Efficacy, safety, and tolerability of arbaclofen in Autistic children and adolescents, the AIMS-2-TRIALS-CT1: a randomized, double-blind, placebo-controlled phase II trial

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Summary

Background Previous trials have indicated the potential of arbaclofen for improving social difficulties among autistic children and adolescents with fluent speech. AIMS-2-TRIALS-Clinical Trial 1 (AIMS-2-CT1) examined whether arbaclofen is superior to placebo in improving social function and other secondary outcomes, along with safety and tolerability profiles.

Methods AIMS-2-CT1 is a multi-site, placebo-controlled double-blind, parallel group Phase II randomized clinical trial. Recruitment was conducted in 7 sites in Spain, United Kingdom and France between September 2019 and September 2022. Eligible participants were randomized 1:1, stratified by age and site, for a 16-week treatment period. Age of participants ranged from 5 to 17 years of age. Primary outcome: Socialization domain of the

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Vineland Adaptive Behavior Scales change. Secondary outcome measures: CGI–S (Clinical Global Impression–Severity), CGI–I (Clinical Global Impression–Improvement), Social Responsiveness Scale (SRS-2), Autism Impact Measure (AIM), behavioral measurements (CBCL, ABC-C) and Quality of Life (PedsQL). Safety and tolerability were assessed via several instruments. Clinical trial registration: EudraCT number: 2018-000942-21 and ClinicalTrials.gov registry number: NCT03682978. Last protocol v.9.1, dated June 18th, 2022.

Findings 122 participants (out of 123 randomized) comprised the Intention-to-treat sample (59/63 arbaclofen/placebo); 85%/95% of participants on arbaclofen/placebo completed the study.
Improvements in the primary endpoint and pre-specified key secondary outcomes did not achieve statistical significance [effect size 1.30 (95% CI: −2.6, 5.1)]. Results on all secondary endpoints favored arbaclofen, with significant improvements on many secondary outcomes including the SRS, the AIM Total scores, some subscales of the ABC, and QoL measures. One Serious Adverse Event (psychotic symptoms) was reported on placebo. Sleep-related problems were more frequent on arbaclofen (N = 34, 57.6% in participants on arbaclofen and N = 22, 34.9% in participants on placebo).

Interpretation Although we found no significant effect on the primary outcome, improvements were apparent on several secondary measures of autistic related behaviors as well as quality of life. Arbaclofen shows promise in addressing some autistic difficulties and in improving quality of life, but larger scale trials are needed to further advance our understanding of its potential and to inform future drug development in autism.

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Keywords: Clinical trial; RCT; Arbaclofen; Autism; AIMS-2

Introduction

Autism Spectrum Disorder (ASD), or autism,[ab,1] is a clinically and etiologically heterogeneous neurodevelopmental condition that occurs in approximately 1% of the population. The current defining characteristics of autism are differences in social communication and the presence of repetitive and restricted behaviors and interests, including sensory anomalies, causing clinically significant impairment in social, occupational, or other important areas of functioning.[2] The combination of main features together with other medical conditions and co-occurring psychiatric conditions[3] can significantly impact some autistic people, their families and society[4] and evidence based interventions are needed. Parents of autistic children note communication, emotional and behavior difficulties as their main concerns[5] while autistic individuals themselves prioritize interventions that address their mental health (particularly anxiety), communication and language skills and sensory processing.[6]

There are currently no effective drug treatments for the defining symptoms of autism, and families can turn to non-evidence-based interventions, such as vitamins, diets or off-label drugs.[7] Developing drugs for autism has been challenging because of its clinical and biological heterogeneity and the limited understanding of underlying physiological changes, which together complicate target identification, patient stratification, and the selection of sensitive, clinically meaningful outcome measures.[8] One theory holds that autism is related to alterations in excitatory:inhibitory (E:I) balance, which is implicated in a broad range of brain function, from the establishment and maintenance of neural oscillations, to sensory processing, and complex cognition and social behaviors.[9] Genetic and neurologic evidence for E:I imbalance in autism are reviewed in the study protocol[10] and in Huang et al., 2022.[11]

One of the main players in the excitation–inhibition (E:I) balance is the primary inhibitory neurotransmitter GABA, which plays an important role in behavior and overall brain function. Preclinical studies have shown that GABA agonists can have an impact on demonstrated social differences. GABA receptors are widely distributed throughout brain regions involved in social behavior, and some studies have reported a reduction in the number of these receptors in autistic brains. Moreover, E:I imbalance has been widely associated with atypical sensory input processing across multiple sensory domains and numerous studies have suggested that unusual sensory behaviors may contribute to social difficulties.[12] Arbaclofen (R-baclofen) is an agonist of the GABA-B metabotropic receptor and therefore it would be expected to modulate E:I dynamics. It is hypothesized to

[ab]Due to the different sensitivities with regards to the preferred terms to be used and to accurately report prior research, in this study we used the terms autistic individuals, individuals with autism and individuals with Autism Spectrum Disorders interchangeably (see Keating et al., 2023).

Research in context

Evidence before this study

Preclinical data shows that the non-marketed molecule arbaclofen (an enantiomer of the marketed drug baclofen), a GABA-B agonist, rescues many molecular and behavioral phenotypes in rodent models for autism. These animal findings are broadly supportive of the hypothesis that alterations of excitatory:inhibitory dynamics underlie the social communication differences in autism. Previous clinical trials in Fragile X syndrome and in autism show the molecule to be generally safe and well-tolerated. Efficacy data from a previous trial in autism suggest that arbaclofen might be helpful for socio-communication difficulties in autistic children and young people with fluent language abilities.

Added value of this study

An academic randomized placebo-controlled trial, recruiting from expert sites across Europe, was set up. 122 participants were recruited in Europe between 2020 and 2022 with significant accommodations made (with appropriate regulator approval) due to the Covid-19 pandemic, and 116 participants completed the 16-week protocol. Arbaclofen was generally well tolerated. However, there were more sleep problems (other than somnolence) in the active arm. No significant improvement in the primary outcome measure (VABS-social) was apparent. However, improvements in secondary outcome measures of social withdrawal, peer interactions, repetitive behaviors and quality of life signal the need to continue studying arbaclofen in particular with respect to which groups of individuals with autism may benefit from it. In addition, the extent and features of arbaclofen-associated sleep disturbances will require close monitoring and careful analysis The study was run in parallel to a Canadian study ("ARBA") with an almost identical protocol, in order to allow for subsequent combined analysis.

Implications of all the available evidence

The results obtained warrant further analyses to investigate which participants may benefit from the intervention and whether it is possible to identify a biomarker of response to the treatment to inform targeted future trials. In addition, we show that it is possible to conduct high-quality clinical academic trials, with arguably less economic burden and restraints compared to industry-sponsored trials.

have both pre- and post-synaptic effects, reducing the pre-synaptic release of the excitatory neurotransmitter glutamate, and modulating intracellular signaling in other ways to affect synaptic plasticity (reviewed in Parellada et al., 2023[10]). In rodent models of autism, including the FMR1 knockout and other genetic models, arbaclofen resolves multiple physiologic and behavioral phenotypes, from AMPA receptor turnover to audiogenic seizures and marble burying (reviewed in Huang et al., 2022[11]). In non-autistic comparison individuals, arbaclofen modulated perceptual suppression in the visual cortex, and in autistic individuals, it has been shown to rescue the visual contrast and auditory perception differences between autistic and non-autistic individuals.[11,13,14]

Seaside Therapeutics initially conducted an open-label, flexible-dose phase II trial over eight weeks involving 32 autistic children, administering arbaclofen at doses up to 10 mg three times daily. This preliminary study reported broad improvements in autistic symptoms.[15] Subsequently, a Phase II, double-blind, placebo-controlled II trial (RCT) was conducted in 150 autistic individuals aged 5–21,[16] mean age 11.6, 82.7% male 50.7% with an IQ > 70. After 12 weeks treatment, participants on arbaclofen and placebo showed no difference on the primary outcome measure [Social Withdrawal/Lethargy subscale of the Aberrant Behavior Checklist (ABC)]. However, the arbaclofen group demonstrated a nominally significant improvement on the Clinical Global Impression–Severity (CGI-S). Post-hoc analyses suggested greater therapeutic benefit among the more verbally fluent individuals; and a per-protocol analysis revealed a nominally significant improvement in the Socialization domain of the Vineland Adaptive Behavior Scales, 2nd edition (VABS–2) when rated consistently by the same clinician. Across both studies, arbaclofen was generally well tolerated, with somnolence and labile affect more frequently reported in the treatment group.

In light of the observed findings, the previously undemonstrated efficacy of arbaclofen in improving behaviors in autism and the considerable heterogeneity within the autistic population, which may obscure treatment effects, the present study aimed to assess whether a more specific, targeted, and homogeneous group of verbally fluent children and adolescents might benefit from arbaclofen treatment. A Phase II clinical trial was conducted to further test the drug's tolerability and its efficacy in addressing defining and associated autistic symptoms, as well as its impact on participants' quality of life. The study design was refined based on the protocol and post-hoc findings of Veenstra-VanderWeele, 2017,[16] alongside insights from the AIMS-2-TRIALS network concerning factors influencing placebo response in autism clinical trials.[17]

Methods

Trial design and setting

AIMS-2-CT1 is an international, multi-site, placebo-controlled double-blind, parallel group Phase II

randomized clinical trial. Recruitment was conducted in seven University or outpatient clinics in Spain (Barcelona, Madrid and Salamanca), United Kingdom (London, Glasgow and Newcastle) and France (Paris). AIMS-2-CT1 is one of the many studies conducted within the AIMS-2-TRIALS network (www.aims-2-trials.eu), which aims to apply a precision medicine approach to autism and improve patient outcomes by tailoring treatments to a patient's biological profile. One of the main goals of the network is to quickly set up clinical trials with new or repurposed drugs, built on newly available preclinical advances, with academic sponsorship. Within the partners in the network, there are autistic representatives with lived experience of autism, and advocacy organizations, who were involved in the design and monitoring of the trial, to inform development of iterative versions of the trial design.

Participants

Male and female autistic children and adolescents, aged between 5:0 and 17:11 years at time of consent and with fluent language (as defined by eligibility for modules 3 or 4 of the ADOS-2), were invited to participate. Biological sex data was collected via the participant/legal representative report. Gender data was not collected. Written informed consent was signed by the participant or legal representative and assent provided by participants, following local laws and regulations.

To be enrolled in the study, we considered the following main inclusion criteria: diagnosis of ASD according to the DSM-5 criteria and complex verbal language [defined as qualifying for an Autism Diagnostic Observation Schedule–2, (ADOS–2)[18] Module 3 or 4 assessment, as determined by a clinically-certified ADOS–2 rater supervised by the local research-reliable ADOS–2 lead]; the participant resided with the informant caregiver, was willing to comply with the medication and research protocols and was able to take medication orally; pharmacological treatment and psychotherapeutic/psychosocial interventions affecting behavior were stable for at least 6 weeks and 3 months respectively prior to screening, with no planned changes for the duration of the trial; subjects with a seizure history were on a stable regimen of anticonvulsant medication and seizure free for at least 6 months prior to screening (if not taking any anticonvulsant medication, the participant was required to be seizure free for at least 3 years prior to screening); a negative pregnancy test for female participants of childbearing potential, and all sexually active participants agreeing to use highly effective forms of contraception. The main exclusion criteria were (full exclusion criteria were reported in Parellada et al., 2021)[10]: any medical condition or health-related issue that could interfere with the conduct of the trial, confound its interpretation or endanger the participant's well-being; drugs with known GABA-ergic effects (such as racemic baclofen, vigabatrin, tiagabine, riluzole or benzodiazepines on a regular use), were prohibited.

Randomization and masking

Participants were randomized to arbaclofen or placebo, 1:1, in a stratified manner (site and age group, 5–11 and 12–17 years old), by a randomization website, Interactive Web Response System—IWRS, developed by the Data Management Department of the Julius Center, University Medical Center Utrecht (UMCU). Besides an unblinded, dedicated pharmacist at each individual site, all study team members and participants were blind to allocation. A central unblinded monitor double checked dispensation regularly. Placebo and active medication tablets had the same appearance, mass, color, smell and taste. Arbaclofen drug substance was manufactured by Excella GMBH &Co.KG, Germany; both arbaclofen and placebo tablets were manufactured by CoreRx, Clearwater, Florida (USA), in identical round white orally disintegrating strawberry-flavored tablets in strengths of 5, 10, 15 and 20 mg. They were stored at room temperature and packed in 7-tablet blisters.

Procedures

A flexible dose titration schedule was utilized during the first 5 weeks of treatment. For participants aged 5–11 years at time of consent, the starting dose was 5 mg once daily and increased to a maximum of 15 mg three times a day. For participants aged 12–17 years at consent, the starting dose was 5 mg twice a day and increased to a maximum of 20 mg three times a day. Taper-down period ran from end-visit (16 weeks after treatment initiation) to follow-up visit two weeks later.

Medical checks (including adverse events monitoring) and interviews (with both the participant and parent of legal representative separately) were conducted at screening, visit 1 (baseline, 1–3 weeks after screening) and 2, 4, 6, 8, 12, 16 weeks later (end-visit). Questionnaires were administered at baseline and at 4, 8, 12 and 16 weeks. EEG, blood and urine analysis were conducted at baseline and end-visits. A medical check and interview were conducted two weeks after the end-visit and a follow-up telephone call was done two weeks later to check for adverse events.

Recruitment took place between September 2019 and September 2022. Last patient visit occurred in March 2023. The COVID-19 global pandemic impacted the conduct of the clinical trial in several ways. Adjustments in response to the pandemic varied to accommodate global, national, and regional regulations regarding access to clinical or academic sites and the settings for non-covid related evaluations. In summary, recruitment was halted for around 2–6 months in March/April 2020, the exact dates depending on the country-level lockdown rules. For ongoing participants during the COVID-19 restrictions, some physical visits

were converted into remote visits (with online assessments), vital signs were collected at home with appropriate safeguards or at local pharmacies, and questionnaires and medication were transported to homes. Local monitors needed to be hired and trained and essential tasks delegated from central monitoring. All adjustments were conducted considering, first, the well-being of participants and then the integrity of the trial, with the appropriate amendments to authorities and with the appropriate consultation with the instruments' authors or experts. Specific amendments due to COVID-19 pandemic are included in Supplemental Material S1.

Outcomes

See Supplementary Material S1 for full description and references of the instruments used in the trial.

Primary outcome

The primary outcome was the effect on social function from weeks 0–16 measured with the parent/carer-report interview Socialization domain of the Vineland Adaptive Behavior Scales (VABS-Soc), 3rd Edition™.[19] The VABS assesses a person's current level of everyday functioning across three domains (i.e., communication, daily living skills and socialization). For this, both the standard score (mean = 100, SD = 15) and the mean of the Growth Scale Value (GSV) of each Socialization subdomain (i.e., interpersonal relationships, play, and coping skills) were used. The GSVs provide with a measure of the absolute level of performance, on an equal-interval scale using Rasch calibration, ranging from no ability to maximum ability.

Choice of primary outcome measure

We recognize that social development is shaped by a range of environmental and experiential influences, and pharmacological treatments are not intended to substitute for the educational or psychosocial supports that remain essential. For this study, we adhered to established standards for drug-intervention research, designating a single primary outcome to evaluate efficacy and controlling for potential confounding factors arising from changing or unstable conditions.

Soc-VABS subscale was selected as the primary outcome measure during the study design phase and was therefore specified in the protocol registered on ClinicalTrials.gov. This choice was made to ensure continuity with previous studies and post hoc results from Veenstra-VanderWeele.[16] This is a widely used, comprehensive and standardized instrument to assess the level of adaptive behavior with regards to social functioning, normalized by age. The clinician interview version (90–120 min for completion) was selected, with a systematic training and reliability process and supervision of the administration by an overall lead rater that supervised the lead raters at each site (ASJ). Likewise, lead raters ensured consistency and reliability with the raters at their site. The lead raters also attended regular consensus meetings with one of the authors of the instrument to ensure reliability amongst lead raters. The instrument is available in the three languages used in the study. The same rater administered the interview at baseline and final visits. In person interviews were planned but a protocol modification was put in place (and the corresponding regulatory amendment conducted) due to COVID pandemic restrictions (see Supplemental Material S1).

Secondary outcomes

Key secondary outcome measures were included to cover the whole spectrum of autistic difficulties, associated behavioral difficulties and quality of life. They included the CGI–S (Clinical Global Impression–Severity) and the CGI–I (Clinical Global Impression–Improvement). The CGI-S and CGI-I were completed after the clinical interview with participants and their parents or representatives had been conducted at each visit. Other secondary outcome measures included the standard scores of all other domains of the VABS, the parent-rated Social Responsiveness Scale-2 (SRS2), and the Child Behavior Checklist (CBCL), and raw scores for the Aberrant Behavior Checklist-Community version (ABC-C), the Autism Impact Measure (AIM), and the Pediatric Quality of Life Inventory (PedsQL) questionnaires. The teacher version of the SRS2 questionnaire was also administered, although many participants had remote education for many months and therefore teacher-rated questionnaires could not be administered in these cases. In order to characterize the sample included in the trial, baseline assessment of intelligence quotient with Weschler Scales and severity of autistic symptoms with the Autism Diagnostic Observation Schedule–2 (ADOS–2) were conducted.

Adverse events

The assessment of adverse events was conducted with open questions to both participants and parents/representatives and with the Safety Monitoring Uniform Report Form (SMURF), the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) and the Columbia-Suicide Severity Rating Scale (C-SSRS) completed at each on-site visit. Medical checks consisted of measuring vital signs, height and weight. Safety blood tests included complete blood count, liver enzymes, renal function, non-fasting glucose and drug checks were done at baseline and end-visit. Pregnancy checks in females were conducted monthly. In relation to suicidal ideation/thoughts, as measured with the C-SSRS, 10 patients in placebo and 10 patients in arbaclofen disclosed past/lifetime suicidal ideation. During the trial, more patients in placebo described suicidal thoughts, although this was not significantly superior to the arbaclofen group (all $p > 0.15$).

Exploratory biomarkers

EEG metrics were assessed as exploratory biomarkers to predict clinical changes based on differences in the former. This data will be reported separately.

Statistical analysis

A sample size of 130 was estimated based on a previous clinical trial and feasibility. For reference, a power of 80% would require an effect size of 0.6 for this molecule.[16]

Primary analyses were conducted in the Intention to Treat (ITT) sample, which included all participants randomized who had at least one dose of medication and one post-baseline assessment. Efficacy was defined as the difference between treatment arms at week 16, using Analysis of Covariance (ANCOVA with follow-up score used as the dependent variable and treatment group as a factor), first with the primary outcome measure (VABS) and then with secondary outcome measures. All analyses were adjusted for age and baseline score, and the adjusted mean differences (derived using the standard errors of the ANCOVA model and the Student's t distribution) are reported. Given the high compliance with the protocol and the low proportion of missing data, no imputation was needed.

Hypothesis testing was performed at the 5% level of significance for 2-sided tests. We describe the results as 'nominally significant', when appropriate, because no correction for multiple comparisons was applied. Safety analysis was conducted on all participants taking at least one dose of study medication by calculating the incidence of adverse events in each arm and summarizing laboratory and ECG assessments, physical examinations and vital signs. Due to the exploratory nature of the trial, no correction for multiple comparisons was undertaken.

All the analyses were repeated in the pre-defined Per Protocol (PP) sample comprised by those from the ITT sample that fulfilled compliance/adherence criteria, i.e., having taken at least 70% of the expected medication (by pill count) and having completed at least 80% of the visits.

In addition to the planned statistical plan, we added a responders' analyses (Reliable Change Index, RCI) to the original Statistical Plan, following recent developments of the measurements.[20] We calculated RCI for SRS2-Total and AIM-Total. Details of these calculations are included in Supplemental Material S2.

The statistical analysis was performed by UDIMIFFA using R software version 4.4.2 (The R Foundation for Statistical Computing - Vienna, Austria). A Data Monitoring Committee (DMC) was in place, with biannual meetings to monitor safety during the conduct of the study.

The study protocol was approved by the three independent national ethics committees involved in participant recruitment (Ref for Spain AIMS-2-CT1, France: Ref. SI:19.08.02.53944 and ANSM: MEDAECNAT-2020-03-00003, UK: 18/EM/0335), and has been published in Parellada et al. (2021).[10]

Clinical Trial Registration

EudraCT number: 2018-000942-21 and ClinicalTrials.gov registry number: NCT03682978. Last protocol v.9.1, dated June 18th, 2022.

Role of funding source

The study funder had no role in study design, data collection, data analysis, data interpretation, or report writing.

Results

Population enrolled and baseline characteristics of the sample

One hundred and forty patients were assessed for eligibility, 123 were randomized; 122 participants (102 male and 20 female) were included in the ITT analysis (Madrid = 50 (41%), Paris = 22 (18%), Barcelona = 20 (16.4%), Salamanca = 11 (9%), Glasgow = 4 (3.3%), London = 11 (9%), and Newcastle = 4 (3.3%)). See CONSORT diagram in Fig. 1. Age range at inclusion was 5–17 years (mean 11.67, SD 3.20). See Table 1 for baseline characteristics of the sample. Most participants were of European descent. Mean total IQ score was in the average range and the severity of autistic symptoms was moderate. Supplemental Material S2 and Figs. 2 and 3 show baseline and end-visit scores and coefficient plots on all outcome measures, the age and baseline adjusted differences between the placebo and arbaclofen groups and the statistical value of the differences, with the magnitude of change.

Drug efficacy

No statistical difference was found in the primary outcome measure (VABS-Soc) [effect size β (95% CI) 1.30 (–2.6, 5.1)] (Figs. 2 and 3 and Supplemental Table S2). Neither did we find a significant difference on the CGI-S [effect size β (95% CI) –0.03 (–0.74, 0.69)]. Other secondary outcome measures showed nominally significant improvements, including the SRS2 (Total, Social-Communication and Repetitive Restrictive Behaviors (RRB) Scales) as reported by parents and in the RRB and mannerisms scales as reported by teachers (note that due to pandemic, and minors not attending schools, the teachers' questionnaires could only be completed in 65% of the cases). There were significant improvements in the AIM Total Score and in the Peer Interaction, Atypical Behavior subscales, and also in subscales of the ABC-C (social withdrawal, hyperactivity and Inappropriate Speech) and in the quality of life-emotional impact subscale of the PedsQL. We further controlled for age across all outcome measures; only the

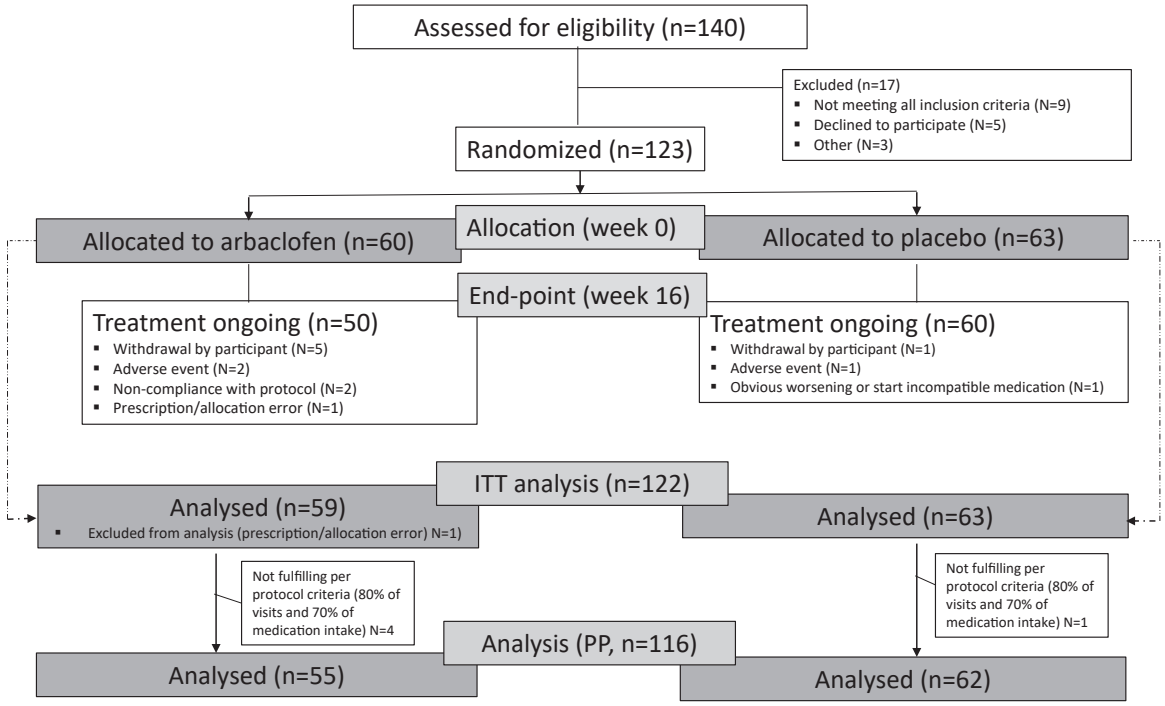

Fig. 1: Trial profile.

VABS COP GSV was affected by age, with older participants showing greater improvement (β [95% CI] = 1.56 [0.51–2.62], p = 0.004). Using the RCI method, we found that that only the SRS2 total T-score as rated by parents showed a clinically significant improvement, with 27% of participants in the arbaclofen group showing a clinically significant improvement, compared with 14% in the placebo group (p = 0.009). See Table 2 and Supplemental Material S2.

	Placebo (n = 63)	Arbaclofen (n = 59)
Sex		
Male	52 (83%)	50 (85%)
Female	11 (17%)	9 (15%)
Age (years)	12.11 (3.18)	11.38 (3.23)
Geographical origin		
Europe	58 (92%)	53 (90%)
South America	3 (5%)	3 (5%)
Central America	0	1 (2%)
North America	0	1 (2%)
Asia	2 (3%)	1 (2%)
IQ		
VIQ	98.10 (21.02)	96.34 (20.54)
NVIQ	100.08 (15.93)	95.98 (17.98)
FSIQ	99.10 (16.49)	96.40 (17.34)
ADOS-2		
ADOS-2 CSS SA	7.08 (2.74)	7.18 (2.50)
ADOS-2 CSS RRB	6.17 (2.84)	6.25 (2.83)
ADOS-2 CSS Total	7.03 (2.65)	7.40 (2.16)

Data are *n* (%) or mean (SD); geographical origin was self-reported; VIQ = verbal IQ; NVIQ = non-verbal IQ; FSIQ = Full-scale IQ; ADOS-2 = Autism Diagnostic Observation Schedule—2nd Edition; CSS = Calibrated Severity Score; SA = Socio-Affective; RRB: Repetitive Restrictive Behavior.

Table 1: **Main descriptors by treatment arm.**

Adverse events

Participants on arbaclofen showed significantly more sleep-related problems (57.6%) than participants on placebo (34.9%), p = 0.02 (Table 3). These included difficulties falling asleep, early wakening or maintaining sleep (36% of the total sample), hypersomnia (36% of all) and other sleep difficulties (nightmares, night walking). Skin conditions were more frequent on placebo. No other significant differences were found. We only observed one Severe Adverse Event (psychotic symptoms), which affected a participant on placebo. Eight participants (6 on arbaclofen, 2 on placebo) withdrew from the study, 3 of them possibly due to adverse events (2 were on arbaclofen and withdraw due to tiredness and with unspecific complains respectively and 1 on placebo, complaining from anxiety and disruptive behavior). Twenty patients needed slower titration or could not reach full expected dose (12 on arbaclofen and 8 on placebo). Main reasons were sleep problems, including somnolence, and nocturnal enuresis and headache, both in arbaclofen and placebo group. See full list of reasons for withdrawal and slow titration in Supplemental Material S3.

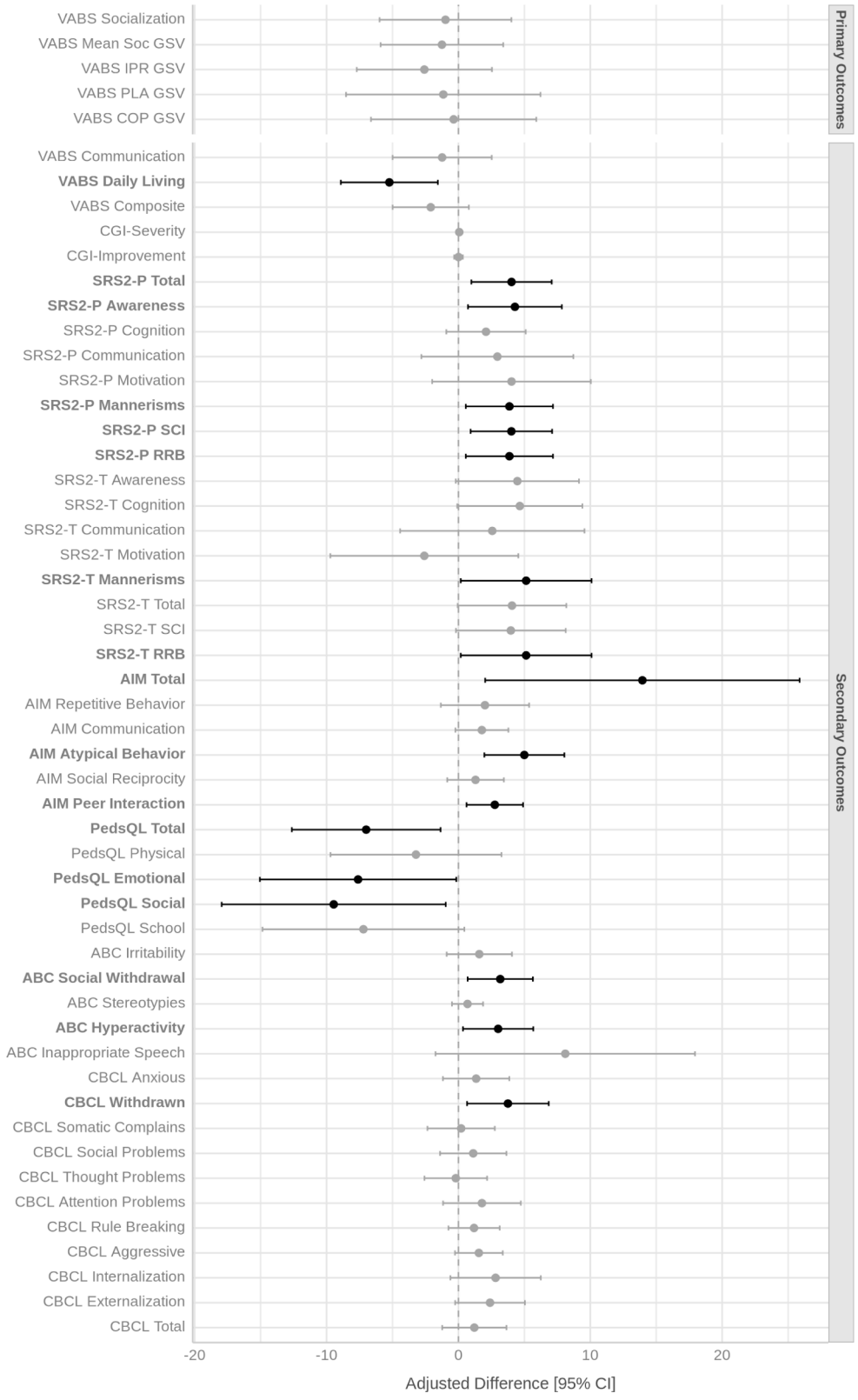

Fig. 2: Coefficient plot for primary and secondary outcomes. For VABS and PedsQL, negative differences indicate improvement; for all other measures, positive differences indicate improvement.

Fig. 3: Baseline and end-visit scores for main outcome measures.

Discussion

We explored the efficacy of arbaclofen on social communication adaptive behavior and associated features frequently associated with autism, and quality of life, in a large sample of children with autism and fluent speech, in a randomized placebo-controlled clinical trial. Adherence to the protocol was very good and there was a favorable safety profile. We found no significant improvement on the primary outcome measure (Socialization domain of the Vineland Adaptive Behavior Scale) or the clinician-rated Clinical Global Impression scales. However, results on many secondary outcome measurements showed improvements on arbaclofen versus placebo, including parent-rated questionnaires on autistic symptoms, i.e., social interaction and communication and repetitive behaviors/sensory profile, measured with the Social Responsiveness Scale, the Autism Impact Measure and the Aberrant Behavior Checklist, and quality of life (PedsQL). QoL is rarely measured in clinical trials in autism, despite being considered one of the most important outcome measures by autistic individuals.[21] Other key contributions of this trial include the multi-site approach, the inclusion of mechanistic biomarkers and efforts to reduce placebo effect,[16] including a limited number of sites, selection of sites with previous experience on the outcome measures to be used, and a clinician-rated primary outcome measure, all key features for improving clinical trials quality.

In this study, we chose the VABS-3 social communication subscale as primary outcome, following post-hoc results in the previous RCT with arbaclofen in autism.[15] In choosing VABS as the primary outcome, we aimed to improve on the trial designs previously used[16] and considered the lack of an alternative such as a robust, replicated and consensus-based outcome measure. Secondary outcome measures in our study were chosen to gather a more comprehensive view of the influence of arbaclofen on autistic and associated-

Clinical outcome	Participant status		
	Overall (*n* = 107)	Placebo (*n* = 56)	Arbaclofen (*n* = 51)
Declined	18 (17%)	15 (27%)	3 (6%)
Stable	67 (63%)	33 (59%)	34 (67%)
Improved	22 (20%)	8 (14%)	14 (27%)

$Chi^2_{(2)} = 9.44$; $p = 0.009$.

Table 2: **SRS responders (*n* and %).**

	Placebo	%	Arbaclofen	%	Chi-square	p
Sleep problems (general)[a]	22.00	34.90	34.00	57.60	6.33	**0.0178**
Higher Normal Daytime Sleepiness[b]	5.00	7.90	7.00	11.90	0.38	0.5420
Mild Excessive Daytime Sleepiness[b]	0.00	0.00	1.00	1.70	0.28	0.4643
Mood/psychiatric symptoms	31.00	49.20	31.00	52.50	0.14	0.7213
Headache	26.00	41.30	19.00	32.20	1.08	0.3499
Suicidality	10.00	5.6	10.00	5.1	0.5	>0.15
Irritability/Behavioral Difficulties	15.00	23.80	15.00	25.40	0.04	1.0000
Concentration/attention problems	5.00	7.90	10.00	16.90	2.30	0.1703
Abdominal pain/gastrointestinal	8.00	12.70	10.00	16.90	0.44	0.6122
Vomiting	11.00	17.50	9.00	15.30	0.11	0.8098
Diarrhea	6.00	9.50	8.00	13.60	0.49	0.5752
Nausea	9.00	14.30	7.00	11.90	0.16	0.7914
Low depressive mood	5.00	7.90	6.00	10.20	0.19	0.7576
Tics	1.00	1.60	5.00	8.50	3.09	0.1060
Decreased appetite	10.00	15.90	5.00	8.50	1.55	0.2743
Restlessness	2.00	3.20	5.00	8.50	1.58	0.2615
Increased appetite	3.00	4.80	5.00	8.50	0.69	0.4811
Anxiety	11.00	17.50	4.00	6.80	3.22	0.0986
Weight gain	1.00	1.60	4.00	6.80	2.09	0.1964
Skin	14.00	22.20	3.00	5.10	7.46	0.0080
Weight loss	1.00	1.60	3.00	5.10	1.18	0.3528
Mood lability	6.00	9.50	3.00	5.10	0.88	0.4932
Lab results	5.00	7.90	1.00	1.70	2.54	0.2086

In bold: significant at p = 0.05 (not corrected for multiple comparisons). [a]This includes all sleep problems other than sleepiness, such insomnia, difficulties to fall asleep, night awakenings, etc. [b]Measured with the ESS-CHAD (Epworth Sleepiness Scale for Children and Adolescents).

Table 3: **Adverse Events reported by treatment arm ordered by decreasing % in the arbaclofen arm.**

behaviors, utilizing standard (SRS2, CGI) or promising (AIM) measurements. The ABC-Social Withdrawal/Lethargy was the primary outcome in the preliminary clinical trial with arbaclofen in autism, but results were negative in that study. Contrasting with these results, we reported a significant difference on several ABC subscale scores, and also in subscales and total scores of questionnaires that measure autistic and associated symptoms, albeit without correction for multiple comparisons. Effect sizes were modest, with ηp^2 between 0.05 and 0.06 for most of the positive results, and around 0.08 for mannerisms/stereotyped behaviors. This magnitude of response is in alignment with the few RCTs in autism with reported positive effects on defining symptoms.[22] With regards to the specific secondary outcome measures chosen, the AIM measures frequency and impact of autistic-related behaviors. It is a relatively new instrument but psychometric properties so far published are very favorable in measuring autistic-related symptoms[23,24]; the SRS2 has been very extensively used in clinical trials and longitudinal studies, demonstrating good psychometric properties when compared with other measures of autism-symptoms and diagnostic tools. It seems to have both trait and state properties having shown stability over time in longitudinal analyses and has been suggested to be sensitive to change following efficacious interventions.[22,25]

The choice of outcome measures for clinical trials in autism is challenging. The complex construct of social behaviors in autism, along with the boundaries between typical and atypical behaviors, how these relate to everyday functioning, and even which social differences - and to what extent - should be a focus for treatment or rather be just accepted, is under significant discussion both within and outside the autistic community.[26] In addition, it remains unclear how much social behaviors can change over the course of a short-term intervention, and how to disentangle such changes from natural developmental trajectories and environmental influences, particularly in children and adolescents. In fact, the use of broad metrics like the social subscale of the VABS, our primary outcome measure, may not be entirely suitable for assessing the effects of a four-month intervention. This scale emphasizes the development of general skills, rather than capturing more specific behaviors or symptoms—such as those targeted by the secondary outcome measures (e.g., AIM, SRS2, ABC, or CBCL)—which may be more sensitive to change through an intervention that acts on a basic mechanism like the excitatory:inhibitory balance, as opposed to one aimed at improving specific skill performance. In addition, the possibility of placebo effect differing for primary and secondary outcome measures should be further studied. In addition, some of the

positive results may reflect type I errors due to the absence of multiple comparison corrections.

With respect to tolerability, arbaclofen demonstrated a good overall tolerability profile; however, more participants receiving arbaclofen experienced sleep-related difficulties. This is a matter of concern given the substantial impact of sleep quality on quality of life in general, and on autistic individuals in particular.

In this study, we aimed to capture a broad range of behaviors commonly associated with functioning, behavioral difficulties, or poor quality of life. Although we gathered participants' perspectives through open clinical interviews that informed the CGI ratings, most questionnaires did not cover the wide range of ages included in the study and were therefore not administered to participants. Another limitation is that participants were patients attending the clinics asking for help or, in the case of the UK, following advertisements in academic clinics. Thus, the recruitment plan did not allow for a more even representation by sex or geographical origin. The variability in recruitment rates across sites may be explained by differences in their academic versus clinical orientation, as well as by local regulatory circumstances—particularly those affecting the reopening of sites after the pandemic lockdown. Nevertheless, this remains an issue that warrants further discussion. As stated in the protocol, this was a Phase II trial, and therefore underpowered to yield statistical differences in the primary outcome, which is in turn the main limitation of this study. However, an effort was made to align the design with that of another study that has been running in parallel in Canada, with a sample size of 90 patients. The data from both studies will be combined once individual results are publicly available.

The AIMS-2-TRIALS Network (https://www.aims-2-trials.es/) has thus proven that it is possible to create a robust network of well-trained academic sites that can conduct clinical trials with ready-to-test new or repurposed molecules across countries and involving participants with different native languages. The design built on learning from previous studies, our own findings on how to reduce placebo effect and including a recently approved mechanistic biomarker (N170) for subsequent predictive analyses.[27] One of the key efforts of the Network is to develop improved methods for identifying patient subgroups that are more likely to respond favorably to specific interventions. This can be achieved by stratifying patients at recruitment based on biomarker data that predicts responsiveness. Clinical data may also aid in identifying potential responder groups. Through the secondary analyses included in this study, we contribute to the methodological advancements needed to achieve this objective. One of the main purposes of the Network is accelerating medicine development connecting basic and clinical, academic and Industry researchers across Europe.

In summary, to run this clinical trial in autism, we designed a multi-site randomized clinical trial[10] following the findings from our own data on the designs that better reduce placebo effect[22]; we conducted the clinical trial in a timely manner even with the context of the COVID-19 pandemic; we explored strategies to identify the most likely responders (which will be published separately, due to space constraints and the fact that the biomarkers were not explored in the entire sample); we engaged in multidisciplinary discussions, including (self-) representatives and all stakeholders willing to enhance the relevance of clinical trials in autism while increasing their precision and translational potential. Our results support the continuation of studies aimed at exploring the efficacy of arbaclofen in children and adolescents with autism and fluent language abilities by showing significant effect on several relevant outcome measures. Larger-scale studies, inspired by the highly promising results we obtained, could pave the way for new therapeutic avenues in autism. However, the extent and specific features of sleep disturbances will need to be carefully considered and analyzed in future studies.

Contributors

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Data sharing statement

We adopt a curated data-sharing approach, meaning that direct access to the data is limited to the study investigators. Other researchers interested in using this data must apply for access by submitting a brief research scope and a motivation letter, detailing the intended purpose of the data, via email to the corresponding author. Data will be made available upon reasonable request. Note that sharing of pseudonymized personal data will require a data-sharing agreement, according to EU law.

Declaration of interests

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Appendix A. Supplementary data

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