Zacks Small-Cap Research

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Jason Napodano, CFA
312-265-9421
jnapodano@zacks.com

scr.zacks.com
10 S. Riverside Plaza, Suite 1600, Chicago, IL 60606

Neurocrine Biosciences, Inc. (NBIX-NASDAQ)

NBIX: Comparing Neurocrine's valbenazine, Auspex SD-809, and Lundbeck's Xenazine...

Current Recommendation	**Buy**
Prior Recommendation	Neutral
Date of Last Change	06/16/2010
Current Price (06/27/14)	$14.62
Target Price	**$18.00**

UPDATE

An interesting race is shapping-up between Neurocrine Bio and fellow San Diego-based biotech, Auspex Pharmaceuticals, as both companies are positioning to do battle in a potential very lucrative area of central nervous system movement disorders based on improving the dosing, safety and tolerability of a 60-year old drug. That drug is tetrabenazine, currently sold in the U.S. as Xenazine® by Lundbeck. Below we provide a brief background on tetrabenazine, take a detailed look at Neurocrine's and Auspex' respective improved versions of the drug, the indications for which these two companies are pursuing, and lay out potential sales opportunities for investors. Our conclusion is that both companies have significant upside based on developing new forms of tetrabenazine and represent good investments at today's level.

SUMMARY DATA

52-Week High	**$19.65**
52-Week Low	**$8.68**
One-Year Return (%)	**14.31**
Beta	**-0.21**
Average Daily Volume (sh)	**445,437**
Shares Outstanding (mil)	**76**
Market Capitalization ($mil)	**$1,127**
Short Interest Ratio (days)	**9.14**
Institutional Ownership (%)	**92**
Insider Ownership (%)	**5**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**36.2**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**13.9**
P/E using 2014 Estimate	**N/A**
P/E using 2015 Estimate	**N/A**

Risk Level	**Below Avg.**
Type of Stock	**Small-Growth**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	0.7 A	0.7 A	0.7 A	0.7 A	2.9 A
2014	0 A	0 E	0 E	0 E	0.0 E
2015					25.0 E
2016					50.0 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	-$0.18 A	-$0.18 A	-$0.17 A	-$0.16 A	-$0.69 A
2014	-$0.17 A	-$0.18 E	-$0.20 E	-$0.22 E	-$0.77 E
2015					-$0.28 E
2016					-$0.02 E

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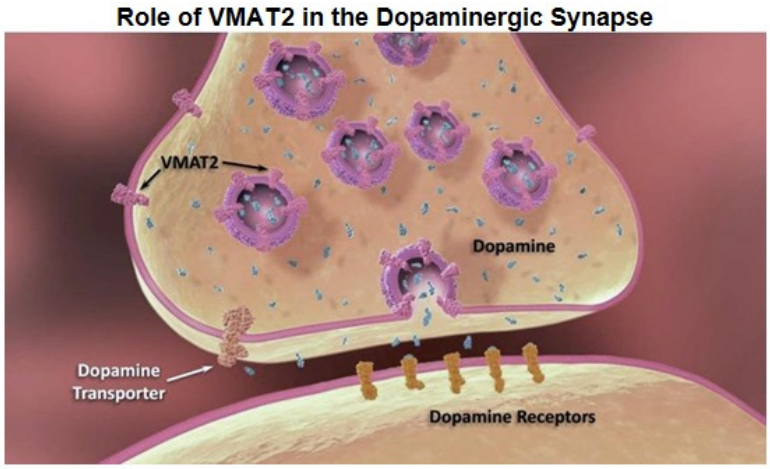
WHAT'S NEW

There is an interesting race shapping-up between Neurocrine Bio and fellow San Diego-based biotech, Auspex Pharmaceuticals, as both companies are positioning to do battle in a potential very lucrative area of central nervous system movement disorders based on improving the dosing, safety and tolerability of a 60-year old drug. That drug is tetrabenazine, currently sold in the U.S. as Xenazine® by Lundbeck. Below we provide a brief background on tetrabenazine, take a detailed look at Neurocrine's and Auspex' respective improved versions of the drug, the indications for which these two companies are pursuing, and lay out potential sales opportunities for investors. Our conclusion is that both companies have significant upside based on developing new forms of tetrabenazine and represent good investments at today's level.

A Closer Look at Tetrabenazine

In 2008, tetrabenazine was approved for the orphan drug indication of treatment of chorea associated with Huntington's disease (HD). Tetrabenazine is an inhibitor of VMAT2, a transporter that serves to package dopamine and other neurotransmitters into vesicles for release into the synapse. The tie between this pharmacological activity and tetrabenazine's therapeutic effect is broadly supported by a plethora of data showing that drugs that increase dopaminergic neurotransmission increase involuntary movement and reduce symptoms of parkinsonism (akinesia), and acute administration of dopamine antagonists has the opposite effect.



Regulatory and Marketing History

Tetrabenazine was initially investigated in the late 1950's as a more efficacious, safer version of reserpine for the treatment of schizophrenia. In 1958, it was approved for this indication in several European countries, but it failed to attract widespread use and was withdrawn from the market in 1962. It was re-introduced in the United Kingdom in 1971 with a broad label for the treatment of "organic movement disorders and tardive dyskinesia", and was approved in the United States as an Orphan Drug with the much narrower label of treatment of chorea in Huntington's disease (HD) in 2008. Tetrabenazine is marketed by Lundbeck under the trade name Xenazine®. U.S. sales in 2013 were $253 million, an increase of 20% over 2012. Orphan Drug exclusivity in the United States expires in August 2015, and there are no unexpired patents. In most Ex-U.S. markets, it is available as a generic, or sold at modest prices due to drug price controls.

Size of the Historical Market for Tetrabenazine

The annual cost of Xenazine® treatment can be estimated as $67,000 based on an average daily dose of 50 mg, the 2008 launch price of $68.50 per 25 mg tablet and 5% annual price increases (this estimated yearly price is consistent with information in Auspex' investor presentation). Using $67,000 as the annual cost and Lundbeck's 2013 sales figures of $253 million, one can estimate roughly 4,000 patients in the U.S (about 15% of the U.S. HD population) are currently being treated with the drug – a surprisingly small number. We believe Xenazine® penetration is low due to the significant side effects and poor tolerability of the drug. We discuss this below.

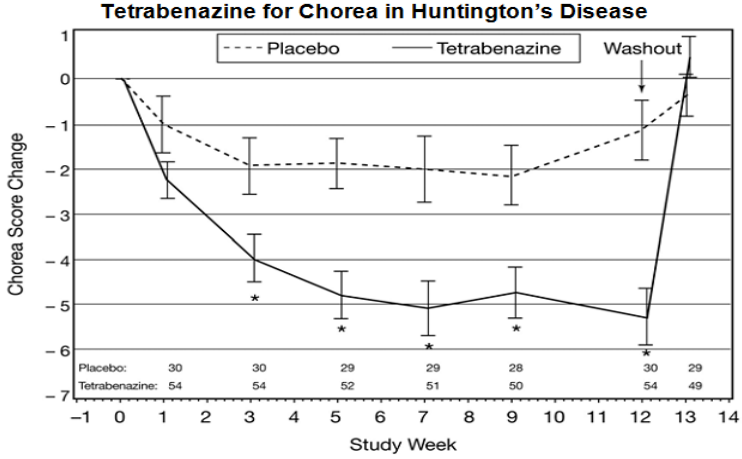
Tetrabenazine's Therapeutic Profile

Tetrabenazine appears highly efficacious for the treatment of a wide range of movement disorders, but has important limitations in terms of its short serum half-life and serious and potentially life-threatening side effects. It is metabolized in part through the action of liver enzyme CYP2D6. This is problematic because high inter-individual variability in CYP2D6 expression leads to high variability in serum levels of drug in response to any given dose. Furthermore, common antidepressants strongly inhibit CYP2D6, thus complicating therapy with substantial drug-drug interactions.

Tetrabenazine was approved by the U.S. FDA for the treatment of HD based mainly on a single, randomized, double-blind, multi-center trial performed on ambulatory patients with HD. Treatment duration was 12 weeks, including a 7-week dose titration period and a 5-week maintenance period, followed by a 1-week washout. The dose of tetrabenazine was started at 12.5 mg per day and titrated upward at weekly intervals in 12.5 mg increments until satisfactory control of chorea was achieved, intolerable side effects occurred, or until a maximal dose of 100 mg per day was reached. The primary endpoint was the Total Chorea Score of the UHDRS (we discuss this below in our section on HD).

As shown to the right, Total Chorea Scores for subjects in the active treatment group declined by an average of 5.0 points during maintenance therapy compared to 1.5 points in the placebo group. This difference was statistically significant. A second, smaller treatment withdrawal trial in 18 patients suggested a similar magnitude effect, but did not demonstrate statistical significance, most likely due to the small sample size. Secondary endpoints such as the effect of treatment on the Cognitive and Functional sub-scores of the UHDRS failed to reach statistical significance, or in some cases showed a trend toward a negative effect of treatment, but an FDA Advisory Panel concluded that these negative outcomes were not clinically significant.

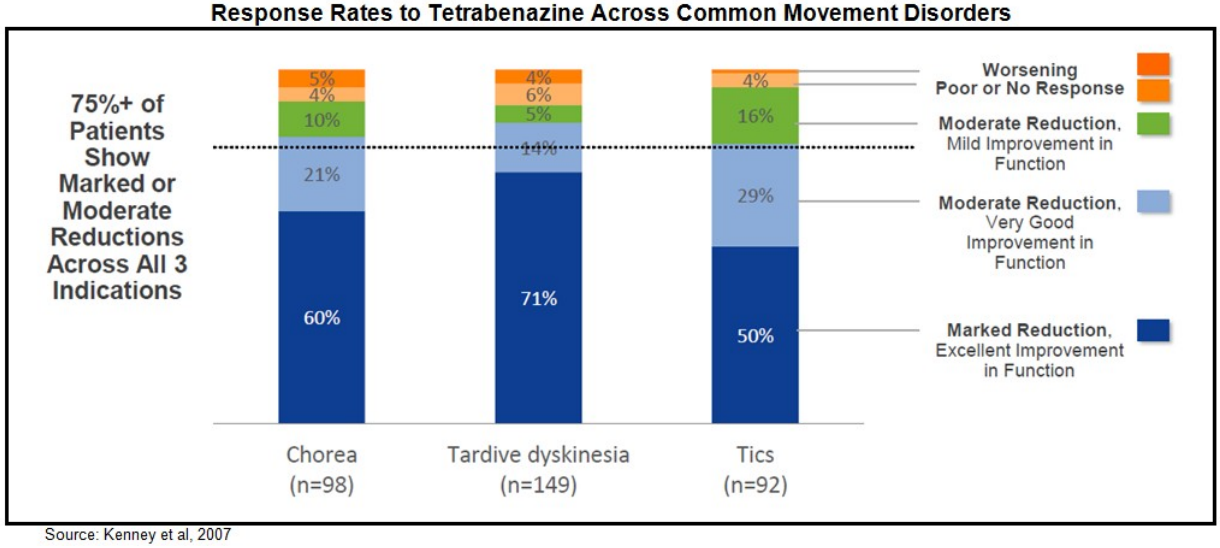
Chorea Score Change vs. Study Week in the Pivotal Trial of Tetrabenazine for Chorea in Huntington's Disease



Source: U.S. FDA

The graph below show the efficacy response rates to tetrabenazine in HD, Tardive Dyskinesia (RD), and Tics (representative of Tourette Syndrome) as found in a retrospective analysis of patients with movement disorders followed over an average of 2.3 years (Kenney et al, 2007). A total of 98 patients had HD, 149 had TD, and 93 had tics (including TS). Approximately 80% of patients in with each type of movement disorder achieved a moderate-to-marked reduction in symptoms when evaluated on a 5 point rating scale.

Response Rates to Tetrabenazine Across Common Movement Disorders



Source: Kenney et al, 2007

For this efficacy analysis one can conclude that tetrabenazine is an effective drug. As such, the low penetration rate in the U.S. must be the result of alternative factors, such as price or safety. As noted above, tetrabenazine is available as a generic in Europe, so price in Europe is not an inhibiting factor in uptake. As a result, we decided to take a look at international penetration rates of tetrabenazine outside the U.S.

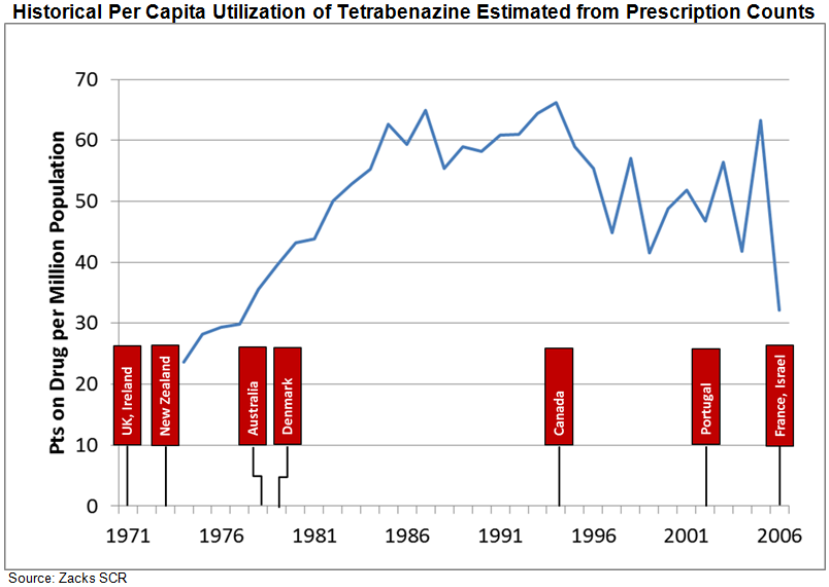
To estimate the size of the market at saturation for a tetrabenazine-like product, we looked at the total number of patients on therapy from 1971 to 2006 using data from the FDA Briefing Document for Xenazine®. We divided this number for each year by the summed population of the countries in which the drug was approved (see below). Notably, tetrabenazine was approved with broad labels for the treatment of "organic movement disorders or tardive dyskinesia" or "hyperkinesias" in three countries between 1971 and 1979, and in a single small country (Ireland) with a slightly less broad label. No additional approvals occurred until 1995, 15 years later. Sales in this set of countries with mostly very broad labeled indications peaked at about 60 patients per 1 million of population.

Historical Approvals of Tetrabenazine for the Treatment of Movement Disorders

Year	Country	Population (Millions) Year of Approval	Approved Indications
1971	U.K.	56.0	Organic movement disorders and tardive dyskinesia
1971	Ireland	3.0	Organic Movement Disorders
1973	New Zeeland	2.8	Organic movement disorders and tardive dyskinesia
1979	Australia	14.4	Organic movement disorders and tardive dyskinesia
1980	Denmark	5.0	Hyperkinesias
1995	Canada	29.1	Organic movement disorders and tardive dyskinesia
2003	Portugal	10.2	Organic movement disorders and tardive dyskinesia
2005	France	60.9	Organic movement disorders and tardive dyskinesia
2005	Israel	6.6	Huntington's chorea and hemiballismus
2007	Italy	58.2	Organic movement disorders and tardive dyskinesia
2007	Netherlands	16.3	Huntington's chorea
2007	Germany	82.9	Huntington's chorea and tardive dyskinesia

Source: U.S. FDA / Zacks SCR

Historical Per Capita Utilization of Tetrabenazine Estimated from Prescription Counts

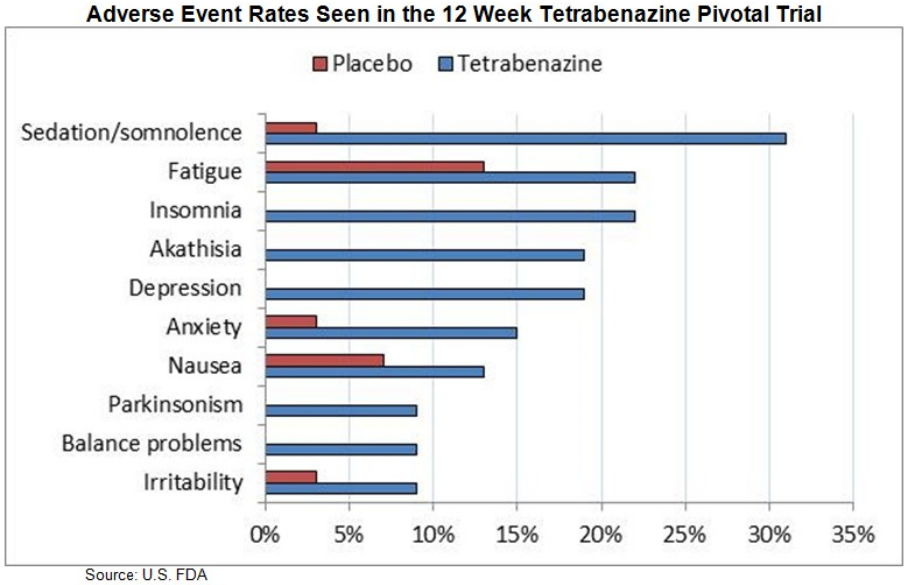


Source: Zacks SCR

The conclusion from this analysis is that penetration rates of tetrabenazine outside the U.S., where price is not a factor, are also rather low. We believe the primary factor limiting tetrabenazine from widespread use is its safety profile, which includes serious psychiatric and movement related side effects. The FDA label for tetrabenazine carries a "Black Box" warning for depression and suicide risk. Suicide risk is already greatly elevated in patients with Huntington's disease and schizophrenia, and this is exacerbated by treatment with tetrabenazine. In the U.S. approval trial described above, 10 of 54 (19%) tetrabenazine treated patients experienced depression or worsening depression compared to none of the placebo-treated patients. Among 187 patients in HD studies of tetrabenazine, one patient committed suicide, a second attempted suicide, and six had suicidal ideation. The Xenazine® label warns physicians of the heightened risk of suicide in patients with Huntington's disease regardless of depression indices. Reported rates of completed suicide among individuals with Huntington's disease range from 3-13%; over 25% of patients attempt suicide at some point in the illness.

As a result of this risk, tetrabenazine is subject to a Risk Evaluation and Mitigation Strategy (REMS) consisting of a Communication Plan designed to ensure that prescribers and dispensing pharmacists are aware of the risks of tetrabenazine. Though not explicitly required by the REMS, the drug is subject to limited distribution through specialty mail-order pharmacies that help monitor use and ensure the delivery of educational materials to prescribers.

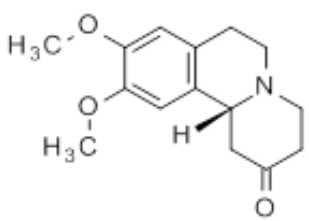
Besides suicidality, additional side effects include symptoms of parkinsonism. This was observed in 15% of tetrabenazine treated subjects in the 12 week HD trial compared to 0% in placebo treated subjects. Akathisia was observed in 19%, and sedation in 31% of tetrabenazine-treated patients vs 0% and 3% of the placebo treated patients. Sedation was the reason upward titration of tetrabenazine was stopped in 28% of patients. Drug induced parkinsonism has the potential to cause more functional disability than untreated chorea for some patients. Tetrabenazine modestly increases the QTc interval and should be avoided in patients with risk factors for cardiac arrhythmias.



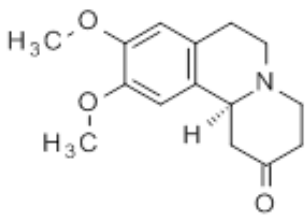
Understanding Tetrabenazine Metabolism

The metabolism of tetrabenazine is quite complicated in part because the drug itself is a 1:1 mixture of enantiomers (racemate). Enantiomers are isomers that have the same relationship as a left-handed and right-handed glove. Owing to the absence of manufacturing scale separation techniques, prior to 1990 most drugs were developed as racemates, but development of single enantiomers is increasingly the norm, as in most cases, only one of the two enantiomers has the desired pharmacological activity.

As non-superimposable mirror images of each other, they have the same molecular weight, chemical formula, melting point, and spectra, but bind to proteins differently in the same sense that only a left handed glove will fit a left hand and only a right handed glove will fit a right hand. In the chemical structures below, the solid wedge represents a bond pointing “up” and out of the page, while the dashed wedge represents a bond pointing downward. These are referred to as the alpha (α) and beta (β) enantiomers.



alpha-DHTB



beta-DHTB

Tetrabenazine is very rapidly metabolized to form compounds that have an –OH group in place of the =O of the parent drug. Each enantiomer of tetrabenazine gives rise to two isomers of this DHTB metabolite, so there are a total of four isomers at this stage. Of these, those derived from (α)-tetrabenazine are active inhibitors of VMAT2 and contribute to the drug's therapeutic effects. Some believe the two DHTBs derived from (β)-tetrabenazine are antagonists at the dopamine D_2 receptor, and may (not proven) contribute to sedation and other tetrabenazine-related side effects.

All four of these DHTB isomers are all metabolized to inactive O-demethylated compounds (ODMs) by the action of cytochrome P450 enzymes in the liver. The α-isomers can be converted to inactive ODM metabolites by either of two cytochrome enzymes, CYP2D6 or CYP3A4. The β-isomers are converted to inactive ODMs solely by CYP2D6. The biochemistry of tetrabenazine metabolism becomes important as we start discussing Neurocrine's and Auspex' respective drugs. However, before we get into the drugs, a discussion of the diseases and potential use indications is warranted.

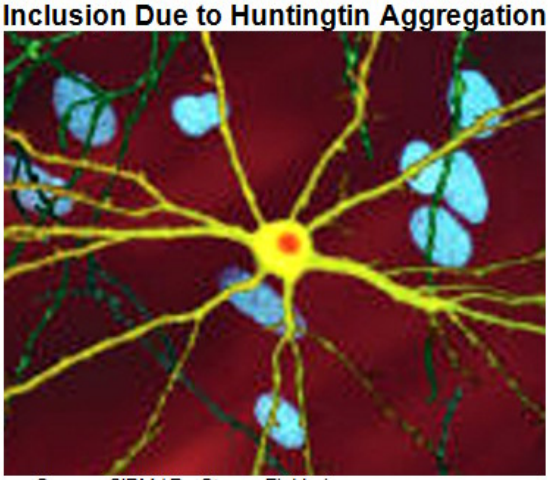
Huntington's Disease

Huntington's disease is an inherited neurodegenerative disorder leading to uncontrolled muscle movement (chorea), cognitive decline, psychiatric illness, and eventually death. The worldwide prevalence is about 5 to 10 persons per 100,000 persons, mainly among persons of Western European descent. Estimates of the U.S. prevalence range from about 20,000 to 30,000 individuals (source: HDSA.org), with the lower estimates mostly being derived from studies performed prior to the advent of genetic testing in 1984.

HD is caused by a mutation in the gene encoding the huntingtin protein. The gene for the huntingtin protein contains a region with a varying number of CAG base pairs, which is the codon for the amino acid glutamine. The number of repeats in unaffected people is normally less than 26. Those with over 40 repeats have 100% penetrance of HD.

The normal function of huntingtin is not known, but the HD variant is toxic to cells. The lengthy polyglutamine sequence encoded by the expanded CAG repeat region leads to the formation of inclusions within the nucleus and cytoplasm of cells, thereby interfering with normal cellular functions. Affected tissues include those in which huntingtin is abundantly expressed, including the brain, muscles, and heart. The region of the brain most strongly affected is the neostriatum of the basal ganglia, a region strongly associated with movement and behavior control.

Microscope image of a Neuron with an Inclusion Due to Huntingtin Aggregation



Source: CIRM / Dr. Steven Finkbeiner

The movement related symptoms of Huntington's disease include

- Chorea – Involuntary movements that are often sudden, incomplete, irregular, and purposeless
- Dystonia – Repetitive muscle contractions that are often associated with a twisting movement
- Bradykinesia and impaired voluntary control – Loss of coordination and difficulty initiating movement

These deficits lead to a progressive loss of function including gait impairment and falls, speech impairment, incontinence, difficulty swallowing and choking.

Below is a video illustrating the impact of chorea via YouTube (link).



Prodromal symptoms are subtle and readily missed. These may include twitching, fidgeting, clumsiness, and changes in gait. These minor deficits typically progress to more profound symptoms such as rigidity, writhing motions, and distorted posture over a period of about three years Chorea is typically a prominent symptom at diagnosis, with dystonia and rigidity becoming more significant later in the disease. In most cases, chorea initially affects the arms and legs, but as the disease progresses it comes to include symptoms such as grimacing, neck, shoulder, and trunk movements. Severity peaks in many patients about 10 years after onset, but in others the frequency and severity of symptoms increases into the late stages of the disease. About 90% of people affected by HD have chorea over their lifetime. About 30% have moderate-to-severe chorea at any given time.

HD-associated cognitive decline leads to impaired executive functions, including planning, abstract reasoning, and decision making. At the onset of motor symptoms, the performance of most patients on standardized cognitive tests is 1.5 standard deviations or more below the mean of unaffected persons. As the disease progresses, memory problems appear, including deficits in both short term and long term memory. Episodic memory (memory of events), procedural memory (how to perform tasks), and working memory (concentration) are all affected, ultimately leading to profound dementia.

Psychiatric symptoms of HD include anxiety, depression, aggression, compulsive behavior, irritability, apathy, delusions, hallucinations, and suicidal thoughts. Suicide is the third most common cause of death among diagnosed HD patients, following aspirational pneumonia and heart failure. The relative contributions of organic brain disease and the patients' fears of end stage disease to the high suicide rate seen in this population are unclear. In end stage disease, patients are typically bedridden and totally dependent on others.

The standard battery used to assess the clinical features and course of HD in clinical trials is known as the Unified Huntington's Disease Rating Scale (UHDRS). The UHDRS has six subsections:

1. Motor assessment
2. Cognitive assessment
3. Behavioral assessment
4. Independence scale
5. Functional assessment
6. Total functional capacity

The most pertinent subscale in the present analysis is the motor assessment score. The 106 point UHDRS motor scale includes measures of chorea, parkinsonism, dystonia, eye movements, and other signs. The 28 point chorea subscale of the motor score rates chorea symptoms on a 0 to 4 scale in seven body regions: Face, Bucco-oral-lingual, Trunk, Right upper extremity, Left upper extremity, Right lower extremity, and Left lower extremity. The maximum (worst) score is 28. In early HD, a 1 point UHDRS total motor score increase is associated with a 10% loss in measures of independent living.

There are no disease-modifying treatments available for HD. As such, the goal of therapy is to control symptoms and maintain function for as long as possible. The Huntington's Disease Society of America has issued treatment guidelines specifically addressing the movement, cognitive, and psychiatric aspects of the disorder.

Psychiatric symptoms for which the guideline recommends pharmacological treatment include depression, anxiety, psychosis, insomnia, obsessions and compulsions, and irritability, which can escalate to violent outbursts. Evidence based treatment guidelines are mostly lacking due to limited trial data on which it can be based. Based on expert opinion, these syndromes are for the most part treated using the same medications that are used in no-HD afflicted persons. SSRIs are preferred to tricyclic antidepressants based on the perception that HD patients may be unusually susceptible to tricyclic antidepressant side effects. Atypical antidepressants are preferred over first generation antidepressants in most patients in order to avoid aggravating chorea.

Similarly, there is a lack of available data to support evidence-based treatment guidelines for most movement disorders in HD. Based on expert opinion, dystonia may be treated with benzodiazepines, baclofen, or dopaminergic drugs developed for Parkinson's disease. In the latter case, careful monitoring for exacerbation of psychosis is recommended. Bradykinesia and rigidity may be treated by similarly, or with amantadine.

An international survey of Huntington disease specialists conducted in 2010 and published in PLOS Currents 2011 by Burgunder et al, found that antipsychotic drugs are typically used as the first-line treatment for HD, with atypical agents such as olanzapine or risperidone being the most common. Switching is common in the event of an inadequate response, and therapy with combinations of tetrabenazine, benzodiazepine, antidepressant, and amantadine often follows. Based on efficacy data, we believe an improved form of tetrabenazine would be moved to first-line or immediate second-line therapy if available.

Tardive Dyskinesia

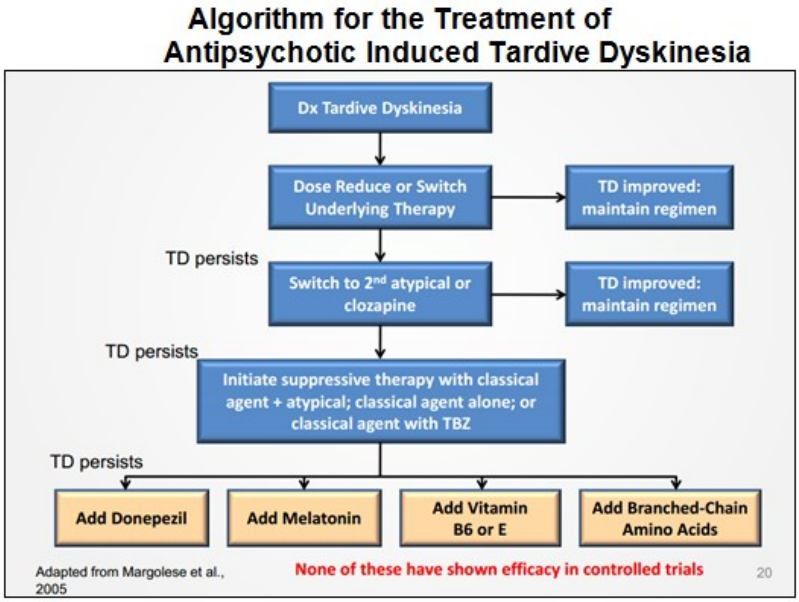
Tardive dyskinesia (TD) is a neurological disorder caused by the long term use of psychiatric drugs (neuroleptics) used in the treatment of schizophrenia. The symptoms of tardive dyskinesia include involuntary and abnormal movements of the jaw, lips, and tongue, including grimacing, sticking out the tongue, and sucking or fish-like movements of the mouth. In some cases, other parts of the body may be affected by rapid, jerking motions (chorea) or slow writhing movements (athetosis). These symptoms cause considerable distress to patients due to the resulting social stigma, and may contribute to poor outcomes such as psychiatric hospitalization by discouraging compliance with treatment. Other medical complications of tardive dyskinesia include difficulty eating, difficulty breathing, and dental problems. The onset of TD is typically insidious, beginning several years after the initiation of treatment. The condition typically reaches maximum severity fairly quickly and then stabilizes in waxing and waning of mild-to-moderate symptoms. Approximately 11% improve if antipsychotic medication is permanently withdrawn.

While modern "atypical" antipsychotic drugs are less prone to cause dyskinesia than older drugs such as haloperidol, perphenazine, and trifluoperazine, the dramatic increase in the use of antipsychotic drugs over the last 25 years has likely led to an overall increase in the incidence of tardive dyskinesia in the population. About one-third of those with long-term exposure are affected. While no population wide survey data of prevalence is available, an estimate of approximately 200,000-500,000 affected individuals can be arrived at based on the incidence of tardive dyskinesia among patients treated long term with neuroleptics (roughly 20-50%) and the incidence of schizophrenia and bipolar disorder in the U.S. population (source: TD Center, *Cloud et al, 2013*).

The etiology of TD is unknown. The most prominent explanatory models include acquired dopamine receptor super-sensitivity (arising from long term dopaminergic blockade), γ-aminobutyric acid (GABA) depletion, cholinergic deficiency, neurotoxicity and oxidative stress, changes in synaptic plasticity, and defective neuro-adaptive signaling. Therapeutic modalities addressing each of these putative pathologies have been evaluated in clinical trials.

The evaluation of disease progression and response to treatment in TD is commonly measured using the Abnormal Involuntary Movement Scale (AIMS) battery (link – AIMS overview and assessment / scoring tool). The first four domains are used to assess the severity of symptoms and their effect on the patient. The fifth serves as a control measure to ensure that movements attributable to dental problems are not mistakenly attributed to neurological disease.

The most widely followed algorithm for the treatment of TD appears to be that of *Margolese et al*, 2005, shown below. The provoking antipsychotic drug is removed or switched, and if no improvement is observed the patient is switched to clozapine, an atypical antipsychotic with reduced movement disorder inducing properties but having a risk of provoking blood disorders that required regular patient testing.



In the event improvement still is not achieved, a second atypical is tried, followed by a fist-generation anti-psychotic. Fourth line therapy involves treatment with tetrabenazine, to which adjunctive therapy with donepezil or various nutritional supplements can be added.

Tourette Syndrome

Tourette syndrome (TS) is a neuropsychiatric disorder whose symptoms consist of multiple motor and vocal tics that are under incomplete voluntary control. The U.S. Centers for Disease Control and Prevention (CDC) estimates the U.S. prevalence at about 0.3% of children age 6-17. This suggests a U.S. patient population of 150,000. We have seen peer-reviewed publications suggest the rate is lower, at only 0.2% (Bitsko et al, 2014) to potentially as high as 0.6% (Comings et al, 1990). The upper-range of estimates suggests a U.S. population of around 300,000.

Most patients experience peak tic severity prior to their mid-teen years, with improvement in the mid-teens to early adulthood. About 10-15% of those affected have a progressive or disabling course that lasts into adulthood. Many individuals with TS experience additional neurobehavioral problems that often cause more impairment than the tics themselves. These include inattention, hyperactivity and impulsivity (attention deficit hyperactivity disorder); problems with reading, writing, and arithmetic; and obsessive-compulsive symptoms such as intrusive thoughts/worries and repetitive behaviors.

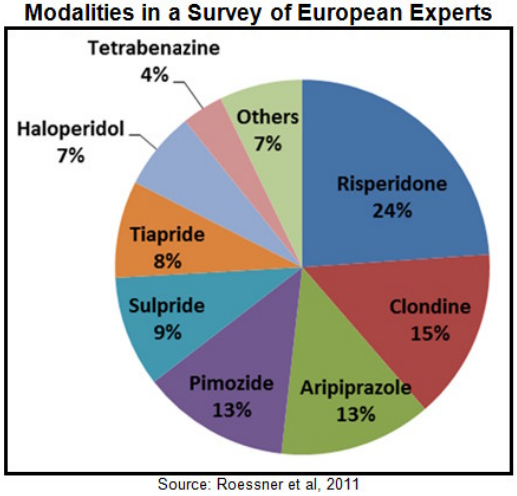
In contrast to the chorea, dystonia, and dyskinesias of HD and TD, the tics of TS are temporarily suppressible, non-rhythmic, and often proceeded by an unwanted premonitory urge. Common presentations include eye blinking, facial grimacing, shoulder shrugging, and head or shoulder jerking. Within an affected individual, the number, severity, and anatomical location of tics vary over time. The most common forms of vocal tic are throat clearing, sniffing, and grunting sounds, but in some affected persons may take the form of spontaneous utterance of objectionable phrases and words and or repeating the statements of others.

Pharmacological treatment of Tourette syndrome is considered when tics interfere with social interactions, school performance, or activities of daily living. The goal of therapy is not complete elimination of tics, but control of the tics to enable social functioning. Many if not most patients receive no treatment at all, or only behavior training exercises, as the extent of disability is usually modest. Furthermore, the most effective agents, including antipsychotic drugs and tetrabenazine, have important side effects.

In the U.S. treatment of moderate tics often involves the use of alpha-2 adrenergic drugs clonidine and guanfacine, especially in the presence of co-morbid ADHD. Efficacy is modest, but side effects are mild. Antipsychotic drugs are used in more severe cases, but have the carry the important risk of side effects such as extrapyramidal effects and tardive dyskinesia. Evidence-based treatment guidelines are virtually non-existent, owing to the heterogeneity of the disorder and the difficulty of conducting trials given the disorder's natural waxing and waning of symptoms.

A survey of European treatment experts published by *Roessner et al* in the European Child and Adolescent Psychiatry in 2011 gave the results below. The article notes that U.S. practitioners are more likely to use clonidine and guanfacine. Tetrabenazine, most likely due to the significant side effects and black box warning for potential suicidality, is not commonly used in Europe or the U.S.

Preferred Tourette Syndrome Treatment Modalities in a Survey of European Experts



Source: Roessner et al, 2011

Improving A 60 Year Old Drug

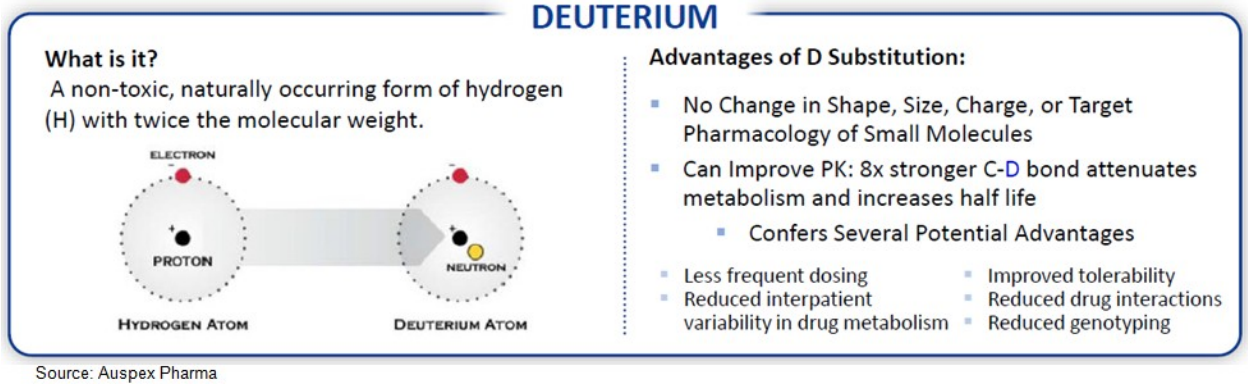
Tetrabenazine is a highly efficacious drug for the treatment of movement disorders, yet utilzation has been limited by severe and life threatening side effects, high inter-individual variability in pharmacokinetics, and the requirement for frequent (TID) administration. A less toxic, more metabolically stable derivative with little or no CYP2D6-mediated metabolic clearance would be a quantum leap in the treatment of HD, TD, and some TS cases, and could potentially achieve sales in excess of $1 billion or more.

Now that investors have a good understanding of tetrabenazine and the markets for which both Neurocrine and Auspex plan to play, we are ready to take a look at each company's respective drug. We start, alphabetically, with Auspex Pharmaceuticals.

Auspex Pharmaceuticals – SD-809

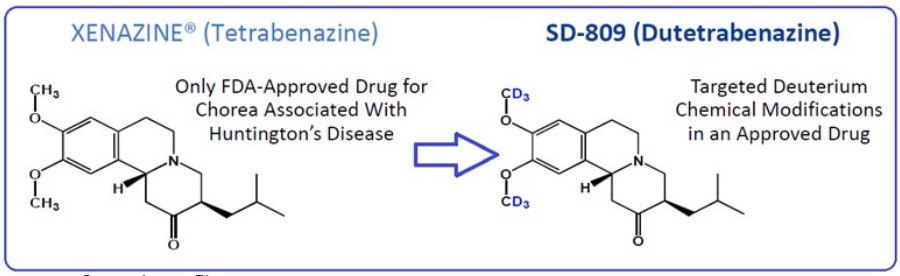
Auspex's platform technology uses deuterium, a stable, non-radioactive, non-toxic, and naturally occuring isotope of hydrogen to design improved variations of existing drugs. Deuterium has a natural abundance of about 1%, and is present in about one in every 50 water molecules on Earth. It has the same size and shape as a hydrogen atom, and differs only in forming very slightly stronger chemical bonds. The removal of a hydrogen atom attached to a carbon atom is the first and rate-limiting step in the metabolism of many drugs. If the hydrogen that is removed in the first step of the metabolic process is replaced by deuterium, the metabolic process is slowed by a factor of up to 8-fold because the C-D bond, which is stronger than a C-H bond, is harder to break (source: Auspex Pharma).

Properties of Deuterium



Source: Auspex Pharma

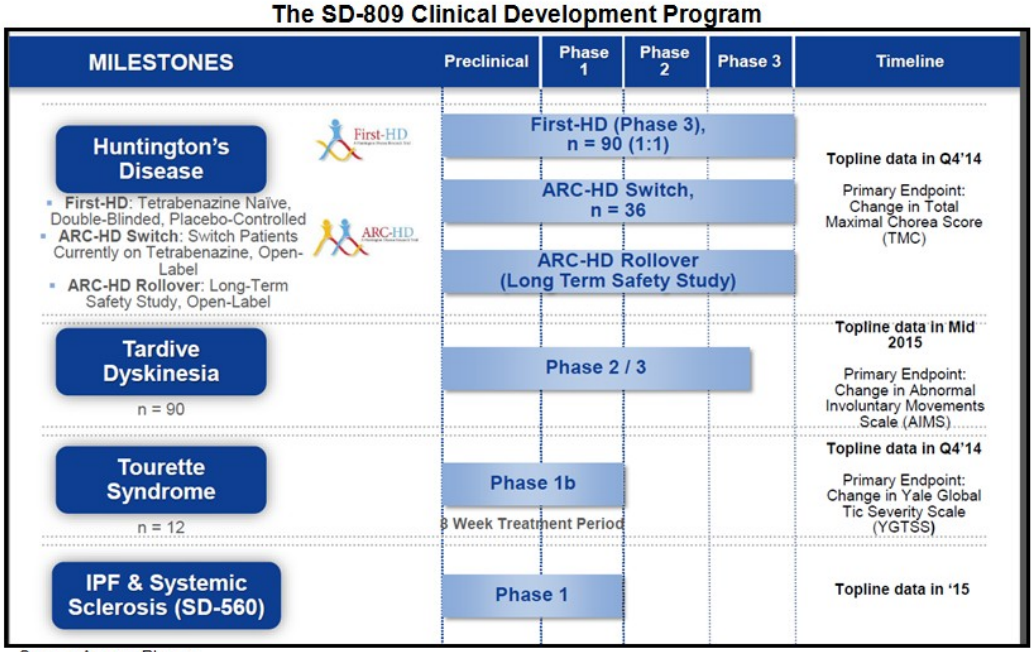
SD-809 is Auspex Pharmaceutical's proprietary deuterium-modified version of tetrabenazine. By replacing all six of the hydrogen atoms on the two methoxyl groups that are demethylated in the dominant deactivation pathway for DHTB, the metabolism is slowed due to the increased strength of the C-D bond.



Source: Auspex Pharma

Auspex is actively pursuing the development of SD-809 for the treatment of HD, TD, and TS. Two Phase 3 trials have been initiated for the treatment of HD, and results are expected in the fourth quarter of 2014. An 8 week Phase 1b trial in adolescent patients with TS was initiated in May 2014, and is also expected to report in the fourth quarter of this year. A 90-patient Phase 2/3 trial in TD is scheduled to begin later in 2014.

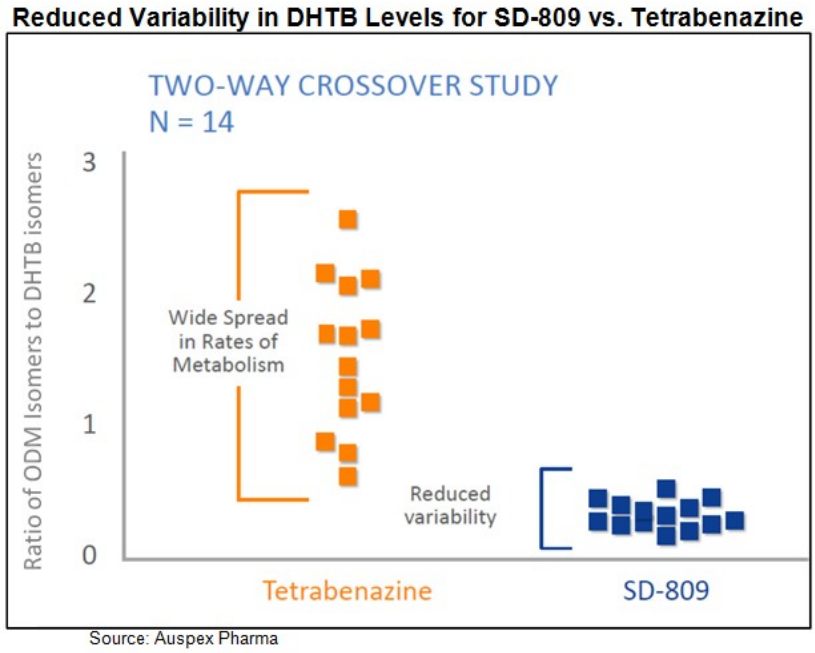
The SD-809 Clinical Development Program



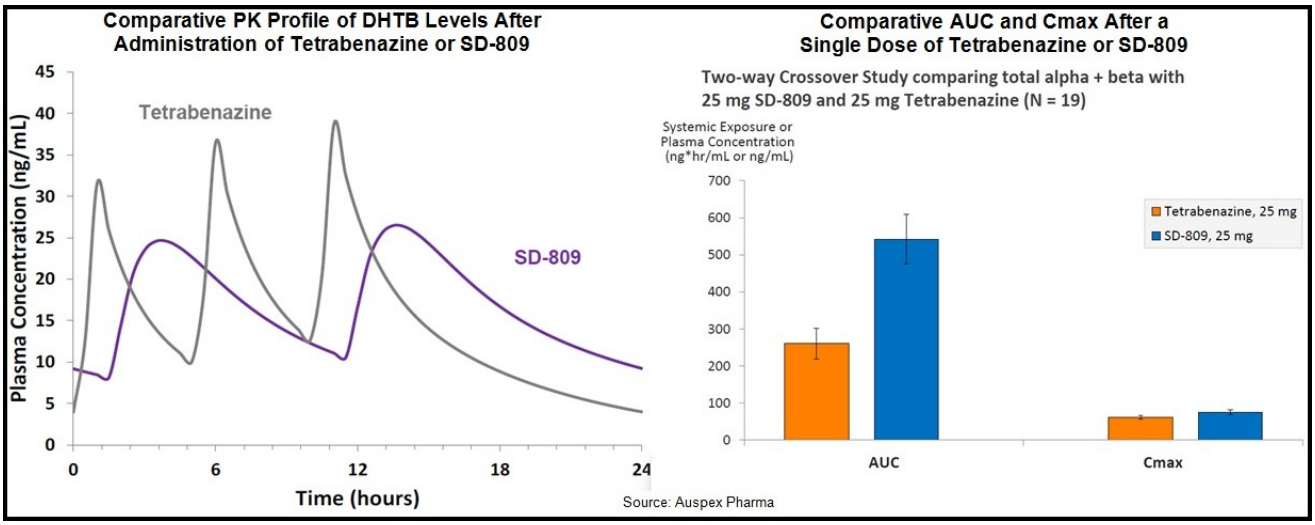
Source: Auspex Pharma

Phase 1 Results in Healthy Volunteers

Error! Reference source not found.shows the results of a Phase 1 crossover study in healthy volunteers treated with a single dose of tetrabenazine or SD-809 in 14 healthy patients. The Y axis shows the ratio of ODM metabolites to DHTB metabolites. Both the ratio (about 0.3 AUC) and the standard deviation of the ODM/DHTB ratio are dramatically reduced on going from tetrabenazine to SD-809. These observations likely reflect an increased serum half-life for SD-809 compared to tetrabenazine. The slowed metabolic pathway and potential involvement of new pathways that do not involve the highly variable CYP2D6 enzyme reduce the need for CYP2D6 genotyping with SD-809.

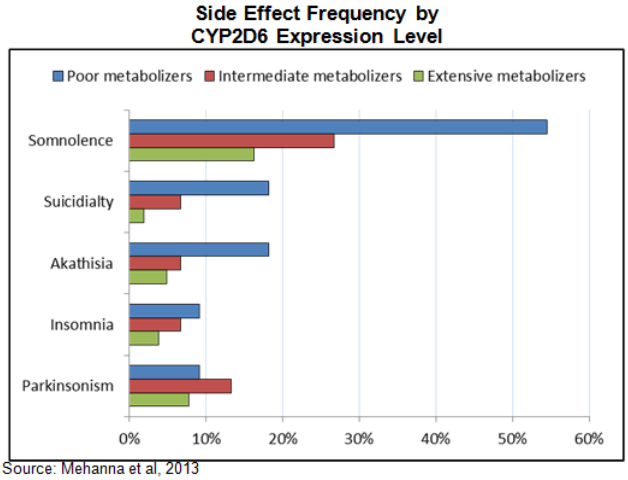


In multi-dose studies comparing 12.5 mg SD-809 administered twice daily (BID) to 12.5 mg tetrabenazine administered three times daily (during waking hours), similar DHTB AUC values were obtained. A much smoother serum drug concentration profile was obtained in the case of SD-809, with C_{MAX} and C_{MIN} values differing by about 14 ng/mL vs 25 for tetrabenazine, which is expected to reduce the need for CYP2D6 genotyping.

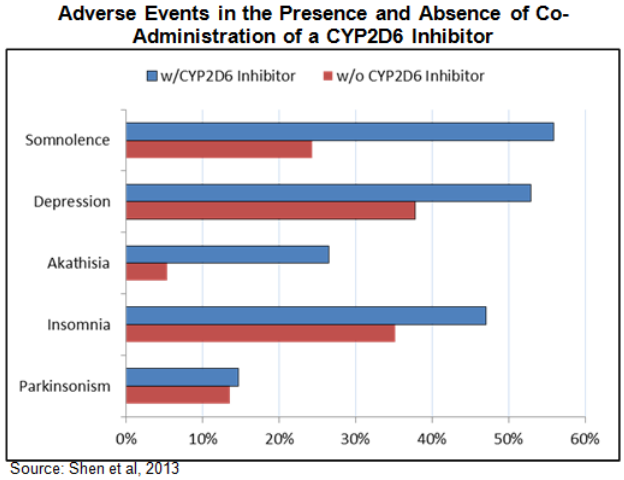


Reducing the need for CYP2D6 genotyping is an important component of the SD-809 story. CYP2D6 is a liver enzyme that plays an important role in tetrabenazine response on both efficacy and tolerability. A retrospective study published by *Mehanna et al* in Movement Disorders in 2013 found that the efficacy and side effects of tetrabenazine is greatly affected in patients with low, medium, or high expression of CYP2D6 (poor, intermediate, and extensive metabolizers, respectively). The authors concluded that side effects such as somnolence, depression/suicidiality, akathisia and insomnia are increased in poor metabolizers relative to extensive metabolizers. The observed level of efficacy for these groups was similar.

A second study published by *Shen et al* in Tremor and Other Hyperkinetic Movements in 2013 evaluated the rate of adverse events in tetrabenazine-treated patients who were co-administered an anti-depressant. The side effects of somnolence, depression, akathisia, and insomnia were increased in those receiving paroxetine or fluoxetine (CYP2D6 inhibitors) relative to those receiving anti-depressants that are not CYP2D6 inhibitors confirmed the importance of previous findings.



Source: Mehanna et al, 2013



Source: Shen et al, 2013

Both of these papers provide suggestive evidence that this subset of tetrabenazine side effects is increased in patients with low CYP2D6 activity relative to those with high CYP2D6 activity. The minimized CYP2D6 effect on Auspex' SD-806, which the company believes will reduced the need for CYP2D6 genotyping, could have a profoundly positive market effect on use if approved. This, of course, will need to be confirmed.

Huntington's Disease: Phase 3 Design

In June 2013, Auspex initiated the First-HD Phase 3 clinical trial (NCT01795859) of SD-809 for the treatment of Huntington's disease. The first of these is First-HD, a randomized, placebo controlled, double blind, parallel group, multi-center trial in 90 tetrabenazine-naïve patients with chorea associated with Huntington's disease. Patients will be randomized 1:1 to receive SD-809 once or twice daily or placebo. They will be individually titrated to their optimal dosage of study drug during the course of the trial, followed by maintenance therapy at that dose. The overall treatment period is 12 weeks in duration with a titration period that lasts eight weeks and a maintenance period that lasts four weeks. The primary endpoint for this trial is change in Total Maximum Chorea score from baseline to maintenance therapy, where final score is defined as the average of values from Week 9 and Week 12 visits. This is the same endpoint that was accepted by the FDA when it considered and approved the NDA for tetrabenazine in 2008. Patients from First-HD may also be eligible to enroll in ARC-HD Rollover, a long-term safety clinical trial described below.

In parallel with First-HD, the company has initiated an additional clinical trial of SD-809, ARC-HD (NCT01897896). One component of ARC-HD, referred to as ARC-HD Switch, is a four-week, open-label "switch" trial in 36 patients with chorea associated with Huntington's disease adequately controlled with tetrabenazine. The objectives of ARC-HD Switch are to evaluate the safety of switching subjects from tetrabenazine to SD-809 and to provide guidance to physicians on how to switch such patients to SD-809. The primary endpoints of ARC-HD Switch are the incidence of adverse events, the duration of time to achieve stable dosing and changes in observed clinical laboratory parameters for patients when treated with tetrabenazine (baseline) as compared to treatment with SD-809.

In ARC-HD Rollover, subjects will return to the clinic at scheduled intervals for evaluation of safety and chorea control. Further adjustments of SD-809 dosing will be made, if necessary, but not more than weekly, and in 6 mg daily increments. Four weeks after the last dose of the study drug, patients will be followed up with by phone to evaluate adverse events and concomitant medication usage. Interim analysis from ARC-HD suggests the drug is working. Top-line results from the First-HD and ARC-HD trials are expected in the fourth quarter of 2014.

Phase 2/3 Trial in Tardive Dyskinesia

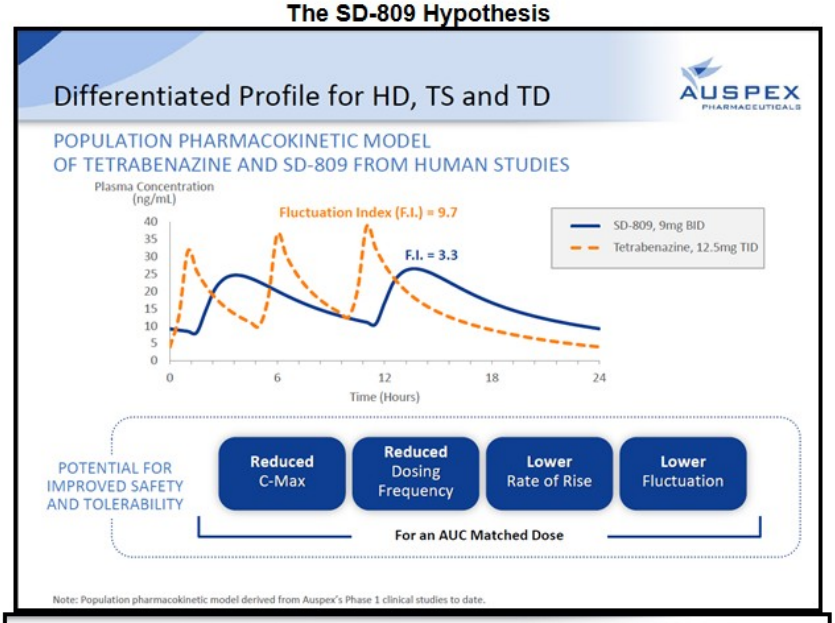
This is a double-blind, placebo-controlled, parallel group study at 30 enrolling sites in the U.S. and Canada. The trial will randomize 90 patients with moderate-to-severe TD 1:1 to receive either SD-809 or placebo for 12 weeks. The primary efficacy endpoint will be the change in AIMS score from baseline to Week 12 as assessed by a central video rater. The key secondary efficacy endpoint is Clinical Global Impression. Safety endpoints include adverse events, vital signs, Physical/neuro/laboratory exams, including ECGs during escalation

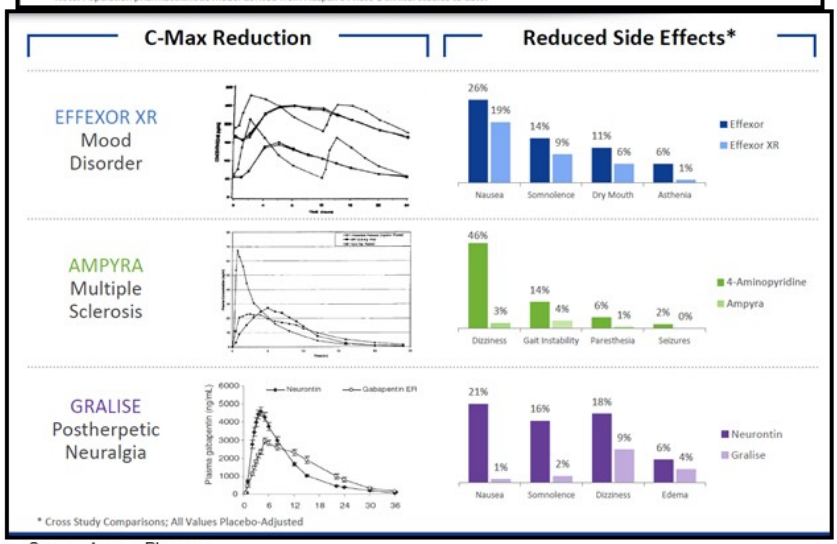
Our Thoughts On SD-809

The Auspex Hypothesis ➔The incorporation of deuterium in place of hydrogen at the sites of primary metabolism results in metabolic clearance being slowed. This will allow the use of less frequent dosing (BID vs. TID) and reproduction of AUC values known to be efficacious for tetrabenazine with lower doses (about half). The C_{MAX} values occurring after each dose will be reduced (because a smaller dose will suffice to provide continuous exposure), and the combination of lower C_{MAX}, less dramatically fluctuating serum levels, and less rapid rise after a dose will provide better tolerability. This reasoning is buttressed by the presentation of examples of other drugs including Effexor®, Ampyra®, and Gralise®, which produced similar efficacy and reduced side effects after reformulation to provide a lower ratio of Cmax to AUC.

The rationale for the SD-809 program is neatly described in the company slide deck from the BioCentury Future Leaders Conference in March 2014.

The SD-809 Hypothesis





Source: Auspex Pharma

One important difference between the case of SD-809 and the examples of improved adverse event profile provided by less frequent dosing cited by Auspex management is that the modified pharmacokinetic profile of SD-809 is obtained by slowing metabolism. In contrast, Effexor® XR, Intermediate Release Ampyra®, and Gralise® are all designed to extend the length of time it takes for the drug to be absorbed – small difference, but potentially

important. A reduced side effect profile is obviously something that the company will prove or fail to confirm in the ongoing Phase 3 trial.

However, based on the company's filings, Auspex plans to seek approval for SD-809 through the 505(b)(2) pathway, an expedited pathway for U.S. FDA approval that allows for substantial reliance on the safety, tolerability, and efficacy or a reference listed drug. In this the case of SD-809, the reference drug is tetrabenazine. Auspex makes note of this in its December 20, 2013 S/1 filing:

Regulatory Strategy for SD-809

We are pursuing a Section 505(b)(2) NDA regulatory strategy, which we expect will allow us to rely in our NDA filing on certain nonclinical and clinical safety findings made by FDA in its approval of the tetrabenazine NDA. Based on our interactions with the FDA, we believe that with the successful completion of First-HD, we will have completed the preclinical studies and clinical trials necessary to submit an NDA under Section 505(b)(2) for SD-809 for the treatment of chorea associated with Huntington's disease. In addition to the results of First-HD, we anticipate that the NDA submission will include the results of ARC-HD Switch, which, if successful, would allow us to provide guidance in our labeling on how to switch patients who are currently on tetrabenazine to SD-809. We also anticipate submitting the results of ARC-HD Rollover, while the FDA is reviewing the NDA. By pursuing the Section 505(b)(2) regulatory pathway for SD-809, our reliance on the FDA's prior findings of safety from tetrabenazine may require any approved labeling for SD-809 to include, in addition to safety information from our clinical trials, certain safety information that is included in the tetrabenazine label, including warnings and other safety information. Moreover, since neither of our ongoing clinical trials is studying SD-809 in a head-to-head comparison with tetrabenazine, if SD-809 is approved by the FDA, we will not be able to make direct comparative claims regarding the safety and efficacy of SD-809 and tetrabenazine. If we meet the primary endpoint of First-HD, we anticipate submitting our Section 505(b)(2) NDA for SD-809 in the fourth quarter of 2014 and, if approved, expect to launch commercial sales in 2015.

The above snap-shot confirms that "no direct comparative claims" can be made. However, the safety, tolerability, and adverse event profile of SD-809 as demonstrated in the Phase 3 trials will be on the label, and physicians are free to compare the two labels and decide for themselves. As such, we believe the marketing message for SD-809 will center around several advantages vs. tetrabenazine. These include: improved dosing from three-times daily (TID) to two-times daily (BID), reduced need for dose titration and CYP2D6 genotyping, and lower side effects vs. that (wink wink) other drug. These are clearly important differentiators, but whether or not the lack of ability to actually go out and market SD-809 as "safer" than tetrabenazine will limit the peak potential of the drug remains to be seen.

In the same S/1 filing we see that Auspex is seeking Orphan Drug designation for SD-809 in HD. However, the U.S. FDA has already granted tetrabenazine Orphan Drug designation for HD with Xenazine®. Initial feedback from the agency leads us to believe it will be an uphill battle for the company to change the FDA's mind without direct head-to-head pivotal studies comparing SD-809 to tetrabenazine. This is something the company is currently not doing, and thus we do not believe SD-809 will be granted Orphan Drug designation.

We are seeking orphan drug designation from the FDA for SD-809 for the treatment of chorea associated with Huntington's disease. Due to our patent protection, our strategy to pursue development of SD-809 in hyperkinetic movement disorders is not dependent on obtaining orphan drug designation and the related marketing exclusivity. We have received initial feedback from the FDA that it believes that SD-809 is the same drug as tetrabenazine, which is already approved for the treatment of this orphan indication, and that SD-809 therefore cannot be designated as an orphan drug for this indication unless we can provide a plausible hypothesis of the clinical superiority of SD-809 to tetrabenazine. We have responded to the FDA's request for additional information to support our belief that SD-809 is not the same drug as tetrabenazine for purposes of orphan drug designation because of the substitution of six specific hydrogen atoms in tetrabenazine with deuterium in SD-809. We are still evaluating whether to pursue orphan designation for the treatment of tardive dyskinesia and/or Tourette syndrome, or certain subsets of those disorders.

Regardless, of the outcome of the Orphan Drug applications – or whether or not the company even pursuing an ODD filing, SD-809 has been granted composition of matter patents (US#8524733) that do not expire until 2031.

Neurocrine Biosciences – Valbenazine

As noted above in our discussion on tetrabenazine, the drug is metabolized into four DHTB isomers, which we can now refer to (for simplicity sake) as (+)-alpha, (+)-beta, (-)-alpha, and (-)-beta. Neurocrine Bio believes that the efficacy in movement and psychiatric disorders such as TD, HD, and TS comes from the (+)-alpha isomer. Published literature seems to support this hypothesis (sources: 1, 2, 3, 4). Literature also support the activity of the (+)-beta isomer; however, some believe the side effect associated with the drug come from the (-)-alpha and (-)-beta isomers. Nevertheless, Neurocrine's approach to develop an improved version of tetrabenazine is to dose what they believe it the primary active metabolite in the (+)-alpha isomer.

More specifically, Neurocrine's NBI-98854 is a prodrug of the (+)-alpha isomer. NBI-98854 is L-Valine (2R,3R,11bR)-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo(a)quinolizin-2-yl ester – or

simply now referred to as valbenazine. The drug has been specifically developed for slowed cleavage, with low VMAT2 activity and attenuated C_{MAX}.

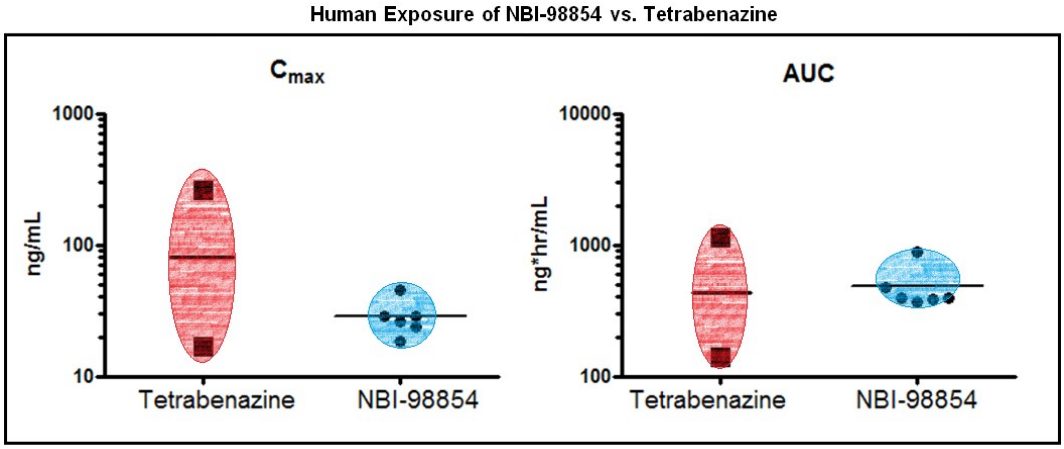
The hypothesis is that dosing the inert parent molecule with a highly selective and potent active metabolite will result in both reduced pharmacokinetic variability and improved safety profile. Additionally, because of the designed slow metabolism, valbenazine can be dosed once daily. More exciting organic chemistry of valbenazine can be explored by investors in the three active patents we found: US#8524733, US#8357697, and US#8039627.

Phase 1 Data & Analysis

Neurocrine conducted a single ascending dose study with NBI-98854 with the primary goal to assess the safety and tolerability of the drug, as well as pharmacokinetics and initial cognitive function tests. Patients were dosed up to 75 mg daily over a 28 day period. Results showed:

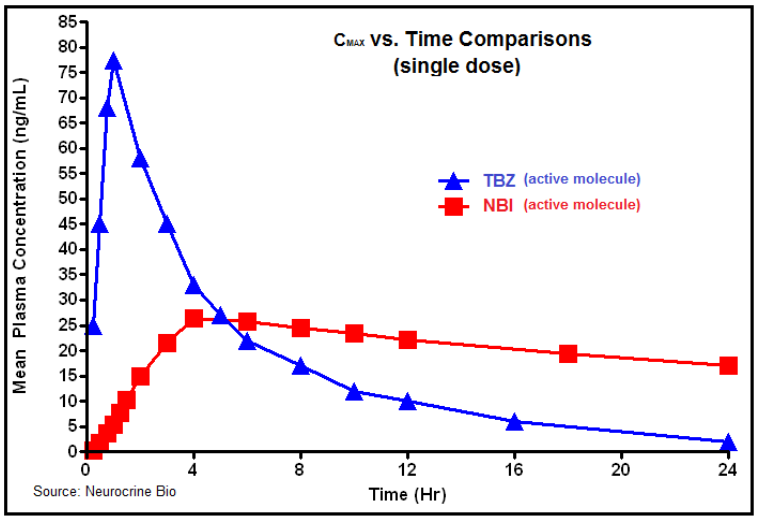
- ✓ No serious adverse events (SAE)
- ✓ No clear treatment emergent adverse events or trends signals
- ✓ No clinically significant ECG changes or QTcF prolongation
- ✓ No clinically significant hemodynamic changes
- ✓ No remarkable laboratory analysis
- ✓ No evidence of sedation, lethargy, and somnolence

When compared to tetrabenazine, valbenazine looks very clean. Below is a representation of the C_{MAX} and AUC data from the Phase 1 study. Investors can see a clear distinction in the variability of the data between NBI-98854 and tetrabenazine.



Source: Neurocrine Bio

Analysis of the blood plasma concentrations of the two drugs confirms that valbenazine can be dosed once daily, which coupled with the initial significant reduction in side effects such as sedation, positioned the drug well against generic alternatives.



Phase 2 KINECT Studies

Recently, Neurocrine Bio completed two Phase 2 studies called KINECT-1 and KINECT-2. KINECT-1 (NCT01688037) enrolled 109 subjects into three arms: a placebo arm (n=54), a straight 50 mg valbenazine for six weeks arm (n=27), and a down-titration arm where subjects started out on 100 mg valbenazine for two weeks then stepped-down to 50 mg for the remaining four weeks (n=26). All subjects had confirmed moderate-to-severe neuroleptic-induced tardive dyskinesia and a diagnosis of schizophrenia or schizoaffective disorder. The primary endpoint of the trial was the change from baseline in the Abnormal Involuntary Movement Score (AIMS) at Week 6 as determined by on-site raters. A key secondary endpoint was clinician-assessed improvement in tardive dyskinesia, as assessed on a 7-point scale.

Neither arm of the trial achieved its primary endpoint of providing a statistically significant improvement in the AIMS score at Week 6 vs placebo. However, examination of the Week 2 data showed that subjects in the 100 mg → 50 mg step-down arm exhibited a nominally statistically significant improvement from baseline in the AIMS when evaluated by a central reviewer. Scores assigned by on-site reviewers were not significantly improved.

		Week 6		
		PBO	50mg	p-value
AIMS Change from Baseline (on-site assessment)				
	LS Mean AIMS ANCOVA (ITT)	-2.5	-3.3	ns
	LS Mean AIMS ANCOVA (PP)	-2.4	-3.0	ns
	Responder Rate (ITT)*	11%	24%	ns
	Responder Rate (PP)*	10%	21%	ns
AIMS Change from Baseline (video assessment)				
	LS Mean AIMS ANCOVA (ITT)	-2.2	-3.5	ns
	LS Mean AIMS ANCOVA (PP)	-1.9	-3.3	ns
	Responder Rate (ITT)*	21%	29%	ns
	Responder Rate (PP)*	18%	28%	ns

** a responder is defined as 50% reduction in AIMS*

		Week 2				
		PBO	50mg	p-value	100mg	p-value
AIMS Change from Baseline (on-site assessment)						
	LS Mean AIMS ANCOVA (ITT)	-1.2	-2.1	ns	-2.1	ns
	LS Mean AIMS ANCOVA (PP)	-1.3	-2.4	ns	-2.5	ns
	Responder Rate (ITT)*	7%	7%	ns	12%	ns
	Responder Rate (PP)*	7%	8%	ns	14%	ns
AIMS Change from Baseline (video assessment)						
	LS Mean AIMS ANCOVA (ITT)	-2.7	-3.9	ns	-4.8	0.034
	LS Mean AIMS ANCOVA (PP)	-2.7	-3.9	ns	-5.5	0.008
	Responder Rate (ITT)*	23%	30%	ns	40%	ns
	Responder Rate (PP)*	23%	31%	ns	48%	0.034

** a responder is defined as 50% reduction in AIMS*

Source: Neurocrine Bio

Despite less than desirable data, Neurocrine was encouraged by the safety and tolerability profile demonstrated in the study. For example, the frequency of treatment-emergent adverse events during the initial two-week period was 17%, 18% and 15% in the placebo, 50mg and 100mg groups, respectively. During the six-week treatment period the frequency of treatment-emergent adverse events was 37% for placebo and 26% for the combined NBI-98854 arms. There were no drug related serious adverse events. Below is a snap-shot of the adverse event profile:

AE	Placebo	50 mg	100 mg
Somnolence	0	2	1
Dry mouth	2	0	0
Bronchitis/URI	2	0	0

In secondary assessments of efficacy, including analysis based on a responder rate and Clinical Global Impression – Tardive Dyskinesia (CGI-TD). Treating clinicians determined that 36% of the subjects taking 100 mg of NBI-98854 were "much improved" or "very much improved" at Week 2 compared to only 8% of the placebo subjects (p=0.002).

With KINECT-1 offering mixed data, Neurocrine got a second-chance to convince investors of valbenazine's value in early January 2014 when the top-line results of KINECT-2 (NCT01733121). KINECT-2 enrolled 102 subjects; and unlike KINECT-1, offered an up-titration schedule where patients could increase dose from the starting 25 mg to 75 mg. According to management, 84% of the patients up-titrated from the 25 mg to the 50 mg dose at week 2, followed by 76% up-titrating to 75 mg at week 4. At the end of the trial, 70% (31 of 44) of the patient population were on the 75 mg dose, 20% (9 of 44) were on 50mg, and 10% (5 of 44) remained on 25mg.

The primary endpoint of the study was change in Abnormal Involuntary Movement Scale (AIMS) from baseline at week 6. Management also provided a responder analysis, which included any subject showing a 50% reduction or greater in AIMS at week 6. Secondary endpoints included a clinician's global impression of change (CGI-TD). Neurocrine analyzed the data from KINECT-2 on an Intent-to-treat (ITT) and Per Protocol (PP) basis. The ITT population includes any subject with at least one dose of blinded study drug (active or placebo) and one post-

treatment AIMS assessment at week 6 (n=89). The PP population excluded any subject randomized to NBI-98854 without quantifiable level of active metabolite at the evaluation time point (n= 78). Below we present the top-line data from the trial:

	Week 6		
	Placebo	NBI-98854	p-value
AIMS Change from Baseline			
Baseline AIMS	7.9	8.0	-
LS Mean AIMS ANCOVA (ITT)	-0.2	-2.6	<0.001
LS Mean AIMS ANCOVA (PP)	-0.3	-3.3	<0.001
Responder Rate (ITT)*	18%	49%	0.002
Responder Rate (PP)*	18%	59%	<0.001

** a responder is defined as 50% or greater reduction in AIMS*

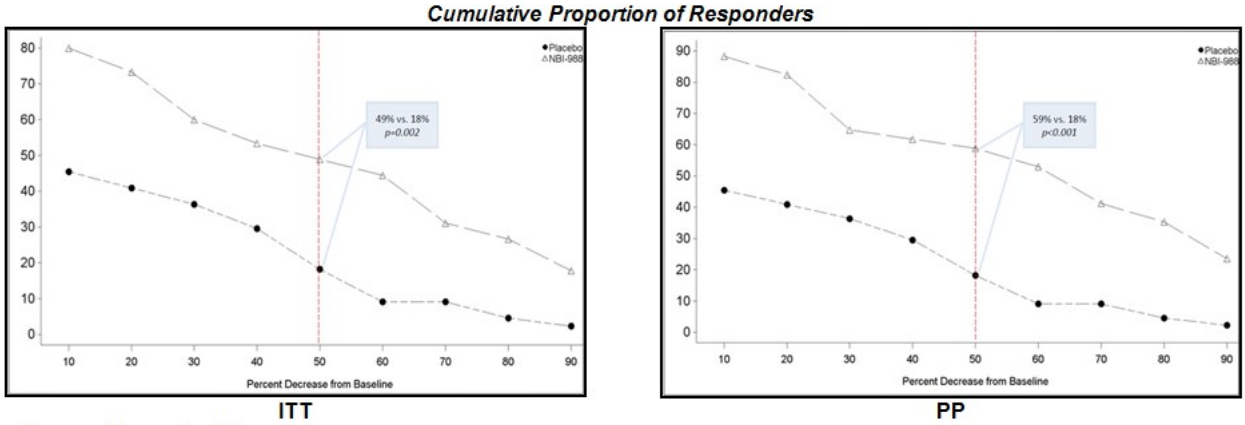
Source: Neurocrine Bio

	Week 6		
CGI-TD	Placebo	NBI-98854	p-value
LS Mean Score (ITT)	3.1	2.2	<0.001
LS Mean Score (PP)	3.1	2.2	<0.001
Responder Rate (ITT)*	16%	67%	<0.001
Responder Rate (PP)*	16%	68%	<0.001

**a responder is defined as "much improved" or "very much improved" (a "2" or "1", respectively) on the CGI-TD. A "4" on the CGI-TD indicates "no change"*

The results were highly statistically significant. This was a dramatic turnaround from the KINECT-1 study where 50 mg of drug failed to separate from placebo at week 6. What seemed to provide the greatest opportunity for success was the change in how the results were analyzed. For KINECT-2, Neurocrine used a centralized rater vs. separate on-site raters in KINECT-1. This allowed for greater standardization of the analysis. We note the U.S. FDA has clearly been amendable to these types of centralized assessments in the past. Other important differences include a marked difference in the baseline AIMS rating for patients between KINECT-1 and KINECT-2. Specifically, the mean baseline AIMS score in KINECT-1 was significantly higher than in KINECT-2 (12.3±5.1 vs. 8.0±4.0). Management noted that the actual patient populations were similar on disease severity but that the difference in baseline varied based on what type of doctor was providing the initial assessment (movement disorder doctors vs. psychiatrists).

Below we present graphical representations of the profound and consistent separation between NBI-98854 and the placebo on measures of responder analysis:



Source: Neurocrine Bio

The safety and tolerability assessment showed that NBI-98854 is a clean drug. That will be very important to the marketing message for Neurocrine when positioning the drug vs. tetrabenazine. During the six-week treatment period the frequency of treatment-emergent adverse events was 33% for placebo and 43% for NBI-98854. There were no drug related serious adverse events. The most common treatment emergent adverse events were fatigue in five subjects (9.8%) randomized to NBI-98854 vs. two subjects (4.1%) in the placebo group, and headache reported by four subjects (7.8%) on NBI-98854 vs. two subjects (4.1%) on placebo.

Discontinuation rates were similar in both the NBI-98854 and placebo treatment groups with five per study arm (none of which were study drug related). We note none of the 10 patients that discontinued during the study were included in the final ITT or PP assessment for the primary outcome. This is the only area where we can nit-pick a little about the results. All patients should be included in the final assessment, not just completers. Nevertheless, given the similar and high (~89%) completion rate for both the drug and placebo in both KINECT-1 and KINECT-2, this does not seem an area of major concern going forward.

Our Thoughts On Valbenazine

Following the results of the KINECT-1 study, valbenazine looked like a dud. It looked like the company either did not dose enough drug or did not maintain patients on an adequate level of drug long enough. As a result of the mixed data, most investors caulked up KINECT-1 as a failure.

Expectations were undoubtable low ahead of the KINECT-2 results. Then, KINECT-2 came out and that all changed. Results from KINECT-2 look solid. We personally had the chance to sit down with Neurocrine management in January 2014 and view some of the before and after videos of patients from KINECT-2. All we can say is – Wow, valbenazine really works! The videos were a slam-dunk case of efficacy in our view. Patients that had significant dyskinesia of the hands, legs, mouth, and tongue all showed dramatic improvements after six weeks on drug. These were likely some of the strongest videos, cherry-picked for investor meetings, but they were still impressive evidence of the drug's efficacy nevertheless.

Management will continue to analyze the data from KINECT-2 over the next few months to further qualify and fully understand the patient population and design characteristics for the planned Phase 3 program. Neurocrine is also working both in-house and with outside consultants to analyze drug exposure and the pooled PK and PD data as it relates to changes in AIMS score seen in both KINECT-1 and KINECT-2. Quite interestingly, recently, Neurocrine went back and analyzed the data from KINECT-1 using the centralized blinded reader protocol from KINECT-2 and found that the KINECT-1 results, although limited by lack of dose, did show statistical significance. We think this helps confirm not only the drug's efficacy but the strong design and execution of management for KINECT-2.

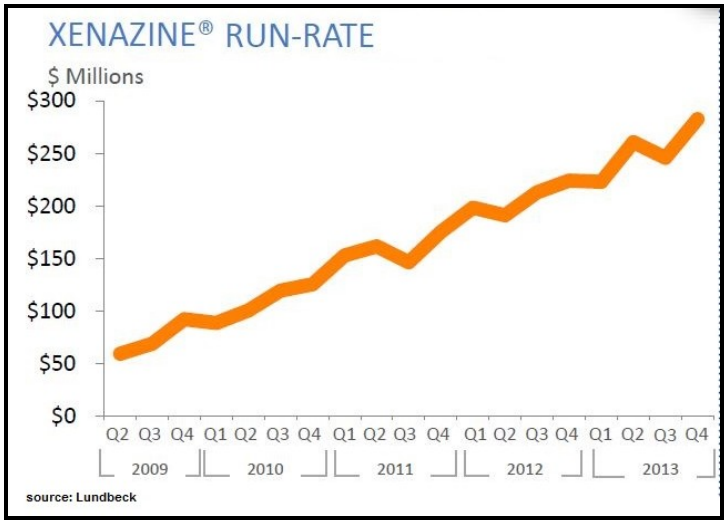
We remind investors that the company has also been doing early-stage toxicology work, namely a hepatic impairment special population study and drug-drug interaction studies to further build up the clinical and pre-clinical data package to bring in front of the U.S. FDA for an "End of Phase 2" meeting. Remember, Neurocrine is not going the 505(b)(2) route to market with valbenazine that Auspex is pursuing with SD-809. As a result, Neurocrine has a lot more "background" work to do before they can submit a package to the FDA, and then hopefully sit down for a face-to-face meeting in the second half of the year.

Neurocrine management has already begun the process of identifying and qualifying additional clinical trial sites for the Phase 3 program. Management's belief is that the Phase 3 program will include two relatively modest sized (150-200 subjects) 12-week pivotal trials, with each having their own 12 month open-label safety extension study. We expect Neurocrine will also conduct, in parallel, a separate additional ~100 subject 12 month open label safety trial. We model the U.S. NDA filing in 2016.

Beyond TD, Neurocrine is still working on completing the pre-clinical juvenile toxicology studies, along with some additional work, so they can file a new investigation new drug (IND) application to the U.S. FDA for Tourette syndrome during the second half of 2014. Following U.S. IND approval, Neurocrine is expected to move quickly into a Phase 2 study for pediatric Tourette syndrome by the end of 2014. Interestingly, we have not heard Neurocrine talk much about pursuing Huntington's disease with valbenazine.

Market Opportunity for SD-809 & Valbenazine

In the U.S., tetrabenazine is approved for the single indication of chorea associated with Huntington's disease. It is subject to a "Risk Evaluation and Mitigation Strategy" (REMS), which primarily features a prescriber education program designed to ensure that physicians are aware of the serious side effects of depression, suicidiality, and parkinsonism. Although not required by the REMS, it is distributed by specialty pharmacies under a restricted distribution system. The U.S. approval summary states that the FDA will monitor tetrabenazine sales to ensure that sales do not substantially exceed those attributable to its approved indication in HD. U.S. sales of tetrabenazine (Xenazine®) were $253 million in 2013, up 20% over 2012.



Protected by Orphan Drug designation in the U.S., it is a generic product in most ex-U.S. markets. The orphan drug exclusivity expires in August 2015, and no unexpired patents protect its exclusivity after that date.

Potential for Generic Competition is Likely Limited

Examination of product availability data for tetrabenazine in European markets suggests that there are currently 3-4 generic manufacturers of tetrabenazine operating in developed markets. Assuming that all of these companies were to enter the U.S. market at the end of Orphan Drug exclusivity would provide a maximum of 5 suppliers in the market (DMF's have been filed by Mylan, Herero, Sun, and Apotek to date). Historically, only limited price reductions have been observed in such situations where a REMS is in place (see Accutane® / generic isotretinoin as an example). Given that the current sales reflect the product of a modest number of patients and a high price for the drug, it is unlikely that additional companies would invest in beginning production knowing that their entry into the market could trigger a price war.

We further note that the FDA has stated that it will act to prevent off-label use of tetrabenazine in non-HD movement disorders. Thus, we assume limited competition for SD-809 and valbenazine in HD, TD, and TS within the "tetrabenazine segment" of these markets.

Positioning In The Market

Analysis of tetrabenazine results in our belief that this is a highly effective drug for the treatment of both HD and TD. Approximately 80 to 85% of HD or TD patients can expect an "excellent" or "very good" response to the drug (*Kenney et al, 2007*). Xenazine® sales of only $253 million in 2013, however, are far below what would be expected given that HD is an Orphan indication with significant pricing (20,000 patients x $67,000 per year = $1.34 billion). The TD market is not an Orphan market, but with at least 150,000 moderate-to-severe TD patients in the U.S. paying "atypical antipsychotic" pricing levels of $10,000 per year still equates to a $1.5 billion market.

One might conclude that the high price of Xenazine® inhibits broad uptake, but use of tetrabenazine outside the U.S. where pricing is far lower is also well below peak estimated based on the drug's efficacy. We believe this is a result of the rather poor tolerability, high side-effects, and potential increased risk of suicide that goes along with tetrabenazine use. As such, a drug with the efficacy of tetrabenazine with much improved safety and tolerability should have a peak sales estimate more representative of the combined total opportunities in HD and TD.

Auspex Strategy is to incorporate deuterium in place of hydrogen at the sites of primary metabolism, resulting in slowed metabolic clearance. This potentially allows for less frequent dosing (BID vs. TID), lower-dosing (about half), less impact of the CYP2D6 enzyme (eliminating the need for genotyping), and better safety and tolerability. Of course, all this will need to be proved in the ongoing Phase 3 FIRST-HD and ARC-HD studies, but the concept of SD-809 offering improved safety and tolerability has been well-validated in the past (see Effexor®, Ampyra®, and Gralise®).

Things that Auspex has going for it include:

- ✓ 505(b)(2) pathway allows them to beat Neurocrine to the market by ~2 years

- ✓ Going after HD allows the company to maintain an extremely high price comparable to Xenazine®
- ✓ Deuterium should not impact the efficacy of SD-809, so assuming the company has selected the correct doses for the Phase 3 studies, we see the outcome of FIRST-HD and ARC-HD as low-risk.
- ✓ Pending Phase 3 data from FIRST-HD later this year should keep biotech investors interested in the story.

Neurocrine's Strategy is to dose only the (+)-alpha isomer of tetrabenazine. The company doses an inactive prodrug that comes active *in vivo*. Dosing the inactive drug minimizes side effects and improved tolerability. The ester acid prodrug is slowly metabolized, allowing for QD dosing compared to TID for tetrabenazine.

Things that Neurocrine has going for it include:

- ✓ The company is pursuing a New Chemic Entity (NCE) with valbenazine, which would provide extended protection and long market exclusivity out to at least 2029, with Hatch/Waxman potential out to 2034.
- ✓ Results from KINECT-2 provide outstanding proof-of-concept for valbenazine. Our interpretation is that this is a highly effective drug with a much-improved side effect and tolerability profile.
- ✓ Company is pursuing the wide-open TD market first with valbenazine.
- ✓ Once daily dosing with aggressive pricing strategy compared to Xenazine®.

Projecting Peak Sales

- **SD-809 in HD**: We assume U.S. approval of SD-809 in HD will target a patient population of around 12,500. We base this off information from the HDSA ranging the total U.S. HD population between 20,000 and 30,000, and then assume only 75% response to therapy (*Kenney et al*, 2007) and 67% eager switching from Xenazine® to SD-809 (our best guess). If Auspex can capture 75% market share from Xenazine® and then penetrate 25% of the untreated market, peak sales estimates are around $400 million with comparable pricing to Xenazine®.

- **Valbenazine in TD**: We assume U.S. approval of valbenazine in TD will target roughly 150,000 of the approximate 200-500,000 total TD patients in the U.S. that are moderate-to-severe in disease state. We assume Neurocrine Bio will charge pricing comparable to atypical antipsychotics, or around $10,000 per year. If Neurocrine can capture 30% market share, peak sales estimates are around $450 million.

So in their initial (most advanced) indications, these are looking like similar sized drugs. The average large-cap pharmaceutical and biotechnology company trades at 5.5x trailing twelve month sales. If we apply an identical 20% discount rate to both companies and assume peak sales for SD-809 and valbenazine in 2022, then these assets are both approximately worth $525 to $575 million in value. Not so coincidently: 1) Auspex current market capitalization is $495 million, and 2) On January 7, 2014 (first day of trading after KINECT-2 top-line results), Neurocrine's market capitalization jumped $535 million (67 million shares outstanding x $8 move in the stock).

Company	Price / Sales
Eli Lilly and Co	2.9
GlaxoSmithKline plc	3.0
Sanofi-aventis	3.2
Pfizer Inc.	3.7
Merck & Co. Inc.	3.9
Johnson & Johnson	4.0
Amgen Inc.	4.6
Cubist Pharma	4.8
Bristol-Myers Squibb	4.8
Valeant Pharma	6.1
Allergan Inc.	7.4
Gilead Sciences Inc.	9.1
Celgene Corporation	9.5
Biogen Idec Inc.	9.6
AVERAGE	**5.5**

Source: Jason Napodano, CFA



The wildcard for both these companies will be what their respective drugs do in follow-on indications. For Auspex, TD is the second indication with SD-809 currently in a Phase 2/3 study. Assuming both SD-809 and valbenazine come to market at the same time in TD, why would anyone pay $67,000 per year for SD-809 when Neurocrine is charging $10,000 for valbenazine? For Neurocrine, that might be impetus to charge more for valbenazine, but movement disorder doctors may give push-back to prescribing such a high price drug for a non-orphan indication. We remind investors that Xenazine® has very limited use off-label in TD, likely because of the high side effect profile and physicians not wanting to "double-up" on side effects already conveyed by atypical antipsychotics. Potential drug-drug interactions may also play an important role in limiting tetrabenazine use in TD patients.

Neurocrine seems content to bypass the HD market for now, focusing on TS as the second indication. Auspex is already in Phase 1b with SD-809. Neurocrine plans to be in Phase 2 for TS in 2015. Safety will be absolutely paramount in TS, as no parent or physician would likely be willing to dose a drug with the side effect profile of tetrabenazine in adolescents for a non-life threating disorder like Tourette syndrome. Valbenazine, with its once-daily dosing, looks to have the advantage over SD-809 in this opportunity, but it is too early to predict market share or sales. There are approximately 150,000 children and young adults that suffer from TS in the U.S., thus representing a fairly sizable market opportunity for both companies.

Conclusion

Auspex Pharmaceuticals currently trades with a market capitalization of around $495 million. This seems fair based on the opportunity in HD alone. Upside comes with the potential use, either approved or off-label, in TD or TS. They have the first-move advantage on Neurocrine and with two pending Phase 3 studies expected to read-out over the next six months this could be a very good investment if the data pans out. Our valuation analysis for Auspex shows the shares modestly under-value, and that projecting sales in HD only. Auspex bulls might argue that our peak sales estimate of $400 million is low assuming the company can gain additional indications or that our discount rate should be lowered after (potentially) two positive Phase 3 trials report late 2014. Bullish forecasts for SD-809 easily yield price targets doubling the current valuation. The primary risk to the Auspex thesis is the potential that the Phase 3 data fails to impress on safety / tolerability. Additionally, several other companies are developing drugs for HD, such as Raptor Pharmaceuticals, Teva Pharmaceuticals, Pfizer, Omeros, and Roche, although none of these compounds are for Huntington's chorea like SD-809. Valeant Pharmaceuticals is also working on a modified slow-release formulation of tetrabenazine, dubbed BVF-018. We do not know the status of this candidate, only that a patent was awarded to Valeant in this regard in June 2012.

Neurocrine Biosciences has given back almost $200 million in value since its initial pop on the top-line results of KINECT-2. Based on our analysis, the $500+ million move was warranted and the shares are attractive based on the pull-back. Neurocrine is taking a slower, yet potentially more solid 505(b)(1) path to market with valbenazine. Of course, Neurocrine's future is split evenly at this point between valbenazine and Phase 3 elagolix at AbbVie (not discussed in this report). Nevertheless, the shares look attractive based on the opportunity for valbenazine in TD alone, with nice potential upside in TS or off-label use in HD. Similar to Auspex, we are being conservative in our peak sales estimate for valbenazine. The potential for a once daily, safer and more tolerable tetrabenazine molecule could easily fetch peal sales double what we currently model. Risks to Neurocrine include potential push-back on the Phase 3 data analysis plan, the U.S. FDA making the company do significantly larger (more expensive) studies with valbenazine than expected, or the development of alternative isomers of tetrabenazine by Valent Pharmaceuticals (see Valeant's 2013 annual report).

PROJECTED FINANCIALS

Neurocrine Biosciences Inc.
Income Statement

Neurocrine Bio	2012 A	2013 A	Q1 A	Q2 E	Q3 E	Q4 E	2014 E	2015 E	2016 E
R&D / Milestones & Fees	**$53.1**	**$2.9**	**$0**	**$0**	**$0**	**$0**	**$0**	**$25.0**	**$50.0**
YOY Growth	*-31.4%*	*-94.6%*	-	-	-	-	-	-	*100.0%*
elagolix Royalties	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-	-
valbenazine sales	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-	-
Total Revenues	**$53.1**	**$2.9**	**$0**	**$0**	**$0**	**$0**	**$0**	**$25.0**	**$50.0**
YOY Growth	*-31.4%*	*-94.6%*	-	-	-	-	-	-	*100.0%*
CoGS / Royalties	$0	$0	$0	$0	$0	$0	$0	$0.0	$0.0
Gross Margin	*100.0%*	*100.0%*	-	-	-	-	-	*100.0%*	*100.0%*
SG&A	$14.5	$13.4	$4.2	$4.2	$4.2	$4.2	$16.8	$16.5	$17.5
% SG&A	*27.3%*	*463.1%*	-	-	-	-	-	*66.0%*	*35.0%*
R&D	$37.2	$39.2	$8.6	$10.0	$12.0	$14.0	$44.6	$40.0	$40.0
% R&D	*69.9%*	*1357.6%*	-	-	-	-	-	*160.0%*	*80.0%*
Operating Income	$1.4	($49.7)	($12.7)	($14.2)	($16.2)	($18.2)	($61.3)	($31.5)	($7.5)
Operating Margin	*2.7%*	*-1720.7%*	-	-	-	-	-	*-126.0%*	*-15.0%*
Interest / Other Income	$3.6	$3.6	$0.9	$0.9	$0.9	$0.9	$3.6	$4.0	$5.0
Pre-Tax Income	$5.0	($46.1)	($11.8)	($13.3)	($15.3)	($17.3)	($57.7)	($27.5)	($2.5)
Taxes	$0	$0	$0	$0	$0	$0	$0	$8.3	$0.8
Tax Rate	*0%*	*5%*	*0%*	*0%*	*0%*	*0%*	*15%*	*30.0%*	*30.0%*
Net Income	$5.0	($46.1)	($11.8)	($13.3)	($15.3)	($17.3)	($57.7)	($19.3)	($1.8)
YOY Growth	-	-	-	-	-	-	-	-	-
Net Margin	*9.5%*	*-1597.4%*	-	-	-	-	*#DIV/0!*	*-77.0%*	*-3.5%*
Reported EPS	**$0.08**	**($0.69)**	**($0.17)**	**($0.18)**	**($0.20)**	**($0.22)**	**($0.77)**	**($0.23)**	**($0.02)**
YOY Growth	*-88.5%*	*-995.4%*					*12.2%*	*-70.6%*	*-91.4%*
Shares Outstanding	65.6	67.3	70.3	73.0	77.0	80.0	75.1	85.0	90.0

Source: Zacks Investment Research, Inc. *Jason Napodano, CFA*

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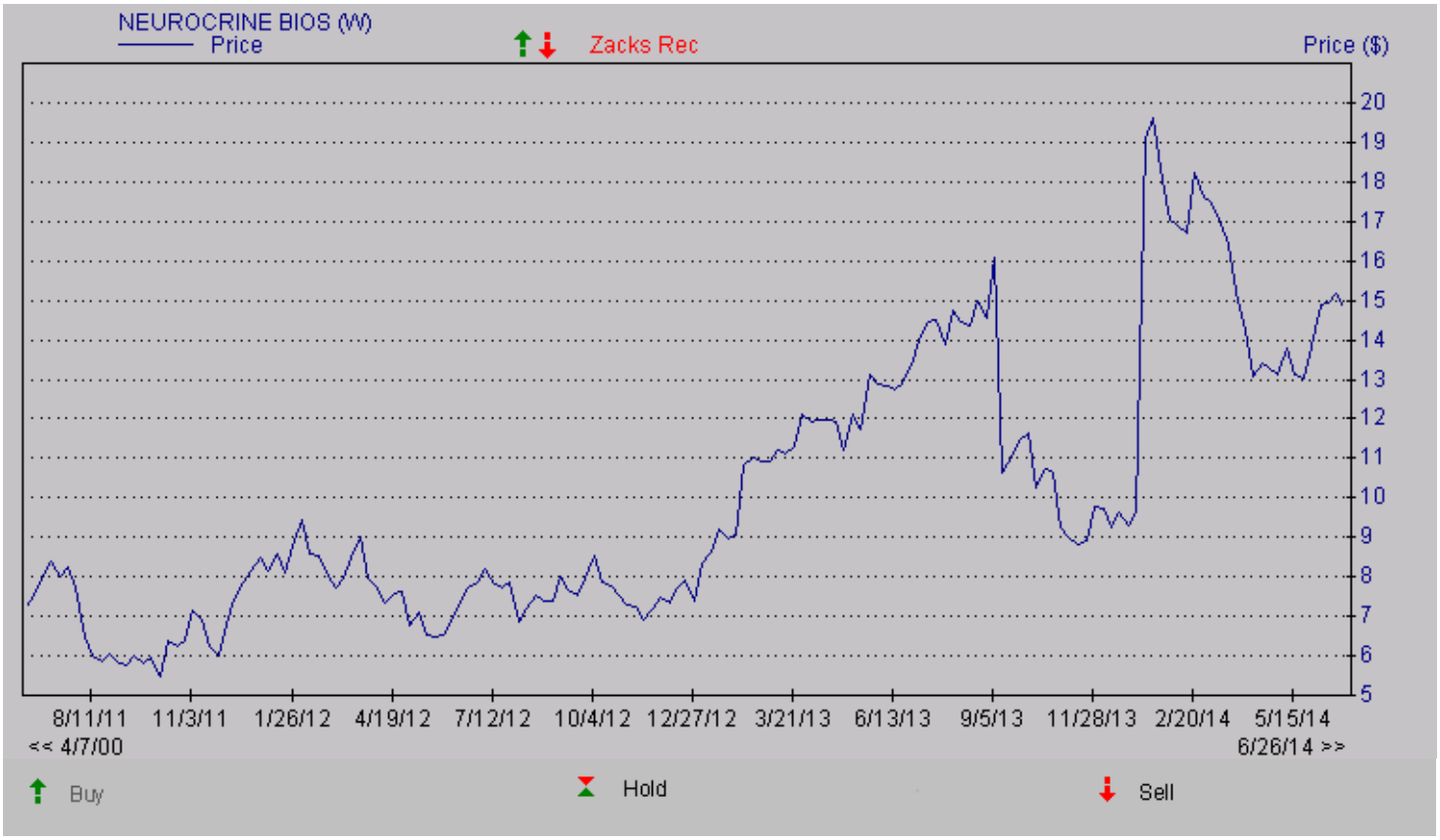

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