NRx Pharmaceuticals, Inc.
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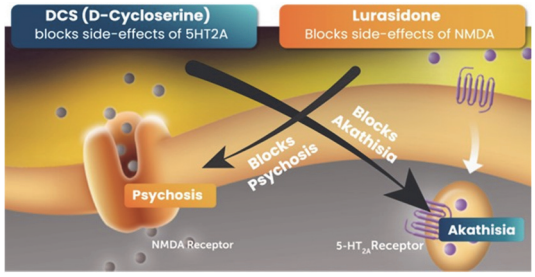
Ticker (Exchange)	NRXP-NASDAQ
Recent Price (12/01/2023)	$0.344
52-week Range	$0.22 - 1.51
Shares Outstanding	81.9 mm
Market Capitalization	$28.2 mm
Average 10-day volume	259,600
Insider Ownership +>5%	22.3%
Institutional Ownership	5%
EPS (Qtr. ended 09/30/2023)	($0.07)
Employees	10

NRx Pharmaceuticals, Inc. (NRXP-NASDAQ)
One-year Stock Chart

DCS-LURASIDONE INTERACTION



COMPANY DESCRIPTION

NRx Pharmaceuticals, Inc. ("NRx" or "the Company") is a clinical stage biopharmaceutical company developing novel therapeutics for the treatment of central nervous system disorders with high unmet medical needs. The Company's foundation product is NRX-101, a patented combination of two FDA-approved drugs—**D-cycloserine (DCS)†**, an **NMDA** receptor modulator; and **lurasidone**, an atypical antipsychotic medication. The Company is assessing the use of NRX-101 in four different indications: suicidal **bipolar depression**, chronic pain, **post-traumatic stress disorder (PTSD)**, and **complicated urinary tract infections (cUTI)**. Development of NMDA antagonists, such as DCS, as antidepressants has been limited by their potential **psychedelic** side effects. Furthermore, **serotonin**-targeted drugs like lurasidone have been limited by their own behavioral side effects, specifically **akathisia**. Professor Daniel Javitt (NRx Co-founder and Chair of its Scientific Advisory) made the simultaneous discovery that: (1) the psychedelic effects of NMDA antagonist drugs could be reversed by combining them with serotonin-targeted compounds; and (2) NMDA inhibitors, in turn, block the akathisia side effect normally associated with serotonin-targeted drugs. The previously undiscovered synergy between these two drug classes is the subject of 48 issued patents and 43 pending patents owned by or licensed to NRx Pharmaceuticals, and as such, is the medical and scientific basis for the Company's technology platform.

KEY POINTS

- NRx entered into a collaboration with Alvogen Pharmaceuticals for the development and commercialization of NRX-101 in suicidal bipolar depression, with the potential for up to $330 million in milestones and double-digit royalties.
- NRx is conducting a single Phase 2b/3 trial of NRX-101 for **Suicidal Treatment Resistant Bipolar Depression (S-TRBD)**, with topline clinical data readout expected by Q1 2024, potentially followed by an NDA application shortly thereafter.
- Under the Alvogen agreement, a successful data readout and completion of a **Type B meeting** with the FDA would trigger a $10 million payment to NRx, at which point, Alvogen would be responsible for all future development and commercialization costs for this indication.
- NRX-101 is also being evaluated for the treatment of chronic pain as a non-addictive substitute for **opioid** products. The Company is planning to start a pharmacokinetic study following result readout of a 200-person U.S. Department of Defense-funded trial in treating chronic pain with DCS.
- NRx is assessing plans to create spinoff companies to complete development of NRX-100 (IV **ketamine**) for acute suicidality and NRX-101 for cUTI, which would potentially provide investors with both capital appreciation and a royalty stream.
- As of September 30, 2023, NRx's cash and cash equivalent position was $8.9 million.

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Executive Overview

NRx Pharmaceuticals, Inc. ("NRx" or "the Company") is a clinical stage biopharmaceutical company developing breakthrough therapeutics for the treatment of life-threatening central nervous system (CNS) disorders with high unmet medical needs. The Company's technology platform targets the brain's N-methyl-D-aspartate (NMDA) receptors for the development of novel therapeutics in the areas of suicidal bipolar depression, chronic pain, post-traumatic stress disorder (PTSD), and complicated urinary tract infections (cUTI).

The Company's focus is on the development of therapeutic product candidates for the treatment of psychiatric diseases modulated by NMDA receptors. NMDA receptors play a crucial role in regulating a wide variety of neurological functions, including breathing, locomotion, learning, memory formation, and **neuroplasticity**. Because of this, they are the target of both therapeutic drugs and drugs of abuse. One such example is ketamine, an NMDA antagonist used as a sedative, anesthetic, off-label as an antidepressant, or recreationally as a hallucinogenic drug of abuse. Another NMDA modulator is D-cycloserine (DCS), an anti-infective originally developed for the treatment of tuberculosis, but found to have potent antidepressant capabilities. However, anecdotal reports suggest that high doses of DCS, ketamine, and other NMDA antagonists can cause psychedelic side effects, which is a potential barrier for at-home therapy.

The Company's foundation product—NRX-101—is a patented oral combination of two FDA-approved drugs: D-cycloserine (DCS), an NMDA receptor modulator; and lurasidone, a serotonin-targeted medication used in the treatment of schizophrenia and bipolar depression. NRX-101 was developed based on 30 years of research conducted by Professor Daniel Javitt (NRx Co-founder and Chair of its Scientific Advisory), related to the role of NMDA receptors in regulating human thought processes, depression, and suicidality.

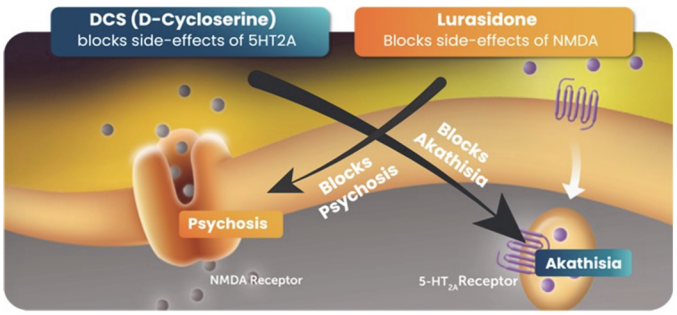
Dual Mechanism of Action–Key Discovery

Development of DCS as an antidepressant has been limited by its potential side effects. However, Professor Daniel Javitt of Columbia University discovered that the psychedelic effects of NMDA drugs could be reversed by combining them with serotonin-targeted drugs, such as lurasidone. Furthermore, a major limitation in the use of serotonin-targeted drugs is its own behavioral side effects, specifically akathisia (a state of agitation, distress, and restlessness associated with generating or exacerbating suicidality in psychotic or depressed patients). Professor Javitt made the simultaneous discovery that NMDA inhibitors, in turn, block the akathisia side effect normally experienced with the use of serotonin-targeted drugs. When administered together, DCS and lurasidone appear to mitigate the most common side effects of the other: lurasidone reduces the risk of psychosis and mania while DCS reduces the occurrence of akathisia (Source: Authorea's *D-Cycloserine for the Treatment Of Chronic Pain*, 2023).

The previously undiscovered synergy between these two drug classes in the treatment of CNS disorders, as illustrated in Figure 1, combined with the efficacy of DCS in the treatment of depression and PTSD, is the subject of 48 issued patents and more than 43 pending patents owned by or licensed to NRx Pharmaceuticals, and as such, is the medical and scientific basis for the Company's technology platform.

Figure 1

DCS - LURASIDONE INTERACTION



Source: NRx Pharmaceuticals, Inc.

NRX-101 Overview

The Company's growing pipeline is powered by its proprietary NRX-101 product candidate (DCS/lurasidone), which NRx is assessing in four different indications: suicidal bipolar depression, chronic pain, post-traumatic stress disorder (PTSD), and complicated urinary tract infections (cUTI).

DCS is a broad-spectrum antibiotic discovered in 1954 and approved for the treatment of tuberculosis. Although its initial development and current use is limited by DCS' potential psychedelic effects, it continues to be used worldwide by the World Health Organization (WHO) primarily for the treatment of tuberculosis. In addition to its anti-infective activity, DCS was discovered to also act as an NMDA antagonist when used at high doses (> 500 mg). Based on this discovery, Professor Javitt and his research partner patented the use of DCS to treat depression. Multiple exploratory clinical studies have demonstrated that administration of DCS can trigger an antidepressant effect, as well as maintain a reduced level of suicidality.

A key factor that makes DCS a potentially attractive oral antidepressant candidate is that, unlike ketamine and other NMDA antagonists, it has shown no potential for addiction or abuse. In addition, the Company believes that since DCS has been used extensively as an antibacterial agent without significant safety concerns this may facilitate regulatory approval since available medications have already undergone the FDA approval process and are able to circumvent testing cycles that are traditionally both costly and protracted.

Manufacturing Capabilities

NRx has completed the transfer of its Phase 3-level commercial drug manufacturing processes to the U.S. The Company has submitted its manufacturing file to the FDA and has completed **Good Manufacturing Practices (GMP)** of all clinical supplies required for its ongoing clinical trials, resulting in 1 million capsules on hand. The completion of this manufacturing milestone allows the Company to decrease ongoing expenditures associated with manufacturing and development of chemical manufacturing controls, and can also accelerate the development of its product candidates as NRx can commence Phase 3 studies without the need to wait for manufacturing readiness.

Bipolar Depression with Suicidality Program

NRx's most advanced program is the use of NRX-101 on bipolar depression with suicidality. NRX-101 is currently in a Phase 2b/3 clinical trial for Suicidal Treatment-resistant Bipolar Depression (S-TRBD), an indication for which the only approved treatment is electroshock therapy. NRX-101 has been awarded **Fast Track designation, Breakthrough Therapy designation,** a **Special Protocol Agreement,** and a **Biomarker Letter of Support** by the FDA, as it aims to be the first oral therapeutic for the treatment of bipolar depression with suicidality.

Bipolar Depression Overview

Bipolar disorder is a mental illness characterized by dramatic shifts in mood, energy, and activity levels that affect a person's ability to think clearly and carry out day-to-day tasks. People with bipolar disorder experience extreme high (mania) and low (depression) moods, the latter of which is associated with suicidal ideation. Patients with bipolar depression are 10 to 30 times more likely to attempt suicide than the general population, with 20% to 60% of them attempting suicide at least once in their lifetime, and between 11% to 20% of bipolar disorder subjects ending their life by suicide (Sources: *Medicina, Vol. 55(8): 403*, 2019, and *Bipolar Disorders, Vol.19: 13-22*, 2017).

Patients who suffer from bipolar depression with **acute suicidal ideation or behavior (ASIB)** (i.e., patients with strong suicidal thoughts, which require stabilization of symptoms in a clinical setting) are first treated, often with ketamine or sedating drugs, to reduce the risk of self-harm. These drugs have only short-term effects, and a stable, non-psychedelic drug is needed to reduce symptoms of depression and suicidal ideation over the long term. Patients with suicidal bipolar depression who are not at immediate risk of self-harm—**sub-acute suicidal ideation or behavior (SSIB)**—are typically treated in an outpatient setting. Between 700,000 and 1 million patients with suicidal bipolar depression are currently in need of treatment in the U.S. alone. The global market for bipolar disorder therapeutics was estimated at $5.9 billion in the year 2022 and is projected to reach $7.8 billion by 2030.

Depression and Suicidality

A key factor in the newly found interest of NMDA antagonists as therapeutic agents is the fact that multiple studies have demonstrated that NMDA antagonists directly inhibit suicidal thoughts, an effect that is distinct from their antidepressant effect. Experts now concur that suicidal ideation, although present in psychiatric disorders such as bipolar depression, PTSD, and **major depressive disorder (MDD)**, should be thought of as a distinct therapeutic target, with the FDA listing suicidal ideation as a separate and independent medical indication.

The Company believes that its focus on suicidality and bipolar depression provides a competitive advantage, as suicidal bipolar depression has not been specifically addressed by pharmaceutical companies, as there are no FDA-approved medicines available for this condition. To the Company's knowledge, NRX-101 is the only oral treatment in development for suicidal ideation in bipolar patients. Clinical trials for bipolar depression either exclude patients with active suicidal ideation, or if suicidal ideation is targeted, exclude bipolar depression, in whom the incidence of suicidal ideation is the highest.

Alvogen Collaboration Agreement

On June 2, 2023, the Company entered into an exclusive global collaboration and license agreement with Alvogen, Inc. (a privately held pharmaceutical company) and Lotus Pharmaceutical Co. Ltd. (an international pharmaceutical company), granting Alvogen an exclusive worldwide license to develop and commercialize NRX-101 for the treatment of bipolar depression with suicidality, as well as a right of first negotiation for other indications and/or potential new products combining DCS with an antidepressant/antipsychotic agent.

NRx is eligible to receive up to $330 million in milestone payments tied to development progress as well as royalty payments. Under the terms of the agreement, NRx is entitled to receive an initial payment of $10 million upon achieving both a successful read-out from the ongoing Phase 2b/3 clinical trial in S-TRB and completion of a Type B meeting with the FDA (expected by Q1 2024), at which point Alvogen will be responsible for all future development, regulatory, and commercialization costs of NRX-101 for this indication.

According to NRx, the Alvogen collaboration provides significant financial and strategic advantages that minimizes the need for future capital raises, as it generates a significant capital influx prior to FDA approval of NRX-101 and eliminates future financial obligations for the Company related to the development, regulatory, and commercialization costs of NRX-101 in bipolar depression indications.

Clinical Development

NRX-101 is currently in a Phase 2b/3 clinical trial for suicidal treatment resistant bipolar depression (S-TRBD). NRX-101 has been granted Fast Track designation, Breakthrough Therapy designation, a Biomarker Letter of Support, and a Special Protocol Agreement by the FDA in bipolar depression with suicidality.

Following positive data from its proof-of-concept STABIL-B Phase 2 study on the use of NRX-101 for bipolar depression with ASIB, which demonstrated a statistically significant benefit of NRX-101 vs. lurasidone in maintaining improvement in depression and suicidal ideation, the Company initiated parallel Phase 2b/3 studies on patients with both bipolar depression with ASIB (stabilized with Ketamine), as well as patients with bipolar depression with SSIB (in an outpatient setting).

During meetings for both trials, the FDA suggested to enroll patients for the ASIB study only after stabilization. The design of this new trial would effectively converge with the SSIB trial. Based on these recommendations, the Company plans to consolidate patients originally expected to enroll in the ASIB study into the SSIB trial and changed the indication to Suicidal Treatment-Resistant Bipolar Depression (S-TRBD), including both patients with ASIB and SSIB, expanding its indication reach to the estimated 700,000 and 1,000,000 people with this condition. Top-line data from this trial is expected in Q1 2024. Following a successful readout, Alvogen will assume further development costs, with the Company planning to file a **New Drug Application (NDA)** as soon as possible thereafter.

Clinical Development of NRX-100 (IV Ketamine) in Acute Suicidality

When NRx met with the FDA in January 2023, the agency encouraged the Company to develop NRX-100 (ketamine) as a labeled drug, rather than rely on prior stabilization of suicidality and depression achieved via the common clinical practice of infusing generic ketamine compounded in licensed pharmacies.

Ketamine has been shown in multiple randomized clinical trials to induce nearly immediate short-term remission from depressive symptoms and from suicidal ideation. Despite the promising clinical findings, and its widely off-label used in clinical settings for the treatment of acute suicidality, ketamine is not approved by the FDA for these indications. As stipulated by the FDA, if NRx's study on patients with bipolar depression and ASIB is to be driven primarily by subjects stabilized with ketamine (as originally designed), an NDA for ketamine would also be required.

Ketamine Data Sharing Agreement

In order to facilitate its NDA application for ketamine, the Company has signed a data sharing agreement with the study leadership of a placebo-controlled trial of ketamine on 156 patients hospitalized for acute suicidality and depression in seven French Government Hospitals (the KETIS trial). Top line data from this trial, published in the British Medical Journal (*BMJ Vol. 376,* 2022), demonstrated a dramatic and statistically significant reduction in suicidal ideation among patients treated with intravenous ketamine, compared to those on placebo. Under the data sharing agreement, NRx has translated the clinical study report, which will be submitted to the FDA, and is converting the electronic, patient level data files to a form suitable for FDA review.

The Company is now in the process of negotiating access to similar patient-level data from a National Institutes of Health (NIH)-funded U.S.-based clinical trial, the findings of which confirm the KETIS trial's results. NRx believes that these multicenter, randomized prospective trials could be sufficient to demonstrate preliminary safety and efficacy of intravenous ketamine in acutely suicidal patients.

Furthermore, on November 6, 2023, the Company announced a development and manufacturing agreement with Nephron Pharmaceuticals, Inc., to develop and manufacture a presentation of ketamine suitable for treating suicidal depression. The Company believes that this agreement, which encompasses GMP manufacturing capabilities, together with the data sharing agreement described above, provides NRx with the necessary requirements for a submission of an NDA for ketamine. The Company's current timeline projects submission of an NDA for ketamine in Q1 2024 with a targeted **Prescription Drug User Fee Act (PDUFA)** date in Q4 2024.

Establishment of a Ketamine-Focused Spinoff Company

According to the Company's business update (November 13, 2023), NRx does not anticipate funding this initiative with its core Company assets and plans to establish a ketamine-focused spinoff company that would potentially provide current and new investors with both capital appreciation and a royalty stream. A term sheet for up to $30 million in anchor financing for a new public entity has been presented to management by a capable investor in a structure where a portion of the equity in the ketamine asset will be allocated to existing shareholders.

Chronic Pain Program

NRX-101 is also being evaluated for the treatment of chronic pain, as a possible non-addicting substitute of opioid products. This program is based on new academic and pre-clinical research showing that NMDA receptors are active at each step of the pain pathway.

Chronic pain—pain persisting or recurring for longer than three months—affects an estimated 20% of the world's population and accounts for nearly one fifth of physician visits. For many chronic pain conditions, the standard of care is the long-term use of analgesics that were originally developed for acute pain, including opioids. The misuse of opioids and its addiction are a serious national crisis that affects public health, with the majority of drug overdose deaths in the U.S., over 75% of the nearly 107,000 in 2021, involving an opioid (Source: CDC's *Understanding the Opioid Overdose Epidemic*). Despite this, few effective non-addictive alternatives to opiates have emerged. The

current opioid crisis, fueled by a failure of non-opioid medication to achieve meaningful clinical relief, creates an acute need for nonaddictive, non-sedating pain medications.

The global chronic pain market was valued at $69.1 billion in 2021 and is expected to reach $140.5 billion by 2030. This growth is driven by an aging population, the prevalence of chronic diseases like diabetes, cancer, neuropathy, multiple sclerosis, and osteoarthritis, as well as an increase in opioid use (Source: *Spherical Insights' Global Chronic Pain Market Size, Share,* and *COVID-19 Impact Analysis and Forecast*, 2023).

Clinical Trails

NRx is awaiting results of a 200-person Phase 2 trial funded by the U.S. Department of Defense (DOD) on the use of DCS in patients with chronic lower back pain, which the Company believes would act as a proof-of-concept study for the use of DCS in chronic pain patients.

In anticipation of these findings, the Company established an **Investigational New Drug (IND)** file for NRX-101 in the treatment of chronic pain. On October 2, 2023, the FDA gave the Company clearance to proceed with pharmacokinetic and human trials under the newly established IND. With this alignment in place and with the current inventory of manufactured NRX-101 on hand for clinical trial use, the Company plans to initiate registrational studies in 2024. Based on the preliminary evidence of efficacy already demonstrated for the use of DCS in chronic pain, NRx plans to seek Fast Track Designation, Priority Review, and Breakthrough Therapy Designation for this critical indication while awaiting near-term results of the DOD-funded trial.

NRx has submitted NRX-101 for consideration by the multibillion dollar **HEAL initiative (HEAL)** and its national consortium of clinical trial sites (EPPICNET), an initiative funded by the U.S. Congress to test innovative non-opioid medicines for chronic pain. The Company believes that NRX-101 represents the first NMDA-targeted non-addictive medicine to be presented to this program. Should the DOD-funded trial yield encouraging data, the Company anticipates that non-dilutive sources of capital will be available, given the national focus on the opioid crisis. Progress in treating chronic pain with NRX-101 may open a far larger market for NRX-101 than the originally targeted psychiatry indications.

Post Traumatic Stress Disorder (PTSD) Program

In September 2022, NRx announced plans to investigate NRX-101 in PTSD. PTSD is a mental health disorder that develops when a person has experienced or witnessed a traumatic, life-threatening, terrifying, or dangerous event. People with PTSD have intense, disturbing recurrent memories of the traumatic event (flashbacks) and negative thoughts related to their experience that last more than a month after the traumatic event has ended, and are severe enough to interfere with school, work, or relationships. Unlike other anxiety disorders, PTSD is significantly associated with depression and suicidal ideation, with people who have PTSD three to five times more likely to have a depressive disorder, as depression in PTSD may be driven by pathways that are similar to those that drive depression in other conditions.

NRx conducted a preclinical study to assess the effects of NRX-101 and high-dose DCS on **fear memory** extinction in rodents. Memory or fear extinction is a process in which a conditioned response gradually diminishes over time as the subject learns to uncouple a response from a stimulus. It is a process that could result in a significant improvement in PTSD symptoms. Both NRX-101 and DCS administration demonstrated the ability to enhance fear memory extinction.

Complicated Urinary Tract Infections (cUTI) Program

NRx is also evaluating NRX-101 for the treatment of complicated UTI (cUTI). The program is based on DCS' antibacterial properties. DCS is currently approved for the treatment of urinary tract infections in some countries and was demonstrated to be effective against pathogens that are increasingly resistant to first- and second-line antibiotics.

Urinary tract infections (UTIs) are the most common outpatient infections in the U.S., accounting for about seven million doctor visits, one million emergency department visits, and more than 100,000 hospitalizations each year (Source: Medstar Health). Although UTIs have been easily treated and cured with antibiotics for decades, in recent years, increased antibiotic resistance of common pathogens that cause urinary tract infections has resulted in a marked increase in hospitalization and death (i.e. cUTI). Complicated UTI is increasingly common in the U.S., with an estimated 3 million new diagnoses annually, making it one of the most common bacterial infections encountered in the hospital setting and among the most common causes of **sepsis** in hospitals (Source: *Forum Infectious Diseases' Vol. 6 (11)*, 2019).

The emergence of multiple drug-resistant organisms has prompted the investigation of older antimicrobials (such as DCS) as well as the development of a number of new antibiotics and combinations for the treatment of antibiotic resistance infections, including cUTIs. In preclinical testing, NRX-101 demonstrated a broad range of potent antibacterial effects against common antibiotic-resistant urinary pathogens in culture medium and in an artificial urine model. The study, commissioned by NRx at Charles River Laboratories (CRL), demonstrated NRX-101's potent *in vitro* activity against reference strains of urinary tract pathogens known to cause cUTIs. These results are consistent with previously reported academic studies that demonstrate potency of DCS in antibiotic-resistant strains of urinary pathogens.

Based on the *in vitro* study performed at CRL, the Company has submitted an IND application, requesting **Qualified Infectious Disease Product (QIDP)**, Fast Track, and Priority Review designation. FDA approval of this IND is expected by year-end 2023.

As with the NRX-100 development project, the Company does not anticipate funding this initiative with core NRx assets and is exploring structures for a new entity that would provide current and new investors with both capital appreciation and a royalty stream.

Cash Runway and Financing

The Company believes that its cash on hand is sufficient to fund operations through the delivery of its upcoming potential milestones, as described on pages 16-17. NRx is conducting key initiatives to minimize the need to utilize current financial assets to continue the development of its different programs, including: (1) funding of ketamine-related and cUTI-related initiatives under new entities (spinoffs) with alternative financing; (2) seeking non-dilutive sources of capital for its chronic pain program, such as its submission for consideration to the HEAL initiative (HEAL), based on the national focus on the opioid crisis; and (3) the significant capital influx prior to FDA approval of NRX-101 resulting from the Alvogen agreement.

CORPORATE INFORMATION (HEADQUARTERS, EMPLOYEES, AND HISTORY)

On May 24, 2021, Big Rock Partners Acquisition Group (BRPA), a special purpose acquisition company, consummated a Plan of Merger with NeuroRx, Inc., a Delaware corporation, and Big Rock Merger Corp., a Delaware corporation and wholly-owned subsidiary of BRPA. Pursuant to the agreement, BRPA changed its name to NRX Pharmaceuticals, Inc. NRx currently employs 10 individuals and is headquartered in Wilmington, Delaware.

Intellectual Property

The Company's intellectual property (IP) portfolio includes robust Composition of Matter patent protection, encompassing five patent families, and including 48 issued and 43 pending patents. The portfolio protects the Company's lead investigational candidate—NRX-101—to at least 2033, covering therapeutic applications for bipolar depression, chronic pain, and PTSD, among others.

NRx's IP protection also includes additional combinations of NMDA antagonists, currently approved antidepressants, and additional 5-**HT2A** antagonists, including dextromethorphan, d-methadone, and S-ketamine, to be used for the treatment of the above conditions, as well as other CNS diseases, such as major depressive disorder (MDD), obsessive compulsive disorder, and other targets.

The Company's initial IP portfolio was acquired through licensing agreements with two entities: Glytech LLC, a Company founded by Professor Daniel Javitt (NRx Co-founder and Chair of its Scientific Advisory Board, biography on page 14); and the Sarah Herzog Memorial Hospital, in Jerusalem, Israel. The Company is required to make certain annual payments, as well as development-based and royalty-based payments to these entities as a result of these agreements.

Both of these IP license agreements grant the Company exclusive license to use technology to develop therapeutic products for the treatment of depression and suicide associated with bipolar disorders, including all products containing DCS (including structural variants) combined with an antidepressant agent or an antipsychotic agent (including but not limited to lurasidone), as well as DCS (including structural variants) for the treatment of all types of bipolar, depressive, and/or anxiety disorders.

Glytech Development and License Agreement

The Company was founded based upon a development agreement with Glytech (signed on August 6, 2015), by which Glytech granted to NRx irrevocable, perpetual, exclusive royalty-free licenses to certain technologies for the development of therapeutic compounds for the treatment of all types of bipolar, depressive, and/or anxiety disorders. The NRx/Glytech IP relationship includes full assignment of a key composition of matter patent (U.S. Patent No. 10,583,138) to NRx by Glytech in January 2021, which covers potential combinations of DCS, other NMDA antagonists, and antidepressant or antipsychotic agents.

Sarah Herzog Memorial Hospital License Agreement

The initial clinical trial of DCS was conducted by Drs. Uri Hersco-Levy and Daniel Javitt at the Sarah Herzog Memorial Hospital (SHMH) in Jerusalem and resulted in a patent owned by SHMH in which Heresco-Levy and Javitt share inventorship. The Company entered into an exclusive license agreement with SHMH, dated April 16, 2019, which grants NRx an exclusive license to U.S. Patent No. 9,789,093, and subsequently filed patent applications for the development of therapeutic products for the treatment of depression and suicide associated with bipolar disorders.

The IP assets initially transferred to NRx as part of these agreements are listed in Figure 2 (page 10). Subsequently, the Company has continued to expand its IP portfolio, including these two key initiatives: (1) obtained license of newly issued U.S. patent No. 11,576,911 from Glytech. The claims of the new patent cover methods for treating a patient suffering from depression, including bipolar depression or major depression, with or without suicidality by administering to the patient an effective amount of the Company's lead product candidate NRX-101; (2) signed a license agreement for U.S. Patent 8,653,120 that claims the use of DCS for the treatment of chronic pain. The Company also signed an agreement with Dr. Vania Apkarian, Professor of Physiology, Anesthesia, Surgery, and Neuroscience Institute, at Northwestern University Feinberg School of Medicine (the inventor) to join NRx's Scientific Advisory Board (SAB).

Figure 2
NRx PATENT PORTFOLIO - AS OF MARCH 2023

Glytech-licensed Patents/Patent Applications		
Jurisdiction	**Patent/Appl. No.**	**Status/Notes**
USA	9,737,531	Granted
USA	9,486,453	Granted
USA	10,660,887	Granted
European Patent Convention	EP 2 872 139	Granted; validated in France, Germany, Ireland, Italy,
European Patent Convention	EP 3 263 108	Netherlands, Poland, Portugal, Spain, Great Britain
Japan	JP 6416762	Granted
Australia	AU 2013288827	Granted
Australia	AU 2018203371	Granted
China	CN 104507477	Granted
China	CN 107875389	Granted
USA	16/166,101	Pending
Israel	IL 271371	Pending
USA	16/812,382	Pending
European Patent Convention	EP 18731195.6	Pending
Japan	JP 2019-568331	Pending
Canada	CA 3,067,162	Pending
Australia	AU 2018284335	Pending
Brazil	BR 11 2019 026449 3	Pending
China	CN 201880051813.X	Pending
Georgia	GE AP201815254	Pending
Mexico	MX/a/2019/015120	Pending
South Korea	KR 10-2020-7000844	Pending
South Africa	ZA 2019/08616	Granted
New Zealand	NZ 760542	Pending
Israel	IL 270916	Pending
USA	17/586,828	Pending
Japan	JP 2019-564867	Pending
Canada	CA 3,064,846	Pending
Australia	AU 2018274767	Pending
Brazil	BR 11 2019 024802-1	Pending
China	CN 201880048653.3	Pending
Georgia	GE AP201815247	Pending
Mexico	MX/a/2019/014113	Pending
South Korea	KR 10-2019-7038209	Pending
South Africa	ZA 2019/08617	Granted
New Zealand	NZ 760544	Pending

SHMH-licensed Patents and Patent Applications		
Jurisdiction	**Patent/Appl. No.**	**Status/Notes**
USA	9,789,093	Granted
Europe	EP 2 670 409	Granted; validated in Switzerland, Germany, Spain, France, Great Britain, Ireland, Italy, Netherlands
USA	17/502,606	Pending
USA	11,013,721	Granted
Canada	CA 2,826,180	Granted
Israel	IL 227611	Granted

NeuroRx-owned Patents and Patent Applications		
Jurisdiction	**Patent/Appl. No.**	**Status/Notes**
USA	10,583,138	Granted

Source: NRx Pharmaceuticals, Inc.

Company Leadership

NRx is led by a highly experienced management team with proven success in pharmaceutical research, development, and commercialization. Biographies of its management team and Board of Directors are provided in the accompanying section.

Management

Stephen Willard, Chief Executive Officer and Director

Mr. Willard brings a wealth of experience in the management of publicly-traded biotechnology companies, together with his background in law and finance. Most recently, he served as CEO of Cellphire Therapeutics, where he grew the company and shepherded their revolutionary human platelet platform through key clinical trials, growing the company and significantly increasing the share price. Prior to Cellphire, he served as CEO of publicly traded Flamel Technologies (now known as Avadel Pharmaceuticals). Mr. Willard is currently serving a six-year term from 2018-2024 as a presidential appointee to the National Science Board. Mr. Willard's career in financial services includes government service as Associate Director of the Federal Deposit Insurance Corporation (FDIC), where he served in the United States Senior Executive Service (SES) from 1991-1994, and on the board of E*TRADE Financial Services from 2000-2014. He has practiced law in New York, London, and Washington, D.C. Mr. Willard earned his undergraduate degree from Williams College and attended Yale University, where he earned a JD in law.

Jonathan C. Javitt, M.D., M.P.H., Chief Scientist, and Director

Dr. Javitt has been a founder of seven successful healthcare IT and biopharma startups with public exits. He has additionally led drug-development engagements for Merck, Allergan, Pharmacia, Novartis, and Pfizer. Dr. Javitt was appointed to healthcare leadership roles under Presidents Reagan, George H.W. Bush, Clinton, and George W. Bush. In the latter role, he was commissioned by President Bush to Chair the Health Committee of the President's Information Technology Advisory Committee (PITAC) and to lead the development of Executive Order 13335, establishing the Office of the National Coordinator for Health IT. In the aftermath of 9/11, Dr. Javitt was appointed a Senior Fellow in the National Security Health Policy Center of the Potomac Institute for Policy Studies to focus on biosecurity preparedness and appointed by President Bush to the Office of the Undersecretary of Defense. He is a graduate of Princeton University, Cornell University Medical College, Harvard School of Public Health, the Wills Eye Hospital, and Johns Hopkins School of Medicine. The Harvard Chan School awarded him the Alumnus of Merit award in 2016 and he continues to serve as Adjunct Professor of the Johns Hopkins School of Medicine. Dr. Javitt has published more than 200 scientific works in the areas of health outcomes and Pharmacoeconomics that have been cited by more than 32,000 scientists. In his role as Chief Scientist of NRx Pharmaceuticals, he continues to lead NRx on scientific matters to advance and expand the Company's pipeline of lifesaving medicines.

Richard Narido, Chief Financial Officer

As Interim Chief Financial Officer, Mr. Narido will serve as the Company's principal financial officer and principal accounting officer. Prior to his appointment as the Company's Interim Chief Financial Officer, Mr. Narido served and held various roles at Lucira Health from March 2021 to April 2023, including most recently as the Chief Financial Officer until Pfizer Inc.'s acquisition of Lucira in April 2023. From July 2018 to March 2021, Mr. Narido served in various roles at Assembly Biosciences, Inc., including most recently as Executive Director, Finance, Controllership and Treasury. From June 2014 to June 2018, Mr. Narido served in various roles at Bio-Rad Laboratories, Inc., including as Americas Head of Finance, Global Commercial Operations. Prior to June 2018, Mr. Narido held various finance roles, including Global Head Finance Reporting and Accounting for Novartis Vaccines and Diagnostics and several industry-related positions, including Business Unit Controller for McKesson Corporation. Mr. Narido started his career with PricewaterhouseCoopers's Financial Audit and Assurance practice. Mr. Narido holds a Bachelor of Science degree from the University of San Francisco and a Master of Science degree from the Pepperdine Graziadio Business School.

Rick Panicucci, Ph.D., Chief Technology Officer

Dr. Panicucci is currently the SVP of CMC at BridgeBio Pharma. Prior to joining BridgeBio, he served as VP of Pharmaceutical Development Services at WuXi STA, where he provided scientific leadership in formulation development and GMP manufacturing. From 2004 to 2015, Dr. Panicucci served as Global Head of Chemical and Pharmaceutical Profiling (CPP) at Novartis. His responsibilities included all small molecule therapeutics across the Novartis portfolio. He also led and developed novel drug delivery technologies for small molecules and biologics and has also led R&D groups at Vertex Pharmaceuticals, Symbollon Pharmaceuticals, Biogen, and Bausch & Lomb. Dr. Panicucci earned a Ph.D. in Chemistry from the University of Toronto and did a Post-Doctoral Fellowship at the University of California, Santa Barbara.

Matthew Duffy, Chief Business Officer

Mr. Duffy has more than thirty years' of experience as both a Healthcare and Wall Street executive. He has extensive drug development-to-market experience, including in CNS, beginning at Pfizer, Inc. in Sales Management and Marketing. He subsequently led drug commercialization activities at Medimmune (Synagis) as head of Marketing and Lev Pharmaceuticals (Cinryze) as head of Commercial Operations. Mr. Duffy has more than 20 years of experience as an investment banker, buy-side and sell-side equity research analyst, and Investor Relations professional. He was/is Managing Director at Roberts Mitani, LLC, at LifeSci Partners, LLC, at Laidlaw LTD (current), and co-founded Black Diamond Research, LLC, a sell-side equity research firm specializing in healthcare/biotechnology. He served on the Board of CorMedix, Inc. (CRMD-NASDAQ) and currently serves on the boards and/or management of Algorithm Sciences, Inc, Lucius Partners, LLC, Voltron Therapeutics, Inc, PD Theranostics, Inc., and AerWave Medical, Inc. Mr. Duffy received his undergraduate degree in Economics from Duke University. He holds Series 7, 63, and 65 securities licenses.

Martin Brecher, M.D., DMSc, MBA, Medical Director

Dr. Breche has more than 30 years of experience in psychiatric drug development and clinical psychiatry. He served as an FDA medical officer, where he led reviews of numerous psychiatry drugs, following which he led the development of novel psychiatry drugs for Hoechst Roussel (iloperidone), Janssen (risperidone), and AstraZenica (Seroquel). He subsequently served as Senior Medical Director for Global Product Development at PPD, a global contract research organization (CRO). He is a graduate of the Massachusetts Institute of Technology (BA), State University of New York, MD, and Wharton School of Management (MBA).

M. Daniel Gordin, Ph.D., Regulatory Affairs Officer

Dr. Gordin is an experienced professional in the field of global drug development with over 35 years of pharmaceutical development. He began his career at the Food and Drug Administration (FDA) as a Pharmacokinetic Reviewer for the Divisions of Neuropharmacology; Pilot Review; Surgical, Dental, and Radiopharmaceuticals; and Metabolism and Endocrine Drug Products, where he was recognized as an Expert Pharmacokinetic Reviewer for the lipid lowering class of drugs. In 1994, Dr. Gordin transitioned to the private sector, working for Leiras Pharmaceuticals, Otsuka, Synthélabo Research, Forest Laboratories, and Novartis Pharmaceuticals in Regulatory Affairs, where he was responsible for formulating and implementing regulatory strategies for the development of innovative pharmaceutical products in CNS, solid organ transplantation, autoimmune, pain, and infectious disease therapeutic areas. Before joining NRx, Dr. Gordin held a leadership position at Sunovion Pharmaceuticals, where he contributed to the development of regulatory strategy in the CNS therapeutic area. Dr. Gordin earned his doctoral degree from the Medical University of South Carolina.

Board of Directors

Patrick Flynn, Audit Committee Chair

Mr. Flynn is a founding investor in NRx. He is an entrepreneur with more than 30 years of senior executive experience. He has provided leadership to numerous successful organizations and has served in a variety of roles, including CEO, COO, CFO, and advisor. Mr. Flynn currently serves as COO of Good Measures, Inc. He co-founded Predilytics, Inc., which was sold to Welltock, Inc. Previously, he served as COO and then as CEO of Health Dialog, which was sold to BUPA International. Mr. Flynn continued with BUPA, opening its business in the GCC and China. He began his career with Bank of America, where he held several positions over the course of 15 years, including Vice President of World Banking and Vice President of Risk Management.

Hon. Sherry A. Glied, Ph.D.

Dr. Glied, whose principal areas of research are in health policy reform and mental health care policy, was named Dean of New York University's Robert F. Wagner Graduate School of Public Service in 2013. From 1989-2013, Dr. Glied was professor of health policy and management at Columbia University's Mailman School of Public Health and served as chair of the department of health policy and management from 1998-2009. In 2010, Dr. Glied was confirmed by the U.S. Senate as Assistant Secretary for Planning and Evaluation at the Department of Health and Human Services, serving in that capacity from July 2010 through August 2012. She had previously served as senior economist for healthcare and labor market policy on the President's Council of Economic Advisers in 1992-1993, under Presidents Bush and Clinton, and participated in the Clinton Health Care Task Force.

Aaron Gorovitz, J.D.

Mr. Gorovitz is a partner of the AHG Group. In addition to his 25 years of legal experience in complex commercial transactions, he has considerable involvement in early-stage biotechnology and health information technology companies.

Chaim Hurvitz

Mr. Hurvitz has served as the Chief Executive Officer of CH Health since May 2011. He previously served as the President of Teva International Group at Teva Pharmaceutical Industries Ltd., from April 2002 to 2010 and was a Director and member of the senior management of Teva Pharmaceuticals Industries Ltd. He serves as the Chairman of Galmed Pharmaceuticals Ltd. and has been its Director since 2011. He has been a Director of TheraCoat Ltd. since October 2010. He is a member of the management of the Manufacturers Association of Israel and head of its pharmaceutical branch. Mr. Hurvitz holds a Bachelor of Arts degree in political science and economics from Tel Aviv University.

Jonathan C. Javitt, M.D., M.P.H., Chief Scientist and Director

Biography on page 11.

Stephen Willard, Chief Executive Officer and Director

Biography on page 11.

Advisors

Prof. Daniel C. Javitt, M.D., Ph.D., Co-founder and Chair, Scientific Advisory Board

Professor Javitt has devoted the past 30 years to the intersection of psychiatry and brain science. He was the first to identify the role of the NMDA receptor in modulating human thought processes in psycho-affective disorders. He is the author of more than 500 scientific publications that have been cited by more than 53,000 scientists together with 10 patents in the field and is one of the most-widely cited authors in neuropsychiatry. His work has merited awards from the American Psychiatric Association and other leading organizations.

Prof. Apkar Vania Apkarian, Ph.D.

Prof. Apkarian is the inventor of US Patent 8,653,120 the use of D-cycloserine to treat chronic pain. He is Professor of Physiology, Anesthesia, Surgery, and Neuroscience at the Northwestern University Feinberg School of Medicine. Dr. Apkarian has been devoted to unravelling brain mechanisms that underlie acute and chronic pain, and more generally how the brain dynamically processes information that gives rise to perception. This has included several decades of research into the use of D-cycloserine in chronic pain. He has published more than 120 peer-reviewed articles in the field that have been cited by more than 33,000 scientists.

Philip T. Lavin, Ph.D., Chief Methodologist

Dr. Lavin is a highly respected biostatistician with more than 30 years experience supporting the design and analysis of clinical trials. Previously, he was a member of the biostatistics faculty at the Harvard School of Public Health, and a member of the Department of Surgery at Harvard Medical School where he was affiliated for more than 25 years. He co-founded Boston Biostatistics in 1983, a company known as Aptiv Solutions. During his career, Dr. Lavin has served as lead biostatistician for 50 U.S. Food and Drug Administration (FDA) approvals, including 38 PMAs—more to date than any other biostatistician. He has also served as a Special Government Employee for 30 years advising the FDA on complex statistical and policy issues. Dr. Lavin is one of the world's most widely published statisticians, having authored more than 250 peer-reviewed publications that have been cited by more than 30,000 scientists.

Prof. Marion Leboyer, M.D., Ph.D., Psychiatry Principal Investigator (EU)

Dr. Leboyer is Professor of Psychiatry at the University of Paris Est Créteil (UPEC) in France. She is head of the DMU IMPACT (University-affiliated department of Psychiatry and Addictology, Hôpitaux Universitaires Mondor, Assistance-Publique-Hôpitaux de Paris). She also runs the laboratory "Translational NeuroPsychiatry," which is part of Mondor Institute for Biomedical research (IMRB, Inserm U955). Since 2007, she is the executive director of a non-profit foundation, "Fondation FondaMental" created by the French Ministry of Research. Dr. Leboyer has authored or co-authored more than 900 peer-reviewed international publications (H-index = 127) and is part of the highly cited researchers (Clarivate) since 2018. In 2022, she was ranked by Research.com best female scientist award (12 in France and 256 in the world among the Top Female Scientist). In December 2021, she received the Inserm Grand Prize. Her research efforts contributed to a better identification of genetic and environmental risk factors associated with major psychiatric disorders towards better understanding of causal mechanisms. In particular, she has contributed to the identification of associations of genetic vulnerability factors, of immune dysfunctions in major mood and psychotic disorders, but also of environmental risk factors as well as brain imaging abnormalities. Her goal is to develop biomarker signatures to better identify homogenous subgroups of psychiatric disorders paving the way to mechanisms-based treatments. Within the 52 French expert networks centers created and coordinated by Fondation FondaMental, several large and deeply phenotyped cohorts of patients have been followed allowing for the construction of shared observational databases and biobanks. These networks have enabled multiple collaborations within different national and international research programs. Dr. Leboyer is the principal investigator of several international and national research projects.

Dennis K. McBride, Ph.D., Chief Strategy Officer and Senior Scientist

Dr. McBride has led numerous national and international initiatives in neuroscience and its interface with information technology, national security, and medical technology/drug development within the federal government, three of which are now multi-billion dollar enterprises. Dr. McBride began his career as a medical scientist in Naval Aviation and ergonomics and served in eight nationally prominent laboratories, including the Defense Advanced Research Projects Agency (DARPA), Naval Aerospace Medical Research Lab, Naval Research Lab, the Office of Naval Research, and the Naval Medical Research Institute. Upon retiring as a highly decorated senior officer (O-6), he assumed leadership of the Potomac Institute for Policy Studies, where he continues to serve as President Emeritus. Following his ten-year term, he was recruited back to the National Defense University to lead the Center for Technology and National Security Policy, culminating his government career as a Senior Executive-4 (Civilian equivalent to Rear Admiral/Vice Admiral). Dr. McBride has served as an adviser to Cabinet Secretaries, U.S. Congressional Committees, and to corporate C-Suite executives. His educational background includes formal enrollment at the University of Georgia, Naval Aerospace Medical Institute (flight surgeon school), the University of Southern California, the London School of Economics, and Harvard Business School, earning a Ph.D. in experimental psychology, four master's degrees, and an additional postdoctoral education in aviation medicine, systems engineering science, and strategic disruption. He has published widely and was elected by faculty in 1999 to full professor. Dr. McBride has served at multiple universities in colleges of Arts & Sciences, Engineering, Public Policy, and Medicine. For the past 12 years, Dr. McBride has served as an adjunct Professor at Georgetown University School of Medicine and co-Director of Georgetown's Regulatory Science Program.

Michael Manyak, MD, Urology Principal Investigator

Dr. Michael J. Manyak is a urologist, author, and corporate medical executive. He previously served as Global Medical Affairs Director for the GlaxoSmithKline urology franchise. He is the Chief Medical Advisor for Crisis Response for Accenture, a Fortune 100 company. He is an Adjunct Professor of Urology and Engineering at The George Washington University (GWU) and a member of the Baylor College of Medicine National School of Tropical Medicine. He is the former Chief Medical Officer for Triple Canopy, Inc., a large international high risk security firm. Dr. Manyak spent 16 years at GWU after his fellowship in biotechnology at the National Cancer Institute. He was selected as the GW Urology Distinguished Alumnus in 2017.

Andrew Nierenberg, M.D., Psychiatry Principal Investigator

Dr. Nierenberg has been at the Massachusetts General Hospital since 1992, where he holds his current positions. He is also Honorary Professor in the School of Medicine, Faculty of Health at Deakin University, Geelong Australia. Dr. Nierenberg has published over 500 papers and has been listed in The Best Doctors in America for the treatment of mood and anxiety disorders in every edition since 1994. In 2000, he was awarded the Gerald L. Klerman Young Investigator Award and in 2014 the Gerald L. Klerman Senior Investigator Award by the Depression Bipolar Support Alliance. In 2013, Dr. Nierenberg was awarded the prestigious Brain and Behavior Research Foundation Colvin Prize for outstanding achievement in mood disorders research. In 2014, he was awarded the Mentorship Award for Exceptional Mentorship in the Research Arena at MGH. In 2014, 2015, and 2016, he was listed among the World's Most Influential Scientific Minds by Thompson Reuters in recognition of ranking among the top 1% of researchers for most cited papers in psychiatry worldwide. Dr. Nierenberg's primary interests are bipolar depression and novel treatments. He lectures extensively, teaches, supervises, and mentors junior faculty, has an active clinical practice, consults to industry, and conducts clinical trials funded by federal, foundation, industry, and philanthropic sources. He serves as a peer reviewer for over 35 psychiatric journals. Dr. Nierenberg is a member of the editorial boards of over 15 journals and is the editor of Psychiatric Annals and is a deputy editor of Depression and Anxiety.

Wayne Pines, Regulatory & Patient Advocacy Advisor

Mr. Pines previously served as Associate Commissioner of the U.S. Food and Drug Administration.

Milestones

Over the past 12 months, NRx has achieved the following key milestones as it seeks to further advance the development of its proprietary drug pipeline closer to FDA approval.

General

- Expanded its Intellectual Property portfolio by licensing two new patents: U.S. patent No. 11,576,911 for its bipolar depression program, and U.S. Patent 8,653,120 for its chronic pain program.
- Completed the transfer of its Phase 3 commercial drug manufacturing processes to the U.S. and completed GMP manufacturing of supplies required for its ongoing clinical trials, resulting in 1 million Phase 3-level capsules.

Bipolar Depression

- Entered into a collaboration with Alvogen Pharmaceuticals and Lotus Pharmaceuticals for global development and commercialization of NRX-101 in suicidal bipolar depression, with potential for up to $330 million in milestones and double-digit royalties.
- Published the STABIL-B trial results in the *International Journal of Bipolar Disorders*, with DCS demonstrating reduction in suicidality and depression scores compared to standard-of-care medication.
- Awarded Fast Track designation, Breakthrough Therapy designation, a Special Protocol Agreement, and a Biomarker Letter of Support by the U.S. Food and Drug Administration for NRX-101 in the treatment of bipolar depression with suicidality.
- Initiated recruitment on two Phase 2b/3 clinical trial of NRX-101 in patients with bipolar depression with acute suicidal ideation and behavior (ASIB) and in patients with bipolar depression with subacute suicidal ideation and behavior (SSIB).
- Consolidated both trials into a single Phase 2b/3 trial of NRX-101 for Suicidal Treatment Resistant Bipolar Depression (S-TRBD), based on comments and guidance from the FDA, expanding its indication reach.
- Contracted with 1nHealth to initiate a recruitment campaign that may cover up to 45 states in the U.S. to recruit sufficient participants for its S-TRBD Phase 2b/3 trial.
- Signed a data sharing agreement with Foundation FundaMental for the use of patient level data of a French study on the use of ketamine in 156 patients hospitalized for acute suicidality and depression in support of an NDA application of ketamine.
- Signed a development and manufacturing agreement with Nephron Pharmaceuticals, Inc., to develop and manufacture a presentation of ketamine suitable for treating suicidal depression, intended to support its NDA application.

Chronic Pain

- Expanded its NRX-101 program to encompass treatment of chronic pain as the next focus of development.
- Granted clearance by the FDA to proceed with human trials to treat chronic pain under the Investigational New Drug (IND) application filed for the use of NRX-101 in chronic pain.

Complicated Urinary Tract Infection (cUTI)

- Submitted an IND application, requesting Qualified Infectious Disease Product (QIDP), Fast Track, and Priority Review designation for NRX-101 in cUTI.

POTENTIAL MILESTONES

Moving forward, the Company has established objectives over the next 12 months as it seeks to achieve approval for NRX-101 commercialization.

Bipolar Depression

- Report topline clinical data of its Phase 2b/3 in S-TRBD in Q1 2024, with the data expected to be used for a registrational filing.
- Receive $10 million milestone payment as part of the Alvogen development agreement pending a successful data readout of the Phase 2b/3 in S-TRBD and a Type B meeting with the FDA.
- File for an NDA with the FDA for NRX-101 in S-TRBD (pending a successful data readout), with commercialization potentially starting in 2024.
- Submit a NDA for ketamine for the treatment of suicidal depression and ASIB by Q1 2024, with a targeted Prescription Drug User Fee Act (PDUFA) date in Q4 2024.

Chronic Pain

- Await result readout of the 200-person DOD-funded trial in treatment of chronic pain with DCS (Q4 2023).
- Commence a registrational pharmacokinetic study under the newly established Investigational New Drug (IND) file of NRX-1011 for treatment of chronic pain.

Complicated Urinary Tract Infection (cUTI)

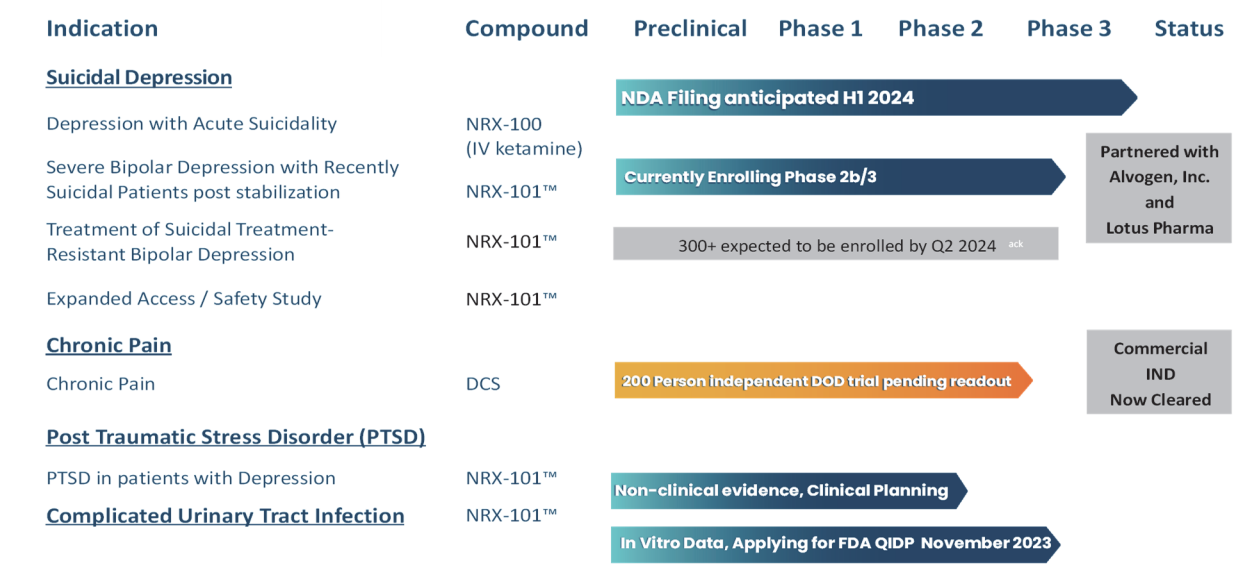
- Approval of IND for NRX-101 in cUTI expected by year-end 2023.
- Spin off a new entity for cUTI.
- File an NDA for NRX-100 for treatment of acute suicidality in depression in Q1 24.

Core Story

NRx Pharmaceuticals, Inc. ("NRx" or "the Company") is a clinical stage biopharmaceutical company developing breakthrough therapeutics for the treatment of life-threatening central nervous system (CNS) disorders with high unmet medical needs. The Company, through its wholly-owned subsidiary, NeuroRx, is focused on using its proprietary technology platform to develop novel therapeutics within the areas of suicidal bipolar depression, chronic pain, post-traumatic stress disorder (PTSD), and complicated urinary tract infections (cUTI). Figure 3 provides a summary of the Company's product pipeline.

Figure 3

NRx PIPELINE



Source: NRx Pharmaceuticals, Inc.

NRx believes that its pipeline provides the Company with three multibillion opportunities with near term milestones, which include: bipolar depression with suicidality, chronic pain, and complicated urinary tract infection (cUTI).

The Company's foundation product—NRX-101—is an oral compound that targets the brain's N-methyl-D-aspartate (NMDA) receptor and is being investigated in a Phase 2b/3 clinical trial for suicidal treatment resistant bipolar depression (S-TRBD), an indication for which the only approved treatment is electroshock therapy. NRX-101 has been awarded Fast Track designation, Breakthrough Therapy designation, a Special Protocol Agreement, and a Biomarker Letter of Support by the U.S. Food and Drug Administration (FDA), as it aims to be the first oral therapeutic for the treatment of bipolar depression with suicidality. NRX-101 was developed based on 30 years of scientific and clinical expertise conducted by Dr. Daniel Javitt (NRx Co-founder and Chair of its Scientific Advisory Board–biography on page 14), related to the role of NMDA receptors in regulating human thought processes in general and in regulating depression and suicidality in particular.

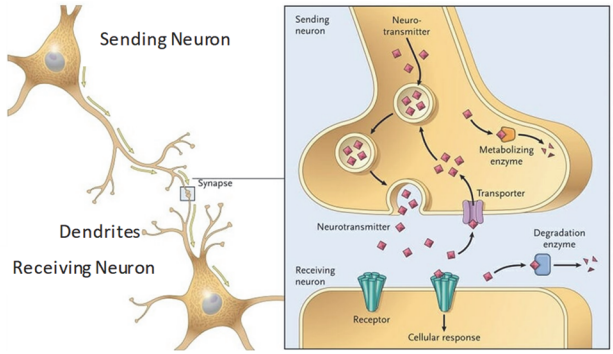
NRX-101 is also being evaluated for the treatment of chronic pain as a possible non-addicting substitute of opioid products. This program is based on new academic and pre-clinical research showing that NMDA receptors are active at each step of the pain pathway. NRx is currently waiting for the data readout of a U.S. Department of Defense (DOD)-sponsored study evaluating D-cycloserine (DCS), a component of NRX-101 and a NMDA antagonist, for the same indication. Since DCS is approved worldwide as an anti-infective, primarily used for the treatment of tuberculosis, the Company expects an abbreviated timeline for this program. NRx is also evaluating the use of NRX-101 for the treatment of both PTSD as well as complicated cUTI.

NMDA RECEPTORS

The Company's main focus is developing its medicinal pipeline targeting psychiatric diseases modulated by NMDA receptors, a type of ion channel receptor found in the nervous system, primarily in the brain.

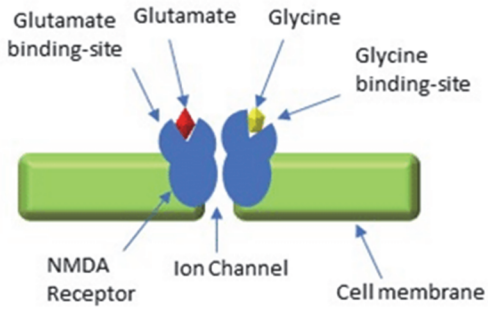
The brain contains cells, called neurons, which send and receive the electrical impulses that control the body. The chemicals that send information from neuron to neuron, controlling their activation, are called neurotransmitters and are an integral part of the chemical pathway that modulates brain activity. Both neurons and neurotransmitters are specialized, each dealing with certain types of information (i.e., one neuron may process information on pain, while another would be involved in visual perception). The activation of a neuron depends on a specific neurotransmitter coupling with its specific receptor—proteins embedded on the post-synaptic membrane of a neuron that receives signals from an adjacent nerve cell (Figure 4).

Figure 4
NEUROTRANSMITTER SYSTEM



Source: Biology Dictionary.

Figure 5
NMDA RECEPTOR



Source: Curegrin.org.

NMDA Function and Role in Neurological Conditions

NMDA receptors play a crucial role in regulating a wide variety of neurological functions, including breathing, locomotion, learning, memory formation, and neuroplasticity (the ability of neural networks in the brain to change, reorganize, or grow, especially in response to learning or following injury or disease). NMDA receptors regulate the structural and functional plasticity of neurons by activating a series of calcium-mediated signaling pathways (Figure 5). NMDA receptor's role in the strengthening of neurons is an important neurological process believed to be the basis of memory formation.

Accordingly, structural and functional impairment of NMDA receptors can lead to neurodegenerative and cognitive disorders, neuropathic pain, epilepsy, and multiple psychiatric disorders (Source: *News Medical Life Sciences'* What are NMDA receptors?). These issues can be derived from either overactivation or deactivation of the NMDA receptors.

Overactivation of the receptor, causing excessive influx of calcium, can lead to **excitotoxicity** and damage to the dendrite spines that connect brain cells to each other, a condition associated with depression-related behavior. At excessive rates of NMDA activity, thoughts and the speed at which new thoughts are generated (ideation) are slowed. People tend to ruminate on those few thoughts, which are often negative and self-destructive in nature. Damage to the dendrites is also thought to be involved in some neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease.

Because of this, blocking NMDA receptors could be useful in treating such diseases. For example, NMDA antagonists have been found to restore lost dendrite spines, reduce depression-related behavior and symptoms, and reduce chronic pain in experimental models and clinical studies (Source: *Science, Vol. 364:6436*, 2019).

However, deactivation or hypofunction of NMDA receptors has been found to induce impairment of synaptic plasticity, as well as various psychiatric problems in humans, including hallucination, mood disorder, delusion, abnormal thinking, agitation, lack of motivation, cognitive deficit, and emotional distress. NMDA hypofunction leads to the excessive release of excitatory neurotransmitters (such as glutamate) in different brain regions, which in turn causes hyperstimulation of postsynaptic neurons and subsequent induction of psychotic conditions (Source: *News Medical Life Sciences*' What are NMDA receptors?). When this happens, thoughts are generated rapidly and, often incoherently, leading to hallucinations and psychosis.

The challenge faced by researchers is to inhibit NMDA receptors while preventing the psychotic problems normally associated with NMDA hypofunction. This could be achieved by preserving NMDA receptors' physiological activity while trying to block its excessive, excitotoxic activity by, for example, the use of antagonists that act as modulators at low concentration but block the receptors when excessively open (Source: *Nature Reviews Drug Discovery, Vol. 5: 160–170*, 2006).

NMDA Antagonists as Antidepressants

Due to their role as a regulator of a wide variety of neurological functions, NMDA receptors are the pharmacologic target of both therapeutic drugs and drugs of abuse. One such example is ketamine, an NMDA antagonist, used as a sedative, anesthetic, off-label as an antidepressant, or recreationally as a hallucinogenic drug of abuse (Source: NIH's National Library of Medicine's *Physiology, NMDA Receptor*).

In 2000, Professor Robert Berman at Yale University made the unexpected discovery that ketamine had potent antidepressant effects. He was conducting a study in which ketamine was being administered to human volunteers to study its psychedelic effects. Unexpectedly, those volunteers reported that symptoms of depression were alleviated. A follow up study on the use of ketamine in subjects with depression showed significant improvement in depressive symptoms within 72 hours after ketamine administration, suggesting a potential role for NMDA receptor-modulating drugs in the treatment of depression (Source*: Biological Psychiatry, Vol. 47(4):351-354*, 2000).

This discovery provided context for the 1959 discovery by Professor George Crane that D-cycloserine (DCS), a newly developed treatment for tuberculosis, was a potent antidepressant. Crane was treating tuberculosis patients when he made the observation. He followed this finding with a placebo-controlled trial that demonstrated the antidepressant effect of DCS (Source: *American Journal of Psychiatry Vol. 115(11):1025-1026*, 1959). At the time, however, there was no understanding of NMDA receptors and their role, much less the understanding that DCS is a potent NMDA inhibitor.

However, anti-depressant research with DCS did not continue due to its potential psychedelic effect at high doses, with researchers favoring another tuberculosis drug, Isoniazid, which was also shown to have antidepressant effects with no psychedelic effects. This led to the development of the first class of antidepressant drugs based on Iproniazid. Of note, Iproniazid was later withdrawn from the market because of its hepatotoxicity. After the effect of NMDA inhibition was discovered, there was a resurgence of interest in DCS and other overlooked NMDA-antagonist medications, for the treatment of depression.

Depression and Suicidal Ideation

A key factor in the newly found interest of NMDA antagonists as therapeutic agents for depression and suicide is the fact that multiple studies have demonstrated that NMDA antagonists directly inhibit suicidal thoughts, an effect that is distinct from their antidepressant effect. For example, in a trial conducted by Professors Michael Grunebaum and Alfred Mann (a member of the NRx advisory board) at Columbia University, ketamine demonstrated a greater reduction in suicidal ideation in depressed patients (Source: *American Journal of Psychiatry, Vol. 175(4):327-335*, 2018). This led to the idea that suicidal ideation, although present in psychiatric disorders such as bipolar depression, PTSD, and major depressive disorder (MDD), should be thought of as a distinct therapeutic target (i.e., an independent medical indication).

Based on clinical data, experts now concur that acute suicidal ideation/behavior (ASIB) and depression are two separate medical targets, with the FDA listing ASIB as a separate indication. Today there is no approved medicine for ASIB in bipolar depression, with standard-of-care consisting of hospitalized observation and, frequently, electroshock therapy (Source: *Psychiatric Advisor's Suicidal Ideation in Bipolar Depression: A Potential New Treatment*, 2017).

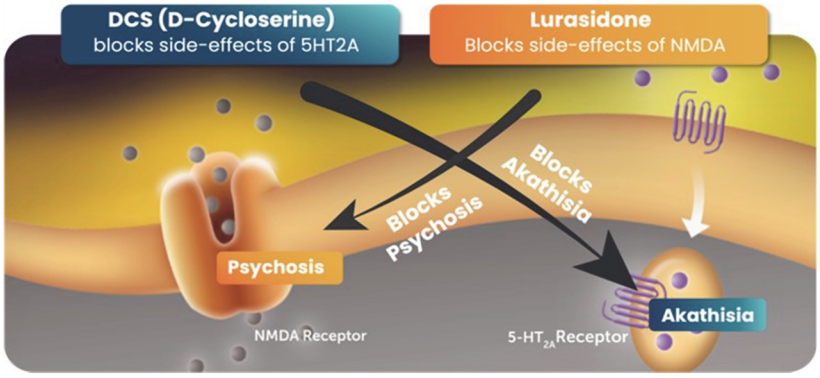
Overcoming the Psychedelic Effects of NMDA Drugs

As previously stated, development of NMDA antagonist in general (and DCS in particular) as an antidepressant was limited by their side effects, as psychedelic effects are incompatible with a medicine for home use. Based on laboratory research that followed the first successful human trial with DCS for depression, Professor Daniel Javitt discovered that the psychedelic effects of NMDA drugs can be reversed by the combination with serotonin-targeted drugs, such as lurasidone (the active ingredient used in the market-leading branded bipolar depression agent).

Furthermore, a major limitation in the use of serotonin-targeted drugs, such as lurasidone, as therapeutic agents is its possible behavioral side effects, especially anxiety, agitation, and akathisia—all of which are associated with generating or exacerbating suicidality in psychotic or depressed patients. However, Professor Javitt made the simultaneous discovery that NMDA inhibitors, in turn, block the akathisia side effect normally experienced with the use of serotonin-targeted drugs (Source: Composition and method for treatment of depression and psychosis in humans, U.S. Patent and Trademark Office #US10583138B2). Since then, NRx scientists have demonstrated, in preclinical and early clinical studies, that combining NMDA and serotonin-targeted agents (in the forms of DCS and lurasidone, respectively) achieves an antidepressant effect that is comparable to that of leading antidepressants, while eliminating the psychedelic effects of NMDA receptor antagonists and also blocking akathisia and reducing suicidal ideation. This relationship, illustrated in Figure 6, is the basis for the creation of the Company's NRX-101 product candidate, which is more fully detailed on pages 24-25.

Figure 6

DCS - LURASIDONE INTERACTION



Source: NRx Pharmaceuticals, Inc.

NRX-101

The Company's growing pipeline is powered by its proprietary NRX-101 product candidate, a patented oral, fixed-dose combination of two FDA-approved drugs: D-cycloserine (DCS), an NMDA receptor modulator; and lurasidone, a 5-HT2a receptor antagonist.

NRX-101 is a potentially rapid-onset and sustained oral treatment regimen currently in a Phase 2b/3 clinical trial for suicidal treatment resistant bipolar depression (S-TRBD), an indication for which the only approved treatment is electroshock therapy. NRX-101 is one of the first oral antidepressants currently in late-stage clinical studies targeting the NMDA-receptor in the brain, which represents a key new mechanism to treat depression. If approved by the FDA, it would be the first medicine regimen targeted to treat S-TRBD. The Company is also assessing the use of NRX-101 in clinical trials for the treatment of chronic pain, PTSD, and cUTI.

NRX-101 has been granted Fast Track designation, Breakthrough Therapy designation, a Biomarker Letter of Support, and a Special Protocol Agreement by the FDA for S-TRBD. Breakthrough Therapy designation was awarded based clinical trial data that demonstrated a statistically significant advantage of NRX-101 vs. lurasidone in maintaining remission from depression and suicidality following a single stabilizing dose of ketamine (pages 29-30).

NRX-101 combination of DCS and lurasidone provides the product candidate with a proprietary dual-mechanism of action that targets both the NMDA and 5-HT2a receptors—two key receptors in the brain.

D-cycloserine (DCS)

Discovered in 1954 as a naturally occurring antibiotic, D-cycloserine (DCS) is a broad-spectrum antibiotic approved for the treatment of tuberculosis. Although its initial development and current use is limited by DCS' potential psychedelic effects, it continues to be used worldwide by the World Health Organization as an anti-infective, primarily used for the treatment of tuberculosis. In the U.S., it is used only for the treatment of antibiotic-resistant tuberculosis.

Although its anti-infective activity is based on its ability to disrupt bacterial cell walls, it was discovered to also act as an NMDA antagonist when used at high doses (> 500 mg). By targeting the NMDA receptor and modulating NMDA activity, DCS seems to foster a normal pace of thought. Based on this discovery, Professors Javitt and Heresco-Levy patented the use of DCS to treat depression. Multiple exploratory clinical studies have since demonstrated that administration of DCS can trigger an antidepressant effect, as well as maintain a reduced level of suicidality.

In addition to depression, DCS has shown promise for other indications based on NMDA's regulatory role in a wide variety of neurological functions. New academic and pre-clinical research shows that NMDA receptors are active at each step of the pain pathway: NMDA antagonists in general and DCS in particular have demonstrated extensive promise for the treatment of chronic pain (Source: Authorea's *D-Cycloserine for the Treatment Of Chronic Pain*, 2023). NRx has also demonstrated potent bactericidal effect against antibiotic-resistant strains of pathogens that cause cUTI.

The Company believes that since DCS has been used extensively as an antibacterial agent without report of significant safety concerns, this may facilitate regulatory approval of NRX-101. Because readily available medications have already undergone clinical trials and approval by the FDA, they are able to circumvent testing cycles and discovery pipeline impediments that are traditionally both costly and protracted (Source: Mid City TMS' *What is D-Cycloserine: How to Repurpose this Antibiotic*, 2023).

DCS Modulation of NMDA Receptors

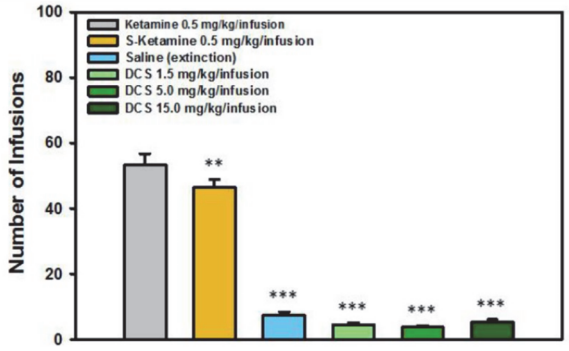
A key factor in the effective use of DCS as a therapeutic agent is the fact that DCS can modulate NMDA activity, acting as a partial agonist at low doses and as a functional NMDA antagonist at high doses. In humans, DCS primarily manifests NMDA agonist effects at doses below 50 mg/d, whereas it primarily manifests NMDA antagonist effects at doses of higher than 500 mg/d, where DCS has been shown to have a clinical antidepressant effect (Source: *International Journal of Bipolar Disorders, Vol. 11: 28*, 2023). This ability to modulate NMDA function in different ways can address a critical concern in the use of NMDA manipulating agents, where the goal is to modulate these receptors in an activity-dependent manner. At low doses, DCS can preserve NMDA receptors' physiological activity, while blocking its excessive activity at higher concentrations (Source: *Neuropsychopharmacology, Vol. 37:4–15*, 2012).

DCS Addiction Potential

Another factor that makes DCS a potentially attractive oral antidepressant candidate is that, unlike ketamine and other NMDA antagonists, it has shown no potential for addiction or abuse. This is important for a short-term antidepressant and critical for a medication to treat chronic pain.

Figure 7

DCS ADDICTION TESTING



Source: Pharmacology Biochemistry and Behavior.

Researchers tested DCS' addictive profile in a standard rodent self-administration model. Following training, where rats learned to self-administer active compounds by pressing a lever, researchers then measured the number of self-administered infusions of rodents in different groups, including ketamine, saline, and DCS at different concentrations (Figure 7). The rats' lever responses in all doses of DCS were only 10% or less of that associated with ketamine infusion and not higher than that of saline infusion. The study concludes that DCS had no abuse potential in nonclinical subjects. These findings provide reassurance that abuse liability is unlikely to be a concern in clinical trials examining DCS in human patients (Source: *Pharmacology Biochemistry and Behavior, Vol. 227–228*, 2023).

Lurasidone, a 5-HT2a Receptor Antagonist

Lurasidone (Latuda®) is a 5-HT2a receptor antagonist currently approved for the treatment of schizophrenia and bipolar depression. The serotonin 5-HT2a receptor is a widely expressed protein receptor that triggers a range of intracellular pathways. 5-HT2A receptors are expressed in many tissues and organs throughout the body, including the CNS, where they are found extensively in brain regions essential for learning, cognitive function, and social interaction. Because of this, abnormal 5-HT2a receptor activity is associated in the pathology of several cognitive and learning disorders, including depression, schizophrenia, obsessive-compulsive disorder (OCD), and drug addiction (Source: Reprocell's *Everything we know about the 5-HT2A (serotonin) receptor*, 2022).

5-HT2a antagonists are primarily used for the treatment of psychosis and bipolar disorders. The most common side effects observed were akathisia (a state of agitation, distress, and restlessness that is a side-effect of antipsychotic and antidepressant drugs), nausea, headache, and sedation. However, although they have demonstrated efficacy in treating bipolar depression, 5-HT2a antagonists have not been shown to decrease suicidal ideation and have an FDA-mandated warning regarding a potential to increase the risk of suicide (Source: *International Journal of Bipolar Disorders, Vol. 11 (28)*, 2023).

NRX-101 Dual Mechanism of Action

NRX-101's combination of DCS and lurasidone has shown promise in counteracting the potential negative effects of each therapeutic compound. Anecdotal reports suggest that high doses of DCS can cause **psychomimetic** side effects, which is a potential barrier for at-home therapy. 5-HT2a antagonists seem to play a role in preventing any potential psychomimetic side effects due to DCS administration (Source: *Frontiers in Psychiatry, Vol. 12*, 2021). Furthermore, administration of DCS has been shown to decrease akathisia induced by 5-HT2a-targeted drugs, including atypical antipsychotic agents, such as lurasidone (Source: *International Journal of Bipolar Disorders, Vol. 11 (28)*, 2023).

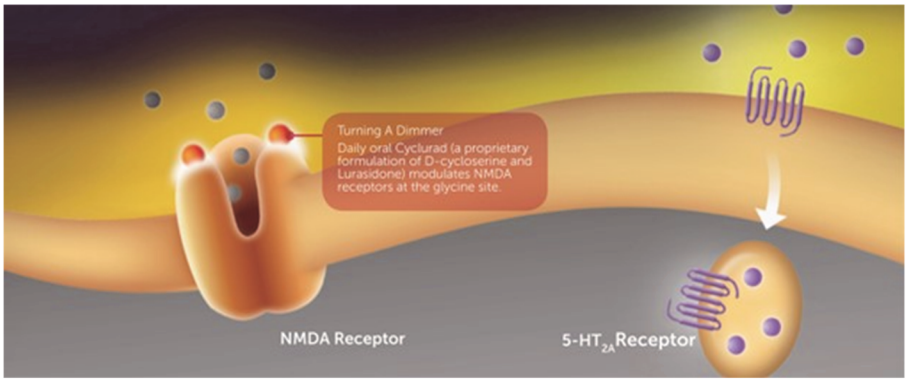
When administered together, DCS and lurasidone appear to mitigate the most common side effects of the other, resulting in a simultaneous blockade of NMDA and 5-HT2a side effects: lurasidone reduces the risk of psychosis and mania while DCS reduces the occurrence of akathisia (Source: Authorea's *D-Cycloserine for the Treatment Of Chronic Pain*, 2023).

The previously undiscovered synergy between these two drug classes, illustrated in Figure 8, in treating CNS disorders combined with the efficacy of DCS in treating depression and PTSD is the subject of 48 issued patents and more than 43 pending patents owned by or licensed to NRx Pharmaceuticals, and as such, is the medical and scientific basis for the Company's technology platform.

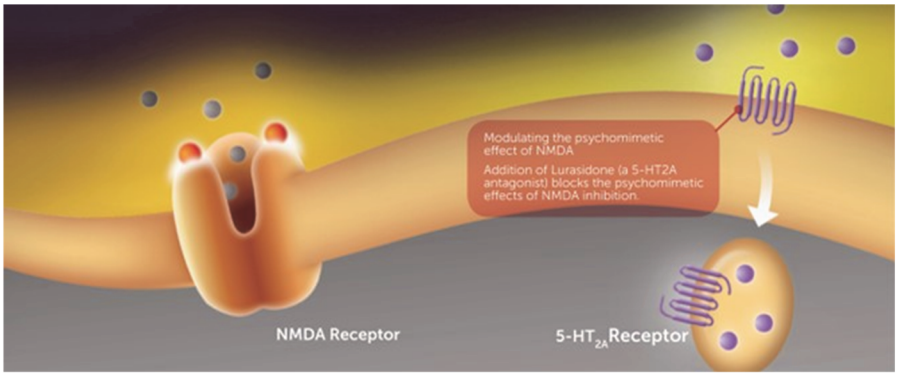
Figure 8

DCS AND LURASIDONE SYNERGY

DCS administration provides theraputic effects on depression and suicidality, while at the same time decreasing akathisia induced by 5-HT2A-targeted drugs



Lurasidone potentially enhances the antidepressant effect while minimizing the risk of psychomimetic side effects of high dose DCS therapy.



Source: NRx Pharmaceuticals, Inc.

The Company believes that NRX-101 possesses potential development advantages over competing therapeutic solutions, including:

- Initial focus on bipolar depression with suicidal ideation and behavior: Most competitors' pipeline products are focused on Major Depressive Disorder (MDD) and exclude bipolar patients from clinical trials. Patients with active suicidal ideation are also routinely excluded from the clinical trials of medicines currently approved for the treatment of bipolar depression.

- Lack of habituation and addiction: Ketamine is a DEA schedule III-controlled substance and is known to be potentially highly addictive. Preclinical habituation studies show no addiction potential for DCS (the NMDA targeting component of NRX-101) and there is no reported history of abuse of DCS in more than 60 years of human use.

- Hallucinations and vomiting have not been a concern in clinical studies with NRX-101: Ketamine and some of its derivatives have been associated with hallucinations and other dissociative side effects in numerous clinical studies. Ketamine must be administered under medical supervision and monitoring of blood pressure.

- NRx's preclinical studies showed no neurotoxicity: Ketamine and other NMDA blocking drugs have the potential to cause brain cell death when abused or used over extended periods of time. Recent FDA guidance requires that proposed NMDA-targeted antidepressants prove the lack of neurotoxicity in histological studies.

Manufacturing Capabilities

NRx has completed the transfer of its Phase 3 commercial drug manufacturing processes to the U.S. The Company has submitted its manufacturing file to the FDA and has released Phase 3 drug manufactured using the expected commercial scale manufacturing processes to be used in NRX-101's Phase 3 trials.

The Company has completed GMP manufacturing of all clinical supplies required for its ongoing clinical trials, resulting in 1 million Phase 3-level commercial process capsules on hand. This initiative is expected to yield stability data sufficient to support a shelf life in excess of two years at time of a potential drug launch (should the clinical trials be successful). The completion of this manufacturing milestone allows the Company to decrease ongoing expenditures associated with manufacturing and development of chemical manufacturing controls. In addition, it can accelerate the development of its product candidates, as the Company can commence Phase 3 studies without the need to wait for manufacturing readiness.

Clinical Development Programs

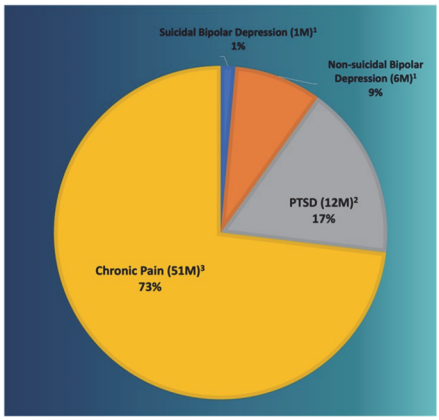
The Company is assessing the use of NRX-101 in four different indications: suicidal bipolar depression, chronic pain, post-traumatic stress disorder (PTSD), and complicated urinary tract infections (cUTI).

NRX-101 has been awarded Fast Track designation, Breakthrough Therapy designation, a Special Protocol Agreement, and a Biomarker Letter of Support by the U.S. Food and Drug Administration (FDA), for the treatment of bipolar depression in patients with suicidality as it aims to be the first oral therapeutic for the treatment of bipolar depression with suicidality. The Company is conducting Phase 2b/3 in patients Suicidal Treatment-Resistant bipolar depression (S-TRBD).

NRX-101 is also being evaluated for the treatment of chronic pain as a possible non-addicting substitute of opioid products; currently waiting for the data readout of a DOD study evaluating DCS for the same indication. NRx is also evaluating the use of NRX-101 for the treatment of both PTSD as well as cUTI. Figure 9 provides an overview of NRX-101 CNS indications.

Figure 9

NRX-101 CNS INDICATIONS



Treatment-resistant Suicidal Bipolar Depression:

Unmet medical need; ongoing Phase 2b/3 clinical trial. Granted Breakthrough Therapy Designation.

Non-suicidal bipolar depression

Currently treated with atypical antipsychotics. All have black box suicide warning on the label.

Chronic Pain

Global Opiate Crisis. Evidence of relief with off-label ketamine. Encouraging early data with cycloserine.

PTSD

Two indicated SSRI drugs. Neither relieves PTSD Symptoms. Both have suicide warnings on label.

Source: NRx Pharmaceuticals, Inc.

According to NRx, its pipeline provides the Company with three multibillion opportunities with near term milestones: bipolar depression with suicidality, chronic pain, and cUTI (Figure 10).

Figure 10

MULTIBILLION MARKET OPPORTUNITIES

Suicidal Bipolar Depression (NRX-100)	Suicidal Bipolar Depression (NRX-101)	Chronic Pain (NRX-101)	Complicated UTI (NRX-101)
• Intravenous Racemic Ketamine	• Partnered with Alvogen	• $70 billion market	• 3 million cases/year
• 180,000 patients with acute suicidality	• 1 million patients	• Extensive non-clinical data	• 90% of organisms are resistant to common antibiotics
• New, compelling clinical trial	• $330 million in potential milestones plus 15% royalty	• Successful Phase 2a trial demonstrating efficacy vs. placebo	• Eligible for FDA Qualified Infectious Disease Product (QIDP) designation
• Failure of nasal ketamine to demonstrate benefit	• 15 more patients to enroll prior to data readout (expected in 2023)	• Awaiting readout of DOD-funded 200-person trial this year	• Priority Review/5 year additional exclusivity
• Company to apply for accelerated approval in 2024	• $10 million milestone on readout	• Non-opioid/non-addictive	
• Potential for $50 -$150 million sales	• Alvogen pays future development costs	• Top Gov't Priority	

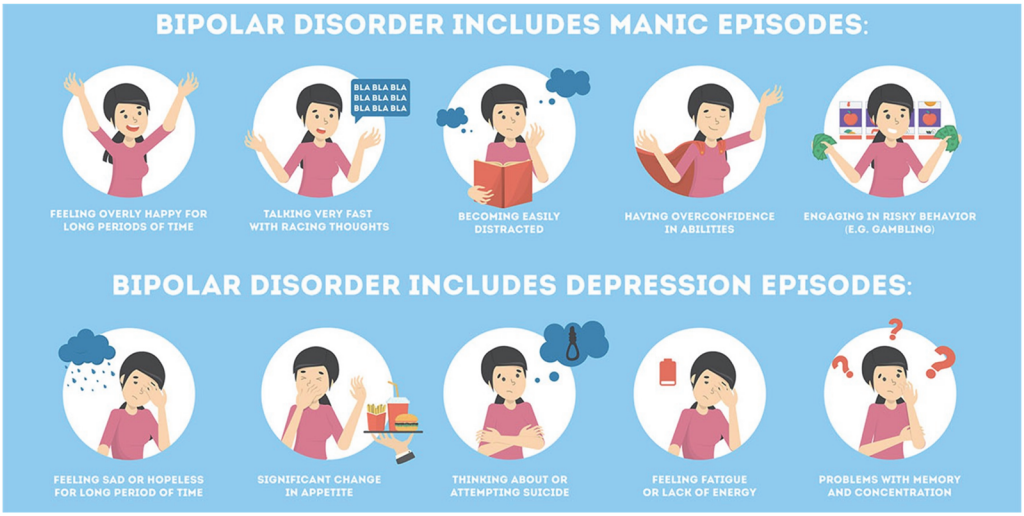
Source: NRx Pharmaceuticals, Inc.

SUICIDAL BIPOLAR DISORDER

Bipolar disorder, sometimes referred to as manic-depressive disorder, is a mental illness characterized by dramatic shifts in mood, energy, and activity levels that affect a person's ability to think clearly and carry out day-to-day tasks. People with bipolar disorder experience extreme high and low moods—known as mania (highs) and depression (lows)—which differ from the typical ups-and-downs most people experience (Figure 11). Bipolar depression (the depressive low mood phase) is a common symptom of this mental illness, and in about half of these individuals, is associated with suicidal ideation (i.e., thoughts of ending one's life).

Figure 11

BIPOLAR DEPRESSION SYMPTOMS



Source: St. Patrick's Mental Health Services.

The condition affects men and women equally, with approximately 46 million people around the world and about 2.8% of the U.S. population (between 5.7 million to 7.0 million individuals) diagnosed with bipolar disorder, and nearly 83% of cases classified as severe (Sources: *National Alliance on Mental Illness (NAMI)* and The *National Institute of Mental Health*).

The 2022 global market for bipolar disorder therapeutics was estimated at $5.9 billion and is projected to reach $7.8 billion by 2030. The growth is driven by the rising awareness of the effects and symptoms of bipolar disorders, government initiatives to improve public knowledge, and innovations in technology that led to combining drugs and therapeutics (Source: *Global Industry Analysts, Inc's Bipolar Disorder Therapeutics - Global Strategic Business Report,* 2023).

Bipolar Depression with Suicidality

Depression in bipolar disorder is the predominant manifestation of the disease, affecting even patients under treatment, and leading to a markedly elevated premature mortality and decreased life expectancy due to suicide. Patients with bipolar depression are 10 to 30 times more likely to attempt suicide than the general population, with 20% to 60% of them attempting suicide at least once in their lifetime, and between 11% to 20% ending their life by suicide (Sources: *Medicina, Vol. 55(8): 403*, 2019, and *Bipolar Disorders Vol.19: 13-22*, 2017).

In March 2022, NRx announced a primary focus on its psychiatry franchise and the late-stage development of NRX-101 for the treatment of bipolar depression in patients with suicidality. NRX-101 specifically targets people with severe bipolar depression who also have acute or sub-acute suicidal ideation. Should these trials in patients with active suicidal ideation demonstrate efficacy, NRx plans to initiate trials in the far broader population, with an estimated seven million patients with chronic/intermittent bipolar depression, nearly all of whom have intermittent thoughts of suicide.

Patients who suffer from bipolar depression with acute suicidal ideation or behavior (ASIB) (i.e., patients with strong suicidal thoughts, which require stabilization of symptoms in a clinical setting) are first treated, often with ketamine or sedating drugs, to reduce the risk of self-harm. These drugs have only short-term effects. A stable, non-psychedelic drug is needed to reduce symptoms of depression and suicidal ideation over the long term. Patients with suicidal bipolar depression who are not at immediate risk of self-harm—sub-acute suicidal ideation or behavior (SSIB)—are typically treated in an outpatient setting. Between 700,000 and 1 million patients with suicidal bipolar depression are currently in need of treatment in the U.S. alone.

Bipolar Depression Treatment Options

Treatment of bipolar disorder normally consists of a combination of psychotherapy and medication, the latter including mood stabilizers, antipsychotics, antidepressants (including lithium), anti-anxiety medication, or a combination of them. In terms of bipolar depression treatment, there are approved drug treatments for the condition, including olanzapine/fluoxetine combination, quetiapine, and lurasidone (monotherapy or adjunctive to lithium or valproate). However, although these options have demonstrated efficacy in treating bipolar depression, they have not shown to decrease suicide ideation, and most include an FDA-mandated warning regarding their potential to increase the risk of suicide (Source: *International Journal of Bipolar Disorders, Vol. 11 (28)*, 2023). Among bipolar disorder patients, the risk of suicidal behavior is among the highest of all psychiatric disorders, despite supposedly effective treatments (Source: *International Journal of Bipolar Disorders, Vol. 8 (1)*, 2020).

This gap between effective treatment of bipolar depression and suicide ideation reinforces the idea that acute or sub-acute suicidal ideation/behavior (ASIB/SSIB) and depression should be treated as two separate medical targets. Currently, there are no approved therapeutics for acute suicidal ideation in bipolar depression, with standard-of-care consisting of hospitalized observation and, frequently, electroshock therapy, which has numerous known side-effects (Source: *Psychiatric Advisor's Suicidal Ideation in Bipolar Depression: A Potential New Treatment*, 2017).

To the Company's knowledge, NRX-101 is the only treatment in development for suicidality in bipolar patients. All other treatments are focused on suicidal ideation associated with depression. For example, a study to assess esketamine for the treatment of suicidal patients will specifically exclude bipolar patients, in whom the incidence of suicidal ideation is the highest.

Alvogen, Inc. Collaboration

On June 2, 2023, the Company entered into an exclusive global collaboration and license agreement with Alvogen, Inc. (a privately-held pharmaceutical company) and Lotus Pharmaceutical Co. Ltd. (an international pharmaceutical company with global presence), for the development of NRX-101 for bipolar depression with suicidality.

Under the license agreement, NRx granted Alvogen an exclusive worldwide, transferable, and sublicensable license to develop, manufacture, and commercialize NRX-101 for the treatment of bipolar depression with suicidality. The agreement also includes a right of first negotiation for new indications outside of the field of bipolar depression with suicidality and/or potential new products containing DCS in combination with an antidepressant/antipsychotic agent.

Alvogen, through its CNS focused Almatica® division, will be responsible for the U.S. commercialization of NRX-101. Lotus Pharmaceuticals will be responsible for commercialization of NRX-101 in markets outside the U.S. through Lotus's direct presence in certain Asian markets or through their export division, which currently has partnerships in numerous markets, including in Europe, Japan, China, Australia, and Latin America.

NRx is eligible to receive up to $330 million in milestone payments tied to development progress and sales targets as well as royalty payments on sales both in the U.S. as well as internationally. Under the terms of the agreement, relating to NRX-101 for the U.S. market, NRx is entitled to receive an initial payment of $10 million upon achieving both a successful read-out from the ongoing Phase 2b/3 clinical trial in S-TRBD and completion of a Type B meeting with the FDA (expected by Q1 2024). Upon payment of the first $10 million milestone, Alvogen will be responsible for all future development, regulatory, and commercial costs of NRX-101 for this indication.

NRx would receive an additional payment of $5 million upon receipt of FDA approval for NRX-101 as well as bonus milestone payments of increasing amounts up to $330 million based on reaching certain net sales targets. NRx is eligible to receive a royalty on net sales between 12% and 16% contingent on certain sales thresholds for the U.S. market and other success-based payments for markets outside of the U.S. Figure 12 provides an overview of the Company's collaboration agreement with Alvogen.

Figure 12

ALVOGEN COLLABORATION OVERVIEW

ALVOGEN COLLABORATION
• NRX-101 in Suicidal Bipolar Depression; right of first negotiation in other fields
• Established global R&D, manufacturing, and commercial operations
• Almatica in the US: CNS focused division of Alvogen
• Lotus in Europe/Asia/Pacific
FINANCIAL TERMS
• Up to $330 million in milestones, based on clinical/regulatory/sales progress
• First $10 million upon delivery of positive data from ongoing trial and Type B FDA meeting minutes
• Double-digit royalties that escalate to the mid-teens on net sales by Alvogen
• Alvogen responsible for substantially all development, regulatory, and commercial costs in this indication

Source: NRx Pharmaceuticals, Inc.

According to the Company, the Alvogen collaboration provides significant financial and strategic advantages that minimizes the need for future capital raises for NRX-101's development and commercialization. This is due to three factors: (1) the resulting significant capital influx prior to FDA approval of NRX-101; (2) no future financial obligation for the development, regulatory, and commercial costs of NRX-101 (Alvogen would be responsible); and (3) no need to build commercial infrastructure for the potential commercialization of NRX-101 in bipolar depression indications.

Clinical Development of NRX-101 in Bipolar Depression with Suicidality

Following positive data from its proof-of-concept STABIL-B Phase 2 study on the use of NRX-101 for bipolar depression with acute suicidal ideation and behavior (ASIB), the Company initiated parallel Phase 2b/3 trials on patients with both bipolar depression with ASIB (i.e., patients with strong suicidal thoughts, which require stabilization of symptoms in a clinical setting), as well as patients with bipolar depression with SSIB (i.e., patients not at immediate risk of self-harm who are typically treated in an outpatient setting). To the Company's knowledge, these studies represent the only known clinical trials in which patients with active suicidal ideation or behavior have been enrolled, as previous studies of oral antidepressants have excluded patients with active suicidality. NRX-101 is also the first investigational oral NMDA-targeted medicine to be developed for patients with suicidal bipolar depression.

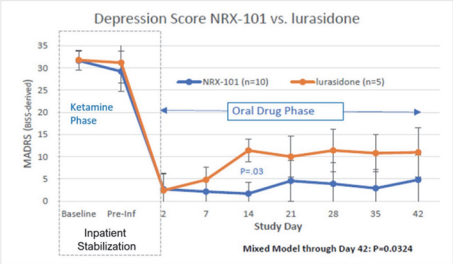
STABIL-B Trial—Phase 2b Study

The Company conducted a proof-of-concept Phase 2b study to assess the use of NRX-101 in patients with bipolar disorder and ASIB, following initial symptoms stabilization with intravenous ketamine compared to the use of lurasidone alone.

Following an intravenous infusion of ketamine (Phase 1), patients with bipolar depression and ASIB received either NRX-101 or lurasidone (Phase 2). Depression was measured by the **Montgomery Åsberg Depression Rating Scale (MADRS)**, and suicidal thinking and behavior was measured by the **Columbia Suicide Severity Rating Scale (C-SSRS)**; global improvement was measured by the **Clinical Global Impression Severity Scale (CGI-S)**.

The proof-of-concept results, presented at the American Congress of Neuropsychopharmacology in 2018 and published in the *International Journal of Bipolar Disorders* (Vol. 11[1]:28, 2023), demonstrated a statistically significant benefit of NRX-101 vs. lurasidone in maintaining improvement in depression from Phase I, after 42 days, with a mean difference between treatments as measure by MADRS (where higher scores indicate a worse severity) of -7.7 points (shown in Figure 13). The use of NRX-101 also resulted in a significant improvement in reducing suicidal ideation, where it lowered both CGI-SS Response Profiles (mean difference between treatments of -2.9) and C-SSRS Response Profiles (mean difference between treatments of -1.5). NRX-101 also resulted in a non-statistically significant decrease in depressive relapse (0% or 0/12 patients vs. 40% or 2/5 patients). Treatment with NRX-101 did not result in any significant safety events and demonstrated improvements in patient-reported side effects. Figure 14 provides an overview of the STABIL-B study results.

Figure 13
STABIL-B STUDY RESULTS



Source: NRx Pharmaceuticals, Inc.

Figure 14
STABIL-B STUDY SUMMARY

- STABIL-B Trial (phase 2b) demonstrated success
- Significant reduction in depression score vs. Standard of Care
- Significant reduction in suicidality score vs. Standard of Care
- No relapses on NRX-101 vs. 40% relapse rate on Standard of Care
- Breakthrough Therapy Designation awarded based on STABIL-B results
- Published in the International Journal of Bipolar Disorders
- 3 Academic trials of DCS have demonstrated confirmatory success

Source: NRx Pharmaceuticals, Inc.

Based on STABIL-B findings, the FDA granted NRX-101 Breakthrough Therapy Designation and a Special Protocol Agreement (SPA) for bipolar depression in patients with ASIB. The Breakthrough Therapy Designation allows for an expedited rolling submission of a New Drug Application (NDA) for investigational drugs that have demonstrated substantial improvement over existing approved therapies, and the SPA allows for a single registrational trial of NRX-101 in severe bipolar depression in patients with ASIB after stabilization with ketamine, using a protocol similar to the STABIL-B trial.

Phase 2b/3 Study—Bipolar Depression and ASIB

In January 2023, the Company initiated a Phase 2b/3 clinical trial of NRX-101 for the treatment of severe bipolar depression with acute suicidal ideation and behavior (ASIB) (requiring hospitalization), which affects approximately 150,000 to 180,000 patients per year in the U.S.

Patients who suffer from bipolar depression with ASIB are first stabilized in a hospital setting, often with ketamine or sedating drugs, to reduce the acute risk of self-harm. These drugs have only short-term effects, and a stable, non-sedating and non-psychedelic drug is needed to reduce symptoms of depression and suicidal ideation over the long term. This long-term effect was seen in the STABIL-B Phase 2 trial of NRX-101, with the Company attempting to replicate this finding in a larger trial.

The Phase 2b/3 trial is a double-blind, adaptive trial with a 2:1 randomization favoring NRX-101 vs. lurasidone alone. The study is seeking to prove that following a successful response to a single infusion of ketamine, treatment with NRX-101 is superior to lurasidone, a widely used drug indicated for the treatment of bipolar depression, in maintaining improvement in symptoms of depression. Patients in the study are initially stabilized in a clinical setting with ketamine, then randomly assigned to NRX-101 or lurasidone.

NRX-101's dual-targeted therapy regimen consists of an initial treatment with intravenous ketamine followed by 6-weeks of daily oral administration of NRX-101. Ketamine is a generic drug and has been widely used for a long time as an antidepressant, although its effect does not last long (usually about a week). NRX-101 is designed to extend ketamine's proven anti-suicidal and antidepressant benefits without its drawbacks.

In February 2023, NRx reported minutes of its FDA meeting on the Phase 2b/3 trials of NRX-101 for severe bipolar depression with ASIB. The purpose of the meeting was to discuss requirements for submitting an NDA for NRX-101. The results of the meeting were as follows:

(1) The FDA discussed a broader indication to patients with severe bipolar depression and Recent Acute Suicidality, which does not require ketamine to be the stabilization agent. This could represent a more straightforward development program, while simultaneously increasing the addressable population for its treatment. This broader indication would enable the Company to potentially demonstrate the use of NRX-101 to maintain stabilization from suicidality in patients stabilized either with ketamine or with other standard of care therapeutic approaches. The FDA noted that, should the results of such a study be driven primarily by subjects stabilized with ketamine, an NDA for ketamine would be required.

(2) The FDA further guided the Company to broaden the study of NRX-101 to include treatment of patients with bipolar depression and chronic/intermittent suicidality. This could enable a pathway for the use of NRX-101 by a broader segment of the approximately seven million individuals in the U.S. with bipolar disorder. A portion of this population is already being addressed in the Company's ongoing Phase 2b/3 trial on patients with bipolar depression and SSIB (not requiring hospitalization), described below. Of note, with this guidance, NRx believes the design of this study has effectively converged with its Phase 2b/3 outpatient trial for bipolar depression with SSIB (described below).

Based on the comments and guidance from the FDA, the Company plans to consolidate patients originally expected to enroll in the in the ASIB study into the SSIB Phase 2b/3 trial, while expanding its indication, placing the ASIB study on hold. This would potentially allow registration of NRX-101 for Suicidal Treatment-Resistant Bipolar Depression (S-TRBD) (including both ASIB and SSIB patients), regardless of the mechanism of stabilization. More information on this change is provided on pages 32-33.

Phase 2b/3 Study—Suicidal Treatment-Resistant Bipolar Depression (S-TRBD)

The Company is engaged in an ongoing clinical trial of NRX-101 in treatment-resistant bipolar depression (S-TRBD) with the objective of demonstrating a decrease in depression and suicidal ideation scores in patients treated with NRX-101 compared to those treated with lurasidone alone.

In Q1 2023, the Company announced the participation of Prof. Andrew Nierenberg, M.D., Head of the Massachusetts General Hospital (MGH) Dauton Family Center for Bipolar Treatment Innovation, as the Principal Investigator of the clinical trial. NRx has now initiated clinical trial sites at Northwestern University (Chicago) and University of Texas, Austin, in addition to commercial research sites.

<u>Original Trial Design –Bipolar Depression with SSIB</u>

The original study, which began enrollment in Q2 2022, was designed as a Phase 2 exploratory study of NRX-101 in patients with bipolar depression and Sub-Acute Suicidal Ideation & Behavior (SSIB) (not requiring hospitalization or stabilization), with all patients being treated in an outpatient setting (www.clinicaltrials.gov NCT NCT03395392). The objective of the trial was to demonstrate a decrease in depression scores (as measured by MADRS) and scores of suicidal ideation (as measured by CGI-SS).

In Q1 2023, the study's independent Data Safety Monitoring Board (DSMB) reviewed both safety and unblinded efficacy data for the first 50 patients in the clinical trial and advised the Company that no safety concerns were identified. Moreover, the DSMB did not identify a futility signal, suggesting that the trial has potential to demonstrate a statistically significant outcome with additional enrollment. On this basis, the DSMB advised management to continue enrolling study participants. Based on the DSMB findings, together with the completion of the Company's Phase 3 commercial stage manufacture process, NRx upgraded the ongoing trial to a Phase 2b/3 study.

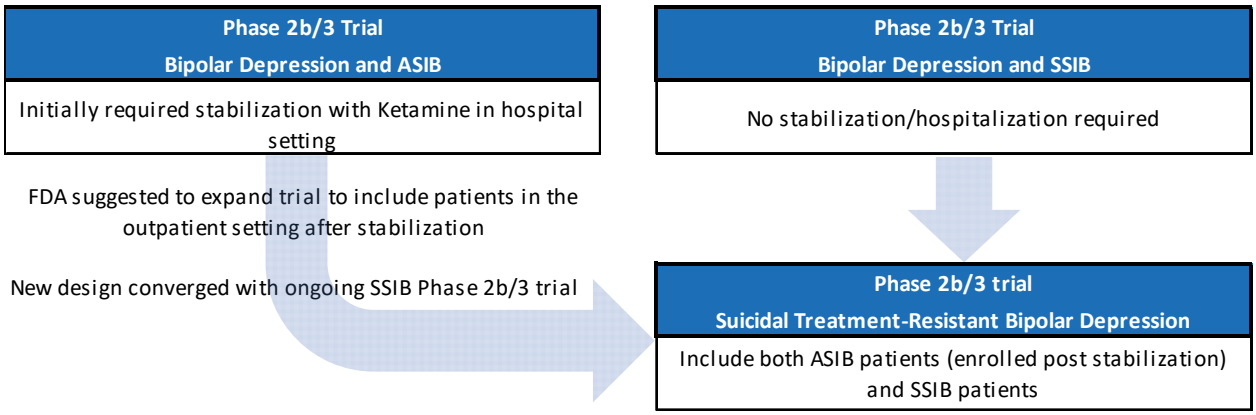
Consolidated Program in Suicidal Treatment-Resistant Bipolar Depression (S-TRBD)

During a Type B meeting with the FDA's Psychiatry Division regarding NRx's bipolar depression and ASIB Phase 2b/3 trial (described on pages 30-31), the FDA suggested to expand its intended use of NRX-101 from the original population of patients with acute suicidality that needed stabilization in a hospital environment, to the broader population of patients with subacute suicidal ideation who are treated in the outpatient setting.

With the FDA's guidance to enroll patients for the acute study in the outpatient setting only after stabilization, the design of this new trial would effectively converge with the currently enrolling Phase 2b/3 trial in patients with SSIB. Based on these recommendations, the Company is evaluating changes to its registrational program for NRX-101 and will seek to consolidate patients originally expected to enroll in the ASIB study into the currently enrolling Phase 2b/3 trial. This would potentially allow registration of NRX-101 for Suicidal Treatment-Resistant Bipolar Depression (S-TRBD), including both patients with SSIB as well as patients with ASIB (regardless of the mechanism of stabilization). An overview of this process is illustrated in Figure 15.

Figure 15

CLINICAL TRIAL EVOLUTION



Sources: NRx Pharmaceuticals, Inc., and Crystal Research Associates, Inc.

This broader indication may also offer significant advantages in commercialization, as the U.S. population of patients with S-TRBD is estimated to be between 700,000 and 1 million people (for whom there is no approved drug), while negating the need for a separate NDA for ketamine in suicidal stabilization.

The Company is completing enrollment of the originally targeted 70 patients, with enrollment expected to continue through November to increase study power. The last patient visit is scheduled for January 2024, with top-line data from this trial expected in Q1 2024. Following a successful readout, Alvogen will assume further development costs. The Company plans to use this trial's data for a registrational filing with the FDA. If the trial is successful, the Company may be able to file an NDA with the FDA for NRX-101 by early 2024, with commercialization starting in 2024. Because NRX-101 is a Breakthrough Therapy, the Company anticipates being able to file an NDA based upon a single, successful Phase 3 trial.

Should these trials in patients with active suicidal ideation (acute or sub-acute) demonstrate efficacy, NRx plans to initiate trials in the far broader population of an estimated seven million patients with chronic/intermittent bipolar depression, nearly all of whom have intermittent thoughts of suicide.

Clinical Trail Compliance

To strengthen compliance to the therapeutic regimen during its trial, the Company is using electronic monitoring, as well as independent internal confirmation of depression and suicidality ratings. This is the same process utilized in the STABIL-B trial that resulted in a high compliance with study medication and high concordance between the psychometric ratings at study sites and those confirmed by the Company's team of raters.

According to the Company, medication compliance, a common problem with trials dealing with bipolar disorder, was tracking at over 90%. In addition, NRx refined its ability to validate the psychometric ratings that are used to assess the MADRS rating, the primary efficacy endpoints for the clinical trial. The Company relies upon a team of veteran raters who both train independent site raters (who conduct site administered depression ratings [i.e., MADRS]) as well as monitor the technical quality of each rating. A standard was set of 90% or better congruence between the Company's veteran rating team and site raters. The Company has recently released preliminary blinded results from the ongoing trial that demonstrate that congruence between the site raters and the veteran raters was tracking above 94% for its 3-point standard and above 97% for the less restrictive 6-point standard. This level of rating congruence exceeds that reported in the peer-reviewed literature (Source: Authorea's *Real Time Quality Assurance Of Depression Ratings In Psychiatric Clinical Trials*, 2023).

Recruitment

In April 2023, the Company contracted with 1nHealth to initiate a recruitment campaign that may cover up to 45 states in the U.S. to recruit sufficient participants for this enlarged trial. The Company has similarly broadened its relationship with Science 37, a Contract Research Organization (CRO) that conducts decentralized clinical trials, to enroll participants identified by the 1nHealth recruitment initiative and randomize them to be treated within the broadened clinical trial. 1nHealth has additionally engaged "The Mighty," a voice-of-the-patient organization with national reach to publicize the clinical trial to the more than 800,000 subscribers who have indicated a focus on bipolar depression and suicidality.

Clinical Development of NRX-100 (Ketamine) in Acute Suicidality

When NRx met with the FDA in January 2023, the agency encouraged the Company to develop NRX-100 (ketamine) as a labeled drug, rather than rely on prior stabilization of suicidality and depression achieved via the common clinical practice of infusing generic ketamine compounded in licensed pharmacies.

The Company believes that ketamine is not only a potentially important treatment for suicidal bipolar depression, but also a potentially enabling therapy for use of NRX-101 in patients with bipolar depression and ASIB. As stipulated by the FDA, if the study on patients with bipolar depression and ASIB is driven primarily by subjects stabilized with ketamine (as originally designed), an NDA for ketamine would also be required. To this end, on October 12, 2023, NRx announced a strategic acceleration of its plans to develop a commercial form of intravenous ketamine (NRX-100) to treat acute depression and suicidality based on recent changes in the regulatory environment and the Company's data cooperation agreement.

Ketamine has been shown in multiple randomized clinical trials to induce nearly immediate remission from depressive symptoms and suicidal ideation. Similar to DCS, ketamine works by targeting the NMDA receptor to rapidly reduce depression and suicidality in people with bipolar disorder. However, the clinical effect of a single ketamine infusion is demonstrated to diminish very quickly (e.g., three days post-intravenous dosing and two days post-intranasal dosing). Moreover, ketamine is an addictive controlled substance that causes hallucinations, has known neurotoxicity, and exhibits abuse potential.

Despite the promising clinical findings, ketamine is not approved for use in suicidal bipolar depression or the reduction of suicidality by the FDA, primarily based on limited data that demonstrates the safety and efficacy of ketamine for these indications. Without an approved form of ketamine for acute suicidality, its benefits will only be available to patients able to pay cash for off-label treatment, because unapproved therapies are not suitable for insurance reimbursement.

This problem is compounded by two recent developments: (1) a long-awaited trial of nasal ketamine for the same indication failed to meet its primary endpoints; and (2) the FDA issued a second warning letter on October 10, 2023, cautioning against the compounding of ketamine, and began a program of rigorous inspections of such pharmacies. The FDA's clear position regarding the illegality of compounded forms of ketamine is likely to further limit access to what appears to be a lifesaving drug.

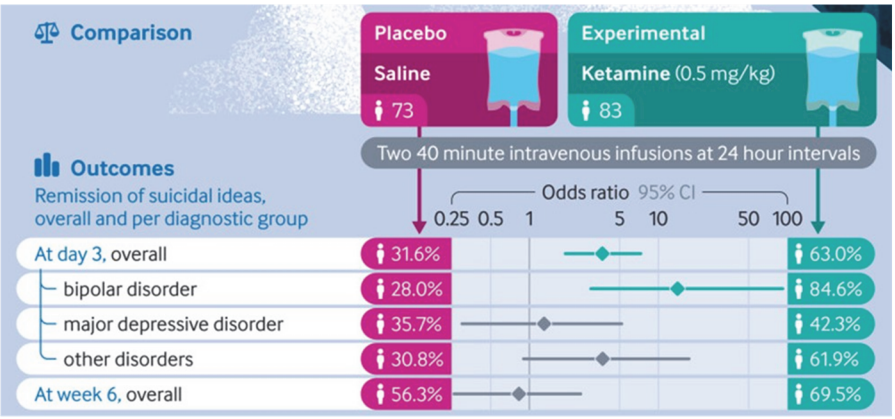
Although NRx believes that ketamine is not suitable as a long-term treatment for depression and suicidality because of its potential for neurotoxicity, addiction, and hallucination, it has long-recognized ketamine's unique ability to provide rapid remission from acute suicidality, especially if paired with a safe, oral drug to maintain the life-saving effect, such as NRX-101. While this may not be a broad commercial opportunity, NRx strongly believes that some form of ketamine must be available for patients with ASIB. However, the cost and logistic implications of studying ketamine in association with suicidal ideation is considerable, in that patients with acute suicidal ideation are frequently admitted to psychiatric hospitals.

In order to facilitate and expedite its NDA application for ketamine, the Company has signed a data sharing agreement with the study leadership of a randomized, placebo-controlled trial of ketamine (versus placebo) on 156 patients hospitalized for acute suicidality and depression in seven French Government Hospitals (the KETIS Trial). NRx approached the Fondation FundaMental, led by Prof. Marion Leboyer, MD, PhD, who served on the NRx Scientific Advisory Board and facilitated establishing the agreement for the use of the patient level data in support of an NDA application.

The top line data from this trial, published in the British Medical Journal (*BMJ Vol. 376,* 2022), demonstrated a dramatic and statistically significant reduction in suicidal ideation among patients treated with intravenous ketamine compared to those on placebo. In a population with high suicidal risks, the use of ketamine resulted in full remission of suicidal ideas after three days in 63% of patients, compared to 31.6% in the placebo group. The trial demonstrated the largest therapeutic effect among the subgroup with bipolar depression (84% vs 28% remission, drug vs. placebo, respectively), which to the Company's knowledge, provides the first clinical evidence that NMDA antagonist drugs, such as ketamine and DCS, may be more effective in treating bipolar depression than in treating major depressive disorder. At week six, remission in the ketamine arm remained high, although non-significantly versus placebo (Figure 16).

Figure 16

KETAMINE STUDY



Source: The British Medical Journal.

Under the data sharing agreement, NRx has translated the clinical study report, which will be submitted to the FDA, and is converting the electronic, patient level data files to a form suitable for FDA review. NRx plans to meet with the FDA in the coming months to discuss a regulatory path for the use of ketamine to treat patients with bipolar depression and ASIB.

The Company is now in the process of negotiating access to patient-level data from a National Institutes of Health (NIH)-funded U.S.-based clinical trial, which confirm the KETIS trial. NRx believes that these multicenter, randomized prospective trials, encompassing more than 240 participants, combined with randomized, prospective data on more than 200 U.S. patients when submitted for review at a patient level, could be sufficient to demonstrate preliminary safety and efficacy of intravenous ketamine in acutely suicidal patients. Data are expected to be transmitted to the FDA by Q4 2023.

The findings of this trial confirm the results reported by Grunebaum and coworkers, as published in the American Journal of Psychiatry (*Vol. 175 (4):327-335, 2018*). The authors tested the acute effect of intravenous ketamine (versus midazolam) on clinically significant suicidal ideation in 80 patients with major depressive disorder. The primary outcome measure was SSI score 24 hours after infusion (at day 1). Adjunctive ketamine demonstrated a greater reduction in clinically significant suicidal ideation in depressed patients within 24 hours compared with midazolam, partially independently of antidepressant effect.

On November 6, 2023, the Company announced a development and manufacturing agreement with Nephron Pharmaceuticals, Inc., a leading manufacturer of sterile injectable drugs, to develop and manufacture a presentation of ketamine suitable for treating suicidal depression. This formulation is expected to overcome some of the formulation deficiencies of existing forms of ketamine (developed for anesthesia) and is expected to have diversion-resistant and tamper-resistant features. The Company believes that this latter aspect is important because of the well-known uses of ketamine as a drug of abuse and as a vehicle for date rape.

Following the data sharing agreement that provides NRx with the required data demonstrating safety and efficacy of ketamine from well-controlled trials, the agreement with Nephron is intended to provide the Company with a ketamine manufacturing process demonstrating adherence to GMP and long-term stability, the last hurdle needed for a submission of an NDA for ketamine. The collaboration aims to produce a proprietary, tamper, and diversion-resistant formulation and packaging of ketamine suitable for treating suicidal depression, with the goal of submitting an NDA for ketamine in Q1 2024 with a targeted PDUFA date in Q4 2024.

Establishment of a Ketamine-Focused Spinoff Company

The Company does not anticipate funding this initiative with its core NRx assets and plans to establish a ketamine-focused spinoff company that would potentially provide current and new investors with both capital appreciation and a royalty stream. A term sheet for up to $30 million in anchor financing for a new public entity has been presented to management by a capable investor and a structure where a portion of the equity in the ketamine asset will be allocated to existing shareholders. This proposal will be discussed at the upcoming annual meeting of shareholders.

Expanded Access Program

As previously discussed, if the NRX-101 ongoing clinical trials demonstrate efficacy, NRx plans to initiate trials in the far broader population of patients with chronic/intermittent bipolar depression, estimated at seven million people. In recommending that NRx pursue this larger indication, the FDA identified the need for a safety database of 1,500 patients, with at least 100 treated for one year. The Company is initiating an Expanded Access Program, as required for all Breakthrough Therapy Medicines, to make this investigational medicine more broadly available for patients who have exhausted approved medicines for bipolar depression and to build that safety database. The Company will seek cost reimbursement for operating this program as permitted under current FDA regulations.

CHRONIC PAIN

In June 2023, concurrent with the announcement of the Alvogen partnership, the Company announced an expansion of its NRX-101 program to encompass treatment of chronic pain as the next focus of development.

Chronic pain—pain lasting beyond the normal healing time and persisting or recurring for longer than three months—affects an estimated 20% of the world's population and accounts for nearly one fifth of physician visits. It often becomes the predominant clinical problem in some patients and its burden on patients, on healthcare systems, and on society has been clearly demonstrated (Source: *Pain Therapy, Vol. 7(1):59-75*, 2018).

The rate of chronic pain and high-impact chronic pain (HICP) (pain that limits life or work activities on most days) among adults is approximately 21% and 8%, respectively. New cases of chronic pain occur more often among U.S. adults than new cases of several other common conditions, including diabetes, depression, and high blood pressure (Source: NIH's *NIH study finds high rates of persistent chronic pain among U.S. adults*). In the U.S., more than one in five adults suffers from chronic pain (20.9% or approximately 51.6 million persons), with the condition linked with depression (Source: CDC's *Chronic Pain Among Adults—United States, 2019–2021*, 2023).

The global chronic pain market was valued at $69.1 billion in 2021 and is expected to reach $140.5 billion by 2030. This growth is driven by an aging population, the prevalence of chronic diseases like diabetes, cancer, neuropathy, multiple sclerosis, and osteoarthritis, and an increase in opioid use (Source: *Spherical Insights' Global Chronic Pain Market Size, Share,* and *COVID-19 Impact Analysis and Forecast*, 2023).

Opioid Crisis

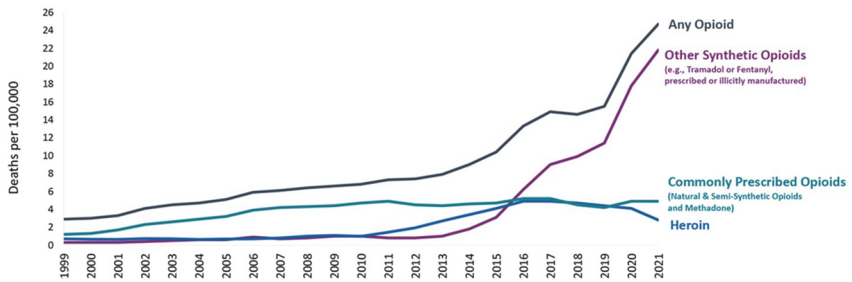
For many chronic pain conditions, the standard of care is the long-term use of analgesics that were originally developed for acute pain. Among these are opioids, which comprise natural, semi-synthetic, or synthetic analgesic molecules with a pharmacological action similar to opium. Opioid substances include pain relievers available legally by prescription, such as oxycodone (OxyContin®), hydrocodone (Vicodin®), codeine, morphine, and many others, as well as illegal drug heroin and synthetic opioids such as fentanyl.

Long-term use of opioids is accompanied by decreasing levels of analgesic response (opioid tolerance), necessitating dose escalation to manage pain. When this occurs, people routinely take more of the substance to elicit the desired response. This ever-increasing dosing places patients at great risk for overdose and addiction.

The misuse of opioids and its addiction are a serious national crisis that affects public health as well as social and economic welfare. In May 2017, during the new FDA's Commissioner Scott Gottlieb's first all-hands address to agency staff, he declared the opioid abuse epidemic as the agency's "greatest immediate challenge." Drug overdose deaths and opioid-involved deaths since then have continued to increase, with the majority of drug overdose deaths in the U.S., over 75% of the nearly 107,000 in 2021, involving an opioid (Source: CDC's *Understanding the Opioid Overdose Epidemic*) (Figure 17). According to the director of the White House Office of National Drug Control Policy, opioid related deaths could dramatically increase to about 165,000 annually by 2025.

Figure 17

OPIOID RELATED DEATHS



Source: Centers for Disease Control and Prevention (CDC).

Chronic pain is at the heart of the opioid crisis, with the widespread burden of chronic pain and the use of opiates to treat the condition considered the main driving force behind the national crisis, resulting in widespread addiction and death. Despite this, few alternatives to opiates have emerged that both treat chronic pain and potentially decrease craving for opiates among chronic pain sufferers. The current opioid crisis, fueled by a failure of non-opioid medication to achieve meaningful clinical relief, creates an acute need for non-addictive, non-sedating pain medication.

NMDA Receptors and Pain

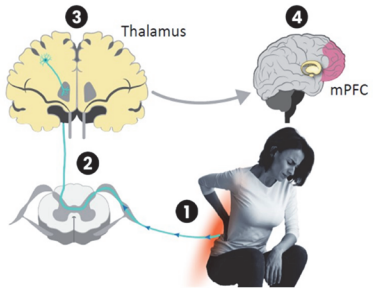
The NMDA receptor activity has been found to play fundamental roles in pain processing, pain sensitization, and chronic pain induced depression, as they are considered integral to pain signaling through the nervous system. Activation of NMDA receptors causes the spinal cord neuron to become more responsive to all of its inputs, resulting in spinal neuron sensitization, leading to a heightened level of pain. Activation of NMDA receptors also causes reduced functionality of opioid receptors. This decreased sensitivity, in turn, translates to opioid tolerance as patients will require higher doses of opioids to achieve the same therapeutic effects (Source: *U.S. Pharmacist, Vol.36(5): HS4-HS8*, 2011).

In experimental models and clinical studies, NMDA antagonists have demonstrated attenuation of neuropathic pain and shown potential in reducing opioid craving, as well as the ability to suppress central sensitization (Source: *Journal of Pain and Symptom Management, Vol. 19(1):2-6*, 2000). For example, the NMDA receptor antagonist ketamine is used off-label to treat various chronic pain syndromes. However, because of its risks for causing physical and psychological dependance, psychomimetic side effects, and neurotoxicity, ketamine is of limited clinical usefulness (Source: Authorea's *D-Cycloserine for the Treatment Of Chronic Pain*, 2023).

Academic and pre-clinical research shows that NMDA receptors are active at each step of the pain pathway, from the focal point of pain, through the peripheral nervous system, up to the spinal cord to the brain, as illustrated in Figure 18. As pain signals reach the brain, the perception of pain is modulated in the thalamus, and memory of the pain is modulated and stored in the cortex. Human brain imaging studies suggest that chronic, neuropathic pain has a strong emotional component that is mediated by the medial prefrontal cortex (mPFC) and can be affected by the use of NMDA antagonists (Source: *Pain, Vol.132(1-2):108-23*, 2007).

Figure 18

NMDA RECEPTORS AND PAIN PROCESSING



1) NMDA receptors help the body recognize physical pain stimuli

2) NMDA receptors control how pain signals move towards the brain by modulating pain transmission at dorsal horn of the spinal cord

3) NMDA receptors help recognize pain signals in the thalamus, and are important for recalling memories of past painful experiences

4) NMDA receptor activity in the medial prefrontal cortex is critical in emotional and cognitive aspects of pain processing

Source: NRx Pharmaceuticals, Inc.

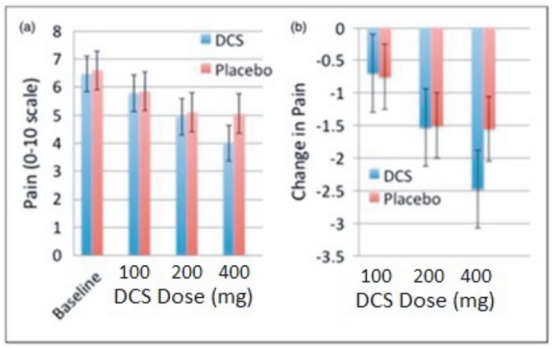
D-Cycloserine (DCS) in Pain Management

As an NMDA antagonist, DCS has been shown to modulate the body's pain response. DCS has demonstrated extensive nonclinical and early clinical efficacy in decreasing the response to nociceptive pain (i.e., pain triggered by pain receptors in the body) and decreasing craving for opioid drugs, with evidence that DCS is both non-addictive and non-neurotoxic. Unlike ketamine and other NMDA antagonist drugs that have the potential to cause addiction and neurotoxicity, DCS does not carry a propensity for dependance or abuse, is not neurotoxic, and has extensive history of long-term use as an anti-infective agent. These factors suggest that DCS is suitable for treatment of chronic pain with no potential to cause addiction or neurotoxicity.

The rationale for treatment of chronic pain with DCS is outlined in a published 2016 pilot study of DCS in the treatment of chronic pain at Northwestern University (Source: *Molecular Pain Vol.12: 1–8*, 2016). The study randomized 41 participants to a placebo-controlled dose-escalation study of 100mg, 200mg, and 400mg (each dose for two weeks) vs. placebo. The primary outcome measure was back pain intensity on a 1-10 rating scale.

Figure 19

DCS IN PAIN MANAGEMENT



Source: NRx Pharmaceuticals, Inc.

Although the trial did not meet the primary endpoint, because separation was not seen at all dosages/timepoints, post-hoc analysis shows a significant reduction in chronic back pain at six weeks vs. placebo, which is the point in time that the 400mg DCS dose was reached (Figure 19).

These results are in line with research conducted by the Company demonstrating that DCS acts as a partial NMDA receptor agonist at lower doses and as a NMDA antagonist at high doses. The 400 mg dose presented in this study roughly corresponds to the 25µg/ml blood level identified by NRx as the threshold at which DCS begins functioning as an NMDA antagonist.

Pre-clinical research has also shown other potential mechanisms of action by which DCS could target chronic pain. Mitochondrial dysfunction has previously been shown to be responsible for maintaining chronic pain after nerve injury. DCS, when administered in combination with pioglitazone, has shown to improve mitochondrial function, attenuating orofacial neuropathic pain and anxiety related behaviors associated with nerve injury in a mouse model of neuropathic pain (Source*: The Clinical Journal of Pain Vol. 34(2): 168–177*, 2018).

Department of Defense (DOD) Study Confirmatory Study

Based on the results of the 2016 pilot study, the research group leading the study embarked on a larger confirmatory Phase 2 clinical trial using the 400 mg dose of DCS in over 200 patients with chronic lower back pain, in which patients were randomly assigned to DCS 400mg/day vs. placebo. The 5-year, $4.9 million trial is being funded by the U.S. Department of Defense (DOD) under the Congressionally Directed Medical Research Program (clinicaltrials.gov NCT03535688). Data collection is complete and statistical results are expected by year-end 2023.

The Company believes that this study can be viewed as a large proof-of-concept study of DCS for the treatment of chronic pain. Positive results are expected to provide a Breakthrough Therapy path towards treatment of chronic pain with DCS and DCS-containing medicines. In anticipation of these findings, the Company established an Investigational New Drug (IND) file for NRX-101 in the treatment of chronic pain.

DCS and Opioid Cravings

There is a strong scientific rationale that DCS may reduce opioid cravings in people who suffer from both chronic pain and addiction. Opioid withdrawal involves both physical and psychological components, similar to other substance-use disorders. Patients may be able to overcome physiological effects of withdrawal, only to relapse after being exposed to drug-taking triggers.

When the opioid antagonist, naloxone, is given to opioid-dependent rats, it triggers an immediate withdrawal syndrome. If rats are confined to a specific area on the test apparatus during acute withdrawal, they develop an aversion to that location. When allowed to move freely in the test apparatus, they will avoid the area that is now associated with withdrawal. Opioid-dependent animals were slow to extinguish this conditioned response; however, administration of DCS accelerated this process. The authors conclude that DCS facilitates extinction of morphine withdrawal-associated place aversion (Source: *Biological Psychiatry, Vol. 67(1): 85–87*, 2010).

These results indicate that administration of DCS might not only have a positive effect in pain management but could also decrease craving for opioid drugs. This, coupled with DCS' lack of addiction potential, could translate into an effective therapeutic agent to treat chronic pain while avoiding the risk of opioid dependance.

NRX-101 in Chronic Pain

NRx is awaiting results of the 200-person Phase 2 trial funded by the DOD. Following the release of these results, the Company plans to initiate a pilot study in the treatment of chronic pain using NRX-101. Based on the preliminary evidence of efficacy already demonstrated for the use of DCS in chronic pain, NRx plans to seek Fast Track Designation, Priority Review, and Breakthrough Therapy Designation for this critical indication while awaiting near-term results of the DOD-funded trial.

On October 2, 2023, the FDA gave the Company clearance to proceed with human trials under the IND application for the use of NRX-101 to treat chronic pain. Subsequently, the FDA provided the Company with a "Study May Proceed" letter, authorizing NRx to proceed with a pharmacokinetic study under the newly established IND. The FDA advised NRx to focus on a specific type of pain in its initial registrational trials, which is consistent with the Company's plan to attempt to replicate the clinically significant benefit previously identified in association with treatment of low back pain. With this alignment in place and with the current inventory of manufactured NRX-101 on hand for clinical trial use, the Company plans to initiate registrational studies in 2024, pending receipt of data from the DOD-funded trial in order to confirm the previously identified efficacy signal and dosing range.

The IND application leverages pioneering research on the use of DCS in the treatment of chronic pain and the recent licensure by NRx of a U.S. Patent (US Patent 8,653,120) for the use of DCS in the treatment of pain. The Company has also recently announced the addition of Dr. Vania Apkarian, Professor of Physiology, Anesthesia, Surgery, and Neuroscience Institute, Northwestern University Feinberg School of Medicine, to the NRx Scientific Advisory Board. Dr. Apkarian is the inventor of the patent and a global expert in pain research and has important experience studying DCS in chronic pain.

NRx has submitted NRX-101 for consideration by the multibillion dollar HEAL initiative (HEAL) and its national consortium of clinical trial sites (EPPICNET), an initiative funded by the U.S. Congress to test innovative non-opioid medicines for chronic pain. The Company believes that NRX-101 represents the first NMDA-targeted non-addictive medicine to be presented to this program. Should the DOD-funded trial yield encouraging data, the Company anticipates that non-dilutive sources of capital could be available, given the national focus on the opioid crisis. Progress in treating chronic pain with NRX-101 may open a larger market for NRX-101 than the originally targeted psychiatry indications.

Additional Synergies of DCS and Lurasidone: Chronic Pain and Depression

NMDA antagonists in general and DCS specifically have demonstrated promise for treating chronic pain. However, the well-known psychomimetic side effects of NMDA drugs have limited their respective use in patients with chronic pain. The combined administration of DCS and lurasidone solves that issue, as DCS and lurasidone appear to mitigate the most common side effects of the other.

Chronic pain and depression are frequently comorbid, sharing common neurobiological pathways. Studies show that the prevalence of pain in depressed patients is 60% to 75%. In a review of over 30,000 adults across four continents, patients who have experienced pain for greater than six months are more than four times as likely to have a depressive disorder than those without chronic pain. Given the strong neurobiological and clinical link between depression and chronic pain, several groups have argued that the treatment of depression should be considered part of a comprehensive strategy for treating chronic pain.

In light of this, the combination of DCS and lurasidone, two proven therapeutics for treating bipolar depression and major depressive disorders, may not only treat chronic pain at various levels of the peripheral and central nervous systems, but may also reduce symptoms of depression that complicate the treatment of chronic pain (Source: Authorea's *D-Cycloserine for the Treatment Of Chronic Pain*, 2023).

POST-TRAUMATIC STRESS DISORDER (PTSD)

In September 2022, NRx announced plans to investigate NRX-101 in PTSD as an additional indication. The Company expects to commence planning for a Phase 2 clinical trial with the study expected to be open for enrollment in 2024.

Post-Traumatic Stress Disorder (PTSD) Overview

PTSD is a mental health disorder that develops when a person has experienced or witnessed a traumatic, life-threatening, terrifying, or dangerous event. These can be single, traumatic instances, or intense, long-lasting traumatic experiences, including war and combat, sexual assault, natural disasters, and mass violence. People with PTSD have intense, disturbing recurrent memories of the traumatic event (flashbacks) and negative thoughts related to their experience that last more than a month after the traumatic event has ended, and are severe enough to interfere with school, work, or relationships.

PTSD may lead to avoidance behavior, negative thoughts, and suicidal ideation. People with PTSD may avoid situations or people that remind them of the traumatic event, and they may have strong negative reactions to something as ordinary as a loud noise or an accidental touch. In the U.S., PTSD affects 13 million people, with five of every 100 adults in the U.S. (5%) having experienced PTSD in any given year, and 1 in 13 people developing PTSD at some point in their life.

Unlike other anxiety disorders, PTSD is significantly associated with depression and suicidal ideation, with people with PTSD three to five times more likely to have a depressive disorder, as depression in PTSD may be driven by pathways that are similar to those that drive depression in other conditions. The association between PTSD and depression also leads to higher suicidal ideation, with people with PTSD who struggle to express their feelings having a higher risk of suicide (Source: *The Recovery Village's PTSD Statistics and Facts*).

The link between PTSD and suicidal ideation has a large effect on the military veteran population. Veterans, especially those who are deployed to a war zone, are more likely to have PTSD than civilians. Post-9/11, the U.S. has lost four times more veterans and service members to suicide than combat, with an estimated 30,177 having died by suicide compared to the 7,057 killed in post-9/11 war operations (Source: Brown University's *Watson Institute: High Suicide Rates among United States Service Members and Veterans of the Post9/11 Wars*).

PTSD Treatment Option

The global PTSD treatment market size was valued at $1.15 billion in 2022 and is projected to grow to $1.60 billion by 2030, primarily driven by the increase in PTSD cases worldwide, rising government initiatives, and the growing demand for better therapeutic options spearheading R&D innovation and the launch of new therapeutic drugs (Source: *Market Research Future's Post-Traumatic Stress Disorder Market Information By Treatment, End Users, And Region - Forecast till 2030*, 2023).

The antidepressant drug class segment dominates the PTSD treatment market, especially the use of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine re-uptake inhibitors (SNRIs) to treat the core symptoms of PTSD. The FDA has approved two SSRIs for the treatment of PTSD—Zoloft (sertraline) and Paxil (paroxetine)—recommended as a first line of treatment. In addition, the symptom relief that medication provides allows many people to participate more effectively in psychotherapy. However, no serotonin-targeted antidepressant has demonstrated an effect in extinction of fear memory in patients, and SSRIs are contraindicated against suicide. In addition, both core symptoms of PTSD (intrusion, avoidance, negative alterations in cognition and mood, alterations in arousal and reactivity) and depression may persist despite the best-available treatment.

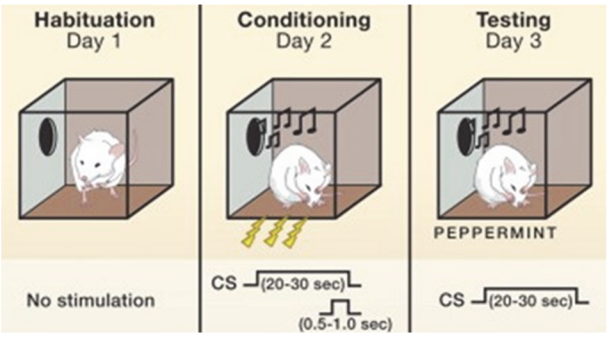
NRX-101 for the Treatment of PTSD

In preclinical and clinical studies, beneficial effects of DCS alone and in combination with antidepressants were observed in the treatment of PTSD. In clinical trials, low dose of DCS (50 mg/day, below the threshold at which DCS begins acting as an antagonist) demonstrated an augmentation of response to psychotherapy for PTSD (Source: *Biological Psychiatry, Vol. 71(11):962-968*, 2012). A related editorial suggests that use of DCS could result in fear extinction through the enhancement of different forms on neuroplasticity, leading to protection against traumatic memory reinstatement, and allowing patients to benefit from psychotherapies and pharmacotherapies for PTSD (Source*: Biological Psychiatry, Vol. 71(11):932-934*, 2012).

Memory or fear extinction is a process in which a conditioned response gradually diminishes over time as the subject learns to uncouple a response from a stimulus. Pavlovian fear conditioning (FC) test, depicted in Figure 20, is a widely used behavioral assay in rodents for measurement of aversive learning and memory relevant to PTSD. In the test, a tone (conditioned stimulus) is paired with a mild electric shock. Once the association is established, the tone induces a fear response (freezing), even without the introduction of an electric shock. However, if after this the tone is presented repeatedly without combination with the electric shock, memory extinction occurs in normal animals, and the subjects learns to disassociate the tone form the electric shock. Since persistence of a traumatic memory in PTSD might be caused by a failure of memory extinction, enhancement of memory extinction might be beneficial for PTSD treatment.

Figure 20

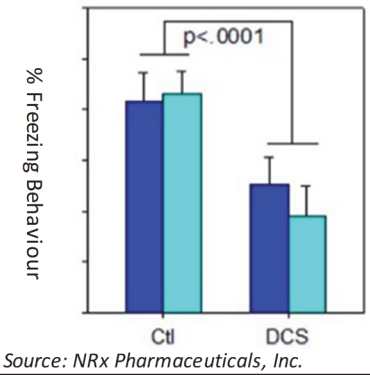
FEAR CONDITIONING MODEL



Source: Cell.com.

Figure 21

DCS IN PTSD MODEL



Source: NRx Pharmaceuticals, Inc.

The fear conditioning rodent model was implemented by NRx to study the effects of NRX-101 and high-dose DCS on fear memory extinction in a preclinical PTSD study. Both NRX-101 and DCS administration demonstrated the ability to enhance fear memory extinction. Rats treated with either NRX-101 or high-dose DCS showed a significant progressive reduction in freezing following conditioning versus the saline administered (control) group (Figure 21).

These finding, together with studies of ketamine's positive effects on PTSD in both humans and rodents, suggest a novel hypothesis on the role of NMDA receptors in PTSD: that excessive plasticity may lead to reactivation of memories of the traumatic event even in the absence of negative reinforcers. Thus, if this is proven correct, use of NMDA antagonists, such as high-dose DCS, may be beneficial to enhance memory extinction and avoid the common pitfalls associated with PTSD.

ANTIBACTERIAL (COMPLICATED URINARY TRACT INFECTION)

NRx is further evaluating NRX-101 for the treatment of complicated UTI (cUTI). The program is based on DCS's antibacterial properties. DCS was originally developed as a broad-spectrum antibiotic approved for the treatment of tuberculosis, and continues to be used worldwide by the World Health Organization (WHO) as an anti-infective, primarily used to treat tuberculosis. In the U.S., it is used only for the treatment of antibiotic-resistant tuberculosis. DCS was never labeled for the treatment of UTI, due to the first- and second-generation antibiotics' effectiveness against the common urinary tract pathogens of the day.

The Company believes that the combination of DCS with a 5-HT2A antagonist in NRX-101 has the potential to treat antibiotic-resistant UTI with decreased propensity to cause unwanted CNS effects. The Company has initiated pre-clinical research to evaluate whether current antibiotic-resistant pathogens are resistant to NRX-101 both in laboratory culture and simulated urine.

As with the NRX-100 development project, the Company does not anticipate funding this initiative with core NRx assets and is exploring structures for a new entity that would provide current and new investors with both capital appreciation and a royalty stream.

Complicated Urinary Tract Infection (cUTI) Overview

Urinary tract infections (UTIs) are the most common outpatient infections in the U.S., accounting for about seven million doctor visits, one million emergency department visits, and more than 100,000 hospitalizations in the U.S. each year (Source: Medstar Health). About half of women and more than one in 10 men will get a UTI in their lifetime, with many people experiencing recurrent UTIs. Worldwide, there are an estimated 150 million cases of UTIs per year, accounting for $6 billion in healthcare expenditures (Source: The Hospitalist's *What makes a urinary tract infection complicated?*).

UTIs are usually caused when bacteria from the skin or rectum enter the urethra. Symptoms include a painful burning sensation while urinating, bloody urine, and more. Normally, UTIs are classified as uncomplicated or complicated. Uncomplicated UTIs can typically be treated on an outpatient basis with a course of antibiotics.

Complicated UTIs (cUTI) on the other hand, are those that carry a higher risk of treatment failure and typically require broader antimicrobial coverage, which leads to longer antibiotic courses and, depending on severity, could require intravenous antibiotics. cUTIs are increasingly common in the U.S., with an estimated 3 million new diagnoses annually, making it one of the most common bacterial infections encountered in the hospital setting and among the most common causes of sepsis in hospitals (Source: *Forum Infectious Diseases' Vol. 6 (11)*, 2019). In the U.S., cUTIs are associated with considerable morbidity and healthcare resource utilization, with cUTI's responsible for over 626,000 hospital admissions a year, comprising about 1.8% of all annual hospitalizations (Source: NIH's *Complicated Urinary Tract Infections*).

Although uncomplicated UTIs have been easily treated and cured with antibiotics for decades, in recent years, increased antibiotic resistance of common pathogens that cause urinary tract infections has resulted in a marked increase in hospitalization and death. As a result of antibiotic resistance—when bacteria become resistant to the medicines used to treat them—a number of antibiotics routinely employed for UTIs have become ineffective, leading to more severe illness, hospitalizations, and mortality, and driving up medical costs. More than 92% of bacteria that cause UTIs are resistant to at least one common antibiotic, and almost 80% are resistant to at least two. At the same time, the fourth-generation antibiotics that are now used to treat cUTI and treat antibiotic resistant pathogens are increasingly associated with systemic side effects (Source: *Scientific America's Antibiotic-Resistant UTIs Are Common, And Other Infections May Soon Be Resistant Too*, 2023).

The emergence of multiple drug-resistant organisms has prompted the investigation of older antimicrobials as well as the development of a number of new antibiotics and combinations, for the treatment of antibiotic resistance infections, including cUTIs.

NRX-101 for the Treatment of Urinary Tract Infection

DCS, a key component of NRX-101, is currently approved for the treatment of urinary tract infection in some countries and, as recently as 2015, was demonstrated to be effective against pathogens that are increasingly resistant to first- and second-line antibiotics. DCS is not widely used, however, because of its known propensity to cause hallucination at therapeutically effective doses.

The mechanism of action of DCS as it relates to the treatment of cUTI is associated with the ability of DCS to kill the bacteria (bactericidal) or arrest bacterial growth (bacteriostatic) depending on its concentration at the infection site. DCS has a structure similar to **D-alanine**, an amino acid required for the synthesis of a key protein that makes up the structure of the bacterial cell wall. By competing with D-alanine, DCS gets incorporated into the bacterial cell wall, weakening it, and resulting in the leakage of cell contents, killing the bacteria and arresting further bacterial growth (Source: MedicineNet).

NRx Preclinical Study

In preclinical testing, NRX-101 demonstrated a broad range of potent antibacterial effect against common antibiotic-resistant urinary pathogens in culture medium and in an artificial urine model. The study, commissioned by NRx at Charles River Laboratories, demonstrated NRX-101's potent in vitro activity against reference strains of urinary tract pathogens known to cause cUTIs. These results are consistent with previously reported academic studies that demonstrate potency of DCS in antibiotic-resistant strains of urinary pathogens. Figure 22 shows the minimum inhibitor concentration (MIC) data of the experiment (MIC value is the lowest concentration of an antibiotic at which bacterial growth is completely inhibited).

Figure 22

NRX-101 IN cUTI

Strain	D-cycloserine	Lurasidone	DCS MIC in combination	Reference
E. coli 35218				
E. coli 25922	256	>142.3	256	256
E. coli 700928	256	>142.3	256	32
E. coli 700336	128	>142.3	256	128
E. coli 2469				
E. coli Xen 16	256	>142.3	256	>256
P. aeruginosa PA01	512	>142.3	512	32
P. aeruginosa 27853	512	>142.3	512	32
P. aeruginosa Xen 41	512	>142.3	128	32
P. aeruginosa BAA 3105	128	>142.3	128-256	16
K. pneumoniae 1705				
A. baumannii 19606				
A. baumannii 1605	512	>142.3	256	32

Source: NRx Pharmaceuticals, Inc.

DCS has the advantage achieving nearly 100% excretion in the urine, while achieving high urinary tract concentration levels with oral administration, suggesting that NRX-101 has the potential to be developed as a safe and effective treatment of cUTI. Because NRx has already completed the Phase 3 manufacture of NRX-101, the Company is in a position to immediately seek investigational human use for this indication.

NRx performed its preclinical testing of NRX-101 against resistant pathogens that appear on the Congressionally-mandated Qualified Infectious Disease Product (QIDP) list and proved in vitro effectiveness against antibiotic-resistant E. coli, Pseudomonas, and Acinetobacter, appearing to meet the requirements for the FDA Qualified Infectious Disease Product (QIDP) designation.

Qualification for QIDP affords a sponsor five years of additional market exclusivity from the FDA, regardless of patent status, together with Fast Track Designation and Priority Review. The Company believes that NRX-101 as an oral medication has the potential to demonstrate benefit in patients who would otherwise require intravenous third and fourth generation antibiotics. Additionally, should NRX-101 succeed in clinical trials, the Company will consider developing a follow-on product that is anticipated to achieve another 20 years of patent exclusivity.

Based on the in vitro study performed at CRL, the Company has submitted an Investigational New Drug application, requesting QIDP, Fast Track, and Priority Review designation. FDA approval of this IND is expected by year-end 2023.

ADDITIONAL POTENTIAL PSYCHIATRY PRODUCTS

The Company's intellectual property portfolio enables NRx to pursue additional combinations of known molecules, including dextromethorphan, d-methadone, and other named NMDA antagonists.

One example is potential product candidate, NRX-102, a new product in exploratory preclinical development, which pairs a fixed dose combination of DCS with Mirtazapine, a currently approved antidepressant. In a 2013 Phase 2 study, clinical data demonstrate the potential efficacy of DCS in combination with an SSRI antidepressant versus an SSRI antidepressant alone in treating patients with treatment resistant MDD.

NRx has also identified additional 5-HT2A antagonists that may be appropriately paired with DCS, in order to capitalize on DCS' ability to inhibit the akathisia induced by SSRI antidepressants.

Existing clinical data have shown DCS to be a useful initial therapeutic agent with which to target the glycine site on the NMDA receptor. However, DCS has mixed agonist/antagonist effects and its antagonist properties are only manifest at high doses of DCS. The Company has identified other small molecule NMDA antagonists that are effective at lower doses and may be paired with 5-HT2A antagonists in order to yield a dual-targeted pro-drug. Accordingly, in the future, the Company plans to explore design initiatives to develop candidate prodrugs that will expand on the dual-targeted properties of NRX-101 and NRX-102.

Examples of this initiative are NRX-201/202, potential candidates that target bipolar depression and MDD/PTSD, respectively. These compounds are anticipated to replace the DCS component of NRX-101/102 with a molecule that is more specifically targeted than DCS at the same glycine site target. The Company's patent portfolio includes issued and pending claims for many such dual-targeted combinations.

Investment Highlights

- NRx Pharmaceuticals, Inc. ("NRx" or "the Company") is a clinical stage biopharmaceutical company developing novel therapeutics targeting the brain's N-methyl-D-aspartate (NMDA) receptors for the treatment of central nervous system disorders with high unmet medical needs.

- The Company's foundation product, NRX-101, is a patented combination of two FDA-approved drugs—D-cycloserine (DCS), an NMDA receptor modulator; and lurasidone, an antipsychotic medication. The Company is assessing the use of NRX-101 in four different indications: suicidal bipolar depression, chronic pain, post-traumatic stress disorder (PTSD), and complicated urinary tract infections (cUTI).

- NRx's technology platform is based on the discovery by Professor Daniel Javitt (NRx Co-founder and Chair of its Scientific Advisory) that: (1) the psychedelic effects of NMDA antagonist drugs could be reversed combining them with serotonin-targeted compounds; and (2) NMDA inhibitors, in turn, block the akathisia side effect normally associate with serotonin-targeted drugs such as lurasidone.

    - The previously undiscovered synergy between these two drug classes is the subject of 48 issued patents and 43 pending patents owned by or licensed to NRx Pharmaceuticals, and as such, is the medical and scientific basis for the Company's technology.

- NRx entered into a collaboration with Alvogen Pharmaceuticals for the development and commercialization of NRX-101 in suicidal bipolar depression, with the potential for up to $330 million in milestones and double-digit royalties.

    - NRx is conducting a single Phase 2b/3 trial of NRX-101 for Suicidal Treatment Resistant Bipolar Depression (S-TRBD), with topline clinical data readout expected by Q1 2024, and potentially an NDA shortly after. The Company may be able to begin commercialization of NRX-101 on this indication in 2024.

    - Under the Alvogen agreement, a successful data readout and completion of a Type B meeting with the FDA (expected by 1Q 2024) would trigger a $10 million payment to NRx, at which point, Alvogen would be responsible for all future development and commercialization costs for this indication.

- NRx is also developing a proprietary form of Ketamine (NRX-100) for the treatment of acute suicidality. The Company has signed a data sharing agreement with the KETIS study leadership (a trial of ketamine on 156 patients hospitalized for acute suicidality in seven French Government Hospitals) and signed a development and manufacturing agreement with Nephron Pharmaceuticals, Inc., to develop and manufacture a presentation of ketamine suitable for treating suicidal depression.

    - The Company believes that these two initiatives provide NRx with the necessary requirements for a submission of an NDA for ketamine (Q1 2024), with a targeted PDUFA date in Q4 2024.

    - NRx does not anticipate funding this initiative with its core NRx assets and plans to establish a ketamine-focused spinoff company that would potentially provide current and new investors with both capital appreciation and a royalty stream.

- NRX-101 is also being evaluated for the treatment of chronic pain, as a non-addicting substitute of opioid products. The Company is planning to start a pharmacokinetic study following result readout of a 200-person U.S. Department of Defense-funded trial in the treatment of chronic pain with DCS.

    - The Company obtained IND approval for NRX-101 in the treatment of chronic pain, and plans to seek Fast Track Designation, Priority Review, and Breakthrough Therapy Designation for this indication.

- NRx is also assessing NRX-101 for the treatment of PTSD and cUTI.
    - Based on the in vitro study performed by NRx in the cUTI indication, the Company has submitted an IND application, requesting Qualified Infectious Disease Product (QIDP), Fast Track, and Priority Review designation. FDA approval of this IND is expected by year-end 2023.
    - As with the NRX-100 development project, the Company does not anticipate funding the cUTI program with core NRx assets and is exploring structures for a new entity that would provide current and new investors with both capital appreciation and a royalty stream.
- NRx finalized transfer of its Phase 3-level commercial drug manufacturing processes to the U.S. and completed production required for its clinical trials (over 1 million capsules).
- The Company believes that its cash on hand is sufficient to fund operations through the upcoming milestones described in this report (page 17). NRx is conducting key initiatives to minimize the need to utilize current financial assets to continue the development of its different programs, including: (1) funding of ketamine-related and cUTI-related initiatives under new entities (spinoffs) with alternative financing; (2) seeking non-dilutive sources of capital for its chronic pain program, such as its submission for consideration to the HEAL initiative; and (3) the capital influx prior to approval of NRX-101 and assignment of development costs resulting from the Alvogen agreement.
- NRx is led by a highly experienced management team with proven success within pharmaceutical research, development, and commercialization.
- As of September 30, 2023, NRx's cash and cash equivalent position was $8.9 million.
- In its November 14, 2023 earnings press release, NRx announced that it had received a $30 million term sheet for the anchor investment in its planned ketamine spinoff.

Competition

As NRx continues to develop and seeks to commercialize its products, the Company may encounter competition from other pharmaceutical and biotechnologies companies, including those that currently market approved products for the indications the Company is targeting, as well as those developing new and innovative therapeutic treatments. Potential competitors may also include academic institutions, government agencies, and other public and private research organizations that seek to establish collaborative arrangements for research, development, manufacturing, and commercialization. The potential competition that NRx may face is profiled in the accompanying section. It is not intended to be an exhaustive collection of the Company's competitors; however, it is believed to be a selection of the type of competition that NRx may face as it strives to commercialize its technologies and product candidates.

All of NRx's programs are based on the same compound (NRX-101), a patented oral, fixed-dose combination of two FDA-approved drugs: D-cycloserine (DCS), an NMDA receptor modulator; and lurasidone, a 5-HT2a receptor antagonist. When administered together, DCS and lurasidone appear to mitigate the most common side effects of the other; lurasidone reduces the risk of psychosis and mania while DCS reduces the occurrence of akathisia. The previously undiscovered synergy between these two drug classes is well protected by intellectual property (IP) assets owned by or licensed to NRx (as described on pages 9-10), and as such, is the medical and scientific basis for the Company's technology platform.

The Company's most advanced program is the use of NRX-101 in bipolar depression with suicidal ideation and behavior. NRx believes that its focus on suicidality and bipolar depression provide a competitive advantage, as suicidal bipolar depression has not been specifically addressed by pharmaceutical companies, with no FDA-approved medicines available today for individuals affected by this condition.

To the Company's knowledge, NRX-101 is the only treatment in development for suicidal ideation in bipolar patients. Clinical trials for bipolar depression either exclude patients with active suicidal ideation, or if suicidal ideation is targeted, focus on Major Depressive Disorder (MDD) and exclude bipolar depression. Patients with suicidal ideation were also routinely excluded from the clinical trials of those medicines currently approved for the treatment of bipolar depression. For example, a study to assess esketamine for the treatment of suicidal patients will specifically exclude bipolar patients, in whom the incidence of suicidal ideation is the highest.

NMDA Receptor Antagonists for Major Depresive Disorder (MDD)

There are currently two drugs for depression that contain an NMDA receptor antagonist. One is a version of an anesthesia drug called ketamine, an NMDA receptor antagonist, which is used as an intravenous (IV) off-label treatment for severe depression, as it can quickly relieve symptoms. In 2019, the U.S. FDA approved a nasal spray version called esketamine, or S-ketamine, under the brand name Spravato. The following year, the FDA expanded the approved use of esketamine to include treating patients with MDD with attempted suicide or thoughts of it. However, the clinical effect of a single ketamine infusion is demonstrated to diminish very quickly (e.g., three days post-intravenous dosing and two days post-intranasal dosing). Moreover, ketamine is an addictive controlled substance that causes hallucinations, has known neurotoxicity, and exhibits abuse potential.

Despite the promising clinical findings, ketamine is not approved by the FDA for use in suicidal bipolar depression or the reduction of suicidality by the FDA. This problem is compounded by two recent developments: (1) a long-awaited trial of nasal ketamine for the same indication failed to meet its primary endpoints; and (2) the FDA issued a second warning letter on October 10, 2023, cautioning against the compounding of ketamine, which is likely to further limit access to what appears to be a lifesaving drug.

In 2022, a second medication was approved for major depression but not bipolar depression, which was a combination drug with the brand name Auvelity (described on page 48), which is composed of two active ingredients—bupropion (an antidepressant) and dextromethorphan (an NMDA receptor antagonist that is also a commonly used cough suppressant).

Other Potential Competitors

Abilify Maintena® (Lundbeck A/S)

Aripiprazole (sold under the brand name Abilify Maintena) is a long-acting once-a-month injection for the treatment of schizophrenia and as maintenance monotherapy treatment of bipolar disorder. Lundbeck also has the following products and product candidates targeting psychiatric and neurological conditions: Rexulti (brexpiprazole), approved as an adjunctive therapy for the treatment of major depressive disorder (MDD); Trintellix (vortioxetine) approved for treatment of MDD; Aripiprazole, a long-acting injectable for the treatment of schizophrenia and bipolar disorder; and product candidate Brexpiprazole, in Phase 3 trials for PTSD.

Auvelity® (Axsome Therapeutics)

Auvelity is a combination of dextromethorphan (an NMDA receptor antagonist that is also a commonly used cough suppressant), and bupropion (an antidepressant), approved by the FDA in August 2022 for the treatment of major depressive disorder (MDD) in adults. Auvelity is the only approved drug for depression that blocks NMDA receptors and is the the first oral depression treatment with a new mechanism of action to gain approval in over 60 years. However, similar to many antidepressants, Auvelity has an FDA warning regarding the increased risk of suicidal thoughts and behavior in pediatric and young adult patients taking antidepressants. Auvelity is not approved for bipolar depression.

Caplyta® (Intra-Cellular Therapies, Inc./Bristol Myers Squibb)

Lumateperone (sold under the brand name Caplyta) is an atypical antipsychotic medication approved for the treatment of schizophrenia as well as bipolar depression, as either monotherapy or adjunctive therapy (with lithium or valproate). It was developed by Intra-Cellular Therapies and licensed from Bristol-Myers Squibb. Lumateperone was approved for medical use in the U.S. in December 2019 with an initial indication for schizophrenia, and became available in February 2020. It has since demonstrated efficacy in bipolar depression and received FDA approval in December 2021 for depressive episodes associated with both bipolar I and II disorders.

Esmethadone (REL-1017) (Relmada Therapeutics, Inc.)

Esmethadone (REL-1017) is a new chemical entity (NCE) and novel NMDA receptor antagonist in late-stage development as an adjunctive treatment for MDD in adults. Clinical trial results showed rapid, robust, and sustained antidepressant effects from REL-1017 in patients with inadequate response to standard treatment, while dipslaying a very favorable safety profile with the lack of meaningful risk of abuse. Relmada is also advancing a clinical-stage program in neurodegenerative diseases based on psilocybin and select derivative molecules.

Latuda® (Sumitomo Dainippon Pharma Co., Ltd.)

Lurasidone hydrochloride (sold under the brand name Latuda) is an antipsychotic medicine used to treat schizophrenia as well as episodes of depression associated with bipolar disorder (bipolar depression). It works by balancing the levels of dopamine and serotonin in the brain, substances that help regulate mood, behaviors, and thoughts. It belongs to a group of medications called antipsychotics. Sumitomo Dainippon Pharma is also conducting a Phase 3 clinical study of its late-stage product candidate, SEP-4199 (non-racemic amisulpride), for bipolar depression in the U.S. and Japan. This program is being conducted as part of a collaboration between Sunovion, its parent company Sumitomo Dainippon Pharma and Otsuka Pharmaceutical Co., Ltd.

Lybalvi® (Alkermes Inc.)

Lybalvi is a combination of an established antipsychotic agent (olanzapine) and a novel μ-opioid receptor antagonist (samidorphan) for the treatment of schizophrenia and bipolar I disorder. Lybalvi is designed to provide the efficacy of olanzapine while limiting the weight gain often associated with olanzapine therapy. In clinical studies, patients treated with Lybalvi demonstrated statistically significantly less weight gain than patients treated with olanzapine. Lybalvi gained FDA approval in June 2021 to treat schizophrenia, as a monotherapy or for the acute (short term) treatment of manic or mixed episodes, and as monotherapy or an adjunct to lithium or valproate for maintenance treatment of manic or mixed episodes that happen with bipolar disorder. Since Lybalvi blocks the effects of opioids, such as heroin, methadone, or opioid pain medicines, attempting to overcome Lybalvi's opioid blockade with high or repeated doses of exogenous opioids could lead to life-threatening or fatal opioid intoxication.

Seroquel® (AstraZeneca Plc/ Cheplapharm Arzneimittel GmbH)

Quetiapine (sold under the brand name Seroquel) is an atypical antipsychotic medication to treat several kinds of mental health conditions, including schizophrenia and bipolar disorder. The FDA originally approved Seroquel in September 1997 for the treatment of psychotic disorders, in January 2004 for short term treatment of acute manic episodes associated with bipolar disorder (bipolar mania), and in October 2006, for bipolar depression. Overall, Seroquel and its extended release formulation Seroquel XR, are indicated for the treatment of schizophrenia, acute depressive episodes in bipolar disorder (as monotherapy or with other medications), long-term treatment of bipolar disorder (as an adjunct to lithium or divalproex), as well as major depressive disorder in adults, among others. In 2019, following the expiration of its patent protection in the U.S. and Canada, AstraZeneca agreed to sell the commercial rights to Seroquel and Seroquel XR in the U.S. and Canada to Cheplapharm Arzneimittel GmbH. AstraZeneca previously divested the rights to Seroquel and Seroquel XR in the UK, Japan, and other major international markets.

Symbyax® (Eli Lilly & Company)

Eli Lilly & Company's Symbyax combines two of the company's billion-dollar blockbuster drugs—fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI), and olanzapine (Zyprexa), an atypical antipsychotic. The fluoxetine and olanzapine combination of two antidepressant-antipsychotic compounds is used to treat depression that is a part of bipolar disorder, and depression in patients who received other antidepressants that did not work well. Olanzapine and fluoxetine work by increasing the activity of certain chemicals, called serotonin, norepinephrine, and dopamine in the brain. These chemicals help relieve the symptoms of depression.

Vraylar® (Abbvie Company [Allergan PLC]/ Gedeon Richter)

Cariprazine (sold under the brand name Vraylar and Reagila), is an atypical antipsychotic, which is used in the treatment of schizophrenia, bipolar mania, bipolar depression, and major depressive disorder. Vraylar obtained FDA approval for the treatment of schizophrenia and bipolar disorder in 2015, and expanded its FDA-approved uses to depressive episodes associated with bipolar disorder (2019) and major depressive disorder (MDD) as an adjunctive treatment (2022). In March 2022, Abbvie and Gedeon Richter announced a co-development and licensing agreement to research, develop, and commercialize novel dopamine receptor modulators for potential treatment of neuropsychiatric conditions. The collaboration is based on the results of preclinical research carried out by Richter and includes several new chemical entities selected for development. AbbVie and Richter have collaborated for 15 years on Central Nervous System (CNS) projects, including products such as Vraylar/Reagila.

Chronic Pain Competitive Landscape

Some of the commonly used medicines to treat chronic pain are opioid pain relievers, nonsteroidal anti-inflammatory drugs, and adjuvant analgesics. However, the standard of care is the long-term use of opioids, including oxycodone (OxyContin®), hydrocodone (Vicodin®), codeine, morphine, and many others. However, their long-term use has led to a serious national crisis related to the misuse and addiction of opioids products. The current opioid crisis, fueled by a failure of non-opioid medication to achieve meaningful clinical relief, creates an acute need for nonaddictive, non-sedating pain medication. Thus, researchers are focusing on the development of non-opioid and non-addictive effective chronic pain therapeutics.

As NRx seeks to develop NRX-101 as a non-opioid/non-addictive therapeutic agents for chronic pain, it can expect to encounter competition from the major companies in the chronic pain market (offering both opioid and non-opioid alternatives), such as Eli Lilly and Company, Pfizer Inc., Abbott Laboratories, Medtronic Plc., Boston Scientific Corporation, Novartis AG, Johnson & Johnson, AstraZeneca PLC, Bristol-Myers Squibb, and others. In addition, it may also encounter competition from smaller companies developing novel non-opioid therapeutics for chronic pain. Examples of these types of companies, include, among others:

(1) *Nementum Pharmaceuticals*: the company's assets include four novel non-opioid products in development to treat pain, both in the U.S. and around the world. Its lead candidate is NTM-006 (in-licensed from Johnson & Johnson), a new chemical entity with a novel mechanism of action in Phase 2 trials for pain as monotherapy or as part of a multimodal regimen;

(2) *Centrexion Therapeutics*: the company's pipeline includes CNTX-6970, an oral candidate for the treatment of inflammatory chronic pain (Phase 2), CNTX-0290, an investigational small molecule for chronic pain (Phase 1), and CNBTX-6016, for neuropathic pain (Phase 1); and

(3) *Vertex Pharmaceuticals*: the company's product candidates include VX-548, in Phase 3 development for the treatment of chronic pain.

Historical Financial Results

Figures 23, 24, and 25 (pages 51-53) provide a summary of NRx's most recent key financial statements for the quarter ended September 30, 2023.

Figure 23
NRx Pharmaceuticals, Inc.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(in thousands, except share and per share data)
(Unaudited)

	Three months ended September 30,		Nine months ended September 30,	
	2023	2022	2023	2022
Operating expenses:				
Research and development	$ 3,314	$ 4,129	$ 10,837	$ 12,571
General and administrative	2,494	5,012	12,344	21,876
Settlement expense	—	—	250	—
Total operating expenses	5,808	9,141	23,431	34,447
Loss from operations	(5,808)	(9,141)	(23,431)	(34,447)
Other (income) expenses:				
Interest income	(119)	(95)	(420)	(119)
Interest expense	40	—	40	3
Change in fair value of convertible note payable	359	—	2,794	—
Change in fair value of warrant liabilities	(26)	37	(27)	(236)
Change in fair value of Earnout Cash liability	—	—	—	(4,582)
Total other (income) expenses	254	(58)	2,387	(4,934)
Net loss	$ (6,062)	$ (9,083)	$ (25,818)	$ (29,513)
Change in fair value of convertible note attributed to credit risk	—	—	22	—
Other comprehensive loss	—	—	22	—
Comprehensive loss	$ (6,062)	$ (9,083)	$ (25,840)	$ (29,513)
Net loss per share:				
Basic and diluted	$ (0.07)	$ (0.14)	$ (0.35)	$ (0.45)
Weighted average common shares outstanding:				
Basic and diluted	81,946,957	66,449,593	74,114,180	65,532,409

Source: NRx Pharmaceuticals, Inc.

Figure 24
NRx Pharmaceuticals, Inc.
CONDENSED CONSOLIDATED BALANCE SHEETS
(in thousands, except share and per share data)

	September 30, 2023 (Unaudited)	December 31, 2022
ASSETS		
Current assets:		
Cash and cash equivalents	$ 8,902	$ 20,054
Prepaid expenses and other current assets	4,187	5,741
Total current assets	13,089	25,795
Other assets	21	21
Total assets	$ 13,110	$ 25,816
LIABILITIES AND STOCKHOLDERS' (DEFICIT) EQUITY		
Current liabilities:		
Accounts payable	$ 3,631	$ 2,076
Accrued and other current liabilities	4,728	4,855
Accrued clinical site costs	575	914
Convertible note payable and accrued interest - short term	10,069	7,703
D&O insurance payable	314	—
Warrant liabilities	10	37
Total current liabilities	19,327	15,585
Convertible note payable and accrued interest - long term	—	2,822
Total liabilities	$ 19,327	$ 18,407
Preferred stock, $0.001 par value, 50,000,000 shares authorized;	—	—
Series A convertible preferred stock, $0.001 par value, 12,000,000 shares authorized; 3,000,000 and 0 shares issued and outstanding at September 30, 2023 and December 31, 2022, respectively	3	—
Common stock, $0.001 par value, 500,000,000 shares authorized; 83,919,554 and 66,442,989 shares issued and outstanding at September 30, 2023 and December 31, 2022, respectively	84	67
Additional paid-in capital	242,533	230,339
Accumulated other comprehensive loss	(22)	—
Accumulated deficit	(248,815)	(222,997)
Total stockholders' (deficit) equity	(6,217)	7,409
Total liabilities and stockholders' (deficit) equity	$ 13,110	$ 25,816

Source: NRx Pharmaceuticals, Inc.

Figure 25
NRx Pharmaceuticals, Inc.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)
(Unaudited)

	Nine months ended September 30, 2023	Nine months ended September 30, 2022
CASH FLOWS FROM OPERATING ACTIVITIES:		
Net loss	$ (25,818)	$ (29,513)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation expense	4	3
Stock-based compensation	1,590	2,862
Change in fair value of warrant liabilities	(27)	(236)
Change in fair value of earnout cash liability	—	(4,582)
Change in fair value of convertible promissory note	2,794	—
Non-cash settlement expense	250	—
Increases (decreases) in operating assets and liabilities:		
Prepaid expenses and other assets	1,554	(1,443)
Accounts payable	1,654	(1,519)
Accrued expenses and other liabilities	(466)	2,991
Net cash used in operating activities	(18,465)	(31,437)
CASH FLOWS FROM INVESTING ACTIVITIES		
Purchase of computer equipment	(4)	(11)
Net cash used in investing activities	(4)	(11)
CASH FLOWS FROM FINANCING ACTIVITIES		
Repayment of note payable	—	(518)
Repayment of convertible note	(2,288)	—
Repayment of insurance loan	(474)	—
Proceeds from issuance of insurance loan	786	—
Proceeds from issuance of Series A preferred stock and warrants issued in private placement, net of issuance costs	1,171	—
Proceeds from issuance of common stock and warrants issued in private placement, net of issuance costs	8,122	22,610
Net cash provided by financing activities	7,317	22,092
Net (decrease) increase in cash and cash equivalents	(11,152)	(9,356)
Cash and cash equivalents at beginning of period	20,054	27,605
Cash and cash equivalents at end of period	$ 8,902	$ 18,249
Supplemental disclosure of cash flow information:		
Cash paid for interest	$ 646	$ —
Non-cash investing and financing activities		
Issuance of common stock as principal and interest repayment for convertible notes	$ 982	$ —
Issuance of common stock warrants as offering costs	$ 75	$ 726
Issuance of common stock for settlement of accrued liability	$ 250	$ 17

Source: NRx Pharmaceuticals, Inc.

Recent Events

11/27/2023—NRx Pharmaceuticals, Inc. announced that Dr. Jonathan Javitt, Founder and Chief Scientist of NRx Pharmaceuticals, will present a corporate overview at the Noble Capital Markets' 19th Annual Emerging Growth Investor Conference on Monday, December 4th, 2023, at the College of Business Executive Education Building at Florida Atlantic University in Boca Raton, FL.

11/13/2023—Announced its financial results for the quarter ended September 30, 2023 and provided a business update.

11/7/2023—Announced that it will release its third quarter 2023 financial results after the market closes on Tuesday, November 14, 2023, via press release.

11/06/2023—NRx Pharmaceuticals, Inc. and Nephron Pharmaceuticals, Inc. (Nephron), a leading manufacturer of sterile injectable drugs, announced the signing of a development and manufacturing agreement to manufacture a presentation of ketamine suitable for treating suicidal depression, an urgent public health need.

10/31/2023—Announced the signing of a development contract to manufacture a presentation of ketamine suitable for intravenous administration under current U.S. Food and Drug Administration (FDA) manufacturing regulations. Existing supplies of ketamine are not labeled for treatment of depression and suicidality and often do not conform to modern manufacturing requirements for single-dose injectable medications. NRx and its manufacturing partner plan to release further information in an upcoming 8K filing.

10/26/2023—Announced further alignment with the FDA Division of Anesthesiology, Addiction Medicine, and Pain Medicine in connection with the development of NRX-101 for treatment of chronic pain. The communication took the form of a “Study May Proceed” letter, authorizing NRx to proceed with opening a pharmacokinetic study under the newly-established Investigational New Drug file for treatment of chronic pain. This is a formal letter that generally follows clearance of an IND and outlines nonclinical and clinical requirements suggested by the review division. The preclinical requirements identified by FDA for this new indication are consistent with the already-implemented preclinical requirements previously identified by the Division of Psychiatry Products for the use of NRX-101 to treat Bipolar Depression, although the duration of some nonclinical studies will be extended for the anticipated longer treatment duration associated with chronic pain.

10/12/2023—Announced a strategic acceleration of its plans to develop a commercial form of NRX-100 (intravenous ketamine) to treat acute depression and suicidality, based on recent data cooperation agreements and on changes in the regulatory environment. The full presentation may be viewed on the Company’s web page Link. Two simultaneous and unexpected developments augment NRx’s renewed focus on offering a commercial form of intravenous ketamine: (1) A long-awaited trial of nasal ketamine for the same indication failed to meet its primary endpoints. (2) The FDA issued a second Advisory on October 10, 2023 cautioning against the compounding of ketamine, which follows its February 16, 2022 warning letter regarding the compounding of nasal forms of ketamine. Sequential warning letters of this nature are frequently followed by enforcement actions, particularly in the case of a DEA scheduled, dangerous drug, such as ketamine.

10/05/2023—Announced that Dr. Jonathan Javitt, Chief Scientist of NRx Pharmaceuticals, is scheduled to present a corporate overview at the 8th Annual Dawson James Conference on October 12th, 2023, at the Wyndam Grand Jupiter in Jupiter Florida. Management will conduct in-person one-on-one meetings throughout the conference and deliver the Company’s presentation.

10/02/2023—Announced that the U.S. FDA gave the Company clearance to proceed with human trials to treat Chronic Pain under the Investigational New Drug (IND) application filed for the use of NRX-101. The IND application leverages pioneering research on the use of D-cycloserine (a key ingredient of NRX-101) in the treatment of chronic pain. NRx Pharmaceuticals plans to seek Fast Track and Breakthrough Therapy Designations from the FDA while awaiting near-term results of Department of Defense (DOD)-funded trial.

09/18/2023—Announced that Stephen Willard, J.D., Chief Executive Officer and Dr. Jonathan Javitt, Chief Scientist of NRx Pharmaceuticals, will present a company overview at the Sidoti Virtual Small Cap Conference on Thursday, September 21, 2023.

09/15/2023—Announced that it signed a data sharing agreement with Foundation FundaMental, led by Prof. Marion Leboyer, MD, PhD, who served on the NRx Scientific Advisory Board, the study leadership of a randomized, placebo-controlled trial of 156 patients hospitalized for Acute Suicidality and Depression in seven French Government Hospitals. This trial demonstrated a dramatic and statistically-significant reduction in suicidal ideation and depression among patients treated with intravenous ketamine. The trial reached its primary endpoint for all patients and demonstrated the largest effect among the subgroup with bipolar depression. At a meeting with the FDA in January 2023, the FDA requested randomized, placebo-controlled data in support of intravenous ketamine for acute suicidality in the inpatient setting. Such trials are extraordinarily complex to organize. In this case, NRx approached Prof. Leboyer and established the current Data Sharing Agreement. The top line data from this trial were published in the British Medical Journal (BMJ Vol, 376, 2022)

09/14/2023—Entered into an agreement with LS Associates, a division of LifeSci Advisors, LLC ("LSA"), pursuant to which LSA will provide certain consulting services to the Company, including but not limited to, arranging for the provision of the Company's Interim Chief Financial Officer. In connection with the agreement, the Company appointed Richard Narido to serve as Interim Chief Financial Officer of the Company. As Interim Chief Financial Officer, Mr. Narido will serve as the Company's principal financial officer and principal accounting officer. The Company also announced that it accepted the resignation of Seth Van Voorhees, Ph.D., former Chief Financial Officer of the Company, which was tendered on September 11, 2023, effective as of September 30, 2023.

09/07/2023—Announced that Stephen Willard, J.D., Chief Executive Officer and Dr. Jonathan Javitt, Chief Scientist of NRx Pharmaceuticals, are scheduled to present a company overview at the H.C. Wainwright 25th Annual Global Investment Conference, in New York City. The presentation is scheduled for September 12, 2023.

08/30/2023—Announced submission of an IND application to the FDA for the use of NRX-101 to treat Chronic Pain. The IND application leverages pioneering research on the use of D-cycloserine (a key ingredient of NRX-101) in the treatment of chronic pain and the recent licensure by NRx of a US Patent for the use of D-cycloserine in the treatment of pain. Nonclinical and substantial clinical data are already on file with FDA for NRX-101, which has already been granted Breakthrough Therapy Designation for the treatment of suicidal bipolar depression.

08/29/2023—Entered into a definitive purchase agreement with accredited investors to purchase 3,000,000 shares of preferred stock at $0.40 per share, which will convert, after six (6) months into 3,000,000 common shares and 3,000,000 warrants to purchase common stock at a purchase price of $0.40 per share; the term on these warrants is five (5) years. These shares may also be converted to common shares at the investor's option should the closing share price of NRx common stock reach $1.20 per share during the six-month period.

08/14/2023—Announced its financial results for the second quarter ended June 30, 2023, and provided a business update.

08/07/2023—Signed a License Agreement for U.S. Patent 8,653,120 that claims the use of D-cycloserine for the treatment of chronic pain in exchange for a commitment to pay milestones and royalties as development milestones are reached in the field of chronic pain. The patent is supported by extensive nonclinical data and early clinical data that suggest the potential for NMDA antagonist drugs, such as NRX-101 to decrease both chronic pain and neuropathic pain while potentially decreasing craving for opioids.

06/20/2023—Announced that Stephen Willard, J.D., Chief Executive Officer and Dr. Jonathan Javitt, Chief Scientist of NRx Pharmaceuticals, will present a company overview at the H.C. Wainwright 4th Annual Neuropsychiatry Virtual Conference on June 26, 2023.

06/09/2023—Announced closing of $6.28 million registered direct offering for the purchase and sale of 9,670,002 shares of common stock at a purchase price of $0.65 per share. In a concurrent private placement, the Company issued unregistered warrants to purchase up to 9,670,002 shares of common stock at an exercise price of $0.6525 per share that are exercisable six months following issuance for five years following the initial exercise date. H.C. Wainwright & Co. acted as the exclusive placement agent for the offering.

06/05/2023—Announced a global collaboration agreement with Lotus Pharmaceuticals, a multinational pharmaceutical company, and Alvogen, a privately owned U.S. based pharmaceutical company, covering the development and commercialization of NRX-101 for suicidal treatment-resistant bipolar depression (for global markets. Under the terms of the agreement, relating to NRX-101 for the U.S. market, NRx is entitled to receive an initial payment of $10 million upon achieving both a successful read-out from the ongoing Phase 2b/3 clinical trial and completion of a Type B meeting with the U.S. FDA. NRx would receive an additional payment of $5 million upon receipt of FDA approval for NRX-101 as well as bonus milestone payments of increasing amounts up to $330 million based on reaching certain net sales targets. In addition to success-based payments, NRx is eligible to receive a royalty on net sales between 12% and 16% contingent on certain sales thresholds for the U.S. market and other success-based payments for markets outside of the U.S Lotus will acquire worldwide rights for NRX-101 for treatment of suicidal treatment-resistant bipolar depression and will be responsible for commercialization of NRX-101 in markets outside of the U.S. Alvogen and Lotus have committed to fund the next registrational study in suicidal treatment-resistant bipolar depression to support approval of NRX-101 contingent upon successful results of the ongoing Phase 2b/3 clinical trial and completion of a Type B meeting with the FDA.

05/16/2023—Announced its financial results for the first quarter of 2023 and provided a business update.

03/30/2023—Announced its financial results for the full year 2022 and provided a business and clinical update.

03/27/2023—Reported that the independent Data Safety Monitoring Board (DSMB) reviewed the safety and efficacy findings of the first fifty enrolled participants in the Company's clinical trial of NRX-101 for the treatment of Severe Bipolar Depression and Subacute Suicidal Ideation or Behavior (www.clinicaltrials.gov NCT NCT03395392). The DSMB found no futility signal at this stage of the trial. Similarly, no safety signals were identified in association with NRX-101 and the DSMB recommended that enrollment in the trial continue as planned. Based on the DSMB findings, the Company has upgraded the ongoing trial to a Phase 2b/3 trial whose results may be used in a future registrational filing, should the primary endpoint be met.

03/09/2023—Announced that it consummated an offering of 3,766,666 shares of common stock and 3,766,666 warrants to purchase common stock at a combined purchase price of $0.75 per share of common stock and associated warrant. The shares of common stock purchased in the offering are subject to restriction on transfer for a period of six (6) months following issuance. The warrants have an exercise price of $0.75 per share, will be exercisable commencing six (6) months following issuance and will have a term of five years from the issuance date. The gross proceeds from the offering are expected to be approximately $2.9 million.

02/22/2023—Announced that the U.S. Patent and Trademark Office has issued U.S. Patent No. 11,576,911. This patent, issued to Glytech LLC, is exclusively licensed to NeuroRx, Inc., a wholly-owned subsidiary of NRx Pharmaceutical. The claims of the new patent cover methods for treating a patient suffering from depression, including bipolar depression or major depression, with or without suicidality by administering to the patient an effective amount of the Company's lead product candidate, NRX-101.

02/13/2023—Reported the minutes of a Type B meeting with the U.S. FDA's Division of Psychiatry Products held on January 11, 2023. The purpose of the meeting was to discuss requirements for submission of a New Drug Application for NRX-101. During the meeting, the FDA suggested a broadening of the addressable population of the indication to include patients stabilized from suicidality either with ketamine (as designed) or with other standard of care therapeutic approaches. The FDA further guided the Company to broaden the study of NRX-101 to include chronic/intermittent treatment of patients with Bipolar Depression and suicidality. This could enable a pathway for the use of NRX-101 by a broader segment of the approximately 7 million individuals in the U.S. with Bipolar Disorder on a long-term basis.

02/02/2023—Reported the recommendations of an independent DSMB, which reviewed the safety findings of the first fifty enrolled participants in the Company's Phase 2 clinical trial of NRX-101 for the treatment of Severe Bipolar Depression and Subacute Suicidal Ideation or Behavior (www.clinicaltrials.gov NCT NCT03395392). The DSMB recommended that enrollment in the trial continue as planned and identified no drug-related Serious Adverse Events or other safety issues of concern. The Company anticipates that the DSMB will examine unblinded study data in March 2023 to assess the study for safety, potential futility, and conditional power.

01/19/2023—Announced that it had a meeting and a written response from the FDA regarding its path for NDA submission for its lead compound, NRX-101. With FDA's written response, it appears that NRx has reached alignment with the FDA regarding its proposed registration manufacturing plan.

01/05/2023—Announced that it will be presenting a scientific update of its Phase 2 and Phase 3 development program for NRX-101 in the treatment of suicidal bipolar depression at the upcoming 6th Annual Neuroscience Innovation Forum by Sachs Associates on January 8, 2023, as part of the activities surrounding the annual J.P. Morgan Healthcare Conference being held in San Francisco.

01/03/2023—Announced that its first clinical trial site has been contracted for its Phase 3 clinical trial of NRX-101 for the treatment of Severe Bipolar Depression with Acute Suicidal Ideation and Behavior (with others expected in near future) and that first dosing of patients is expected in early 2023. NRX-101 is the first investigational medicine to target this condition, for which the only currently approved treatment is Electroconvulsive Therapy.

12/05/2022—Announced the appointment of Carrie M. Carretta, PhD, APN-BC, AHN-BC, PMHNP as Senior Vice President, Clinical Development and Medical Affairs. She will lead the Company's clinical development program and provide medical oversight across all indications. Dr. Carretta will report to the Chief Executive Officer and Director.

12/02/2022—Announced it received written notice on December 1, 2022, from The Nasdaq Stock Market informing NRx Pharmaceuticals that it has regained compliance with the minimum bid price requirement under the Nasdaq Listing Rule 5450(a)(1) (which requires the Company to maintain a minimum closing bid price of $1.00 per share) and the matter is now closed. Nasdaq staff made this determination after NRx Pharmaceuticals' closing bid price was above $1.00 per share for 10 consecutive business days from November 16, 2022, to November 30, 2022.

Risks and Disclosures

This Executive Informational Overview® (EIO) has been prepared by Crystal Research Associates, LLC ("CRA") with the assistance of NRx Pharmaceuticals, Inc. ("NRx" or "the Company") based upon information provided by the Company. CRA has not independently verified such information. Some of the information in this EIO relates to future events or future business and financial performance. Such statements constitute forward-looking information within the meaning of the Private Securities Litigation Act of 1995. Such statements can only be predictions and the actual events or results may differ from those discussed due to the risks described in NRx's statements on forms filed from time to time.

The content of this report with respect to NRx has been compiled primarily from information available to the public released by the Company through news releases and other filings. NRx is solely responsible for the accuracy of this information. Information as to other companies has been prepared from publicly available information and has not been independently verified by NRx or CRA. Certain summaries of activities and outcomes have been condensed to aid the reader in gaining a general understanding. CRA assumes no responsibility to update the information contained in this report. In addition, for year one of its agreement, CRA has been compensated by the Company in cash of fifty thousand dollars and has been awarded options for its services in creating this report and for quarterly updates.

Investors should carefully consider the risks and information about NRx's business, as described below and more fully detailed in the Company's recently filed Form 10-K, filed with the SEC on March 31, 2023. Investors should not interpret the order in which considerations are presented in this document or other filings as an indication of their relative importance. In addition, the risks and uncertainties covered in the accompanying sections are not the only risks that the Company faces. Additional risks and uncertainties not presently known to NRx or that it currently believes to be immaterial may also adversely affect the Company's business. If any of such risks and uncertainties develops into an actual event, NRx's business, financial condition, and results of operations could be materially and adversely affected.

This report is published solely for information purposes and is not to be construed as an offer to sell or the solicitation of an offer to buy any security in any state. Past performance does not guarantee future performance. For more complete information about the risks involved of investing in the Company, as well as for copies of this report, please contact NRx by calling (484) 254-6134.

Share price suppression associated with Naked Shorting

Shareholders and others have repeatedly noted that the Company's share price appears to be adversely affected by short sales of stock that frequently accompanies positive news. While covered short sales (i.e., those sales that are accompanied by borrowing of an existing share of stock) is legal, "naked" shorting, without an underlying borrowed share, is not. A recent Federal Court decision holds brokerages liable for damages to companies associated with persistent naked short positions.

In Q3 2023, the Company contracted with ShareIntel, Inc. to examine disparities between NRx stock positions as reported by brokerages and NRx shares reported by DTC, the electronic clearinghouse for the Nasdaq exchange. The Company announced that persistent disparities of approximately 1 million to 1.5 million shares were identified. The Company's has now instructed its counsel to initiate outreach to the compliance departments of the identified brokerages, demanding that all uncovered short positions in the Company's stock be closed via a forced delivery of shares. The Company has been advised by counsel that this action has resulted in share appreciation when implemented by other issuers of Nasdaq stock.

Risk Factors Summary

The following section provides a summary of key risk factors identified by NRx. Since this is only a summary, a much more comprehensive listing of significant risk factors that the Company may encounter is provided in NRx's most recent Annual Report, Form 10-K, filed with the SEC on March 31, 2023.

https://app.quotemedia.com/data/downloadFiling?webmasterId=101533&ref=317378716&type=PDF&symbol=NRXP&companyName=NRX+Pharmaceuticals+Inc.&formType=10-K&dateFiled=2023-03-31.

- NRx has a limited operating history upon which to base an investment decision. The Company has not been profitable historically and may not achieve or maintain profitability in the future.
- The Company needs to raise additional capital to operate its business. If it fails to obtain the capital necessary to fund operations, NRx will be unable to continue as a going concern or complete its product development.
- NRX-101 is in clinical testing and the Company cannot predict with any certainty if or when it might submit an NDA for regulatory approval.
- NRx has not yet scaled manufacturing of its drug products to levels that are required for sustained sales.
- The Company has been, and may become involved in, disputes, claims, arbitration, and litigation.
- If NRx fails to obtain or maintain FDA and other regulatory clearances for its products, or if such clearances are delayed, the Company will be unable to commercially distribute and market its products in the U.S.
- NRx's products will face significant competition in the markets for such products and future products may never achieve market acceptance. The Company is faced with rapid technological change and developments by competitors may render its products or technologies obsolete or non-competitive.
- The Company is currently operating in a period of economic uncertainty and capital markets disruption, which has been significantly impacted by geopolitical instability due to ongoing military conflict worldwide.
- NRx's relationships with customers and payors will be subject to applicable anti-kickback, fraud and abuse, transparency, and other healthcare laws and regulations, which could expose the Company to criminal sanctions, civil penalties, contractual damages, reputational harm, and administrative burdens.
- Managing NRx's growth as it expands operations may strain Company resources.
- Failure to achieve and maintain effective internal controls over financial reporting in accordance with Section 404 of the Sarbanes-Oxley Act could impair the Company's ability to produce timely and accurate financial statements or comply with applicable regulations and have a material adverse effect on its business.
- Even if a drug product is approved, regulators may impose limitations on the use or marketing of such product.
- If NRx is unable to design, conduct, and complete clinical trials successfully, its drug candidates will not be able to receive regulatory approval. The Company cannot predict whether regulatory agencies will determine that the data from clinical trials of its product candidates supports marketing approval.
- There is no guarantee that regulators will grant NDA approval of NRx's current or future product candidates.
- If an adverse event occurs during a clinical trial, the regulators or an internal review board may delay or terminate the trial.

- Discussions and guidance of clinical trials are not binding obligations on the part of regulatory authorities. The results of NRx's current or future clinical trials may not support its product candidate claims or may result in the discovery of unexpected adverse side effects.

- Delays in the commencement or completion of pharmaceutical development, manufacturing, or clinical efficacy and safety testing could result in increased costs and delay the Company's ability to generate revenues.

- Even if NRx's products are approved by regulatory authorities, if the Company or its suppliers fail to comply with ongoing FDA regulation or if NRx experiences unanticipated problems with its products, these products could be subject to market restrictions or withdrawals.

- Conducting clinical trials of the Company's drug candidates or commercial sales of a drug candidate may expose NRx to expensive product liability claims and the Company may not be able to maintain product liability insurance on reasonable terms or at all.

- If the Company pursues development of its NRX-100 drug candidate, the use of a controlled substance subjects it to DEA scrutiny and compliance, which may result in additional expense and clinical delays, and may generate controversy. In addition, the use of controlled substances may limit the availability of the active ingredients needed for NRX-100.

- Modifications to NRx's products may require new NDA approvals and some of the Company's other product candidates will require Risk Evaluation and Mitigation Strategies.

- NRx's business relies on certain licensing rights that can be terminated in certain circumstances.

- The Company's business depends upon securing and protecting critical intellectual property. If NRx is found to be infringing on patents or trade secrets owned by others, the Company may be forced to cease or alter its product development efforts, obtain a license to continue development or sale of the Company's products, and/or pay damages.

- Breaches by NRx's employees or other parties may allow trade secrets to become known to the Company's competitors.

- NRx may not receive royalty or milestone revenue relating to its product candidates under its collaboration and future license agreements for several years, or at all.

- The Company does not have direct control of third parties performing preclinical and clinical trials. If such third parties do not perform as contractually required or expected, NRx may not be able to obtain regulatory approval for or commercialize its products.

- NRx has no manufacturing capabilities and depends on other parties for manufacturing operations. These manufacturers may fail to satisfy the Company's requirements and applicable regulatory requirements.

- NRx's issuance of additional shares of Common Stock or convertible securities could make it difficult for another company to acquire it, may dilute investors' ownership of the Company's shares, and could adversely affect NRx's stock price. Future sales, or the perception of sales, of Common Stock by NRx or its existing stockholders could cause the market price for its Common Stock to decline.

- The Company qualifies as a "smaller reporting company" within the meaning of the Securities Act, which could make NRx's securities less attractive to investors and may make it more difficult to evaluate the Company's performance.

- Anti-takeover provisions in the Company's governing documents and under Delaware law could make an acquisition of NRx more difficult, limit attempts by Company stockholders to replace or remove current management, and limit the market price of NRx's Common Stock.

- Certain of the Company's stockholders have effective control of NRx, and their interests may conflict with NRx's or investors in the future. The Company is no longer a "controlled company" under the corporate governance rules of NASDAQ. However, NRx continues to rely on certain exceptions from corporate governance standards.

- If NRx fails to meet the applicable continued listing requirements of NASDAQ Global Market, NASDAQ may delist its common stock, in which case, the liquidity and market price of the Company's common stock could decline.

- NRx does not intend to pay dividends on its Common Stock for the foreseeable future. However, NRx announced in its November 15, 2023 earnings call that it anticipated a royalty payment to shareholders from sales of NRX-100 both via those ketamine spinoff shares allocated to current shareholders and via ketamine royalties that would be distributed to NRx Pharmaceuticals.

Glossary

5-HT2a—A widely expressed protein receptor that belongs to the serotonin receptor family. 5-HT2A receptors are expressed in many tissues and organs throughout the body, including the central nervous system, where they are found extensively in the brain region essential for learning, cognitive function, and social interaction.

Acute Suicidal Ideation Or Behavior (ASIB)—Patients with strong suicidal thoughts, which require stabilization of symptoms in a clinical setting.

Akathisia—A feeling of muscle quivering, restlessness, and inability to sit still, sometimes a side effect of antipsychotic or antidepressant medication.

Biomarker Letter of Support—A letter issued to a requester that briefly describes the U.S. Food and Drug Administration (FDA)'s Center for Drug Evaluation and Research's (CDER) thoughts on the potential value of a biomarker and encourages further evaluation.

Bipolar Depression—The depressive low mood phase of bipolar disorders, bipolar depression is a common symptom of this mental illness, and in about half of these individuals is associated with suicidal ideation.

Bipolar Disorder—A mental health condition that causes extreme mood swings that include emotional highs (mania or hypomania) and lows (depression).

Breakthrough Therapy Designation—A U.S. Food and Drug Administration (FDA) process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

Clinical Global Impression Scale (CGI-S)—The Clinical Global Impression – Severity scale (CGI-S) is a seven-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis.

Columbia Suicide Severity Rating Scale (C-SSRS)—A suicidal ideation and behavior rating scale created by researchers at Columbia University, University of Pennsylvania, University of Pittsburgh, and New York University to evaluate suicide risk.

Complicated Urinary Tract Infections (cUTI)—A urinary tract infection that carries a higher risk of treatment failure and typically requires longer antibiotic courses.

D-alanine—An amino acid required for the synthesis of a key protein that makes up the structure of the bacterial cell wall.

D-cycloserine (DCS)—A broad-spectrum antibiotic and anti-infective originally approved for the treatment of tuberculosis, it was discovered to act as a NMDA antagonist at high doses with potent antidepressant capabilities.

Excitotoxicity—A process by which nerve cells suffer damage or death when the levels of otherwise necessary and safe neurotransmitters, such as glutamate, become pathologically high, resulting in excessive stimulation of receptors.

Fast Track Designation—A designation by the U.S. Food and Drug Administration (FDA) of an investigational drug for expedited review to facilitate development of drugs that treat a serious or life-threatening condition and fill an unmet medical need.

Fear Memory—A memory of a traumatic event that causes a fear of its recurrence.

Good Manufacturing Practices (GMP)—A system of regulations promulgated by the FDA for ensuring that manufacturers, processors, and packagers of drugs, medical devices, some food, and blood take proactive steps to ensure that their products are produced and controlled according to quality standards.

HEAL initiative (HEAL)—A U.S. National Institutes of Health (NIH)-wide effort to improve prevention and treatment strategies for opioid misuse and addiction and to enhance pain management.

Investigational New Drug (IND)—A request from a clinical study sponsor to obtain authorization from the FDA to administer an investigational drug or biological product to humans in a clinical trial setting.

Ketamine—A synthetic compound and NMDA antagonist used as an anesthetic and analgesic drug and also (illicitly) as a hallucinogen.

Lurasidone—An antipsychotic medication used to treat schizophrenia and bipolar disorder sold under the trade name Latuda®, among others.

Major depressive disorder (MDD)—A mood disorder having a clinical course involving one or more episodes of serious psychological depression that last two or more weeks each, and are characterized by a loss of interest or pleasure in almost all activities, a decrease in energy, difficulties in thinking or making decisions, loss of self-esteem or feelings of guilt, and suicidal thoughts or attempts.

Montgomery Åsberg Depression Rating Scale (MADRS)—A generic, clinician-rated scale, which covers all DSM-IV criteria of major depressive disorder except psychomotor retardation and agitation.

Neuroplasticity—The ability of the brain to form and reorganize synaptic connections, especially in response to learning or experience or following injury.

New Drug Application (NDA)—The vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an IND become part of the NDA.

NMDA (N-methyl-D-aspartate)—A receptor of glutamate (the primary excitatory neurotransmitter in the human brain). NMDA receptors play a crucial role in regulating a wide variety of neurological functions, including breathing, locomotion, learning, memory formation, and neuroplasticity.

Opioid—A class of drugs that derive from, or mimic, opium. Opioids work in the brain to produce a variety of effects, including pain relief. As a class of substances, they act on opioid receptors to produce morphine-like effects.

Post-Traumatic Stress Disorder (PTSD)—A condition of persistent mental and emotional stress occurring as a result of injury or severe psychological shock, typically involving disturbance of sleep and constant vivid recall of the experience, with dulled responses to others and to the outside world.

Prescription Drug User Fee Act (PDUFA)—Once the FDA accepts a filing for the approval of a drug, the agency must complete its review process within 10 months (or 6 months if the drug is given a priority review designation). The date at the end of the review period is referred to as the PDUFA date.

Psychedelic—Relating to or denoting drugs (such as LSD) that produce hallucinations and apparent expansion of consciousness.

Psychomimetic—A substance or drug that mimics the symptoms of psychosis, including delusions and/or delirium, as opposed to only hallucinations.

Qualified Infectious Disease Product (QIDP)—An FDA designation designed to promote the development of antibacterial and antifungal drugs to treat serious or life-threatening infections. It was introduced in the Generating Antibiotic Incentives Now (GAIN) Act in 2012. QIDP designation confers particular advantages, including priority review, fast-track designation, and an additional five years' market exclusivity if a product is licensed.

Sepsis—A serious condition that happens when the body's immune system has an extreme response to an infection. Sepsis occurs when chemicals released in the bloodstream to fight an infection trigger inflammation throughout the body, causing damage multiple organ systems, shock, and possible death.

Serotonin—A neurotransmitter whose biological function is complex, touching on diverse functions including mood, cognition, reward, learning, memory, and numerous physiological processes such as vomiting and vasoconstriction.

Special Protocol Agreement—A process in which sponsors may ask to meet with the FDA to reach agreement on the design and size of certain clinical trials, clinical studies, or animal studies.

Sub-Acute Suicidal Ideation or Behavior (SSIB)—Patients with suicidal thoughts not at immediate risk of self-harm who are typically treated in an outpatient setting.

Suicidal Treatment Resistant Bipolar Depression (S-TRBD)—Treatment-resistant bipolar disorder (TRBD) is a term used when a bipolar patient displays a minimal or an inadequate response to standard treatments. In suicidal TRBD, this comes with suicidal ideation, including both acute and sub-acute Suicidal Ideation and Behavior (ASIB/SSIB).

Type B meeting—Meetings with the FDA held to discuss the overall development program for products granted Breakthrough Therapy designation status.

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