STX209 (Arbaclofen) for Autism Spectrum Disorders: An 8-Week Open-Label Study

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Abstract

STX209 (arbaclofen), a selective GABA-B agonist, is hypothesized to modulate the balance of excitatory to inhibitory neurotransmission, and has shown preliminary evidence of benefit in fragile X syndrome. We evaluated its safety, tolerability, and efficacy in non-syndromic autism spectrum disorders, in an 8-week open-label trial enrolling 32 children and adolescents with either Autistic Disorder or Pervasive Developmental Disorder—Not Otherwise Specified, and a score ≥17 on the Aberrant Behavior Checklist (ABC)—Irritability subscale. STX209 was generally well-tolerated. The most common adverse events were agitation and irritability, which typically resolved without dose changes, and were often felt to represent spontaneous variation in underlying symptoms. Improvements were observed on several outcome measures in this exploratory trial, including the ABC-Irritability (the primary endpoint) and the Lethargy/Social Withdrawal subscales, the Social Responsiveness Scale, the CY-BOCS-PDD, and clinical global impression scales. Placebo-controlled study of STX209 is warranted.

Introduction

Although the number of children and adults diagnosed with autism spectrum disorders (ASD) has increased over the last decade, (CDC *2012*) only two pharmacologic agents (risperidone and aripiprazole) are FDA-approved for use in this population. These agents are indicated for the treatment of irritability in youth with autistic disorder. Irritability, marked by severe tantrums, aggression and self-injury, is common and impairing, but not a core deficit of the disorder.(McPheeters et al. *2011*; Huffman et al. *2011*) The use of these atypical antipsychotics targeting irritability associated with autistic disorder was based on empirical extension of their effects in other disorders and previous reports on use of typical (older generation) antipsychotics in ASD, rather than specifically on a neurobiological understanding of the pathophysiology of ASD.

The development of "targeted treatments"(Geschwind *2009*; Hagerman et al. *2010*) for neuropsychiatric and neurodevelopmental disorders is a newer concept, wherein potential treatments are identified on the basis of a specific understanding of molecular and cellular pathophysiology. Although ASD has been the subject of ever increasing research, its etiologic heterogeneity has challenged efforts to identify a biological target for intervention (State *2010*). One approach to this dilemma is to study single gene disorders associated with high rates of comorbid ASD, such as fragile X syndrome (FXS) and tuberous sclerosis (Hagerman et al. *2010*).

FXS is the most common known single gene risk for ASD, accounting for an estimated 1–3 % of all cases of ASD (Kumar and Christian *2009*). The most extensively validated model of the pathophysiology of FXS is that neurobehavioral impairment results from abnormal synaptic plasticity, driven by excessive signaling downstream of the metabotropic glutamate receptor type 5 (mGluR5) (Bear et al. *2004*). These impairments, ranging from elevated synaptic protein synthesis and seizure susceptibility to abnormal dendritic spine morphology, can be rescued in preclinical FXS models by down-modulating mGluR5 signaling through either pharmacologic or genetic strategies (Krueger and Bear *2011*). Even mature animals with the FXS mutation can show signs of pharmacological rescue by decreasing mGluR5 signaling.(Michalon et al. *2012*).

The relevance of FXS to non-syndromic (idiopathic) cases of ASD is supported by genetic studies of ASD, which suggest that the largest group of genes associated with non-syndromic ASD belongs to a network of genes that are involved in synaptic function.(Gai et al. *2012*) Specific genes that have been suggested to be implicated include *GRM5*, which codes for mGluR5, and several genes that code for proteins involved in the signaling cascade downstream of mGluR5 (Kelleher et al. *2012*; Skafidas et al. *2012*). Although findings are not uniformly consistent, behavioral pharmacology studies show that mGluR5 antagonists or negative allosteric modulators of mGluR5 rescue the impairments in social behavior that are seen in several putative mouse models of ASD, such as the BTBR mouse (Silverman et al. *2012*), the *Nlgn3*- knockout mouse (Baudouin et al. *2012*), and mice exposed prenatally to valproic acid (Gandal et al. *2010*). Furthermore, current models of FXS and ASD posit a pathophysiologic role for an elevated excitatory to inhibitory (E:I) ratio in neurotransmission (Rubenstein and Merzenich *2003*; Paluszkiewicz et al. *2011*). Recent optogenetic studies in mice show that elevation of the E:I ratio results in the impairment of social behaviors, and that subsequent augmentation of inhibitory neurotransmission can reduce this impairment.(Yizhar et al. *2011*) In patients with syndromic and idiopathic ASD, abnormally high E:I ratios may be reflected in seizure susceptibility, sensory hyper-responsiveness, anxiety, and increases in cortical activation, especially in the amygdala, when confronted with social stimuli (Watson et al. *2008*; Rubenstein and Merzenich *2003*).

Another potential therapeutic agent that is being tested in FXS and ASD is STX209 (arbaclofen), a specific GABA-B receptor agonist. Although STX209 is not an mGluR5 antagonist, it acts presynaptically to reduce glutamate release (Kang et al. *2012*), and may thus, by reducing glutamatergic activity, have a mechanism that converges with that of mGluR5 antagonists. Research in animal models of FXS demonstrates that STX209, like selective mGluR5 antagonists, reduces elevated protein synthesis, susceptibility to audiogenic seizures, and abnormalities in dendritic spine morphology (Henderson et al. *2012*). In idiopathic ASD, post-mortem studies also have observed reductions in GABA-B receptor binding in cingulate cortex, fusiform gyrus, and elsewhere in the brain (Fatemi et al. *2009*; Oblak et al. *2010*).

In a Phase 2 clinical trial that enrolled 63 children and adults with FXS, treatment with STX209 was associated with improvements on the Aberrant Behavior Checklist (ABC)—FXS Social Avoidance scale, a subscale of the ABC that was recently factor- analyzed for potential use specific to the FXS population (Berry-Kravis et al. *2012*). This scale consists of four highly-

correlated items that are all found in the original "Lethargy/Social Withdrawal" subscale of the ABC (ABC-LSW). Further post hoc analyses showed that STX209 was associated also with improvement on global measures and on the Vineland Adaptive Behavior Scales—Socialization domain in the subset of 27 subjects with more severe social impairment (as measured by the ABC-SW) at baseline.

The study we now report on was designed as a preliminary investigation of whether STX209 also might have beneficial effects in patients with ASD not associated with FXS. While animal research and the clinical trial in FXS, both reviewed above,

suggest that a GABAergic agent such as STX209 might have beneficial effects in the social domain, we examined a broad range of outcomes in this exploratory study. The ABC-Irritability subscale was chosen to be the primary outcome measure, because it is known to be sensitive to change in pharmacologic trials for ASD, which has not been demonstrated for any measure of social outcomes.

Methods

This study (clinicaltrials.gov identifier NCT00788073) was approved by all relevant Institutional Review Boards. Informed consent was provided for all subjects by their parents or legally-authorized representative, and assent was provided by subjects, as appropriate. The study was sponsored by Seaside Therapeutics, Inc.

Subjects

This study enrolled children and adolescents, aged 6–17 years, who met DSM-IV criteria for either Autistic Disorder or Pervasive Developmental Disorder, Not Otherwise Specified (PDD–NOS). Subjects also were evaluated for diagnostic corroboration using the Autism Diagnostic Interview-Revised (ADI-R), but no criterion score was required for entry. Subjects also were required to have a baseline score of 17 or greater on the ABC-Irritability subscale, and a score of 4 (moderate) or worse on the Clinical Global Impression of Severity scale (CGI-S). Subjects were not permitted to enroll if they had a known genetic diagnosis that is associated with ASD (e.g., FXS, tuberous sclerosis, or copy number variant associated with ASD), but genetic testing was not performed as part of this trial. Other medical exclusion criteria included a history of seizure disorder, unless the subject was on a stable regimen of antiepileptic drug(s) and seizure-free for at least 6 months. Pregnant females were not allowed to enroll.

Up to two concurrent psychoactive medications were allowed if dosing had been stable for at least 4 weeks prior to study entry, and remained stable throughout the study. Patients receiving antipsychotic medications were not permitted to enroll, given their significant and potentially confounding side effect profile, and because of their known benefits on symptoms of irritability, which comprised the primary outcome of the study. Use of vigabatrin, tiagabine, and riluzole also were prohibited, due to their potentially confounding GABA-ergic and/or glutamatergic mechanisms. Similarly, educational and behavioral interventions were required to be stable starting 3 months prior to study enrollment and to remain stable throughout the study. Regular school vacations were not regarded as disruptions in educational programming.

Study Design

The study was an eight-week, open-label trial, conducted at eight sites in the USA. After a screening period of up to 30 days, STX209 was started at a dose of 1 mg BID, then increased

every 3–4 days to a maximum dose of 10 mg BID (ages 6–11 years) or 10 mg TID (ages 12–17 years). Study visits were conducted at Weeks 2, 4, 6, and 8, with additional phone calls during up-titration of study drug and as needed. Planned dose increases were halted if subjects were "very much improved" (score of 1 on the CGI-Improvement (CGI-I) scale. If subjects did not tolerate their new, higher dose, then the dose was reduced to the previous tolerated level. For each subject, the highest dose that was associated with acceptable tolerability was declared the optimal tolerated dose (OTD). Subjects continued on their OTD for the remainder of the 8-week treatment period. After completion of assessments at the 8-week time point, subjects were tapered off of study drug over 1–2 weeks, or more slowly as tolerated, in very few cases.

Assessments and Analysis

A broad battery of efficacy assessments was administered, including the ABC, the CGI-S, the CGI-I, the Social Responsiveness Scale (SRS), the Children's Yale-Brown Obsessive Compulsive Scale—modified for PDD (CY-BOCS-PDD), the Child and Adolescent Symptom Inventory-4 (CASI) Anxiety scale, the Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale-IV, the Vineland Adaptive Behavior Scales (VABS), visual analog scales (VAS) for 3 target behaviors nominated by the subjects' parents or primary caregivers, and the Leiter-R Brief IQ score. The ABC-Irritability subscale was the primary outcome measure, chosen in alignment with the primary outcome used in the approval studies of risperidone and aripiprazole. Safety assessments included spontaneously reported adverse events (coded according to the Medical Dictionary for Regulatory Activities, MedDRA, version 12.0), physical examination, electrocardiograms (ECG), and standard clinical laboratory tests.

All efficacy analyses reported below are from the full, intent-to-treat (ITT) study population. Statistical analyses included measurements from baseline and all treatment visits, using repeated measures analysis of variance techniques, with terms for time and age group (child vs. adolescent). *p* values reported below are for the comparison of baseline to end-of-treatment.

Results

Forty-six subjects underwent screening for study enrollment, and 32 (29 male) met all inclusion and exclusion criteria. Demographics and baseline characteristics of the subjects are provided in Table 1.

Table 1

Subject characteristics

Total number of subjects	32
Age	
6–11 years	12
12–17 years	20
Sex (M/F)	29/3
Race (>1 response permitted)	

Caucasian	31
African-American	1
Other	1
Ethnicity: non-Hispanic/Hispanic	29/3
DSM-IV diagnosis	
Autistic disorder	27
PDD–NOS	5
ADI-R autistic disorder (yes/no)	29/3
Concomitant psychoactive medication (any)	21
Psychostimulants	5
Alpha-adrenergics	6
SSRI/SNRI	4
Anti-epileptics	3
IQ (mean ± standard deviation)	56 ± 22

Twenty-five of 32 subjects completed the study, with 2 discontinuing due to adverse events (1 for increased impulsivity, increased aggression, and increased oppositionality; 1 for agitation). Five subjects discontinued for other reasons (1 withdrew consent; 1 lost to follow-up; 1 for a planned tonsillectomy; 1 switched directly to racemic baclofen at Week 8, rather than taper off STX209 as required by study protocol; and 1 at investigator's discretion). There was 1 serious adverse event (worsening aggression), which occurred during the planned taper of study medication at the end of the treatment period.

STX209 was generally well-tolerated. The most common adverse events were agitation (22 %), irritability (22 %), fatigue (16 %), psychomotor hyperactivity (16 %), insomnia (13 %) and diarrhea (13 %). Other events occurring in more than 5 % of the subjects are listed in Table 2. A large majority of the adverse events were rated as mild in severity, and resolved without dose changes. Most of the events reflecting potential activation (e.g., agitation, irritability, hyperactivity) were transient and resolved spontaneously, and were often judged to be manifestations of the spontaneous variability in underlying symptoms and unrelated to drug administration. Indeed, many subjects who were rated as globally "much improved" had transient events of this nature. Clinical laboratory assessments and ECGs did not show any treatment-associated abnormalities.

Table 2

Adverse events reported in ≥5 % of subjects

Adverse event	Frequency (%)
Agitation	22
Irritability	22
Fatigue	16
Psychomotor hyperactivity	16
Diarrhea	13
Insomnia	13
Aggression	9
Disturbance in attention	9
Headache	9
Nasopharyngitis	9
Abdominal pain, upper	6
Cough	6
Decreased appetite	6
Dizziness	6
Streptococcal pharyngitis	6
Self-injurious behavior	6
Upper respiratory tract infection	6
Vomiting	6

Broad positive changes with drug treatment on a number of outcome measures were seen in the ITT population of this open-label trial. On the primary endpoint, the ABC-Irritability scale, subjects showed improvement from a baseline score of 27.0 ± 7.61 (mean ± standard deviation), to 17.7 ± 10.35 at Week 8 ($p < 0.001$). Improvements on this scale were seen at all study visits (Weeks 2, 4, 6, and 8), and no difference in effect was seen in the younger children compared to the adolescents. The magnitude of improvement increased slightly from Week 2 to 4, without notable change thereafter. Subjects also showed significant improvement on the ABC-Lethargy/Social Withdrawal scale, from a score of 17.3 ± 8.18 at baseline, to 12.6 ± 9.30 at Week 8 ($p = 0.001$), with improvement apparent by Week 2 (Fig. 1), and with no effect of age group. Significant improvements also were seen on the Social Responsiveness Scale, the CY-BOCS-PDD, the ADHD-IV Rating Scale, and the other subscales of the ABC, except for the Inappropriate Speech subscale, which showed marginal change (Table 3). An increase was noted on the Vineland-Communication domain standard score, and a marginal increase on the Vineland

Adaptive Behavior Composite Score, but not on the other domains of the Vineland or on the Leiter-R (data not shown).

Fig. 1

Aberrant Behavior Checklist subscale scores by study week. Scores on the irritability and the social withdrawal subscales are shown. *Error bars* indicate standard error of the mean

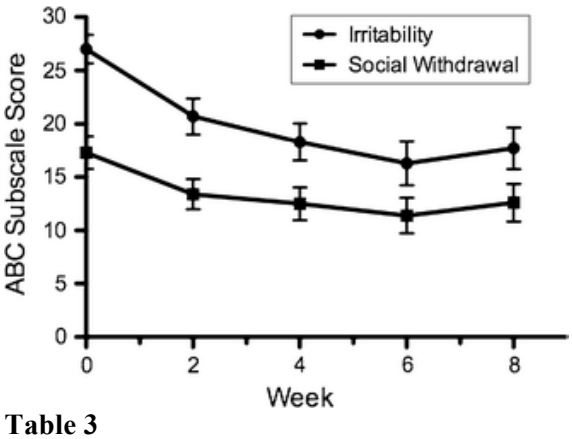

Table 3

Efficacy results

Measure	Baseline	Week 8	*p* value
ABC-Irritability	27.0 ± 7.61	17.7 ± 10.35	<0.001
ABC-Lethargy/Social withdrawal	17.3 ± 8.18	12.6 ± 89.30	0.001
ABC-hyperactivity	29.7 ± 12.14	21.1 ± 12.01	<0.001
ABC-inappropriate speech	7.0 ± 3.53	6.0 ± 4.04	0.081
ABC-stereotypy	9.3 ± 6.77	6.6 ± 6.90	0.002
Social responsiveness scale (total score)	117.0 ± 33.75	103.0 ± 29.62	0.037
CY-BOCS-PDD	14.8 ± 4.12	11.6 ± 4.95	<0.001
ADHD-IV rating scale (total score)	34.2 ± 11.38	26.1 ± 12.95	<0.001
CASI-anxiety	20.4 ± 10.56	16.5 ± 13.79	<0.001
CGI-I	–	2.5 ± 0.92	–
CGI-S	5.1 ± 0.91	4.4 ± 1.16	–

In addition to the improvements in specific aberrant and functional behaviors, improvements were observed on the clinician-rated CGI-I and the CGI-S global assessments (Table 3). At Week 8, CGI-S scores had improved in 14 subjects (50 % of those with data available), worsened in 2,

and were unchanged in 12. On the CGI-I, 20 subjects (71.4 % of those with data) had Week 8 scores of "1"("very much improved") or "2" ("much improved"), scores that are generally felt to reflect clinically meaningful change. Thirteen (13) subjects (41 %) were classified as "responders" in the domain of social function, according to a rigorous post hoc definition, requiring improvement of at least 25 % on the ABC-Social Withdrawal score and a CGI-I score of "very much" or "much improved."

Discussion

Over the past two decades, the majority of ASD medication trials have tested agents that are approved for use in other neuropsychiatric disorders, such as psychosis, depression, anxiety, and ADHD, but that have uncertain mechanistic relevance to ASD. Some of these medications have clear value in the management of interfering symptoms and behaviors associated with ASD. Improvements in social behaviors have been noted in some trials, though these findings often derive from secondary analyses [e.g., studies of risperidone (Scahill et al. *2012*)], or are from open-label studies, (Aman et al. *2009*) or are from populations with specific comorbidity [e.g., hyperactivity in trials of methylphenidate and guanfacine (Scahill et al. *2006*; Jahromi et al. *2009*)]. By contrast, few studies have prospectively aimed to demonstrate an impact on the core social and communicative symptoms of ASD. The emerging cellular- and molecular-level mechanistic understanding of ASD is leading to the development and testing of compounds focused on core deficits. In the open-label study reported here, STX209, a GABA-B agonist selected to reduce the hypothesized excessive glutamatergic and deficient GABAergic signaling in ASD, showed beneficial effects on measures of irritability, social function and communication, as well as on global improvement. These results are consistent with the hypothesis that modulation of cell signaling pathways that are perturbed in fragile X syndrome may be relevant to other cases of ASD as well.

The improvement seen on the ABC-Irritability subscale, the primary endpoint of this open-label study, suggests that STX209 may have efficacy in the same domain for which risperidone and aripiprazole have proven efficacy. The baseline ABC-Irritability scores for subjects in this study were comparable to those reported in the prior pivotal trials of risperidone and aripiprazole. Although the degree of improvement observed during open-label STX209 treatment here (ABC-I decrease of 34 %) was less than that seen in the initial risperidone controlled study (decrease of 57 %), it was more similar to that found in the aripiprazole flexible-dose study (decrease 44 %).

Subjects also showed significant improvement on the ABC-Lethargy/Social Withdrawal subscale (ABC-LSW), which assesses aspects of social avoidance and motivation. STX209 was associated with a reduction in ABC-LSW scores of 27 % from baseline. We note that the subjects in this study were children and adolescents with ASD who had significant levels of irritability, as in previous trials of atypical antipsychotics for ASD. In a controlled study of risperidone, a significant group effect was seen, with a decrease of 46 % on risperidone versus 26 % on placebo. An open-label risperidone trial showed reductions of 59 and 69 % for medication-only and medication + parent training, respectively. A reduction of 44 % was seen in the flexibly-dosed aripiprazole study, but this change was not significantly different than in the placebo-treated group. In addition, we observed parallel improvements on the Social Responsiveness Scale, which provides a wide-ranging assessment of social behaviors and social cognitive ability, and on the Vineland Communication subscale, adding convergent validity to changes seen in ABC-LSW ratings. Although the overall magnitude of improvements in ABC-SW with STX209 are not greater than those seen in other treatment studies of children with ASD accompanied by serious behavioral problems, these results offer the first empirical findings and some support for the role of GABAergic treatments in ASD. These data support additional, larger-scale, controlled studies

with STX209 or other GABAergic compounds. Studies in subjects with lower levels of irritability will be needed to determine whether the effects in the social domain are primary or are secondary to reductions in irritability.

The results of this study are limited primarily by its open-label design. This is of particular importance in ASD research in which there is a long history of positive open-label findings focused on core impairments followed by negative results in subsequent placebo-controlled trials (D. J. Posey et al. *2008*). Placebo effects are evident in virtually all neuropsychiatric trials, and trials in ASD are no exception, as found in the studies of aripiprazole and citalopram. We note that in the earlier randomized, controlled trial of STX209 for patients with FXS, STX209 was not associated with greater improvement than placebo on the ABC-Irritability subscale. Placebo effects historically have been the highest in ASD trials focused on core social impairment with placebo response rates in the 30–40 % range noted (D. Posey et al. *2009*). Our reliance on parent-report measures in this trial of a novel compound may have increased expectancy bias. Thus, we acknowledge that the broad improvements found on essentially all of the behavior rating scales may reflect such a general placebo effect. Alternatively, it may be possible that effective treatment of the core pathophysiology of ASD could result in broad symptomatic improvement.

Even assuming that STX209 is effective for core pathophysiology in ASD, the smaller or non-significant improvements in functional and cognitive measures in this study may be the consequence of the relatively short 8-week duration of treatment, and the need for longer-term educational/behavioral intervention in combination with pharmacotherapy to effect change in these parameters. It is notable also that only 41 % of the subjects met rigorous criteria in the responder analysis. This raises questions about the symptom target, entry criteria and duration of future trials. For example, given the recognized heterogeneity of ASD, future trials may enroll distinct subpopulations to test new treatments. The ABC-LSW scale has now demonstrated reliability, validity and sensitivity to change in the open-label context of the current study. However, it may be argued that it targets a relatively narrow domain of social disability in a disorder characterized by a broad range of social deficits.

Some subjects in this study exhibited a worsening of underlying symptoms such as agitation, irritability, and aggression. Although it is possible that these events represent a deleterious drug effect, many of these events may reflect spontaneous variability in underlying symptoms. This interpretation is consistent with the results of a placebo- controlled study of STX209 in FXS, in which rates of adverse events such as irritability and aggression were higher on placebo than on STX209. Other adverse events in this study did not present significant clinical concerns, and the relative lack of sedation and somnolence contrast with the well-known tolerability profile of racemic baclofen.

A placebo-controlled trial of STX209 is needed to determine whether the beneficial effects on irritability and social behavior seen in this study will be superior to placebo. Placebo comparison also provides a more rigorous evaluation of adverse events and

overall safety. Regardless of the results for STX209, however, the development of treatments based on the increasingly more refined neurobiological understanding of ASD holds the strongest hope for identifying new therapies that target disease pathophysiology and potentially alter the developmental trajectory of patients at risk for or affected by ASD.

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