CLINICAL STUDY REPORT
AIMS2-CT1 trial - EUDRACT 2018-000942-21

Arbaclofen in Children and Adolescents with Autism Spectrum Disorders.

SUMMARY DOCUMENT

Rationale: Autism Spectrum Disorder (ASD) is a clinically and etiologically heterogeneous neurodevelopmental condition affecting approximately 1% of the population. The defining symptoms of ASD are deficits in social communication and the presence of repetitive and restricted behaviours and interests, but also sensory anomalies. In addition, up to 70% of individuals have one or more psychiatric and/or medical comorbidities. Currently, there are no effective medical treatments for the core symptoms of ASD. The aim of our project is to conduct a double blind Randomized Controlled Trial (RCT) in adolescents with autism, in order to modulate social function with a molecule that impacts GABA/glutamate equilibrium. Arbaclofen is a selective GABA-B receptor agonist and augments GABA-ergic activity, inhibits presynaptic release of glutamate, inhibits postsynaptic transmission, and modulates intracellular signaling. Through elevation of GABA-ergic inhibitory activity arbaclofen may act to alleviate ASD symptoms associated with social anxiety and emotional hyperarousal.

Objective: Primary objective was to examine the effect of arbaclofen vs. placebo on social function in patients with ASD between the age of 5 and 17 randomized to arbaclofen or placebo during 12 weeks of treatment. Secondary objectives included differences in functioning, adaptive domains, social communication behaviours, associated other problem behaviours, and the safety and tolerability were assessed.

Study design: A Phase II Randomized, Double-Blind, Placebo-Controlled Study. We tested arbaclofen vs. placebo in high functioning, verbal, ASD individuals - both males and females - between the age of 5 and 17 (130 in European countries).

Study population: Participants between 5 and 17 years of age, residing with the interviewed caregiver, presenting complex language (as defined in ADOS-2) with a diagnosis of ASD according to the DSM-5 criteria. Pharmacological and educational regimes affecting behaviour must have been stable prior to screening. Pregnancy test must be negative for females of childbearing potential.

Intervention: Randomization of study subjects was performed 1:1 into both treatment arms to either arbaclofen or placebo. A 16-week treatment period provided adequate time for titration of the study drug to the optimal dose.

Main study parameters/endpoints: Primary objective was to examine the effect of arbaclofen vs. placebo on social function in patients with ASD between the age of 5 and 17 randomized to Arbaclofen or placebo during 12 weeks of treatment (Socialization domain of the Vineland-3; Vineland Adaptive Behavior Scales). Secondary objectives included differences in global functioning (Clinician's Global Impression), adaptive domains (Vineland-3 other adaptive domains: communication and daily living skills),

social communication behaviours (BOSCC, SRS-2 and AIM), associated problem behaviours (CBCL, Children Behaviour Checklist, and ABC-C, Aberrant Behaviour Checklist), and the safety and tolerability were assessed. Quality of life was also measured (PedsQL). We additionally used EEG measures and DNA sampling to explore potential underlying physiology.

Results: In total, 137 individuals signed up for the study and 122 were randomized. Sixty-three patients received placebo and 59 arbaclofen. The mean age in the placebo group was 12.11(SD=3.18) years and 11.38(SD=3.23) years in the arbaclofen arm. As expected, there was a significantly higher number of males than females in both groups. Their average full IQ was 97.89 (SD=18.56) for the placebo group and 98.48(SD=19.36) for the arbaclofen one. The difference between means was not significant. Similarly, mean ADOS severity scores were 7.02(SD=2.68) for the placebo group, and 7.43(SD=2.18) for the arbaclofen group, for which difference between means were not significant either. Completion rates were high, with 95.2% in the placebo group vs 84.7% in the arbaclofen arm. During the full duration of the trial, sleep problems were significantly reported more in the arbaclofen group, although it was never severe enough to stop the study and normally corrected by adjusting the dose. Only one SAE was reported. However, this patient was allocated to the placebo arm.

We found no significant differences in our primary outcome (i.e. Vineland-3 Socialization domain) between treatment arms (p = .07). Analyses on secondary outcome variables revealed, however, significant differences between groups for the Social Responsiveness Scale (SRS-2) total score as well as in the Social awareness and mannerisms subscales, both reported independently by parents and teachers. There were also significant differences in the Autism Impact Measure (AIM) total score, and in the atypical behaviour and peer interaction subscales, all of them favouring arbaclofen. Quality of life, measured by the PedsQL also showed a significant increased after treatment in those in arbaclofen.

Conclusions: The exposure to arbaclofen did not show an improvement in our main primary outcome, social adaptive behaviour measured with the Vineland interview of adaptive behaviour. However, several secondary outcomes reported significant improvement in social skills of different degrees, such as social awareness, peer interaction and atypical behaviour, as well as other behavioural changes, such as less mannerisms. Overall, the quality of life of these patients seemed to improve.