ACS Chemical Neuroscience

VIEWPOINT

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ACS Chemical Neuroscience Molecule Spotlight on STX209 (Arbaclofen)

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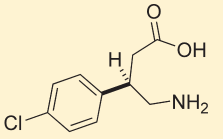
ABSTRACT: STX209 (arbaclofen) is a γ-amino butyric acid type B ($GABA_B$) receptor agonist from Seaside Therapeutics currently in clinical trials for autism spectrum disorders (ASD). The company has initiated a phase 2b study after positive results from a phase 2a trial, announced September 2010 (http://www.seasidetherapeutics.com/sites/default/files/STX209_ASD_P2b Trial_Initiation%206%2021%202011%20Final.pdf).

KEYWORDS: STX209, autism spectrum disorder (ASD), GABA



STX209 (arbaclofen or (*R*)-baclofen)
Seaside Therapeutics' $GABA_B$ receptor agonist

Autism spectrum disorders (ASDs) are a group of develop mental disorders and are characterized by three fundamental symptoms: (1) difficulties with social interactions, (2) verbal and nonverbal communication deficiencies, and (3) obsessive interests and/or repetitive behaviors.[1] As these issues are "spectrum disorders", they can vary in intensity from mild to disabling and affect each individual differently. It is estimated the nearly 1% of children are diagnosed with an autism spectrum disorder, with boys being diagnosed nearly 4 times that of girls. Within the definition of ASD, there are three types (or classifications): (1) autistic disorder, usually entails significant language delays, social and communication delays, and behavioral challenges; (2) Asperger's syndrome, generally milder symptoms of autistic disorder and generally do not have language or intellectual disabilities; and (3) pervasive developmental disorder, individuals that meet some, but not all, of the criteria for the above. The symptoms of the disorders begin before the age of 3 and persist throughout the person's lifetime. Unfortunately, there is no cure for autism, and, just as importantly, there is no FDA-approved treatment for the core symptoms of ASD resulting in a critical unmet medical need for these individuals and their families.

Recently, Seaside Therapeutics announced the successful completion of a phase 2a clinical trial with their clinical candidate, STX209.[2] STX209 is a γ-amino butyric acid type B receptor agonist ($GABA_B$). STX209 is the active *R*-enantiomer of baclofen, or arbaclofen, a clinically used agent for spasticity for over 30 years. Due to the agonist activity of arbaclofen at the $GABA_B$ receptor, the molecule inhibits presynaptic release of glutamate and thus blocks downstream signaling of $mGlu_5$.[2,3] It is thought that the action on downstream $mGlu_5$ and treating deficiencies in GABA transmission would allow for STX209 to be a viable treatment for ASD.

In September, 2010, Seaside Therapeutics reported on the positive results for STX209 in an open-label phase 2a study conducted in patients with ASD. STX209 achieved statistical significance on the primary end point of the study, improvement on the Irritability subscale of the Aberrant Behavior Checklist (ABC-I). In addition to the Irritability subscale, statistical significant improvement was also seen on the Social Withdrawal subscale (ABC-SW).[4] These results add to the already positive results seen in a randomized, placebo-controlled study of STX209 in patients with fragile X syndrome (FXS). Due these positive results, a number of clinical trials have been initiated on STX209 including a phase 2b study aimed at evaluating the effects on social impairment in children and adults with ASD, a phase 3 study in adolescents and adults with FXS (May 2011), and an additional phase 3 in children with FXS expected to start in summer 2011. Although STX209 is still under clinical evaluation and success is nowhere near assured, these early stage results have led to significant hope in the autism community that a real treatment option can be discovered in the near future.

REFERENCES

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Received: June 27, 2011
Accepted: June 29, 2011
Published: July 06, 2011