of participants), mild bradycardia (N = 22, 58%), mild headache (N = 14, 75%), and mild tachycardia (N = 12, 50%)	University of Wisconcin	Brown et al; *Clinical Pharmacokinetics,* 2017
Analyze acute, short- and long-term subjective effects of psilocybin in healthy humans from previously conducted double-blind, placebo-controlled experimental studies	Retrospective analysis	1-4 doses of oral psilocybin (45-315 µg/kg)	110	Healthy adults	Collected data from eight studies demonstrated that psilocybin was safe and well-tolerated under the conditions tested; low abuse potential demonstrated.	The most frequent self-reported adverse experiences were mild headache and mild lethargy (fatigue, exhaustion, or lack of energy) immediately after psilocybin administration. For these events, normal function was largely restored after 24 hours.	University of Zurich	Studerus et al; *J Psychopharmacol,* 2011

Source: Usona Institute, H.C. Wainwright & Co.

Psilocybin Has Demonstrated Potential in Depression in Prior Studies

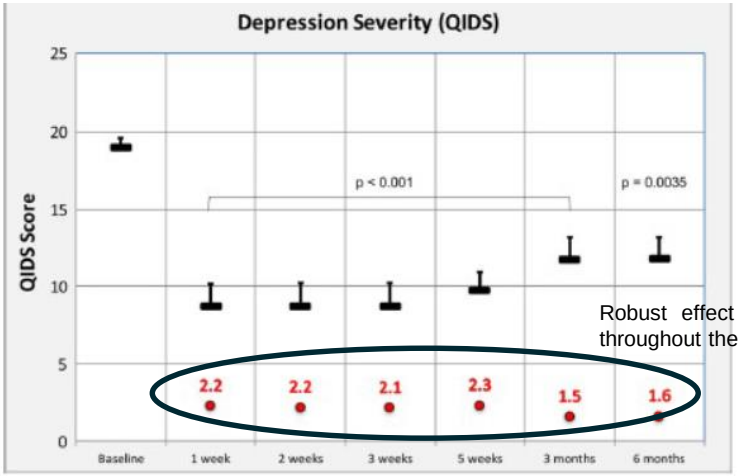
Study	Trial Design	Dose	N	Population	Outcome	Notable Safety	Investigator	Source
Determine safety and efficacy outcomes for up to 6 months in an open-label trial of psilocybin for treatment-resistant depression	Open-label, dose-escalating feasibility study	Oral psilocybin, 1x 10 mg (low dose), 1x 25 mg (high dose) one week apart	20	Adults with moderate or severe depression	Depression severity as measured by the QIDS (self-reported) and HAM-D (clinician-administered) ratings both improved. Nine and four participants, respectively, met the criteria for response and remission at the week five time point; reductions in depressive symptoms were observed for six months.	Mild to moderate transient anxiety (N = 15; 79%), and mild to moderate headache (N = 8; 42%). Five participants (26%) reported transient nausea, but there were no cases of vomiting.	Imperial College of London	Carhart-Harris et al; *Lancet Psych,* 2016, and Carhart-Harris et al; *Psychopharmacol,* 2018
Investigate the efficacy of a single psilocybin dosing session versus placebo (in conjunction with psychotherapy) to treat clinically significant anxiety or depression	Randomized, double-blind, placebo-controlled, crossover	0.3 mg/kg oral psilocybin or 250 mg oral placebo	31	Adults with cancer diagnosis	When compared to placebo, a single dose of psilocybin produced a significant acute and sustained reduction in combined anxiety and depressive symptoms as measured by the total Hospital Anxiety and Depression Scale (HADS) score.	The most common adverse events that occurred during the psilocybin dosing sessions (before and after crossover, N = 28) included elevated systolic (>160 mm Hg) and diastolic BP (>100 mm Hg), headache and migraine, anxiety, and nausea.	NYU	Ross et al; *J Psychopharmacol,* 2016

Source: Usona Institute, H.C. Wainwright & Co.

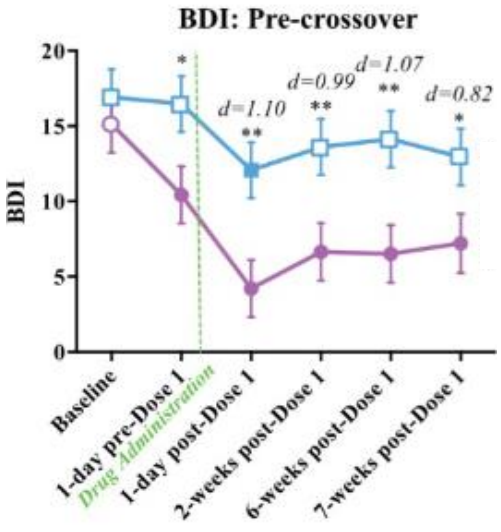
Transient increases in blood pressure, headaches, and nausea are common in historical trials evaluating psilocybin in psychiatric indications. These transient side effects are not dissimilar to those experienced with esketamine, which was approved for TRD, and MDMA, which is in Phase 3 development for PTSD. We discuss esketamine and MDMA in greater detail later on in this report.

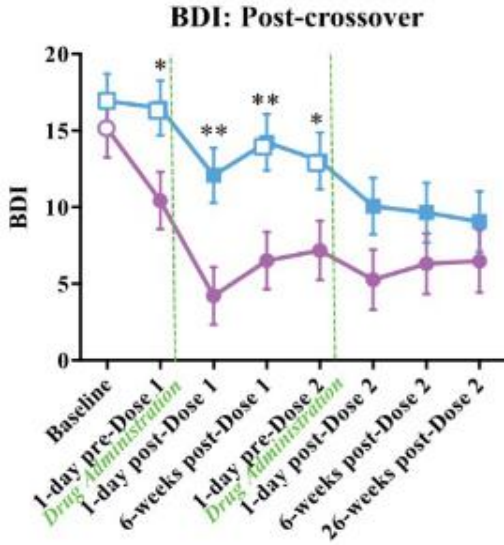
Psilocybin Has Demonstrated Potential in Depression in Prior Studies

QIDS values to assess self-reported depression point to fast onset of action with long duration for psilocybin in depression



Robust effect size throughout the trial.





	BDI				STAI				SHAPS			HAM-D		GAF	
	Baseline	1 Week	3 Mos	6 Mos	Baseline	1 Week	3 Mos	6 Mos	Baseline	1 Week	3 Mos	Baseline	1 Week	Baseline	1 Week
Mean (*SD*)	34.5 7.3	11.8 11.1	19.2 13.9	19.5 13.9	68.6 6.1	44.8 15.7	56.5 13.3	53.8 13.3	6.6 4.1	1.9 2.7	3.3 4.2	24.1 5.4	9.3 7.6	48.9 10.3	74.2 16.05
Difference vs base-line (*SD*)	-	– 22.7 10.6	– 15.3 13.7	– 14.9 12.0	-	– 23.8 15.2	– 12.2 12.7	– 14.8 14	-	– 4.6 4.1	– 3.3 4.6	-	– 14.8 7.8	-	+ 25.3 17.1
Cohen's d value	-	2.5	1.4	1.4	-	2.2	1.2	1.5	-	1.3	0.8	-	2.3	-	1.9
***p* value**	-	$p < 0.001$	$p < 0.001$	$p < 0.001$	-	$p < 0.001$	$p < 0.001$	$p < 0.001$	-	$p < 0.001$	$p = 0.005$	-	$p < 0.001$	-	$p < 0.001$

Source: Ross et al., 2016.

A change in the HAMD-17 of at least 7 points is considered clinically meaningful, so a change of nearly 15 is robust in our view, demonstrating potentially early onset of action. Moreover, perhaps as interesting is the longer-term efficacy demonstrated on the BDI with an effect size of 1.4 over six months, demonstrating potentially robust duration of action.

Note: in the above chart, mean values (black horizontal bars) as calculated for the 19 study completers, with error bars included. QIDS scores of 16-20 are considered to reflect severe depression. Cohen's d values vs baseline are shown in red, all contrasts vs baseline yielded p values of < 0.001 with the exception of the 6-month contrast which was p = 0.0035. Also note, in the above table, Clinician administered ratings (HAM-D and GAF) were completed at baseline and one-week post-dosing only.

Source: Carhart-Harris et al., 2016, Hengartner, Ploderl, 2018, H.C. Wainwright & Co.

Psilocybin Has Demonstrated Potential in Additional Indications

Study	Trial Design	Dose	N	Population	Outcome	Notable Safety	Investigator	Source
Investigate the effects of psilocybin dose (low vs high dose) on a variety of outcome measures relevant to anxiety or depressive disorders exacerbated by cancer diagnosis	Randomized, double-blind, crossover	Oral psilocybin, 1x 0.014 mg/kg or0.042 mg/kg (low dose) / 1x 0.31 mg/kg or 0.43 mg/kg (high dose)	56	Adult cancer patients	Following the first post-dose assessment 92% of participants in the high-dose first group met standard criteria for depressive symptom clinical response and 60% met criteria for symptom remission as per the GRID-HAMD measure (p <.001 and p<.01, respectively), compared with 32% and 16% respectively in the low-dose first group. In the high-dose first group 76% met criteria for anxiety symptom clinical response and 52% met criteria for symptom remission at first post- dose assessment as per the HAM-A measure (p<.001 and p<.01, respectively), compared with 24% and 12% respectively in the low-dose first group.	Episodes of elevated systolic blood pressure (>160 mm Hg) occurred in 18 of 53 (34%) high dose sessions, as compared to 17% (N = 9) of the low dose “placebo” sessions. Episodes of elevated diastolic blood pressure (>100 mm Hg) occurred in 7 of 53 (13%) high dose sessions, and 1 of 52 (2%) of the low dose sessions. One participant experienced a transient peak blood pressure (214/114 mm Hg) in high dose session.	Johns Hopkins	Griffiths et al; *J Psychopharmacol,* 2016
Quantify acute effects of psilocybin in alcohol-dependent participants and provide preliminary outcome and safety data	Single-group, dose-escalating proof of concept study	Oral psilocybin, 1x 0.3 mg/kg, and 1x 0.3 or 0.4 mg/kg four weeks apart	10	Adults with active alcohol dependence	Mean percent of drinking days (days with any consumption of alcohol) decreased during weeks 5-12 relative to baseline (27.2 ± 23.7%; 95% CI 9.0-45.4, p = 0.009), and relative to weeks 1-4 (21.9 ± 21.8%; 95% CI 5.1-38.6, p = 0.017) prior to psilocybin administration. Mean percent of heavy drinking days (days where male participants consumed five or more drinks containing 14 g of alcohol, or female participants consumed four or more drinks containing 14 g of alcohol) also decreased during weeks 5-12 relative to baseline(26.0 ± 22.4; 95% CI 8.7-43.2, p = 0.008) and weeks 1-4 (18.2 ± 20.0%; 95% CI 2.8-33.5, p = 0.026)	The most common adverse event was mild headache (5 of 10 participants, 50%), which resolved within 24 hours following psilocybin administration.	University of New Mexico	Bogenshutz et al; *J Psychopharmacol,* 2015

Over the prior 20 years, academic research centers have generated data pointing to potential for psilocybin treatment in various psychiatric conditions including addiction (alcohol, tobacco), mood disorders (anxiety, obsessive compulsive disorder), and cancer-related depression and anxiety.

Source: Usona Institute, H.C. Wainwright & Co.

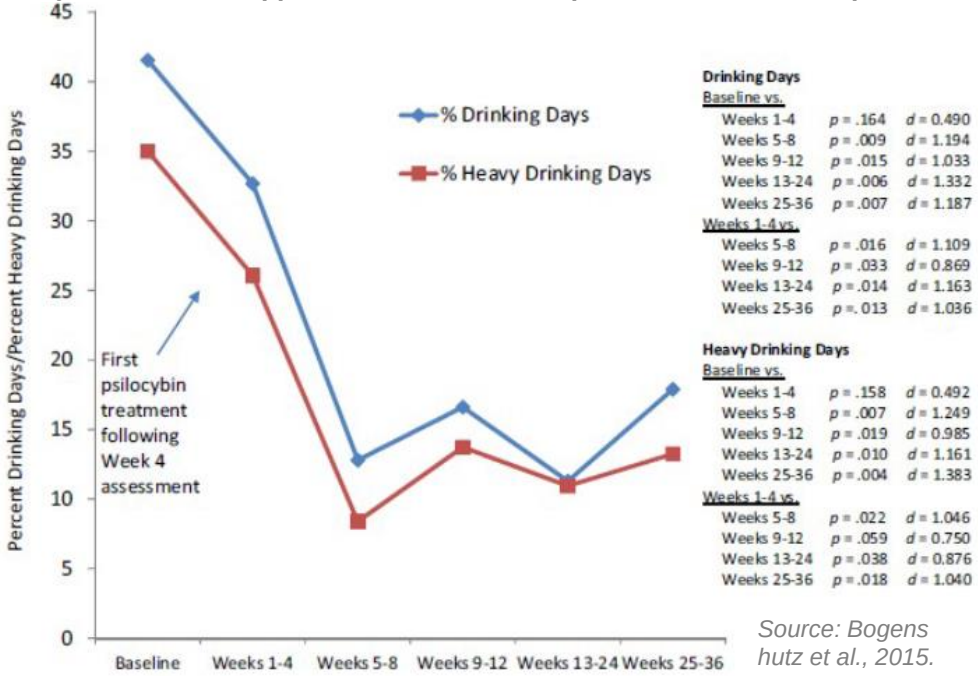
Psilocybin Has Demonstrated Potential in Additional Indications

Study	Trial Design	Dose	N	Population	Outcome	Notable Safety	Investigator	Source
Determine the safety and feasibility of psilocybin as an adjunct to tobacco smoking cessation treatment.	Open-label, dose-escalating	Oral psilocybin, 1x 20 mg/70 kg (low dose). 1x 30 mg/70 kg (high dose), and 1x optional dosing (lowor high)	15	Psychiatrically healthy, nicotine-dependent adult smokers	Twelve of 15 participants (80%) reported seven-day point prevalence abstinence at the six-month follow-up, and 11 (73%) were biologically confirmed to have quit smoking. Three participants (20%) tested positive for smoking at the six-month follow-up.	Baseline values for mean maximal systolic BP increased from125 ± 10 mm Hg to 153 ± 11 mm Hg, mean maximal diastolic BP increased from 71 ± 8 mm Hg to 87 ± 11 mm Hg, and mean maximal HR increased from 68 ± 9 to 87 ± 11 beats per minute following psilocybin administration.	Johns Hopkins (Tobacco)	Johnson et al; *J Psychopharmacol,* 2014
Evaluate efficacy ofpsilocybin for advanced- stage cancer patients	Randomized, double-blind, placebo-controlled, crossover	0.2 mg/kg (1x oral psilocybin, 1x oral placebo)	12	Adults with advanced cancer (various types)	Beck Depression Inventory (BDI) scores for psilocybin through two weeks post-dose did not attain statistical significance. However, long-term follow-up through six months showed a drop of nearly 30% from pre-administration to month one with statistical significance achieved at month six (p=.03).	Mean maximum systolic BP increased from 117 ± 4.3 mm Hg to 138.9 ± 6.4 mm Hg, mean maximal diastolic BP increased 69.6 ± 2.7 mm Hg to 75.9 ± 3.4 mm Hg, and mean maximal heart rate increased from 70.4 ± 4.3 beats per minute to 81.5 ± (5.8) beats per minute.	Harbor-UCLA	Grob et al; *Arch Gen Psychiatry,* 2011
Explore safety for human consumption of 4 doses of psilocybin in a small sample of symptomatic Obsessive Compulsive Disorder patients	Open-label, dose-escalating, proof of concept	Oral psilocybin, 1x 100 µg/kg (low dose), 1x 200 µg/kg (medium dose) and 1x 300 µg/kg (high dose) sequentially, with 1x 25 µg/kg (very low dose) inserted randomly	9	Adults with OCD	Decreases in OCD symptoms of a variable degree (23-100%) were observed in all subjects during at least one dosing session per the YBOCS (Yale-Brown Obsessive Compulsive Scale).	One participant experienced hypertension which was not associated with psychic anxiety or somatic symptoms.	University of Arizona	Moreno et al; *J Clin Psychiatry,* 2006

Source: Usona Institute, H.C. Wainwright & Co.

Psilocybin Has Demonstrated Potential in Additional Indications

Psilocybin treatment appeared to demonstrate potential in alcohol dependence



Drinking Days

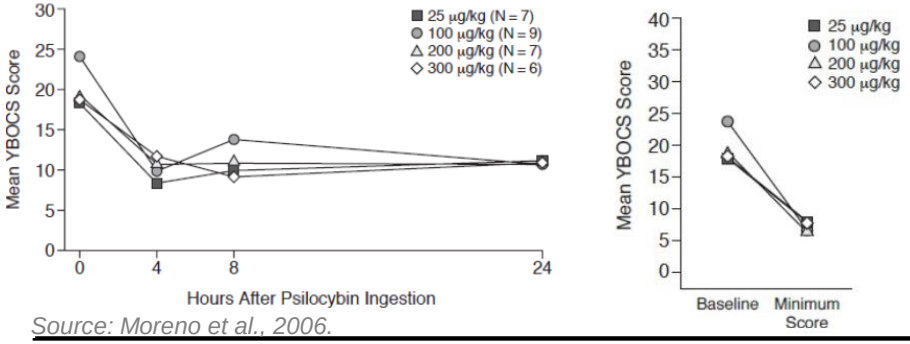
Baseline vs.		
Weeks 1-4	$p = .164$	$d = 0.490$
Weeks 5-8	$p = .009$	$d = 1.194$
Weeks 9-12	$p = .015$	$d = 1.033$
Weeks 13-24	$p = .006$	$d = 1.332$
Weeks 25-36	$p = .007$	$d = 1.187$
Weeks 1-4 vs.		
Weeks 5-8	$p = .016$	$d = 1.109$
Weeks 9-12	$p = .033$	$d = 0.869$
Weeks 13-24	$p = .014$	$d = 1.163$
Weeks 25-36	$p = .013$	$d = 1.036$

Heavy Drinking Days

Baseline vs.		
Weeks 1-4	$p = .158$	$d = 0.492$
Weeks 5-8	$p = .007$	$d = 1.249$
Weeks 9-12	$p = .019$	$d = 0.985$
Weeks 13-24	$p = .010$	$d = 1.161$
Weeks 25-36	$p = .004$	$d = 1.383$
Weeks 1-4 vs.		
Weeks 5-8	$p = .022$	$d = 1.046$
Weeks 9-12	$p = .059$	$d = 0.750$
Weeks 13-24	$p = .038$	$d = 0.876$
Weeks 25-36	$p = .018$	$d = 1.040$

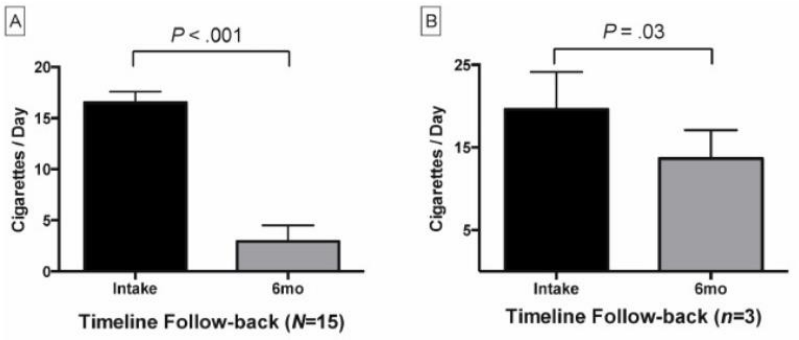
Source: Bogens hutz et al., 2015.

OCD symptoms improved dramatically post-psilocybin treatment



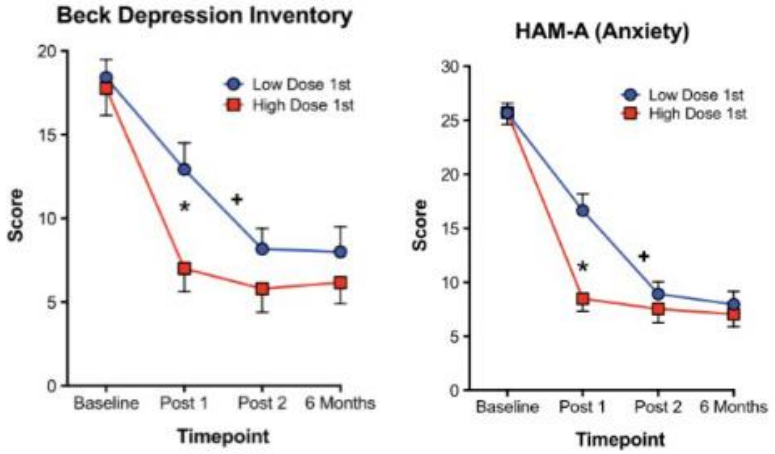
Source: Moreno et al., 2006.

Timeline follow-back data at the six-month time point for (A) the entire study population, and (B) the three participants who tested positive for smoking at the six-month follow-up demonstrates psilocybin utility in smoking cessation



Source: Johnson et al., 2014.

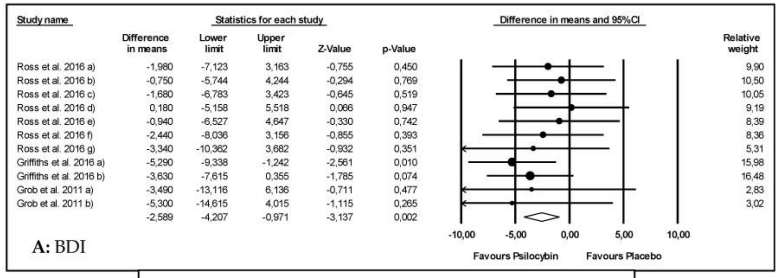
Psilocybin treatment demonstrated a benefit in depression and anxiety associated with cancer diagnosis



Source: Griffiths et al., 2016.

Forest Plots in Depression and Anxiety Favor Psilocybin in Meta Analysis

Becks Depression Inventory (BDI)

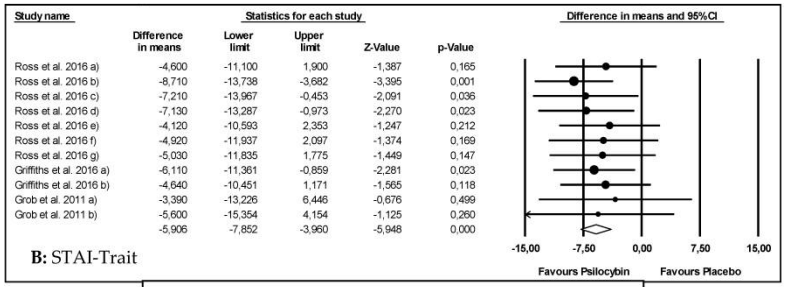


Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Ross et al. 2016 a)	-1,980	-7,123	3,163	-0,755	0,450	9,90
Ross et al. 2016 b)	-0,750	-5,744	4,244	-0,294	0,769	10,50
Ross et al. 2016 c)	-1,680	-6,783	3,423	-0,645	0,519	10,05
Ross et al. 2016 d)	0,180	-5,158	5,518	0,066	0,947	9,19
Ross et al. 2016 e)	-0,940	-6,527	4,647	-0,330	0,742	8,39
Ross et al. 2016 f)	-2,440	-8,036	3,156	-0,855	0,393	8,36
Ross et al. 2016 g)	-3,340	-10,362	3,682	-0,932	0,351	5,31
Griffiths et al. 2016 a)	-5,290	-9,338	-1,242	-2,561	0,010	15,98
Griffiths et al. 2016 b)	-3,630	-7,615	0,355	-1,785	0,074	16,48
Grob et al. 2011 a)	-3,490	-13,116	6,136	-0,711	0,477	2,83
Grob et al. 2011 b)	-5,300	-14,615	4,015	-1,115	0,265	3,02
	-2,589	-4,207	-0,971	-3,137	0,002	

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 4.443$; df = 10; p-Value= 0.925; $I^2 = 0$

Test for overall effect: $z = -3.137$, p-Value = 0.002

State-Trait Anxiety Inventory (STAI)-Trait

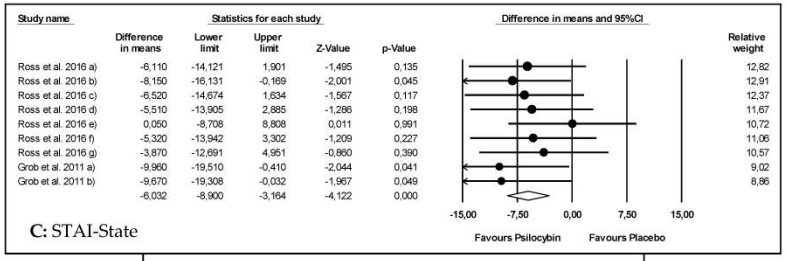


Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
Ross et al. 2016 a)	-4,600	-11,100	1,900	-1,387	0,165
Ross et al. 2016 b)	-8,710	-13,738	-3,682	-3,395	0,001
Ross et al. 2016 c)	-7,210	-13,967	-0,453	-2,091	0,036
Ross et al. 2016 d)	-7,130	-13,287	-0,973	-2,270	0,023
Ross et al. 2016 e)	-4,120	-10,593	2,353	-1,247	0,212
Ross et al. 2016 f)	-4,920	-11,937	2,097	-1,374	0,169
Ross et al. 2016 g)	-5,030	-11,835	1,775	-1,449	0,147
Griffiths et al. 2016 a)	-6,110	-11,361	-0,859	-2,281	0,023
Griffiths et al. 2016 b)	-4,640	-10,451	1,171	-1,565	0,118
Grob et al. 2011 a)	-3,390	-13,226	6,446	-0,676	0,499
Grob et al. 2011 b)	-5,600	-15,354	4,154	-1,125	0,260
	-5,906	-7,852	-3,960	-5,948	0,000

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.520$; df = 10; p-Value= 0.991; $I^2 = 0$

Test for overall effect: $z = -5.498$, p-Value < 0.001

STAI-State



Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Ross et al. 2016 a)	-6,110	-14,121	1,901	-1,495	0,135	12,82
Ross et al. 2016 b)	-8,150	-16,131	-0,169	-2,001	0,045	12,91
Ross et al. 2016 c)	-6,520	-14,674	1,634	-1,567	0,117	12,37
Ross et al. 2016 d)	-5,510	-13,905	2,885	-1,286	0,198	11,67
Ross et al. 2016 e)	0,050	-8,708	8,808	0,011	0,991	10,72
Ross et al. 2016 f)	-5,320	-13,942	3,302	-1,209	0,227	11,06
Ross et al. 2016 g)	-3,870	-12,691	4,951	-0,860	0,390	10,57
Grob et al. 2011 a)	-9,960	-19,510	-0,410	-2,044	0,041	9,02
Grob et al. 2011 b)	-9,670	-19,308	-0,032	-1,967	0,049	8,86
	-6,032	-8,900	-3,164	-4,122	0,000	

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.606$; df = 8; p-Value= 0.891; $I^2 = 0$

Test for overall effect: $z = -4.122$, p-Value < 0.001

Source: Vargas, Luís, et al., H.C. Wainwright & Co.

Public Companies Mentioned in This Report

atai Life Sciences (ATAI; Buy; Trucchio)
COMPASS Pathways (CMPS; Buy; Trucchio)
Cybin Inc. (CYBN; Buy; Trucchio)
FactSet (FDS; not rated)
Field Trip Health (FTRP; Buy; Trucchio)
J&J (JNJ; not rated)

Source: FactSet, H.C. Wainwright & Co.

C$ in millions, unless otherwise noted

	Jun-20	Sep-20	Dec-20	Mar-21	Jun-21	Jun-21	Sep-21	Dec-21	Mar-22	Jun-22	Jun-22	Jun-23		
	F2020A	**F1Q21A**	**F2Q21A**	**F3Q21A**	**F4Q21A**	**F2021A**	**F1Q22E**	**F2Q22E**	**F3Q22E**	**F4Q22E**	**F2022E**	**F2023E**	**F2024E**	**F2025E**
Revenues	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
% chg	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Cost of sales	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
% chg	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
% of sales	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Gross profit	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
% chg	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
% of sales	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
bp chg	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Research and development expenses	**0.0**	**0.0**	**0.3**	**0.6**	**1.3**	**2.2**	**1.3**	**1.3**	**1.3**	**1.3**	**5.2**	**10.2**	**15.2**	**20.2**
% chg	NM	NM	NM	NM	NM	NM	NM	314.9%	109.1%	0.0%	132.7%	96.7%	49.2%	33.0%
% of sales	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
General and administrative expenses	**0.3**	**0.2**	**0.5**	**1.0**	**0.8**	**2.5**	**0.8**	**0.9**	**0.9**	**1.0**	**3.7**	**4.5**	**6.5**	**8.5**
% chg	NM	NM	NM	NM	NM	752.6%	319.0%	96.2%	-4.8%	17.8%	47.5%	21.8%	44.8%	30.9%
% of sales	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Sales and marketing expenses	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**5.0**
% chg	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
% of sales	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Share-based compensation	**0.2**	**0.0**	**0.4**	**0.0**	**1.6**	**2.0**	**1.6**	**1.7**	**1.7**	**1.8**	**6.8**	**9.6**	**12.0**	**17.0**
% chg	NM	NM	NM	NM	NM	951.4%	NM	NM	NM	NM	238.1%	41.4%	25.4%	41.7%
% of sales	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Total operating expenses	**0.5**	**0.2**	**1.1**	**1.6**	**3.8**	**6.7**	**3.8**	**3.9**	**4.0**	**4.1**	**15.6**	**24.2**	**33.6**	**50.6**
% chg	NM	NM	NM	NM	NM	1292.2%	NM	241.9%	143.8%	8.0%	132.6%	55.1%	39.0%	50.5%
% of sales	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Operating income (loss)	**(0.5)**	**(0.2)**	**(1.1)**	**(1.6)**	**(3.8)**	**(6.7)**	**(3.8)**	**(3.9)**	**(4.0)**	**(4.1)**	**(15.6)**	**(24.2)**	**(33.6)**	**(50.6)**
% chg	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
% of sales	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
bp chg	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
EBITDA	**(0.5)**	**(0.2)**	**(1.1)**	**(1.6)**	**(3.8)**	**(6.7)**	**(3.8)**	**(3.9)**	**(4.0)**	**(4.1)**	**(15.6)**	**(24.1)**	**(33.5)**	**(49.9)**
% chg	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
% of sales	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
D&A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.7
Total other income/(expenses)	**0.0**	**(3.1)**	**(0.7)**	**(0.0)**	**(1.1)**	**(4.9)**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Pre-tax income (loss)	**(0.5)**	**(3.4)**	**(1.8)**	**(1.7)**	**(4.8)**	**(11.7)**	**(3.8)**	**(3.9)**	**(4.0)**	**(4.1)**	**(15.6)**	**(24.2)**	**(33.6)**	**(50.6)**
% chg	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
% of sales	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Taxes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tax rate	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
IFRS net income (loss)	**(0.5)**	**(3.4)**	**(1.8)**	**(1.7)**	**(4.8)**	**(11.7)**	**(3.8)**	**(3.9)**	**(4.0)**	**(4.1)**	**(15.6)**	**(24.2)**	**(33.6)**	**(50.6)**
% chg	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
% of sales	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
IFRS EPS	**($0.03)**	**($0.12)**	**($0.03)**	**($0.02)**	**($0.06)**	**($0.20)**	**($0.05)**	**($0.04)**	**($0.04)**	**($0.04)**	**($0.16)**	**($0.18)**	**($0.17)**	**($0.16)**
% chg	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Shares outstanding	14.3	27.4	54.2	67.3	81.7	57.7	82.2	98.6	99.1	115.5	98.9	134.8	200.9	320.6

Source: Company filings, H.C. Wainwright & Co. estimates

C$ in millions, unless otherwise noted

	Jun-20	Sep-20	Dec-20	Mar-21	Jun-21	Jun-21	Sep-21	Dec-21	Mar-22	Jun-22	Jun-22	Jun-23		
	F2020A	**F1Q21A**	**F2Q21A**	**F3Q21A**	**F4Q21A**	**F2021A**	**F1Q22E**	**F2Q22E**	**F3Q22E**	**F4Q22E**	**F2022E**	**F2023E**	**F2024E**	**F2025E**
Net income (loss)	**(0.5)**	**(3.4)**	**(1.8)**	**(1.7)**	**(4.8)**	**(11.7)**	**(3.8)**	**(3.9)**	**(4.0)**	**(4.1)**	**(15.6)**	**(24.2)**	**(33.6)**	**(50.6)**
Depreciation and amortization	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.7
Change in fair value of convertible debentures	0.0	0.0	0.3	(0.1)	(0.1)	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Accretion of lease liabilities	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Depreciation of right-of-use assets	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Reverse takeover transaction cost	0.0	3.1	0.0	0.0	0.0	3.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Share-based compensation	0.2	0.0	0.4	0.0	1.6	2.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
All other	0.0	0.0	0.0	0.0	(0.0)	(0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Changes in working capital														
Inventories	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Receivable and other assets	0.0	0.0	(0.4)	(1.1)	(1.1)	(2.6)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
HST recoverable	(0.0)	(0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other assets	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Prepaid expenses - non-current	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Trade and other payables	0.1	0.0	0.2	(0.1)	0.5	0.7	0.2	0.2	0.2	0.2	0.8	0.8	1.0	1.0
Total changes in working capital	**0.1**	**(0.0)**	**(0.1)**	**(1.2)**	**(0.6)**	**(1.9)**	**0.2**	**0.2**	**0.2**	**0.2**	**0.8**	**0.8**	**1.0**	**1.0**
Cash from operating activities	**(0.2)**	**(0.2)**	**(1.3)**	**(2.9)**	**(3.9)**	**(8.4)**	**(3.6)**	**(3.7)**	**(3.8)**	**(3.9)**	**(14.8)**	**(23.3)**	**(32.5)**	**(48.9)**
Cash acquired from reverse takeover transaction	0.0	1.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Proceeds from sale of marketable securities	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Purchases of intagible assets	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Purchases of property and equipment	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	(1.0)	(4.0)	(7.0)
Cash from investing activities	**0.0**	**1.0**	**0.0**	**0.0**	**0.0**	**1.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**(1.0)**	**(4.0)**	**(7.0)**
Proceeds, IPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Payments of IPO costs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Convertible debenture	0.0	0.0	0.4	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Payments made to lease liability	0.0	0.0	0.0	(0.0)	(0.0)	(0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Proceeds from shares to be issued	0.0	0.0	0.0	0.2	(0.2)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Proceeds, offering of shares, net	0.8	0.0	4.6	0.9	6.8	12.3	0.0	9.5	0.0	9.5	19.0	28.5	47.5	95.0
Proceeds from exercise of warrants, net	0.0	0.0	0.0	0.0	0.7	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Proceeds, exercise of stock options, net	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
All others	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cash from financing activities	**0.8**	**0.0**	**5.0**	**1.1**	**7.3**	**13.4**	**0.0**	**9.5**	**0.0**	**9.5**	**19.0**	**28.5**	**47.5**	**95.0**
Net changes in cash	0.5	0.8	3.7	(1.8)	3.3	6.0	(3.6)	5.8	(3.8)	5.6	4.2	4.2	11.0	39.1
Beginning cash and equivalents	0.0	0.5	1.4	5.0	3.2	0.5	6.6	3.0	8.9	5.1	6.6	10.8	14.9	25.9
Effect of exchange rate changes.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Less: Restricted cash	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Ending cash and equivalents	**0.5**	**1.4**	**5.0**	**3.2**	**6.6**	**6.6**	**3.0**	**8.9**	**5.1**	**10.8**	**10.8**	**14.9**	**25.9**	**65.0**
Free cash flow	**(0.2)**	**(0.2)**	**(1.3)**	**(2.9)**	**(3.9)**	**(8.4)**	**(3.6)**	**(3.7)**	**(3.8)**	**(3.9)**	**(14.8)**	**(24.3)**	**(36.5)**	**(55.9)**
FCF/share	($0.01)	($0.01)	($0.02)	($0.04)	($0.05)	($0.15)	($0.04)	($0.04)	($0.04)	($0.03)	($0.15)	($0.18)	($0.18)	($0.17)

Source: Company filings, H.C. Wainwright & Co. estimates

C$ in millions, unless otherwise noted

	Jun-20	Sep-20	Dec-20	Mar-21	Jun-21	Jun-21	Sep-21	Dec-21	Mar-22	Jun-22	Jun-22	Jun-23		
	F2020A	**F1Q21A**	**F2Q21A**	**F3Q21A**	**F4Q21A**	**F2021A**	**F1Q22E**	**F2Q22E**	**F3Q22E**	**F4Q22E**	**F2022E**	**F2023E**	**F2024E**	**F2025E**
Cash and cash equivalents	0.5	1.4	5.0	3.2	6.6	6.6	3.0	8.9	5.1	10.8	10.8	14.9	25.9	65.0
Marketable securities	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Inventories	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Receivable and other assets	0.0	0.0	0.4	1.5	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3
HST recoverable	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other assets	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total current assets	**0.6**	**1.4**	**5.5**	**4.8**	**9.9**	**9.9**	**6.3**	**12.2**	**8.4**	**14.1**	**14.1**	**18.2**	**29.2**	**68.3**
Property and equipment, net	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.9	4.8	11.1
Intangible assets, net	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Right of use asset	0.0	0.0	0.0	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Prepaid expenses - non-current	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total assets	**0.6**	**1.4**	**5.5**	**5.0**	**10.1**	**10.1**	**6.5**	**12.4**	**8.6**	**14.3**	**14.3**	**19.4**	**34.2**	**79.6**
Trade and other payables	0.1	0.1	0.4	0.3	0.4	0.4	0.6	0.8	1.0	1.2	1.2	2.0	3.0	4.0
Current portion of lease obligation	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Convertible debenture	0.0	0.0	0.7	0.6	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total current liabilities	**0.1**	**0.1**	**1.0**	**0.9**	**0.9**	**0.9**	**1.1**	**1.3**	**1.5**	**1.7**	**1.7**	**2.5**	**3.5**	**4.5**
Lease liability	0.0	0.0	0.0	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Total liabilities	**0.1**	**0.1**	**1.0**	**1.1**	**1.1**	**1.1**	**1.3**	**1.5**	**1.7**	**1.9**	**1.9**	**2.7**	**3.7**	**4.7**
Share capital	0.8	3.7	6.6	8.1	13.2	13.2	13.2	13.2	13.2	13.2	13.2	13.2	13.2	13.2
Additional paid-in capital	0.0	0.0	0.0	0.0	0.0	0.0	0.0	9.5	9.5	19.0	19.0	47.5	95.0	190.0
Shares to be issued	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Contributed surplus	0.2	1.4	3.5	2.9	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
Accumulated deficit	(0.5)	(3.8)	(5.7)	(7.3)	(12.1)	(12.1)	(15.9)	(19.7)	(23.7)	(27.7)	(27.7)	(51.9)	(85.6)	(136.2)
Total stockholders' equity (deficit)	**0.5**	**1.3**	**4.4**	**3.9**	**9.0**	**9.0**	**5.3**	**10.9**	**7.0**	**12.4**	**12.4**	**16.7**	**30.6**	**74.9**
Total liabilities + stockholders' equity	**0.6**	**1.4**	**5.5**	**5.0**	**10.1**	**10.1**	**6.5**	**12.4**	**8.6**	**14.3**	**14.3**	**19.4**	**34.2**	**79.6**

Source: Company filings, H.C. Wainwright & Co. estimates

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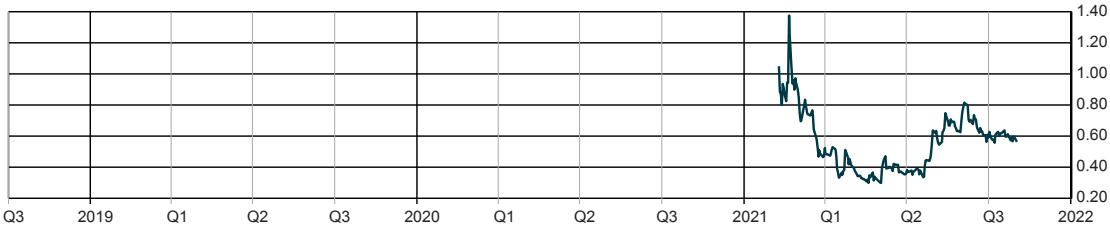
RETURN ASSESSMENT

Market Outperform (Buy): The common stock of the company is expected to outperform a passive index comprised of all the common stock of companies within the same sector.

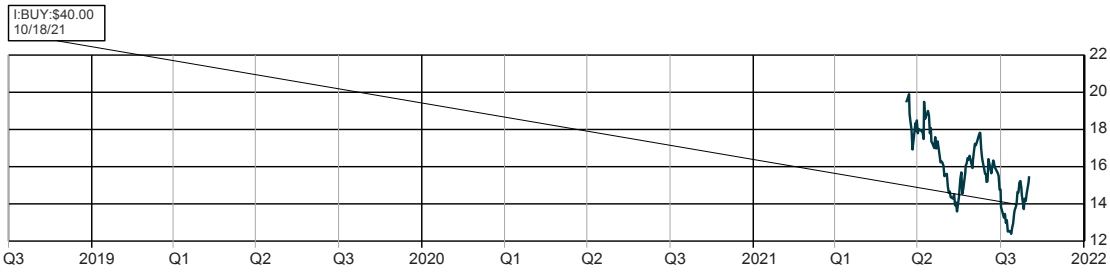
Market Perform (Neutral): The common stock of the company is expected to mimic the performance of a passive index comprised of all the common stock of companies within the same sector.

Market Underperform (Sell): The common stock of the company is expected to underperform a passive index comprised of all the common stock of companies within the same sector.

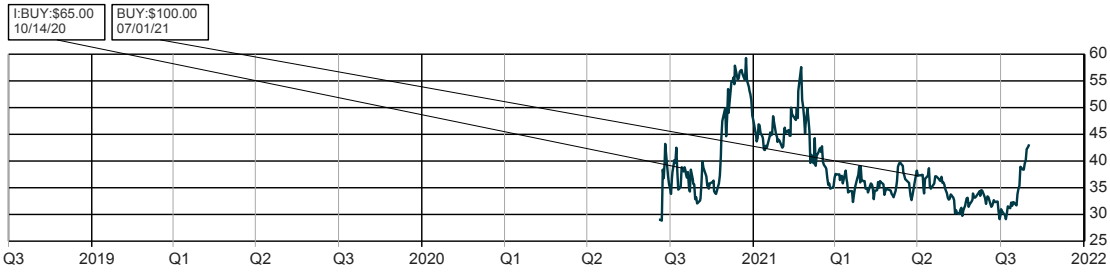
Rating and Price Target History for: Mindset Pharma Inc. (MSSTF-US) as of 11-01-2021



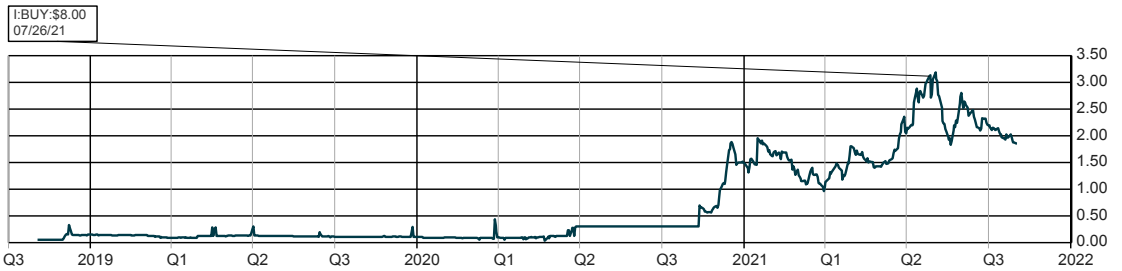
Rating and Price Target History for: Atai Life Sciences N.V. (ATAI-US) as of 11-01-2021



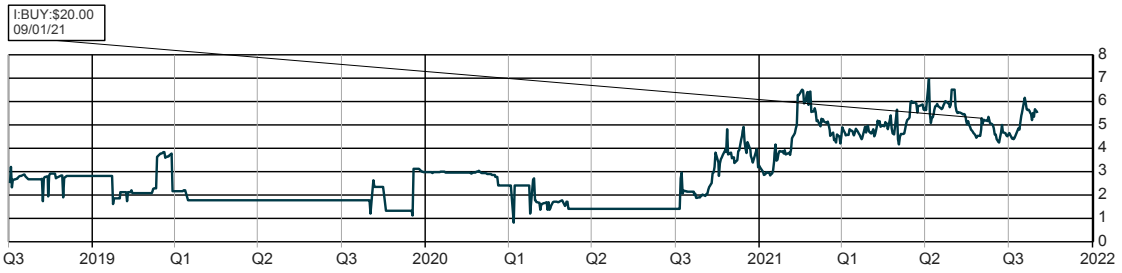
Rating and Price Target History for: COMPASS Pathways Plc (CMPS-US) as of 11-01-2021



Rating and Price Target History for: Cybin Inc. (CYBN-US) as of 11-01-2021



Rating and Price Target History for: Field Trip Health Ltd. (FTRP-US) as of 11-01-2021



Related Companies Mentioned in this Report as of Nov/02/2021					
Company	Ticker	H.C. Wainwright Rating	12 Month Price Target	Price	Market Cap
Atai Life Sciences N.V.	ATAI	Buy	$40.00	$15.52	$2632
COMPASS Pathways Plc	CMPS	Buy	$100.00	$43.06	$1870
Cybin Inc.	CYBN	Buy	$8.00	$1.85	$300
Field Trip Health Ltd.	FTRP	Buy	$20.00	$5.50	$313

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Distribution of Ratings Table as of November 1, 2021				
			IB Service/Past 12 Months	
Ratings	Count	Percent	Count	Percent
Buy	543	90.20%	199	36.65%
Neutral	55	9.14%	14	25.45%
Sell	1	0.17%	0	0.00%
Under Review	3	0.50%	1	33.33%

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