Zacks Small-Cap Research

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Cerecor, Inc.

(CERC-NASDAQ)

CERC: Initiating on Cerecor, Inc.; Developing Novel Treatments for Psychiatric Conditions…

Based on our probability adjusted DCF model that takes into account potential future revenues from CERC-301 and CERC-501, CERC is valued at $12/share. This model is highly dependent upon the clinical success of CERC-301 and CERC-501 and will be adjusted accordingly based upon future clinical results.

Current Price (05/23/16)	$3.21
Valuation	**$12.00**

INITIATION

Cerecor, Inc. (CERC) is developing treatments for patients with neurological and psychiatric disorders. The company has two compounds currently in Phase 2 clinical trials: CERC-301, an NMDA receptor subunit 2B (NR2B) antagonist, as an adjunctive treatment for major depressive disorder (MDD) and CERC-501, a kappa opioid receptor (KOR) antagonist, for smoking cessation. The company also has a preclinical compound, CERC-406, which is a catechol-O-methyltransferase (COMT) inhibitor for the treatment of residual cognitive impairment in patients with MDD.

Cerecor's compounds offer a unique mechanism of action, proof-of-concept for the molecule or target, and biomarkers to guide development for each targeted condition, which could translate to safer and more efficacious options than what is currently available.

SUMMARY DATA

52-Week High	**$6.65**
52-Week Low	**$2.67**
One-Year Return (%)	**N/A**
Beta	**N/A**
Average Daily Volume (sh)	**25,020**
Shares Outstanding (mil)	**9**
Market Capitalization ($mil)	**$28**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**16**
Insider Ownership (%)	**7**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**

Risk Level	**N/A,**
Type of Stock	**N/A**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	0.0 A	0.0 A	0.0 A	0.0 A	0.3 A
2016	0.0 A	0.0 E	0.0 E	0.0 E	0.0 E
2017					0.0 E
2018					0.0 E

Earnings per Share
(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	- A	- A	- A	- A	-$4.71 A
2016	-$0.32 A	-$0.31 E	-$0.32 E	-$0.32 E	-$1.27 E
2017					-$1.04 E
2018					-$0.95 E

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WHAT'S NEW

Initiating Coverage

We are initiating coverage of Cerecor, Inc. with a valuation of $12.00/share. Cerecor is a clinical stage biopharmaceutical company developing treatments for patients with neurological and psychiatric disorders. We believe that each of Cerecor's lead compounds represent potential best-in-class treatments due to their novel mechanisms of action and potentially better safety profile compared to currently available therapeutic options. The company's lead compounds are:

- **CERC-301 – Adjunctive Treatment for Major Depressive Disorder**: CERC-301 is an antagonist of the N-methyl-D-aspartate (NMDA) receptor, which is a receptor subtype of the glutamate neurotransmitter system. The compound is currently in a Phase 2 clinical trial for the treatment of patients with major depressive disorder (MDD) who are not adequately responding to their current antidepressant medication and are severely depressed. As opposed to current standard of care anti-depressants that can take weeks or months to produce a significant reduction in depression symptoms, CERC-301 has the potential to have a rapid onset of action, likely in a matter of days. The rapid onset of action is due to the specific blockade of the NMDA receptor subunit 2B (NR2B), which also could potentially lead to fewer side effects than other non-selective NMDA receptor antagonists.

- **CERC-501 – Substance Use Disorders and Adjunctive Treatment for MDD**: CERC-501 is a potent and selective antagonist of the kappa opioid receptor (KOR), which is believed to be involved in modulating stress, mood, and addictive behaviors. The compound is currently in a proof-of-concept Phase 2 clinical trial in smoking cessation. In addition, two externally funded clinical trials are being conducted with CERC-501 in treating cocaine addiction and mood disorders.

- **CERC-406 – Cognitive Impairment**: CERC-406 is the lead preclinical candidate from the company's proprietary compounds of catechol-O-methyltransferase (COMT) inhibitors. The company is planning to develop CERC-406 as a treatment for residual cognitive impairment syndrome in patients with MDD.

CERC-301 is currently being investigated in the Clin301-203 clinical trial, a Phase 2 randomized, double blind, placebo controlled study evaluating the antidepressant effect of 12 mg and 20 mg doses of CERC-301 in MDD patients currently experiencing a severe depressive episode despite stable ongoing treatment with either an SSRI or SNRI. A total of 104 subjects are expected to enroll and we anticipate top-line results being released in the first half of 2017.

CERC-501 is currently being investigated in the Clin501-201 clinical trial, which is a Phase 2 randomized, double blind, placebo controlled trial to evaluate the effects of 15 mg of CERC-501 on tobacco withdrawal and reinstatement and to assess craving, mood, and anxiety during 18 hours of abstinence in 66 heavy cigarette smokers. Results from this study are expected in the second half of 2016.

Cerecor recently completed an initial public offering (IPO) in October 2015 where a total of 4,000,000 units were sold for $6.50 per unit. Each unit consisted of one share of common stock, one Class A warrant to purchase one share of common stock at an exercise price of $4.55, and one Class B warrant to purchase one-half share of common stock at an exercise price of $3.90. Net proceeds from the IPO were approximately $23.6 million, and we estimate the company's current cash position of $16.6 million is enough to fund operations through the end of 2016.

INVESTMENT THESIS

Major Depressive Disorder

Depression is a serious international public health problem that can lead to significant morbidity and mortality. The American Psychiatric Association's (APA) *Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* classifies the depressive disorders as major depressive disorder, disruptive mood dysregulation disorder, persistent depressive disorder, and depressive disorder due to other medical conditions. Common symptoms among all patients with depressive disorders are the presence of sad, empty, or irritable mood along with cognitive impairments that affect a person's ability to perform normal functions. The differences in the types of depressive disorder are due to duration, timing, or cause of the condition.

DSM-5 diagnosis of major depressive disorder (MDD) requires at least five of the following symptoms occurring during the same two-week period.

- Diminished interest/loss of pleasure in almost all activities (required for MDD diagnosis)
- Depressed mood (could be exemplified by irritability in children/adolescents)
- Significant weight change or appetite disturbance (in children could be inability to achieve expected weight)
- Sleep disturbance
- Psychomotor agitation
- Fatigue/low energy
- Feelings of worthlessness
- Diminished mental capacity, indecisiveness
- Recurrent thoughts of death/suicide ideation/suicide attempt

Depression screening tests are commonly used to screen for depression and other psychiatric disorders. The most widely used screening tool is the Patient Health Questionnaire-9 (PHQ-9). The PHQ is a three-page questionnaire that can be completed by the patient and can be used for making criteria-based diagnoses of depressive and other mental disorder commonly seen by primary care physicians (Spitzer *et al*., 1999). PHQ-9 is the 9-item depression module from the full PHQ, with each item scored on a scale of 0-3 to measure severity.

It is currently unclear exactly what causes MDD, however it likely involves a complex interplay between neurotransmitter supply and the regulation of various receptors. Most studies point to a central role of the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) as a contributing factor, however additional neurotransmitters are also likely involved, including norepinephrine, dopamine, glutamate, and brain-derived neurotrophic factor (BDNF) (Dunlop *et al*., 2007).

A number of antidepressant medications are known to work by increasing the levels of the monoamine neurotransmitters serotonin, norepinephrine, and/or dopamine. This resulted in the formulation of the "monoamine hypothesis" of depression. This hypothesis postulates that the deficiency of one or more neurotransmitters is responsible for the clinical characteristics of depression. However, there are a number of reasons to believe that the monoamine hypothesis does not fully explain the cause of depression. While antidepressant medications cause a sudden increase in monoamine neurotransmitters, it takes several weeks of treatment in order for patients to begin experiencing clinical benefit. In addition, reduction of monoamine neurotransmitters does not affect the mood of healthy people (Krishnan *et al*., 2008). Other factors that are hypothesized to contribute to the development of depression are differences in brain structure, certain personality types, and past instances of abuse.

In 2010, the U.S. Centers for Disease Control (CDC) reported that the prevalence of depression in adults from 2006-2008 was 9%, with 3.4% meeting the criteria for major depression (CDC, 2010). An additional report by the U.S. National Comorbidity Survey Replication stated that 16 million adults in the U.S. suffer from a depressive episode during a 12-month period. Morbidity associated with depression takes the form of completed suicide, which is the tenth leading cause of death in the U.S. (CDC).

Treatment of Depression

There are three main types of treatment for depression: pharmacotherapy, psychotherapy, and electroconvulsive therapy (ECT).

Pharmacotherapy: The drugs utilized to treat MDD include selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, serotonin-dopamine activity modulators (SDAMs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). It typically takes two weeks of treatment before a clinical response can be achieved. Antidepressant medications are typically very effective, with treatment failures typically due to medication noncompliance.

SSRIs: Examples of these drugs include citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft). These compounds are utilized as a first-line treatment due to their ease of dosing and low toxicity. Common side effects include gastrointestinal upset, sexual dysfunction, and fatigue.

SNRIs: This class of drugs includes venlafaxine (Effexor), desvenlafaxine (Pristiq), duloxetine (Cymbalta), and levomilnacipran (Fetzima). These compounds are typically used as a second-line treatment for those that don't respond to SSRIs, but can be used first-line in those that have concurrent pain or fatigue associated with their depression. The side effects for SNRIs are similar to those for SSRIs.

Atypical antidepressants: Examples of these drugs include bupropion (Wellbutrin), mirtazapine (Remeron), and trazodone (Desyrel). They are all effective as monotherapies in treating depression and are typically used in combination therapy for more difficult to treat patients.

SDAMs: Examples of this class of drugs include brexpiprazole (Rexulti) and aripiprazole (Abilify). They work as partial agonists of 5-HT1A and dopamine D2 receptors and as antagonists of 5-HT2A and noradrenaline alpha1B/2C receptors. Brexpiprazole is used as adjunctive therapy for depression. Side effects of these medications include weight gain, agitation, and restlessness.

TCAs: These medications include amitriptyline (Elavil), clomipramine (Anafanil), desipramine (Norpramin), and doxepin (Sinequan). TCAs have long been know to be effective in treating depression, however they are used less commonly now due to their side effect profile, which includes blurred vision, drowsiness, weight gain, and constipation, and considerable toxicity in the case of overdose.

MAOIs: These drugs include isocarboxazid (Marplan), phenelzine (Nardil), selegiline (Emsam), and tranylcypromine (Parnate). They are used in a variety of mood and anxiety disorders. Side effects include insomnia, anxiety, weight gain, and sexual dysfunction.

The Agency for Healthcare Research and Quality (AHRQ) compared the effectiveness of 12 second-generation antidepressants and found that they were mostly similar, although they did vary with respect to onset of action and side effects that could affect quality of life (AHRQ, 2008). No matter which medication is prescribed, the American College of Physicians recommends that clinicians assess patient status, therapeutic response, and adverse effects within 1 to 2 weeks of starting therapy and if no treatment response is seen by 6 to 8 weeks to try a different medication (Qaseem *et al*., 2008). Pharmacologic treatment is typically continued for 4 to 9 months after a satisfactory response following a depressive episode.

Psychotherapy: Psychotherapy is the first-line treatment for children and adolescents under the age of 18 who have depression. There are a number of different psychotherapies, with the most studied form being cognitive behavior therapy (CBT). CBT usually lasts for between 10 and 20 minutes and includes behavioral strategies and cognitive restructuring for the purpose of changing negative thoughts. Additional psychotherapy treatments include behavioral activation, interpersonal therapy, and problem-solving therapy.

Electroconvulsive therapy: This therapy involves the electrical inducement of seizures to provide relief from depression and is used as a last line of treatment. The overall effectiveness rate appears to be approximately 50% (Dierckx *et al*., 2012). Risks associated with the procedure include those found with the use of general anesthesia, post-procedure confusion, and rarely memory difficulties.

Problems With Current MDD Treatment Options

While currently available antidepressant treatments are successful for some patients, there exist a number of less than ideal characteristics surrounding clinical outcomes with their use. This was exemplified in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Fava *et al*., 2003), a study conducted by the National Institute of Mental Health that involved one or more acute treatment steps to achieve symptom remission in a total of 4,041 patients with MDD. The results of the study showed that:

- The average time to remission was 5.4 to 7.4 weeks. In other words, MDD patients did not begin to see clinical benefit for over a month. For patients with severe MDD and suicide ideation, the lag in time between the beginning of treatment and clinical efficacy is too long and is one of the biggest drawbacks to currently available MDD treatments.

- Only 36.8% of MDD patients achieved remission from their clinical symptoms after 12 weeks of treatment. Overall, 51.4% of patients failed to respond to treatment, which was defined as achieving a 50% reduction in symptoms.

These two points underscore the biggest problems facing physicians who are treating patients with MDD. The lack of efficacy for a majority of patients when trying an antidepressant medication for the first time means that a doctor may need to switch patients' medications in order to identify one the patient responds to. In addition, the slow onset of action (average response rates of 5.4 to 7.4 weeks in the STAR*D study) means that depression symptoms can persist for many weeks following diagnosis and the initiation of treatment. Lastly, common side effects seen with current antidepressant medications (drowsiness, gastrointestinal disturbance, sexual dysfunction) are just one more reason that more potent and faster-acting antidepressants are greatly needed for patients suffering from MDD.

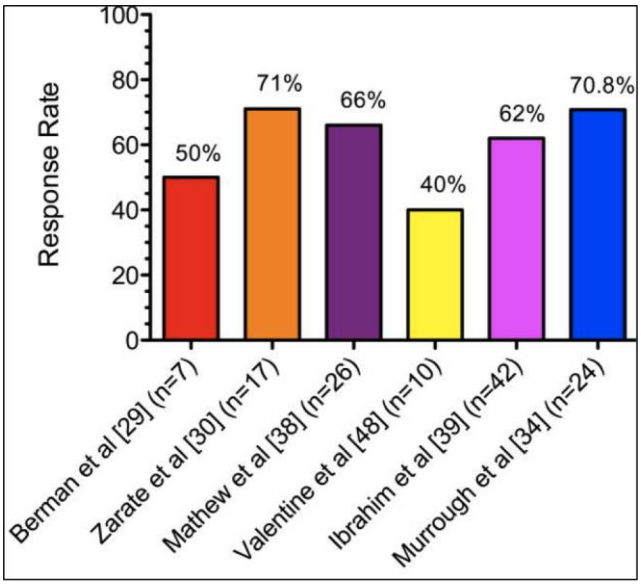
NMDA Receptor Antagonists Offer an Alternative Approach to Treating MDD

Glutamate is a major neurotransmitter in the central nervous system. Glutamate receptors are classified into two groups: the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor and the N-methyl-D-aspartate (NMDA) receptor are *ionotropic* receptors while metabolic and heterotrimeric GTP-binding protein-linked glutamate receptors (mGluRs) are *metabotropic* receptors (Palmada *et al*., 1998). The NMDA receptor has received particular attention due to its activation causing a cascade of potential antidepressant-like effects including an increase in the production of BDNF (Sanacora *et al*., 2008).

NMDA receptors are named due to the fact that N-methyl-D-aspartate binds to them in a selective fashion, and does not bind to the other glutamate receptors. They are composed of various subunits to form three different subtypes: GluN1, GluN2, and GluN3 (or NR1, NR2, and NR3). There are eight variants of the NR1 subunit, four different NR2 subunits (referred to as NR2A through D), and two NR3 subunits (Paoletti *et al*., 2007).

There are a number of recent studies that show the NMDA receptors contribute to the pathophysiology of MDD (Serafini *et al*., 2013). This may be the result of an imbalance in glutamate signaling that can lead to NMDA agonism, which ultimately leads to enhanced excitatory activity in neural circuits involved in depression. Traditional monoamine antidepressants are known to interfere with glutamate system function by reducing glutamate release and synaptic transmission along with regulating NMDA receptor activity (Musazzi *et al*., 2013). However, as discussed above, these effects take time, but point to the opportunity to have a rapid effect on depression through NMDA antagonism.

Ketamine, a drug that has been utilized for over 50 years as a dissociative anesthetic, is a known antagonist of the NMDA receptor. It was first studied as a treatment for depression in 2000 in a study involving seven patients with MDD that received a single sub-anesthetic dose (Berman *et al*., 2000). The results showed significant improvement in depressive symptoms within 72 hours of treatment with ketamine. These results were followed up by additional single-dose studies that showed very similar results (Zarate *et al*., 2006; Valentine *et al*., 2011). Multiple-dose studies have also been published showing the efficacy of ketamine in treating MDD (aan het Rot *et al*., 2010; Murrough *et al*., 2013). Ketamine also appears to have anti-suicidal properties, as shown in studies involving patients with chronic (DiazGranados *et al*., 2010) and acute (Larkin *et al*., 2011) suicide ideation. The effect of ketamine in multiple depression studies is summarized in the following figure, which shows the peak response rates for a series of trials that tested ketamine in patients with MDD (Murrough *et al*., 2012).



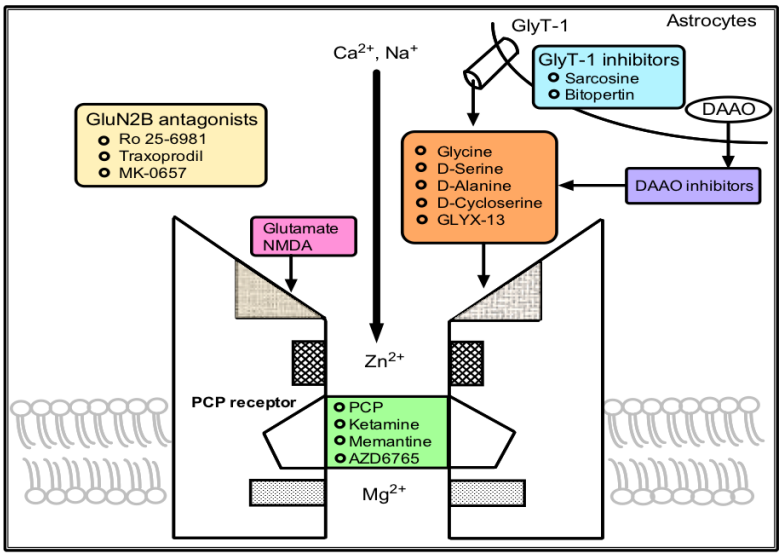
Source: Murrough *et al*., 2012

Preclinical studies show that ketamine exerts its anti-depressant effects through a number of different signaling pathways. Treatment with ketamine results in increased phosphorylation and activation of the mTOR signaling pathway, leading to a sustained induction of synaptic proteins that lasts for a similar length of time as the therapeutic response (Li *et al*., 2010). The neuronal and antidepressant effects of ketamine are blocked by administration of rapamycin, which is an inhibitor of mTOR signaling. Ketamine also results in an increase in extracellular glutamate in the prefrontal cortex (Moghaddam *et al*., 1997), likely the result of disinhibition of glutamate transmission (Homayoun *et al*., 2007). Lastly, BDNF signaling is likely involved in ketamine's effects based on studies showing that the effects are blocked when tested in mice with BDNF deficits (Liu *et al*., 2012).

While shown to be quite effective at rapidly reducing depressive symptoms, ketamine has a number of side effects that preclude its widespread use including the fact it is a psychotomimetic that can result in toxicity and a schizophrenic-like syndrome when abused (Behrens *et al*., 2007). What is needed is a drug that has the rapid anti-depressive action of ketamine but without the toxic side effects.

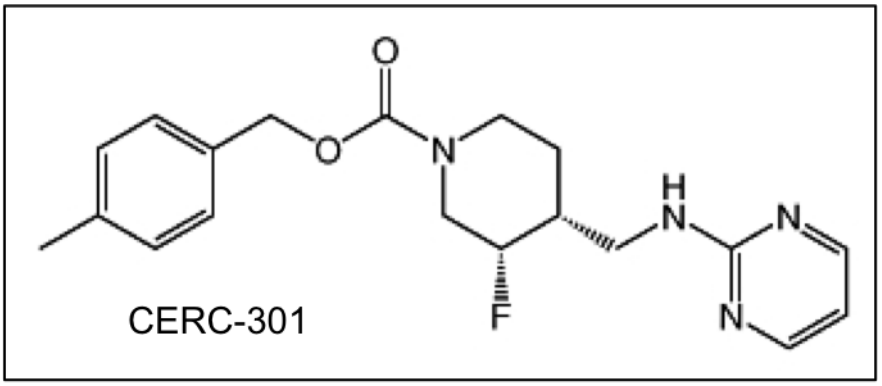
CERC-301 is a Selective NR2B Antagonist

The current understanding about the role of different NMDA receptor subtypes is that compounds that act as subunit-selective modulators are likely to be as efficacious but safer and with less abuse potential than non-selective NMDA receptor antagonists such as ketamine. There are a number of different compounds currently under development that target various NMDA receptor subunits, as shown in the following figure.



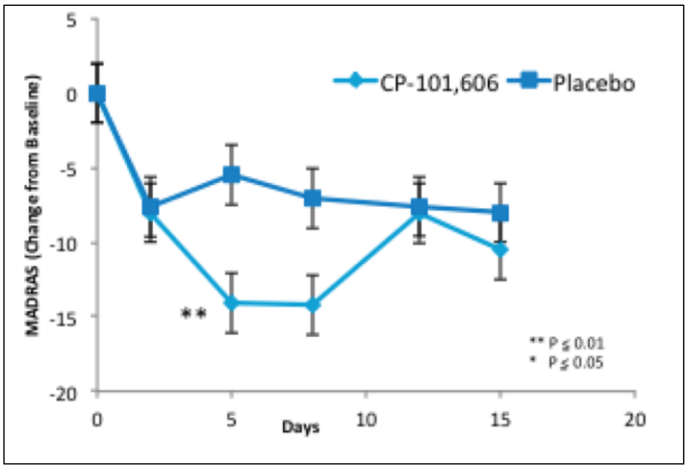
Source: Hashimoto *et al.,* 2013

Cerecor is developing CERC-301, an orally available and NR2B-specific receptor antagonist, as an adjunctive medication in patients with severe MDD who are not responding to their current antidepressant treatment. CERC-301, then MK-0657, was acquired by Cerecor from Merck in 2013 through an exclusive worldwide license. Merck conducted preliminary trials of CERC-301 in healthy subjects, but failed to demonstrate clinically significant changes in mental status, however changes in blood pressure were observed which is consistent with the compounds mechanism of action.



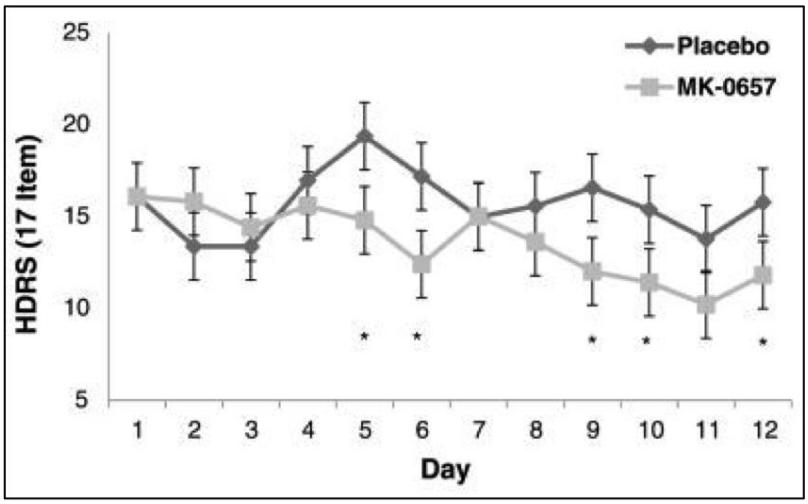
Source: Mony *et al*., 2009

Previous studies with other NR2B-selective antagonists have shown the potential for this class of compounds to be utilized in treating MDD. In 2008, a randomized, double blind clinical trial was performed in patients with MDD who were refractory to standard of care treatment to test CP-101,606, an NR2B-selective antagonist (Preskorn *et al*., 2008). In this study, patients were first treated in an open-label fashion for six weeks with the SSRI paroxetine followed by a single blind placebo infusion. Those who did not respond to paroxetine (n=30) were then randomized to a single infusion of CP-101,606 or placebo followed by four additional weeks of paroxetine. As the following figure shows, patients treated with CP-101,606 exhibited a greater change in the Montgomery-Asberg Depression Rating Scale (MADRS), which is a scale used by psychiatrists to measure the severity of depressive episodes, than those treated with placebo.



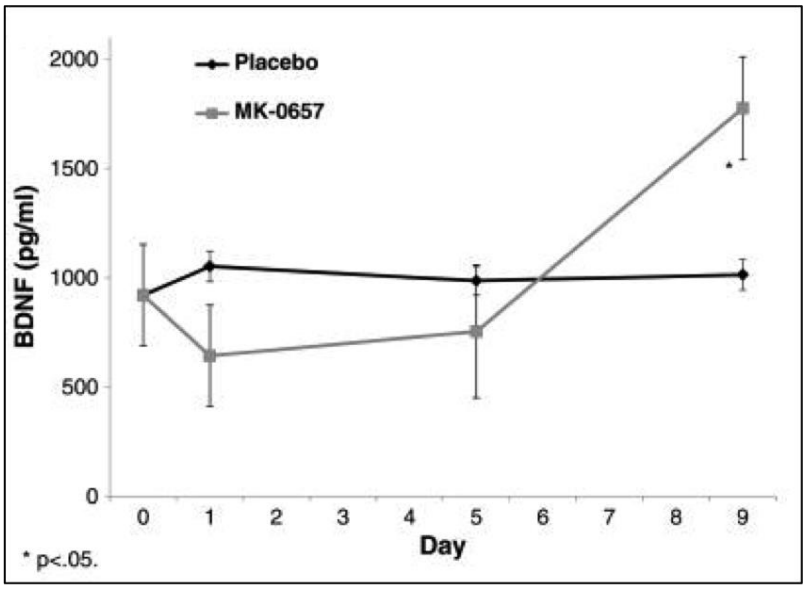
Source: Preskorn *et al*., 2008

Merck initially developed MK-0657 for the treatment of Parkinson's disease, and when the compound failed to show efficacy in early studies in Parkinson's the company discontinued development. At the time it was discontinued, MK-0657 was being tested in a clinical study of patients with treatment resistant MDD (NCT00472576), however only 5 of the planned 21 patients were enrolled in the trial (Ibrahim *et al*., 2012). Patients in the study had one drug-free week followed by randomization to receive MK-0657 (4-8 mg/day) or placebo for 12 days. At day 12, the study drug was discontinued, the subjects were drug-free for 14 days, and then crossed over to the other treatment condition. Results showed that there was no significant improvement in patients receiving MK-0657 compared to placebo as assessed by the primary outcome measure (MADRS). However, MK-0657 was shown to improve depressive symptoms when assessed by the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI). The following figure shows the statistically significant difference in HDRS on day 5 of treatment between MK-0657 and placebo treatment.



Source: Ibrahim *et al*., 2015

Interestingly, there was a statistically significant increase in plasma levels of BDNF following nine days of treatment with MK-0657, indicating that the compound was working how it was theorized and in line with other NMDA antagonists.



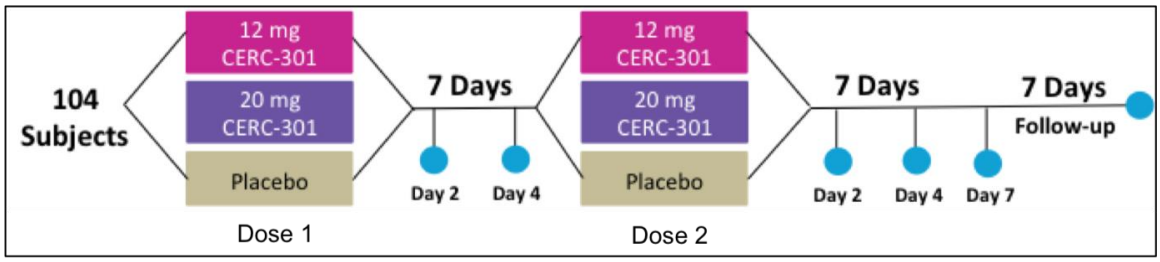
Source: Ibrahim *et al*., 2012

Cerecor initiated a Phase 2 clinical trial of CERC-301 in November 2013 (NCT01941043). The 135-patient, placebo controlled trial consisted of MDD subjects who were resistant to SSRI or SNRI treatment and had recent active suicidal ideation. Patients were treated for 28 days with 8 mg/day of CERC-301 and the primary outcome was the change in HDRS on day 7. In March 2015, Cerecor announced that the 8 mg dose used in the study did not meet the primary objective, however the drug was shown to be safe and well-tolerated. In a separate pharmacokinetic/pharmacodynamics study, 48 patients were safely treated with daily doses of CERC-301 of up to 20 mg, thus indicating that higher doses of CERC-301 could be utilized in future clinical trials.

Study Clin301-203

Cerecor is currently conducting the Clin301-203 clinical trial, a Phase 2 randomized, double blind, placebo controlled study evaluating the antidepressant effect of 12 mg and 20 mg doses of CERC-301 in MDD patients currently experiencing a severe depressive episode despite stable ongoing treatment with either an SSRI or SNRI (NCT02459236). A total of 104 subjects are expected to enroll and we anticipate top-line results being released in the first half of 2017.

The primary outcome of the study is the antidepressant effect of both doses of CERC-301 compared to placebo averaged between two and four days' post-treatment as assessed by the 6-item unidimensional subset of the HDRS known as the Bech-6. This is a subscale of the HDRS that should allow for the detection of acute drug effects along with the duration of the drug effect. Key secondary objectives include evaluating the antidepressant effect of CERC-301 by the full HDRS and the 7-item unidimensional subset known as Santen-7. Additional analyses will include the antidepressant effect at two, four, and seven days after each dose as well as 14 days after the last administration of study drug by the Bech-6, Santen-7, HDRS, Clinically Useful Depression Outcome Scale-Anxiety Self Report (CUDOS-A-SR), and the Snaith-Hamilton Pleasure Scale Self Report (SHAPS-SR). Qualified site raters will administer the clinically-administered tests and the study subjects will administer self-reported scales. There are a total of nine study visits, however four of them will be conducted by phone to alleviate the burden on the subjects. The figure below gives a graphical representation of the study.



Source: Cerecor, Inc.

In comparison to the previous Phase 2 trial that Cerecor conducted with CERC-301, there are a number of attributes to the Clin301-203 study that we believe could lead to a greater likelihood of success. Cerecor is testing a higher dose of CERC-301 (12 mg and 20 mg) compared to the first Phase 2 study that only evaluated 8 mg/day. In addition, subjects will take the medication on an empty stomach in order to increase the bioavailability of the drug. Both of these changes will result in maximum drug concentration being two to four times higher in subjects in the Clin301-203 study than in the previous study. Other factors that make the Clin301-203 study more likely to be successful include a more rigorous inclusion/exclusion criteria, recruitment of subjects from psychiatric clinical referrals and depression clinical study databases, and the use of the Bech-6 scale, which is more sensitive to acute changes from fast-acting antidepressants.

CERC-301 Granted Fast Track Status by FDA

On October 7, 2014 Cerecor announced that the U.S. Food and Drug Administration (FDA) has designated CF-301 as a Fast Track product for the treatment of MDD. The Fast Track program was put into place under the FDA Modernization Act of 1997 and is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. A company that receives Fast Track designation is eligible for the following:

- More frequent meetings with the FDA to discuss the drug's development plan and ensure that the appropriate data is being collected to support drug approval.
- More frequent written communication from the FDA about things such as clinical trial design.
- Eligibility for accelerated approval and priority review, including the submission of a New Drug Application (NDA) or a Biologics License application (BLA) on a rolling basis. What this means is that a company can submit completed sections of an NDA or BLA as they are completed and have them reviewed by the FDA, rather than waiting until every section of the application is completed before the entire application can be reviewed.

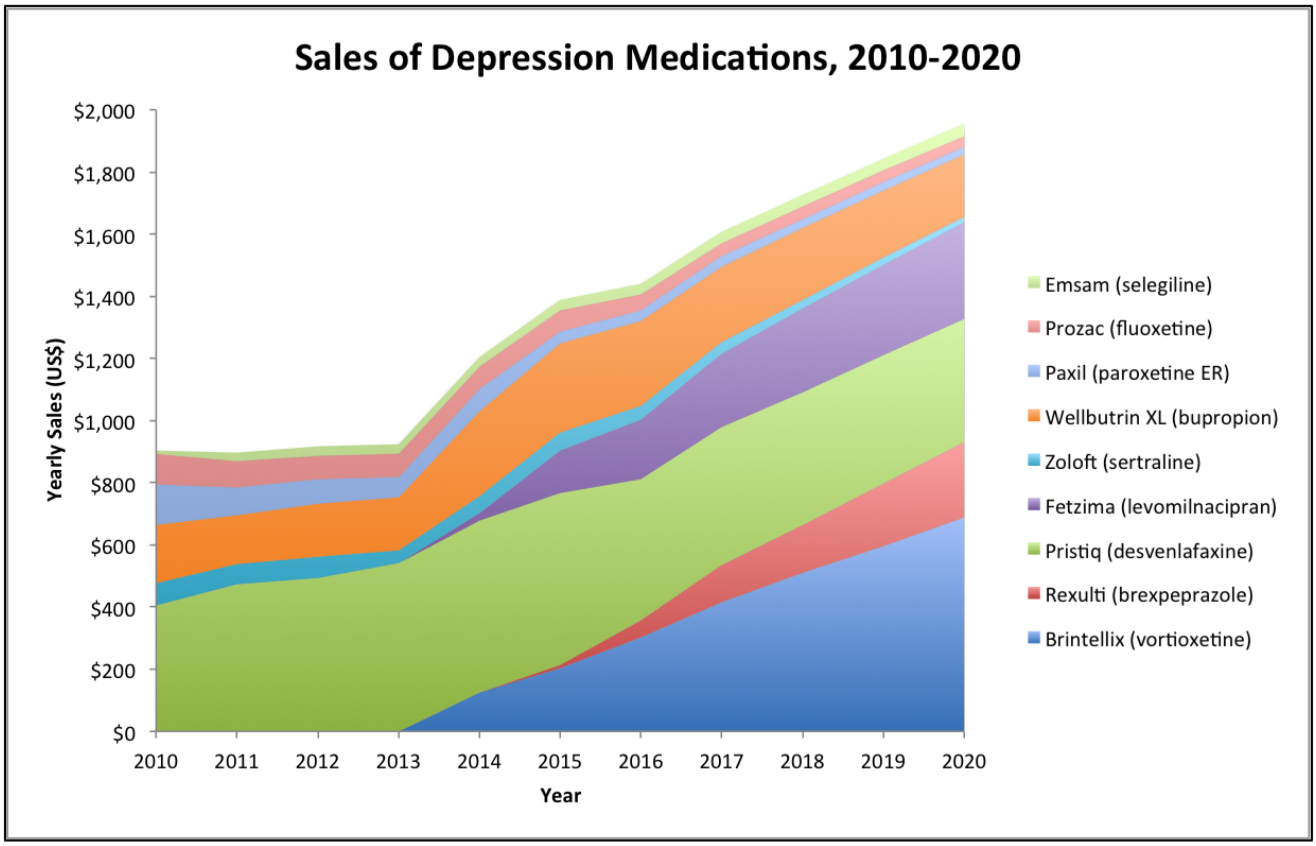
CERC-301 could become a novel fast-acting antidepressant medication, however since no other antidepressants are approved with a similar clinical outcome it will be very important for Cerecor to be able to have continual input from the FDA regarding clinical study design to ensure the proper data is obtained for eventual approval of the drug.

Opportunity in MDD

The treatment of depression represents a significant market opportunity. As mentioned above, approximately 16 million adults in the U.S. will suffer from a major depressive episode during any 12-month period. Of those, approximately 4 million are treated with drug therapy, which is the current target market for CERC-301. Due to the increasing prevalence of generic medications, many 'Big Pharma' companies have exited the space or are waiting for smaller biotech companies to produce positive early-stage results before re-entering the market. With an

increased understanding of the disease and better treatment target validation, a company such as Cerecor could realize a significant jump in value with positive clinical results.

The following chart shows the U.S. sales of different prescription depression medications from 2010-2020. The data after 2015 is from consensus analyst's forecasts (EvaluatePharma). Growth in the market is going to be supplied by new entrants to the market such as Brintellix, Rexulti, and Fetzima. Even with a number of different treatment options available, there is still plenty of room in the market for an effective treatment with a differentiated mechanism of action.



Source: EvaluatePharma; Zacks SCR

There are currently five other programs in development by other companies for compounds that are rapid onset antidepressants or anti-suicide treatments:

- **Esketamine**: This is the S(+) enantiomer of ketamine. It is being developed by Johnson and Johnson as an intranasally administered adjunct treatment for patients with MDD and is currently in a Phase 3 clinical trial.

- **Rapastinel**: This is an intravenously administered peptide that is a partial agonist of the glycine site of the NMDA receptor being developed as a adjunctive treatment for MDD by Allergan. It recently received Breakthrough Therapy designation from the FDA and Phase 3 clinical trials should be underway soon.

- **NRX 1074**: This is an orally administered small molecule drug that acts as a partial agonist of the glycine site of the NMDA receptor being developed as a adjunctive treatment for MDD by Allergan. Phase 2 clinical trials are set to get underway in 2016.

- **AZD8108**: This is an orally administered NMDA receptor antagonist being developed by AstraZeneca. It has completed Phase 1 studies.

- **AV-101**: This is a prodrug of 7-chloronurenic acid, which is a selective antagonist of the glycine site of the NMDA receptor antagonist and is being developed by VistaGen Therapeutics. The compound is currently in a Phase 2 clinical trial for the treatment of MDD.

Substance Use Disorder

Drug abuse is a significant public health problem. According to the 2013 National Survey on Drug Use and Health (NSDUH), which is an annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA):

- An estimated 24.6 million Americans aged 12 or older (9.4% of the population) were illicit drug users. Illicit drugs are defined as marijuana, cocaine, heroin, hallucinogens, inhalants, or prescription-type psychotherapies used nonmedically. The rate of current illicit drug use appears to be increasing, as the rates ranged from 7.9% to 8.7% from 2002 to 2009.

- An estimated 6.3% of the population (16.5 million people) reported heavy drinking (binge drinking on at least 5 days in the past 30 days)

- An estimated 66.9 million Americans aged 12 or older (25.5% of the population) were current users of a tobacco product. The majority of these (55.8 million) were cigarette smokers

Cigarette smoking is the leading cause of preventable death in the U.S. and is responsible for approximately 480,000 deaths each year (CDC). In addition, life expectancy for those who smoke is at least 10 years shorter than for nonsmokers (Jha *et al*., 2013). While smoking rates continue to decrease, there are still an exceptionally high number of Americans that smoke, resulting in an estimated $170 billion spent each year for illnesses caused by tobacco use.

Co-Occurrence of MDD and Substance Abuse

It is estimated that up to one-third of patients with MDD also suffer from substance abuse disorder (Davis *et al*., 2008). A study of over 40,000 adults found that in those suffering from alcohol abuse disorder, approximately 20% of them also met the criteria for MDD (Pettinati *et al*., 2011). Many patients use illicit drugs as a means to "self-medicate" and alleviate the feelings of low self-esteem, hopelessness, and despair that are common among those with MDD. However, even though patients abuse drugs due to the perceived relief of symptoms, in fact those substances can make depressive episodes worse, leading to heightened negative thoughts and increased self-destructive behavior. Depression can also make it more difficult to quit abusing a substance and make it more likely to suffer a relapse. Unfortunately, current treatment options for co-occurring disorders consists of either treatment for the psychiatric condition or the treatment of the addiction, but not the underlying connection between the two. For example, naltrexone is FDA-approved for the treatment of alcohol dependence but is not approved as either an antidepressant or anti-anxiety agent. Varenicline is an anti-smoking agent, however one of its side effects is depression. Thus, there is a clear unmet need for treatments that are effective at treating both the psychiatric and addiction aspects of co-occurring conditions.

Link Between Substance Abuse and Depression Involves Kappa Opioid Receptors

The link between substance abuse and depression may have to do with stress. A continually stressful environment can increase the risk of clinical depression and substance abuse, and both stress and mood play a significant role in addiction relapse (Watkins *et al*., 2000). Kappa opioid receptors (KORs) and their ligand dynorphin are localized to portions of the brain involved in reward and stress and are believed to play a role in mood, stress, and addictive disorders (Shippenberg *et al*., 2007). Preclinical models show that stress produces a prodepressive phenotype through the activation of KORs.

A significant amount of evidence has been accumulated showing how the KOR sits at the nexus of reward/mood/addictive behaviors, including:

- Cocaine abuse leads to upregulated expression of dynorphin, which can lead to depressive symptoms upon cessation of cocaine use (Sivam, 1989). Similar results are seen with other drugs of abuse such as heroin (Solecki *et al*., 2009) and alcohol (Przewlocka *et al*., 1997).

- Stress leads to an increase in dynorphin levels (Przewlocki *et al*., 1987).

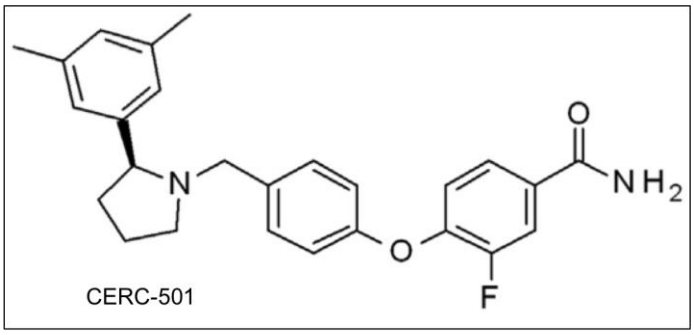
- Activation of KORs produces depressant-like behavior in animal models (Carlezon *et al*., 2006).

- KOR antagonists exhibit antidepressant-like effects in animal models (Mague *et al*., 2003).

For a comprehensive overview of the role that the KOR plays in depression, stress, and substance abuse, please see the article "The kappa opioid receptor: from addiction to depression, and back" (Lalanne *et al*., 2014). All of the above referenced results point to agonist activity of the KOR/dynorphin system as being at the crossroads between stress, depression, and substance abuse. The data also suggest that KOR antagonists could be utilized as antidepressants, to treat anxiety, and for the suppression of withdrawal symptoms. However, up until recently no KOR antagonists that could be tested in the clinic existed.

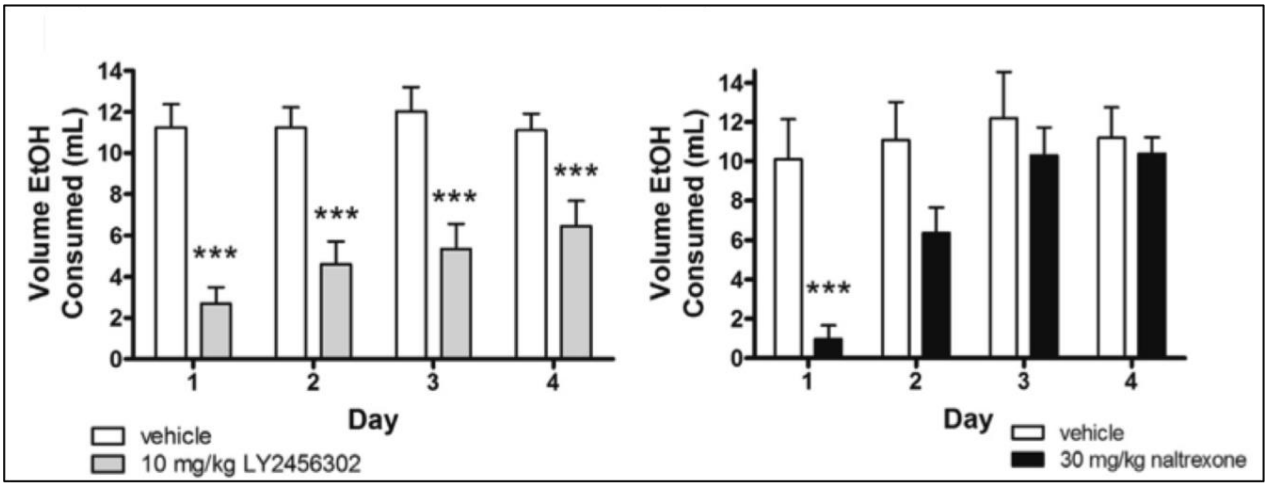
CERC-501 is a Highly Selective KOR Antagonist

Cerecor is developing CERC-501, an orally available, highly specific KOR antagonist, as a treatment for substance use disorder, adjunctive treatment of MDD, and potentially for co-occurring disorders. Cerecor acquired the rights to CERC-501, then LY2456302, through an exclusive, worldwide license from Eli Lilly and Company in February 2015.



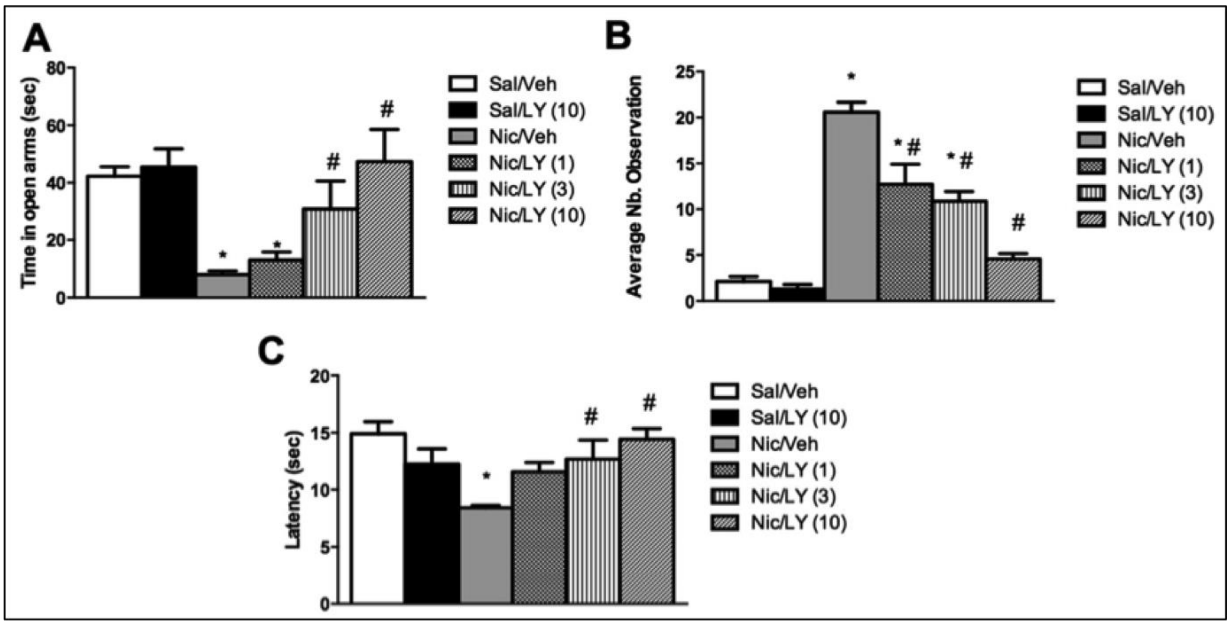
Source: Rorick-Kehn *et al*., 2014

CERC-501 is highly selective for the kappa opioid receptor as it has 21-fold higher affinity for the kappa opioid receptor compared to the mu receptor and 135-fold higher affinity over the delta opioid receptor (Mitch *et al*., 2011). Preclinical studies showed that CERC-501 dose-dependently produced an antidepressant-like response in the forced swim test and significantly attenuated continuous ethanol self-administration in female rats with a history of high ethanol intake (Rorick-Kehn *et al*., 2014). The following figure shows that CERC-501 (LY2456302) significantly reduced ethanol consumption on each of the four days of treatment, while naltrexone was only effective on day 1, with tolerance developing by day 2.



Source: Rorick-Kehn *et al*., 2014

The ability of CERC-501 to treat nicotine withdrawal was studied in an established rodent model where mice were chronically treated with nicotine for two weeks and then studied for withdrawal behaviors 18-24 hours after removal of nicotine with and without CERC-501 (Jackson *et al*., 2015). The following figure shows that pretreatment with 3 and 10 mg/kg CERC-501 significantly A) decreased the expression of anxiety-related behaviors; B) decreased expression of somatic withdrawal signs; and C) decreased the expression of hyperalgesia. These data support the notion that CERC-501 alleviates physical and affective nicotine withdrawal signs in mice and could be effective in supporting smoking cessation.

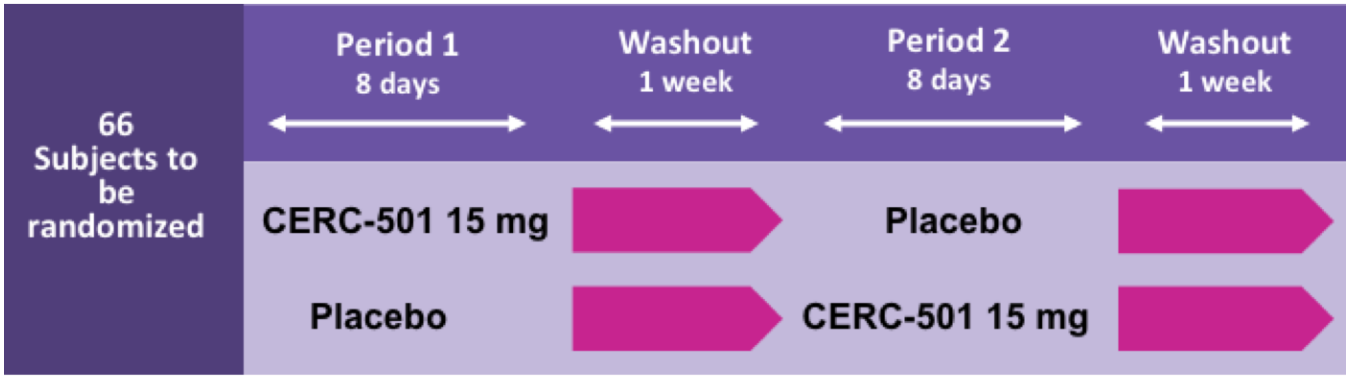


Source: Jackson *et al*., 2015

The safety, tolerability, and pharmacokinetics of CERC-501 was tested in a Phase 1 clinical trial in healthy subjects (Lowe *et al*., 2014). Single doses of 2 mg to 60 mg and multiple doses of 2, 10, and 35 mg were administered alone and in combination with ethanol. There were no clinically significant findings and all doses were well tolerated. In addition, there was no evidence for any interaction with ethanol.

Study Clin501-201

Cerecor is currently conducting the Clin501-201 clinical trial, which is a randomized, double blind, placebo controlled trial to evaluate the effects of 15 mg of CERC-501 on tobacco withdrawal and reinstatement and to assess craving, mood, and anxiety during 18 hours of abstinence in 66 heavy cigarette smokers (NCT02641028). The following graphic gives an overview of the study showing the crossover design, which allows the subjects to be their own control and also significantly increases trial power.



Source: Cerecor, Inc.

Each period of the trial consists of a seven-day treatment period followed by a single testing day on Day 8. The testing day consists of nicotine deprivation for 18 hours, beginning on the evening of Day 7, and continuing to mid-day of Day 8. This is followed by a smoking lapse test, where subjects are presented with a tray of their preferred brand of cigarettes and an ashtray. The subjects will be told they can smoke as much as they like for 50 minutes (delay period), however for each five-minute block of time a subject delays smoking, they receive a financial reward. Following the smoking of the first cigarette or the end of the 50-minute period, subjects will be provided with eight cigarettes of their preferred brand and allowed to smoke for 60 minutes (self-administration period). The number of cigarettes smoked will be recorded. The primary endpoints of the study are the number of minutes and seconds to the start of tobacco use during the delay period and the number of cigarettes smoked during the self-administration period. Results from this study are expected in the second half of 2016.

External Clinical Trials of CERC-501

There are currently two external clinical trials being conducted that involve CERC-501:

- Impact of the KOPr Antagonist OpRA Kappa in Persons at Specific Sages of Cocaine Addiction Trajectory, Versus Normal Volunteers. This is a single-site study being conducted under the leadership of Dr. Mary Kreek of The Rockefeller University Hospital.

- A Phase 2 Study to Evaluate the Kappa Opioid Receptor As a Target for the treatment of Mood and Anxiety Spectrum Disorders by Evaluation of Whether LY2456302 Engages Key Neural Circuitry Related to Hedonistic Response. This six site clinical trial is being conducted under the leadership of Dr. Andrew Krystal.

Cerecor may end up sponsoring one or both of those trials, depending upon the results of the Clin501-201 study. The NIMH was conducting an additional clinical study of CERC-501 for treatment-resistant depression, however that study was discontinued due to slow study progression.

Opportunity in Treating Nicotine Use

There are approximately 67 million Americans who use tobacco products. Of these, approximately 69%, or 46 million individuals, are interested in quitting. A little more than 50% (24 million) attempted to quit in the past year, and of those only 6% were successful (CDC). Thus, there is a huge unmet medical need for those who would like to quit use of tobacco products but are unable to do it on their own. Currently, there are very few therapeutic options available to help control nicotine addiction. The total market for smoking cessation in 2015 was close to $800 million, which was split approximately 50/50 between over the counter (OTC) medications and Chantix® (varenicline).

Cognitive Dysfunction in MDD

One of the primary mediators of functional impairment in patients suffering from MDD is cognitive dysfunction, which is a loss of basic intellectual functions such as memory, problem solving, reasoning, and learning. Most of those who suffer from MDD complain of some type of cognitive impairment. Criterion items for a diagnosis of MDD include a diminished ability to think or concentrate along with indecisiveness. Numerous studies have shown differences between healthy subjects and those with MDD in areas such as attention, executive function, learning, and memory along with cognitive affective bias, which results in focus moving away from positive stimuli and toward negative stimuli (Murrough *et al*., 2011).

While cognitive dysfunction may improve in those successfully treated for MDD, there is ample evidence to support the notion that certain cognitive deficits can persist. A 3-year study of those with MDD showed cognitive dysfunction in 94% of patients during acute depressive episodes and 44% during partial or full remission (Conradi *et al*., 2011). This suggests that cognitive dysfunction may be separate from mood symptoms in those suffering from MDD and that a subset of MDD patients would likely benefit from a treatment targeted to alleviate cognitive dysfunction.

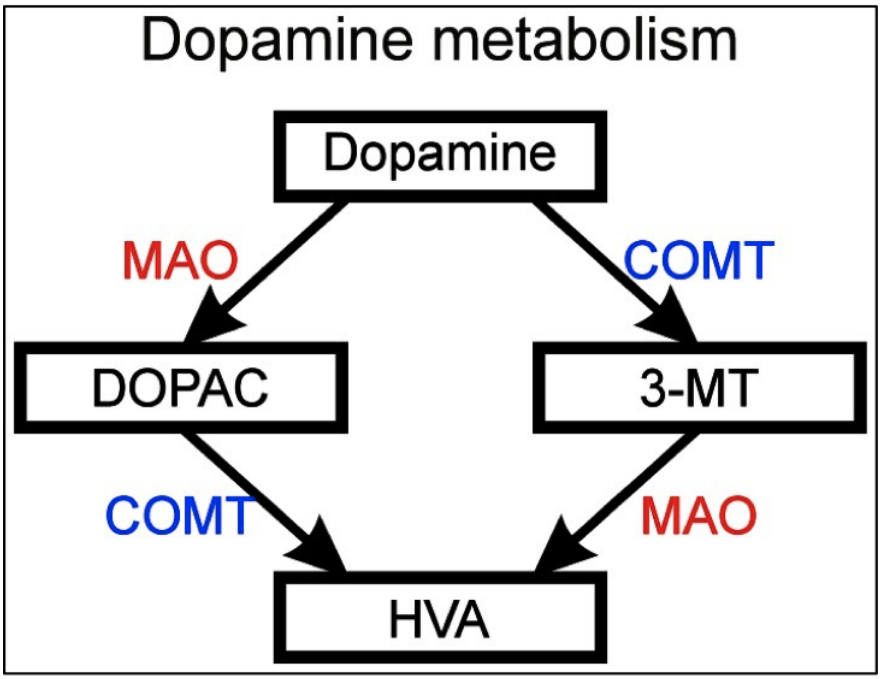
COMT as a Target for Treating Cognitive Dysfunction

Catechol-O-methyltransferase (COMT) is a promising candidate gene for modulating cognition function and dysfunction. The *COMT* gene encodes for two distinct isoforms: soluble-COMT (sCOMT) and membrane-bound COMT (mbCOMT) (Männistö *et al*., 1999). mbCOMT is expressed in the brain and has a much higher affinity for dopamine than sCOMT (Chen *et al*., 2011). Dopamine has a critical role in higher-order cognition in humans, impacting both thought and emotion, particularly in the pre-frontal cortex (Goldman-Rakic, 1999). COMT is responsible for the degradation of dopamine in the PFC. The level of dopamine in the brain is very tightly controlled, with too much or too little having negative consequences. Thus, since COMT is a key regulator of dopamine level, it has emerged as a prime target for augmenting cognitive function and COMT inhibition has been theorized to potentially impact executive function in patient's suffering from various ailments including Parkinson's disease and schizophrenia.

A couple of key characteristics of COMT inhibition are likely to facilitate drug development: genetic variability in the *COMT* gene and a readily available biomarker.

- **Genetic Variability**: Genetic studies have proven that a single nucleotide polymorphism in the *COMT* gene due to an adenine to guanine transition results in a methionine (Met) to valine (Val) substitution at amino acid 158 of the COMT protein (Lachman *et al*., 1996). The Val form of the enzyme leads to higher COMT protein levels and approximately 40% greater enzymatic activity compared to the Met form (Chen *et al*., 2004). These differences have real-world implications, as homozygous Val-COMT carriers have decreased performance on tests of executive control when compared to homozygous Met-COMT carriers (Malhotra *et al*., 2002). Drugs that target the dopaminergic system interact with these genetic variants, as shown by amphetamine improving cognitive performance in homozygous Val-COMT carriers but impairing it in homozygous Met-COMT carriers (Mattay *et al*., 2003). Thus, targeting those individuals that carry Val-COMT is likely to prove beneficial, as that group of patients appear most likely to benefit from pharmacological intervention.

- **Biomarker**: Inhibition of COMT is easily monitored through the quantification of the level of two compounds in the cerebrospinal fluid. The figure below shows that dopamine can be broken down via one of two pathways. The first step is catalyzed by either COMT to yield 3-methoxytyramine (3-MT) or monoamine oxidase aldehyde dehydrogenase (MAO) to yield 3,4-dihydroxyphenylacetic acid (DOPAC). The second step involves the conversion of DOPAC to homovanillic acid (HVA) by COMT or 3-MT to HVA by MAO. Thus, inhibition of COMT results in an accumulation of DOPAC (as no 3-MT is created from dopamine) and a decrease in HVA (as the DOPAC that was manufactured in step 1 can not be converted to HVA). The levels of each of the compounds can be correlated to the level of COMT inhibition.



Source: researchgate.net

COMTi Platform and CERC-406

In 2013, Cerecor acquired the rights to the COMT inhibitor (COMTi) platform from Merck. The platform comprises a group of COMT inhibitors that are selective for mbCOMT compared to sCOMT. The selectivity offered by these compounds is likely to lead to fewer off-target toxicities and side effects that were seen with previous COMT inhibitors such as tolcapone (liver toxicity) and entacapone (diarrhea). Cerecor's compounds are designed to fully penetrate the blood-brain barrier and to be highly selective for mbCOMT, potentially leading to higher efficacy with lower doses.

The lead compound from the COMTi platform is CERC-406, an orally available small molecule that has low inhibitory activity for sCOMT. The company is initially planning to develop CERC-406 as an adjunctive medication for patients with residual cognitive impairment due to MDD. CERC-406 was selected in part based on preclinical data showing a lower potential for periphery inhibition of COMT, rapid absorption and bioavailability, accessibility to the brain, and a favorable dose-dependent biomarker profile in rodents. The company is hopeful that CERC-406 will

be effective in homozygous Val-COMT patients who have higher levels of COMT activity and lower levels of dopamine in the PFC, thus potentially restoring proper levels of dopamine and positively impacting cognitive function. Preclinical studies of CERC-406 are continuing with an IND filing likely in 2017.

Financials and Capital Structure

As of March 31, 2016, Cerecor had approximately $16.6 million in cash and cash equivalents, which we estimate is enough to fund operations through the rest of 2016. This was mainly due to the company's initial public offering in October 2015 that resulted in gross proceeds of $23.7 million. As of March 31, 2016, the company had approximately 6.8 million warrants outstanding with exercise prices of $3.90 (2.3 million warrants) and $4.55 (4.5 million warrants) and expiration dates of April 2017 and October 2018, respectively. If all those warrants were exercised, they would bring in an additional $29.5 million in gross proceeds.

As of May 9, 2016, the company had approximately 8.65 million shares outstanding. In addition, there are approximately 1.5 million stock options and 7.5 million warrants for a fully diluted share count of 17.6 million.

Intellectual Property and License Agreements

Cerecor has a number of issued patents and patent applications covering the company's most advanced programs, which are summarized below. Each of the expiration dates listed does not take into account any potential patent term extensions or market exclusivity periods.

CERC-310: There are three patent families that cover CERC-301. The first family includes composition of matter and use claims with the U.S. patent having an expiration date of August 31, 2026. The second patent family consists of patents in the U.S., Germany, France, and Great Britain that include composition of matter claims (for the U.S. patent only) and generic use claims. The U.S. patent in the second family has an expiration date of June 3, 2022. The third family includes U.S. provisional patent applications that include composition of matter, methods of use, and methods of manufacture claims. If issued, any patent from those applications would expire in 2035 at the earliest.

CERC-501: This compound is covered by a single patent family with dozens of issued patents and pending patent applications that cover composition of matter and varying use claims. The expiration date of the two U.S. patents is January 13, 2029.

CERC-406 and COMTi Platform: The COMT patent portfolio includes three patent families, with each family consisting of patent applications in the U.S. and other advanced nations around the world. Any patents issued from the pending applications will expire no earlier than 2031.

Merck CERC-301 License

Cerecor entered into an exclusive licensing agreement with Merck in 2013 that granted the company rights related to certain small molecule compounds that inhibit or antagonize the activity of the NR2B receptor. The agreement included an upfront payment of $1.5 million, milestone payments of up to $40.5 million due upon the achievement of various development and regulatory milestones, and sales milestone payments of up to $15 million. In addition, Cerecor will pay a high single-digit royalty on net sales of NR2B antagonists.

Lily CERC-501 License

Cerecor entered into an exclusive license agreement with Eli Lilly in 2015 for rights relating to certain small molecule compounds that are potent and selective KOR antagonists. The agreement included an upfront payment of $1.0 million, milestone payments of up to $19 million due upon the achievement of various development and regulatory milestones, and sales milestone payments of up to $30 million. In addition, Cerecor will pay a tiered royalty rate ranging from mid-single digits to low-double digits on net sales of KOR antagonists.

Merck COMTi License

Cerecor entered into an exclusive license agreement with Merck in 2013 for rights to small molecule compounds that inhibit the activity of COMT. The agreement included an upfront payment of $0.2 million, milestone payments of up to $6.15 million due upon the achievement of various development and regulatory milestones for each COMT product, and a low single-digit royalty on net sales of COMT products.

Risks to Consider

Clinical Development Risk: Both CERC-301 and CERC-501 are in Phase 2 clinical studies and while there is preclinical data to support the development of both drugs, there is no guarantee that they will generate positive clinical trial results. In addition, while no safety concerns have been raised through prior preclinical and clinical testing, it is possible that unforeseen serious adverse events could be revealed for either drug during testing in a larger patient population. CERC-406 is still in preclinical development, thus there is no guarantee that it will proceed to clinical testing and no guarantee that it will generate positive results.

Intellectual Property Risk: Cerecor is dependent upon the exclusive licensing agreements signed with Merck and Eli Lilly for CERC-301, CERC-501, and the COMTi platform. Failure to adhere to the terms of those agreements by Cerecor could result in either or both companies cancelling the agreement(s) and preventing Cerecor from continuing development of those compounds and/or not having the ability to sell them once approved.

Additional Capital Will be Required to Complete Product Development: As of March 31, 2016, Cerecor had cash and cash equivalents of $16.6 million, which we believe will be sufficient to fund operations through the end of 2016. However, the company will need to raise additional capital to move the lead product candidates through Phase 3 clinical testing. Depending upon how the capital is raised, current shareholders could face significant dilution.

MANAGEMENT PROFILES

Uli Hacksell, PhD – Chief Executive Officer, President, and Chairman of the Board of Directors

Dr. Hacksell was appointed CEO & President of Cerecor in January of 2016. Dr. Hacksell also serves as Chairman of the Board of Directors, a position he has held since May of 2015. Prior to Cerecor, Dr. Hacksell served as Chief Executive Officer of Acadia Pharmaceuticals, Inc. from September 2000 to March 2015 and was a member of its Board of Directors. Prior to Acadia, Dr. Hacksell held various senior executive positions at Astra AB, including Vice President of Drug Discovery and Technology, President of Astra Draco, one of Astra's largest research and development subsidiaries, and Vice President of CNS Preclinical R&D at Astra Arcus, another Astra subsidiary. Dr. Hacksell is currently Chairman of the Board of Directors of Glionova Therapeutics and is also a member of the Board of Directors of InDex Pharmaceuticals and Uppsala University. He received a Master of Pharmacy and a Ph.D. in Medicinal Chemistry from Uppsala University.

Ronald Marcus, MD – Chief Medical Officer

Dr. Marcus has served as Cerecor's Chief Medical Officer and Head of Regulatory Affairs since May 2015. He has more than 20 years of experience in the development of neuroscience drugs at both Spinifex Pharmaceuticals and Bristol-Myers Squibb. Dr. Marcus was most recently the Chief Medical Officer at Spinifex, where he was responsible for driving clinical development and regulatory strategy of its lead compound for neuropathic pain. Prior to that, Dr. Marcus held various positions at Bristol-Myers Squibb including Group Director of Neuroscience Strategic Unit and Executive Director of Neuroscience Global Clinical Research. In this role, he was Early Development Team Leader for neuropathic pain, schizophrenia, and migraine compounds and Life-Cycle Management Team Leader for Abilify®, which included the development of Abilify® for the adjunctive treatment of depression. Dr. Marcus has authored more than 80 peer-reviewed publications. He received his B.A. in Psychology from the University of Virginia and his M.D. from SUNY Buffalo. He completed his psychiatry residency and the National Institute of Mental Health research fellowship at Cornell University, New York Hospital-Westchester Division.

Mariam Morris – Chief Financial Officer

Mariam E. Morris joined Cerecor as Chief Financial Officer in 2015, leading Cerecor through its initial public offering and currently serves as the Company's Secretary and Treasurer. Mariam is a seasoned financial executive and comes to Cerecor with over 20 years of experience and having owned her own consulting firm for the past six years. While consulting, Mariam worked with several businesses as out-sourced CFO and CBO roles. Prior to owning her own firm, Mariam was the Chief Financial Officer of Sucampo Pharmaceuticals. (NASDAQ: SCMP). Her years of experience include strategic planning, investor relations, human resources, internal controls for public and private companies, SOX compliance, and oversight of human resources and information technology. Mariam has significant SEC reporting, tax, acquisition, technical accounting, budgeting, treasury, operations and project management experience. She has a Masters in Taxation from Old Dominion University, a B.A. in Accounting from Texas Tech University, and is a member of the AICPA and TSCPA.

John Kaiser – Chief Business Officer

Mr. Kaiser serves as Cerecor's Chief Business Officer with responsibilities for corporate strategy, strategic marketing, and business development and led the company to acquire both CERC-301 and CERC-501 in 2013 and 2015, respectively. Prior to joining Cerecor, Mr. Kaiser founded Denysias Bioscience, LLC, a biopharmaceutical company focused on developing new therapies for neuropsychiatric disorders, where he served as Chief Executive Officer. At the same time, Mr. Kaiser also served as President of Kaiser & Associates Consulting, a boutique consulting firm providing strategic corporate and commercial expertise to the biopharmaceutical industry. From 2008-2009, Mr. Kaiser served as Vice President of Commercial and Business Development at ACADIA Pharmaceuticals Inc. Before ACADIA, Mr. Kaiser held numerous positions of increasing responsibilities at Eli Lilly and Company for more than 25 years. He currently serves on the Board of Directors of NHTherapeutics. Mr. Kaiser received his B.S. in pharmaceutical sciences from the James L. Winkle College of Pharmacy at the University of Cincinnati.

VALUATION

Cerecor is a clinical stage biopharmaceutical company developing treatments for patients with neurological and psychiatric disorders. We believe that both of Cerecor's lead compounds represent potential best-in-class treatments due to their novel mechanisms of action and potentially better safety profile compared to currently available therapeutic options. Cerecor currently has a market cap of less $30 million, thus we believe the market is vastly undervaluing the company's assets, particularly CERC-301, which we believe has blockbuster potential as a treatment for major depressive disorder (MDD).

CERC-301

N-methyl-D-aspartate (NMDA) receptors are a type of glutamate receptor that recent research shows contribute to the pathophysiology of MDD. NMDA antagonism is viewed as a means to exert a rapid clinical response in MDD. Ketamine, a drug that has been utilized for over 50 years as a dissociative anesthetic, is a known antagonist of the NMDA receptor. Clinical studies have shown that treating MDD patients with ketamine results in significant improvements in depressive symptoms within 72 hours after treatment. While shown to be quite effective at rapidly reducing depressive symptoms, ketamine has a number of side effects that preclude its widespread use including the fact it is a psychotomimetic that can result in toxicity and a schizophrenic-like syndrome when abused. What is needed is a drug that has the rapid anti-depressive action of ketamine but without the toxic side effects.

NMDA receptors are composed of various subunits to form three different subtypes: GluN1, GluN2, and GluN3 (or NR1, NR2, and NR3). There are eight variants of the NR1 subunit, four different NR2 subunits (referred to as NR2A through D), and two NR3 subunits. The current understanding about the role of different NMDA receptor subtypes is that compounds that act as subunit-selective modulators are likely to be as efficacious but safer and with less abuse potential than non-selective NMDA receptor antagonists such as ketamine.

Cerecor's lead asset is CERC-301, an orally available and NR2B-specific receptor antagonist, which is being developed as an adjunctive medication in patients with severe MDD who are not responding to their current antidepressant treatment. Previous studies with other NR2B-selective antagonists have shown the potential for this class of compounds to be utilized in treating MDD. Cerecor is currently conducting the Clin301-203 clinical trial, a Phase 2 randomized, double blind, placebo controlled study evaluating the antidepressant effect of 12 mg and 20 mg doses of CERC-301 in MDD patients currently experiencing a severe depressive episode despite stable ongoing treatment with another MDD medication. We anticipate topline results from this study in the first half of 2017.

CERC-501

It is estimated that up to one-third of patients with MDD also suffer from substance abuse disorder, in which patients use illicit drugs as a means to "self-medicate" and alleviate the feelings of low self-esteem, hopelessness, and despair that are common among those with MDD. However, even though patients abuse drugs due to the perceived relief of symptoms, in fact those substances can make depressive episodes worse, leading to heightened negative thoughts and increased self-destructive behavior. Depression can also make it more difficult to quit abusing a substance and make it more likely to suffer a relapse. Unfortunately, current treatment options for co-occurring disorders consists of either treatment for the psychiatric condition or the treatment of the addiction, but not the underlying connection between the two. For example, naltrexone is FDA-approved for the treatment of alcohol dependence but is not approved as either an antidepressant or anti-anxiety agent. Varenicline is an anti-smoking agent, however one of its side effects is depression. Thus, there is a clear unmet need for treatments that are effective at treating both the psychiatric and addiction aspects of co-occurring conditions.

The link between substance abuse and depression may have to do with stress. A continually stressful environment can increase the risk of clinical depression and substance abuse, and both stress and mood play a significant role in addiction relapse (Watkins *et al*., 2000). Kappa opioid receptors (KORs) and their ligand dynorphin are localized to portions of the brain involved in reward and stress and are believed to play a role in mood, stress, and addictive disorders (Shippenberg *et al*., 2007). Preclinical models show that stress produces a prodepressive phenotype through the activation of KORs.

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Valuation Methodology

We value Cerecor using a probability adjusted discounted cash flow model that takes into account potential future revenues for CERC-301 and CERC-501. We do not include CERC-406 in our model yet due to the fact that it is still in preclinical development.

For CERC-301, we anticipate that Cerecor will partner the drug and ultimately receive a net 15% royalty on net sales. This takes into account the high single-digit royalty that would be due to Merck upon commercialization of CERC-301. We model for a price of $20 per day in the U.S. and $16 per day in the rest of the world and assume that patients would take the drug for approximately nine months out of the year. Our model calls for a Phase 3 clinical program to get underway in 2018, an NDA filing in 2020, and approval in 2021. We believe approval outside the U.S. would be approximately one year later.

We estimate there are approximately 16 million adults in the U.S. that suffer from MDD each year and approximately 25% of those are treated pharmacologically, which translates to a target population of four million individuals. Outside the U.S., we conservatively estimate another four million individuals are treated with anti-depressants each year. With peak market penetration of 10%, this translates into peak worldwide revenues for CERC-301 of approximately $4 billion. Applying a 10% gross-to-net adjustment, a 96% patient compliance, a 15% net royalty rate, and an 18% discount rate leads to a net present valuation for CERC-301 of $216 million.

For CERC-501, we only include the use of the drug in smoking cessation in our model and have not included any potential revenues from the drug as a treatment for MDD as Cerecor is not conducting trials in that treatment area right now. We anticipate that Cerecor will partner the drug and ultimately receive a net 12% royalty on net sales. This takes into account the tiered royalty rate ranging from mid-single digits to low-double digits that will be due to Eli Lilly upon commercialization of CERC-501. We model for smoking cessation treatment with CERC-501 to cost approximately $180 in the U.S. and $90 outside the U.S. Our model calls for approval of CERC-501 in the U.S. in 2021, and outside the U.S. in 2022.

We estimate there are approximately 55 million smokers in the U.S. and that approximately 45% of those will attempt to quit each year. Outside the U.S., we estimate approximately 80 million smokers with 33% of those attempting to quit each year. We model for peak market penetration of 10% in the U.S. and 5% outside of the U.S., which leads to potential peak worldwide revenues of approximately $500 million. We apply a 12% gross-to-net adjustment, a 96% patient compliance, a net 12% royalty rate, and an 18% discount rate, which leads to a net present valuation for CERC-501 of $21.2 million.

Combining the net present value for CERC-301 and CERC-501 along with the company's current cash total and expected operating burn of $40 million we arrive at a net present value for the company of $213.8 million. Dividing this by the company's fully diluted share count of approximately 17.6 million shares leads to a valuation of $12/share. The stock is currently trading at a significant discount to this valuation, and we believe that positive data from the company's ongoing Phase 2 clinical trials is likely to cause an increase in the share price more in alignment with our valuation.

PROJECTED FINANCIALS

Cerecor, Inc.
Income Statement

Cerecor, Inc.	2015 A	Q1 A	Q2 E	Q3 E	Q4 E	2016 E	2017 E	2018 E
CERC-301	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	
CERC-501	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	
CERC-406	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	
Research & Development	$6.6	$2.3	$2.3	$2.3	$2.3	$9.2	$11.0	$13.0
General & Administrative	$4.4	$2.6	$2.6	$2.6	$2.7	$10.5	$12.0	$14.0
Other Expenses	$0	$0	$0	$0	$0	$0	$0	$0
Operating Income	($11.0)	($4.9)	($4.9)	($4.9)	($5.0)	($19.7)	($23.0)	($27.0)
Operating Margin	-	-	-	-	-	-	-	
Non-Operating Expenses (Net)	$0.5	($0.2)	$0.1	$0.2	$0.2	$0.3	$0.5	$0.5
Pre-Tax Income	($10.5)	($5.1)	($4.8)	($4.7)	($4.8)	($19.4)	($22.5)	($26.5)
Income Taxes Paid	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($10.5)**	**($5.1)**	**($4.8)**	**($4.7)**	**($4.8)**	**($19.4)**	**($22.5)**	**($26.5)**
Net Margin	-	-	-	-	-	-	-	
Reported EPS	**($4.71)**	**($0.59)**	**($0.55)**	**($0.47)**	**($0.40)**	**($1.98)**	**($1.50)**	**($1.47)**
YOY Growth	-	-	-	-	-	-	-	
Basic Shares Outstanding	2.2	8.7	8.7	10.0	12.0	9.8	15.0	18.0

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

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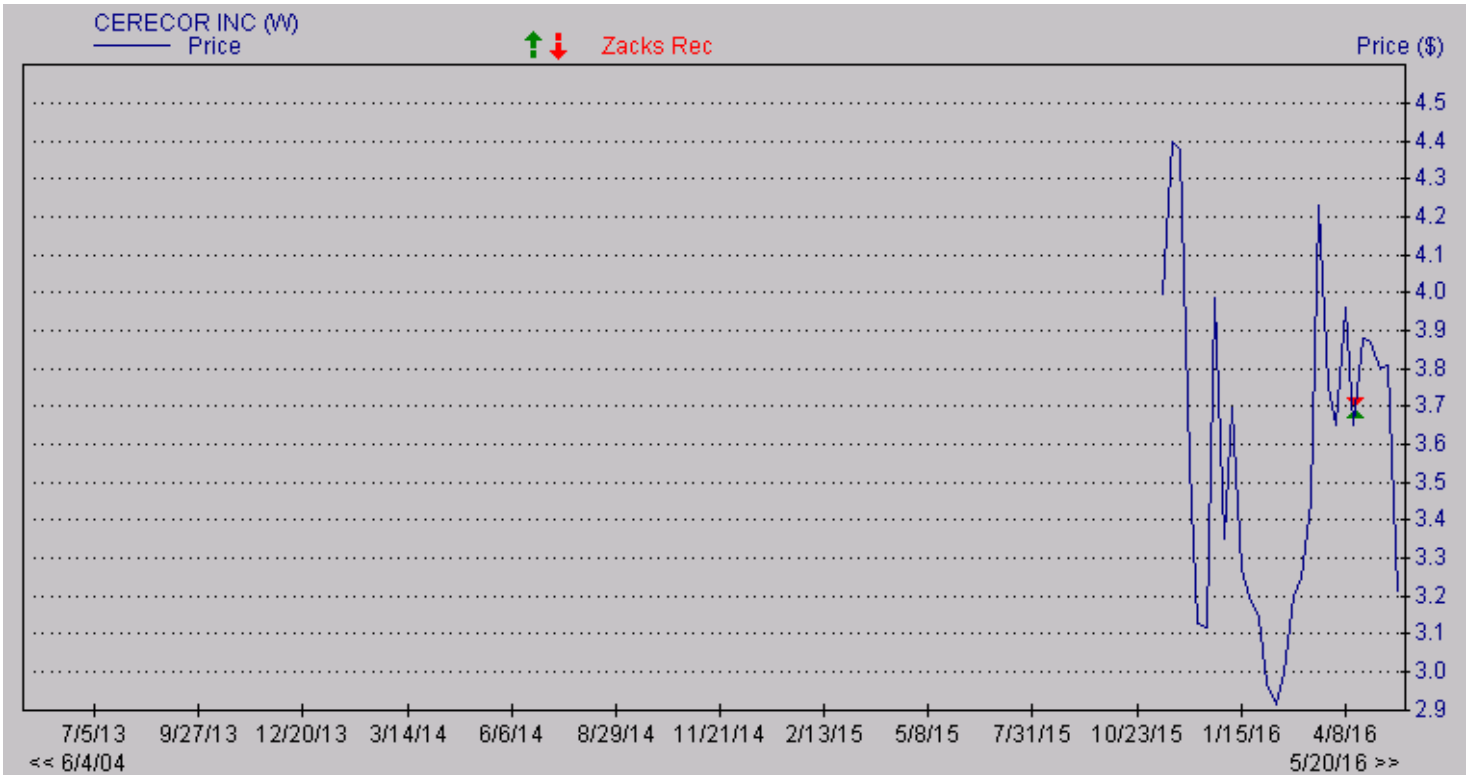
HISTORICAL STOCK PRICE



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