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Safety and efficacy of aviandr in patients with generalized anxiety disorder: A multicenter, randomized, double-blind, placebo-controlled, dose-finding, pilot study

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ABSTRACT

Generalized anxiety disorder (GAD) is associated with an imbalance in the functioning of the stimulating neurotransmitter systems in human's brain. We studied the safety and therapeutic efficacy of aviandr, the new noradrenergic and specific serotonergic antidepressant, for GAD patients in the phase II, double-blind, placebo-controlled, randomized, multicenter, pilot trial at 17 clinical sites of the Russian Federation. 129 eligible patients were 18 years and older and met the criteria for GAD diagnosis. The patients were randomly assigned (1:1:1) to receive oral aviandr at daily dose of 40 mg (cohort 1, n = 41) or 60 mg (cohort 2, n = 43) or placebo (cohort 3, n = 43) for 8 weeks. The patients were assessed by the Hamilton anxiety scale (HAM-A), Hamilton Depression Scale (HAM-D), Clinical Global Impression Scale (CGI-S), Visual Analogue Scale and vital signs. At week 8, the decreases of the HAM-A score were achieved in 53•7%, 47•7% and 16•3% in cohorts 1, 2 and 3, respectively. Changes of HAM-A, HAM-D, CGI-S, and CGI-I scores in aviandr-treated patients were superior to placebo ($p <$ 0•001). The psychic components of anxiety decreased on the first day, throughout the 8 weeks of treatment and on a follow-up week after aviandr discontinuation. Aviandr (40 mg daily dose) reduced drowsiness compared to baseline, was safe, well-tolerated and did not cause serious or severe adverse events or signs of withdrawal syndrome within one week after treatment completion. Aviandr at both 40 and 60 mg daily doses demonstrated therapeutic efficacy in GAD patients over placebo.

1. Introduction

The GAD impacts 7•3% of the world's population. The rates of GAD for the African countries are lower (5•3%) compared to those in Europe (10•4%). During 2019 in US, about one in six (15.6%) adults aged 18 and over experienced symptoms of anxiety in the past 2 weeks that were either mild (9•5%), moderate (3•4%), or severe (2•7%) (Terlizzi and Villarroel, 2020). Based on statistics of 2020 in the US, 18•1% of adults had an anxiety disorder: 8•7% specific phobia, 6•8% social phobia, 3•1% generalized anxiety disorder and 2•7% panic disorder. Severity of

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symptoms of GAD differed by sociodemographic characteristics, anxiety levels are much higher in high-income countries compared to low-income countries (Ruscio et al., 2017). In US it is the most common mental disorder and there is a constant increase in anxiety disorders worldwide in recent years. The COVID-19 pandemic has created enormous problems associated with mental disorders in humans worldwide Czeisler et al. (2015)[i] Goularte et al., 2021 (Cénat et al., 2021) - more than 33% (May 14 through July 21, 2020) of American adults consistently reported symptoms of anxiety or depressive disorder, according to statistics from the Household Pulse Survey conducted by the National Center for Health Statistics (NCHS) in collaboration with the Census Bureau (Pedrosa et al., 2020).

Considering the current situation with the spread of the mental disorders in humans worldwide, the search for the new effective and safe drugs for the treatment of these diseases is highly needed. Current recommendations for the treatment of anxiety and trauma-related disorders in Europe and the US include various classes of drugs: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), noradrenergic and specific serotonergic antidepressants (NaSSA), benzodiazepines, antipsychotics and others (Sartori and Singewald, 2019).

Despite the large number of studies in the field of mental disorders and neurosciences that are conducted worldwide, new drugs to treat anxiety disorders and depression are rarely approved for use. For example, the last multimodal antidepressant with an anti-anxiety effect to enter the market, Vortioxetine, was approved in the United States and Europe in 2013. A large number of drugs are still under development. Although novel drugs (in terms of the mechanism of action) are being studied, it is too early to talk about their efficacy and safety. And already approved drugs has a number of use restrictions related to tolerability. In this regard, the question arises of the search for new medicinal agents to treat anxiety disorders and depression.

The Avineuro Pharmaceuticals Inc. and ChemRar Research and Development Institute LLC developed a new molecule - aviandr (AVN-101, CD-008-0045) with a mechanism of action fundamentally different from SSRI, thus it is void of the negative side effects of the SSRI group of drugs. The pharmacological properties of aviandr are very similar to Mirtazapine, however, according to the results of Phase I and Phase II studies, are not demonstrating undesirable side effects characteristic of Mirtazapine: such as increased appetite, weight gain, and drowsiness. Aviandr is the potent inhibitor of an adrenergic 2A, 2B, and 2C (Ki = 0•41–3•6 nM) receptors, serotonergic 5-HT2A, 5HT-2C, 5-HT6, and 5-HT7 (Ki = 0•15–2•0 nM) receptors and histamine H1 (Ki = 0•58 nM) and H2 (Ki = 89 nM) receptors (Ivachtchenko et al., 2016). MTZ is a H1 receptor antagonist with very strong inverse agonist activity (Anttila et al., 2001), therefore it can cause powerful sedative and hypnotic effects. Unlike MTZ, aviandr is a histamine H1/H2 antagonist with no inverse agonist activity and in addition exhibits picomolar inhibitory activity with respect to 5-HT7 receptors (Ki = 0 • 15 nM) (Ivachtchenko et al., 2016). This receptor profile makes it possible to avoid the negative effects typical of SSRIs and to consider Aviandr as a new drug to treat anxiety and depressive disorders. Aviandr has demonstrated the positive effects in animal models of both impaired and innate cognition. It also exhibited significant anxiolytic and antidepressant capabilities in animals (Ivachtchenko et al., 2016).

Safety, tolerability and pharmacokinetics of the aviandr drug when administered as a single 2 mg/4 mg/10 mg/20 mg dose in healthy male volunteers were studied in two Phase I clinical trials (data not published). The aviandr drug showed favorable safety profile. The AEs documented in the studies, in most cases involved the Central Nervous System, were mild in severity, short-term in duration and required no treatment. There was no relation found between AE occurrence and the study drug administration. There have been no SAEs documented throughout the studies. After single administration, the exposure of aviandr was linearly dependent from the drug dose. According to PK data, time to reach maximum concentration (Tmax) was 1 h, elimination half-life (T1/2) was about 8 h.

In 2017 a phase I clinical trial (data not published) was conducted to assess safety of the aviandr drug increasing doses after the single and multiple dosing. 40 mg (20 mg BID) and 60 mg (20 mg 3 TID) daily doses of the aviandr drug were studied in the trial, the multiple dosing duration was 4 days. The aviandr drug showed favorable safety profile and high tolerability in the study. There were no AEs related to the study drug throughout the study. AEs were observed only in volunteers who received a 40 mg daily dose of the drug.

The objective of this study was to evaluate dosing regimen and to assess the safety and efficacy of aviandr in GAD patients.

2. Methods

2.1. Study design

Multicenter, randomized, double-blind, placebo-controlled, parallel-group [1:1:1] dose-finding pilot study to assess the safety and efficacy of aviandr in GAD patients was conducted at 17 sites in the Russian Federation. Before the start of the clinical study, the study design was reviewed by Independent Ethics Committees (IECs) and written approval was received for all study sites. All the participants provided a written acceptance of the terms. The study was conducted in accordance with the International Conference on Harmonization of Good Clinical Practice and the principles of the Declaration of Helsinki. The phase II clinical trial protocol of aviandr was approved by the Ministry of Health of the Russian Federation and registered in the US National Library of Medicine (NCT04524975).

2.2. Participants

A total 135 participants were screened, of which 129 participants were included in the study and divided into 3 cohorts. 129 patients were included in safety population and 128 patients were included in MITT population. All the patients were Caucasian, average age 42•5 ± 13•1 years (age of 18 years and older is one of inclusion criteria), 75•0% of patients were women who met the International Guidelines for the Diagnosis and Statistics of Mental Disorders (DSM-V) and criteria classification of diseases (ICD-10). The diagnosis of GAD was established by a psychiatrist based on the medical history, clinical interview and detailed psychiatric screening assessments that included HAM-A and CGI-S scales. Inclusion criteria by HAM-A values at Screening and Randomization Visit (Week 0): -overall score ≥ 20; - rating by items 1 (Anxious mood) and 2 (Tension) is ≥ 2 points; and by CGI-S scale: score ≥ 4 (moderate severity and higher).

Participants were excluded if they had a current comorbid diagnosis of a depressive episode, recurrent depressive disorder, bipolar affective disorder, psychosis, schizophrenia, panic disorder, phobic anxiety disorders (agoraphobia, social phobia, unspecified phobic anxiety disorder), post-traumatic stress disorder, eating disorders, somatoform disorders, obsessive-compulsive disorders. Other exclusion criteria included: psychotherapy within 3 months prior to screening and/or at the time of enrollment into the study; being considered at risk for suicide by the investigator, having previously attempted suicide, or currently demonstrating active suicidal ideation; any uncontrolled concomitant somatic disease, including that with a stable treatment regimen.

2.3. Randomization and masking

This study was double-blind, e.g. during the investigational therapy phase, neither the patients nor the investigators knew which therapy and in which doses were prescribed. 129 patients were randomized to the study into three cohorts at a ratio of approximately 1:1:1. The process of the patient randomization and drug vial allocation was performed using an Interactive Web Response System (IWRS). During each

visit, except for visit 3 (week 2), IWRS allocated study drug package numbers for the patient until the next visit, each package contained 3 vials (morning, afternoon, evening) corresponding to the patient group. Aviandr and placebo were in capsule and identical in appearance. They were prepacked in bottles and consecutively numbered for each patient according to the randomization schedule. Package and vial numbers have been accurately documented in patient's source documents and corresponding dispensing forms. All study team members collecting outcome data at the study visits were blinded to randomized treatment.

The capsules of aviandr and placebo were manufactured by JSC Chemical Diversity Research Institute (Russian Federation) by order of ChemRar Research Institute Ltd., Russian Federation.

2.4. Procedures

During the first phase (introductory period: week −1 and week 0) all the patients received orally a placebo. During the second phase (study therapy: week 0 through week 8) the patients of cohort 1 received orally 1 capsule of aviandr (20 mg) before breakfast and before dinner, and 1 placebo capsule before lunch; the patients of cohort 2 received orally 1 capsule of aviandr (20 mg) before breakfast, lunch, and dinner. The patients of cohort 3 received orally 1 placebo capsule before breakfast, lunch, and dinner. During the third phase (observation period: week 9) all the patients received a placebo. The timing of visits and assessments are provided in Table 1.

2.5. Outcomes

The primary outcome was selected in accordance with Guideline on the clinical investigation of medicinal products indicated for generalized anxiety disorder London, January 20, 2005 CPMP/EWP/4284/02. HAM-A is the most useful scale for assessment patients with GAD in most clinical trials (Hamilton, 1959; Matza et al., 2010; Maust et al., 2012).

The primary outcome of the study was treatment response frequency under different daily doses of aviandr at week 8 in patients with GAD. With 41–43 patients in each cohort, the treatment response was considered as a 50% and more decrease of the overall score by HAM-A from baseline level to detect clinically significant differences between aviandr regimens and placebo.

The secondary outcomes of the study included evaluation of the safety, efficacy, pharmacokinetic and pharmacodynamic parameters of aviandr versus placebo in patients with GAD within 8 weeks of therapy and follow-up week after drug discontinuation.

Secondary outcomes included change of the overall score from baseline level by the scales of HAM-A, the sum of score by subscales of mental and somatic anxiety of HAM-A, by items 1 (anxious mood) and 2 (tension) of HAM-A, the overall scores by HAM-D, VAS, CGI-S and CGI-I, assessment of withdrawal symptoms by change in scores on psychometric scales at week 9 compared to week 8 and baseline; the trough concentration (C_{trough}) and concentration of aviandr and its metabolite M1 1 h after its administration at weeks 4 and 8, occurrence of AEs and SAEs based on individual complaints, physical examination results, vital signs, ECG data and laboratory tests.

Safety of aviandr was assessed based on the incidence of AEs and SAEs recorded on the subjective complaints, physical examination, vital signs, ECG and laboratory tests. Registration of AEs and SAEs was performed from the moment the patient signed the informed consent form (before taking the first dose of the study drug) and up to 30 days after the patient's last visit to the research center or the last procedure under the protocol. During the trial we recorded any AEs that came to our attention. At the end of the trial medical records were further checked for formal therapy complaints, AEs and SAEs.

2.6. Statistical analysis

The primary endpoint of the study was the proportion of patients reaching 50% decrease of the total score by Hamilton Anxiety Rating Scale (HAM-A) at Week 8 as compared to baseline level.

According to the paroxetine clinical trial in patients with generalized anxiety disorder, in paroxetine group the mean decrease of the overall score by Hamilton Anxiety Rating Scale (HAM-A) on Weeks 6 and 8 were ~12 that corresponds to 50% decrease of generalized anxiety disorder

Table 1
Schedule of study procedures and assessments.

Phase\Procedures	Screening and run-in period	Study Intervention Period				Follow-up period	ED
Visit	V1	V2	V3	V4	V5	V6	
Week	W1	W0 (Rand.)	W2	W4	W8 (ED)	W9	
Informed consent & Patient registration	X						
Demographics & Medical History	X						
HARS assessment	X	X	X	X	X	X	X
HAMD assessment	X	X	X	X	X	X	X
CGI-S assessment	X	X	X	X	X	X	X
CGI-I assessment		X	X	X	X	X	X
VAS assessment	X	X	X	X	X	X	X
Questionnaire for assessment of anxiety quality	X						
Vital signs	X	X	X	X	X	X	X
Weight/height, BMI	X			X	X		X
Physical examination	X			X	X		X
Clinical laboratory tests:							
- Hematology	X			X	X		X
- Blood chemistry	X			X	X		X
- Genotyping for cytochrome CYP2D6				X			X
- Pharmacokinetic studies				X	X		X
- General urinalysis	X			X	X		X
- Urine tests for prohibited drugs and pregnancy	X	X	X	X	X	X	X
12-lead ECG	X			X	X		X
Eligibility	X	X					
Randomization		X					
IP administration	X	X	X	X	X		
The return and registration of IMP		X	X	X	X	X	X
The issuance r of a patients' diary	X	X	X	X	X		
The return of patients' diary.		X	X	X	X	X	X
Adverse event assessment	X	X	X	X	X	X	X
Concomitant medication assessment	X	X	X	X	X	X	X

symptoms severity. In placebo group the mean decrease of the overall score by HAM-A were 9•3 that corresponds to 38% decrease of generalized anxiety disorder symptoms severity. Moreover, up to 80% patients were positive in decrease of the overall score for 8 weeks of paroxetine treatment, and 30–40% reached complete remission in comparison with 20% patients from placebo group (Rickels et al., 2003).

For this study of CD-008-0045 we assume that the therapy at Week 8 will be considered successful only in case when no less than 50% of patients reach the decrease of overall score by Hamilton Anxiety Rating Scale (HARS) by 50% and more (p1). Similar value in the placebo group should not exceed 30% of patients (p0).

The sample size was based on the exact single stage phase II assessment at one-sided $\alpha = 0.05$ and 80% power (A'hern, 2001). Continuous variables with a normal distribution were expressed as mean (SD) and compared using ANOVA test for parametric data and Kruskal-Wallis test for nonparametric data. The primary efficacy outcome was the proportion of patients who achieved a 50% reduction in HAM-A at week 8 from baseline at week 0. The dosing regimen was considered having a different effect than placebo if observed in 17/39 (43•6%) or more patients of aviandr cohorts 1 and 2 and less than in 17/39 (43•6%) of patients in placebo cohort 3. The efficacy was assessed in the Modified Intention to Treat (MITT) set, which consisted of all the randomized patients who received at least one dose of the study drug and had at least one post-baseline score (week 0) on the HAM-A. The aviandr cohorts were compared to the placebo using the criterion $\chi 2$.

The secondary efficacy outcome was the change from baseline to end of study (week 8) in the HAM-A totals score, total score of the mental and somatic anxiety subscales of HAM-A, total scores of HAMD, CGI-S, CGI-I, and VAS. Scale change score was analyzed using Linear Mixed Effect Model (LME) that included treatment as factor, center as random factor and baseline total score as a covariate. The mean values of least squares and 95% confidence intervals were calculated using least-squares means function of R statistical package (version 3.5.2). The effect of each aviandr regimen, in comparison with placebo, CGI-I response ("much improved", "very much improved" or "minimally improved" at week 8) was evaluated with criterion $\chi 2$. Analyses of the primary and secondary outcomes were evaluated at 0•050 level.

Applicable statistical analysis methods, consistent with the EEC Recommendations N 19 of November 3, 2020, were used for the data missing at the assessment visit. Patients who could not complete the treatment course in accordance with the protocol were included in the analysis of efficacy outcomes using the method of last observation carried forward (LOCF). This means that the variables taken as criteria for the treatment efficacy were assessed in these patients at the time of dropout from the study. All the statistical analyses were performed with the R statistical package (version 3.5.2).

The AEs recorded by investigators were mapped to preferred terms with use of a MedDRA dictionary (version 21•1). Only treatment-emergent AEs (TEAEs) were summarized. Each individual AE was counted only once based on the maximum intensity recorded, regardless of the number of times the patient experienced the event.

3. Results

3.1. Efficacy of aviandr treatment

According to the screening questionnaire for assessment of anxiety quality in almost all the patients, anxiety affected the subjective sensation of impaired cognitive functioning. The presence of reactive lability (anxiety was provoked by external circumstances) was noted by 62% of the patients. Most patients had signs of personality disorder (accentuations), since the intensity of anxiety disorders was influenced by specific situations (narcissi personality traits, such as "anxiety intensifies when I look bad", "when I think that I am being ignored", "when I compare myself to others"); psychasthenia traits ("when I can't complete the task strictly according to the instructions", "when something goes wrong"), as well as the anxiety associated with the need to restrain anger. Sedation as a possible side effect of anti-anxiety treatment was relevant for 48% of the patients. The most relevant treatment targets for patients, in addition to anxiety were stress tolerance, working efficiency and cognitive functioning.

135 patients with GAD were screened and 129 of them were randomized to 3 cohorts – aviandr 40 mg/day (n = 42), aviandr 60 mg/day (n = 44) and placebo (n = 43) (Fig. 1). Baseline demographic and clinical characteristics of patients with GAD are summarized in Table 2.

The efficacy of aviandr dosage regimens in reducing of anxiety in patients with GAD was considered the primary outcome of the study. The main population for efficacy analysis was the MITT set. The treatment response rate in HAM-A at week 8 in MITT population is shown in Table 3. At week 8, 53•7% (cohort 1) and 47•7% (cohort 2) of patients achieved a 50% decrease of the total score in the HAM-A from baseline. At the same time, in placebo cohort 3, there was a decrease in only 16•3% of patients. Both aviandr cohorts 1 and 2 were significantly different from the placebo cohort 3 ($p < 0•001$) in the number of patients responding to the treatment. Thus, both aviandr cohorts (40 mg/day and 60 mg/day) reached primary outcome and were considered effective in reducing anxiety in GAD patients.

The changes in the total HAM-A score for cohorts 1 and 2 in the secondary outcome analysis are presented in Table 4. The mean changes in HAM-A, CGI-S, CGI-I, and VAS from baseline to week 8 in MITT population are presented in Fig. 2. Patients in cohorts 1 and 2 produced significant improvement in the HAM-A total score compared to patients in cohort 3 ($p = 0•002$). Patients in cohorts 1 and 2 also show improvement on both psychic and somatic anxiety subscales of the HAM-A versus these in cohort 3 [psychic anxiety: $p = 0•005$ and $p = 0•001$, respectively; somatic anxiety: $p = 0•002$ and $p = 0•008$, respectively]. It should be noted that in cohorts 1 and 2, the psychic component of anxiety was reduced, which was detected already in the first days of aviandr administration (Fig. 2C) and continued during the observation period after drug discontinuation. The somatic component decreased its severity somewhat later, but even here the positive dynamics persisted after drug discontinuation (Fig. 2B).

The improvement in HAMD differed significantly for cohort 1 (decrease by 2•09 point; $p = 0•008$) and cohort 2 (decrease by 2•55 point; $p = 0•001$) as compared to cohort 3. It is worth noting that in cohort 1, there is a correlation between the dynamics of anxiety and depressive disorders, and the Pearson coefficient of correlation in cohort 1 was 0•91 ($p < 0•001$) and in cohort 2 it was 0•81 ($p < 0•001$).

At week 8, a significant decrease in the total CGI-S score as compared to the baseline was observed in cohort 1 (decrease by 0•42 point) and cohort 2 (decrease by 0•41 point) versus placebo ($p = 0•030$ and $p = 0•020$), respectively. The change in CGI-I total scores was significantly improved for cohorts 1 and 2 as compared to cohort 3 (decrease by 0•82 and 0•64 points; $p = 0•001$ and $p = 0•009$), respectively.

Response rates measured by the CGI-I scale were additional secondary outcomes. On the CGI-I scale, response rates for aviandr were significantly different from cohort 3 (cohort 1 was 82•9%, $p < 0•001$ and cohort 2 was 81•8%, $p = 0•016$). Since drug intake was completed one week before the end of the study, post-drug discontinuation analysis was performed. During this period, the conditions' severity among patients in both aviandr cohorts continued to decrease significantly on the CGI-S scale (Fig. 2E), which meant the absence of a withdrawal syndrome. This trend was not observed in placebo cohort 3. On the CGI-I scale, positive dynamics continued only in cohort 1 after discontinuation of aviandr (Fig. 2F).

The VAS scale was used to assess the AEs of anti-anxiety therapy such as somnolence (Fig. 2G). In cohort 2, the mean VAS score on the last day of therapy was 15•4 ± 18•0, the change from the baseline was −7•8 ± 26•5, which meant a slight decrease in sleepiness, but the change was not statistically significant. In cohort 1, the mean VAS score was 15•6 ± 13•4, the change from the baseline was −11•2 ± 16•3, which indicated a significant decrease ($p = 0.001$) of this symptom. The same effect was

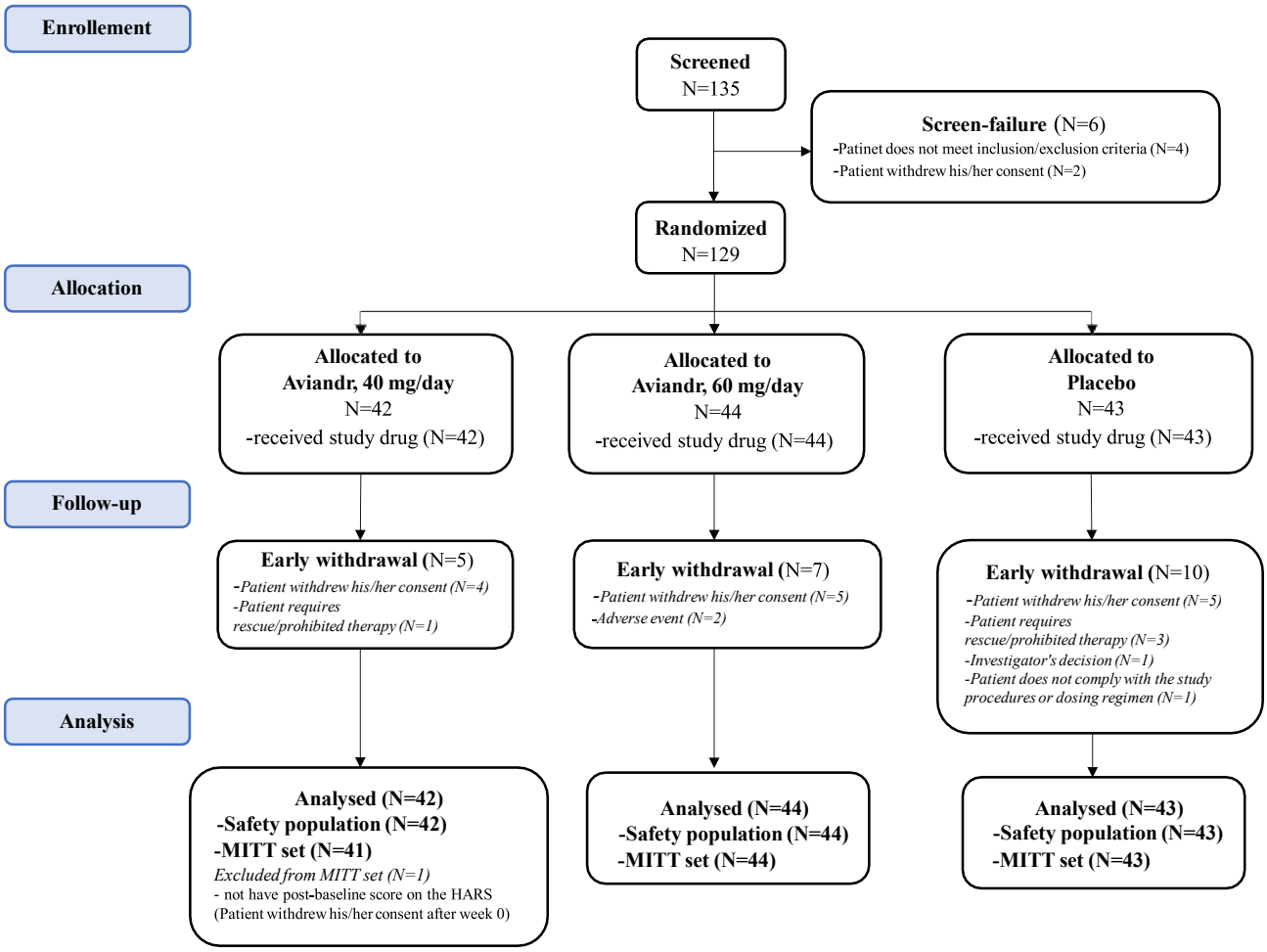

Fig. 1. Flow diagram of multicenter, randomized, double-blind, placebo-controlled study of safety and efficacy of aviandr in GAD patients.
The main *reasons for screening failure* were: the main diagnosis didn't meet inclusion criteria, or concomitant disease.
Reasons for withdrawal were following:
• «Investigator consider it necessary based on the aggravation of GAD symptoms » - 1 patient from Placebo (2.3%);
• «Patient recalled its acceptance to participate in the study » - 5 patients from the group CD-008-0045 60 mg (11.4%), 4 patients from the group CD-008-0045 40 mg (9.5%) and 5 patients from Placebo (11.6%);
• «Patient doesn't follow administration of prescribed doses of the study drug, or procedures related to the study » - 1 patient from Placebo (2.3%);
• «Patient needs salvage or forbidden therapy (aggravation of GAD symptoms that needs administration of benzodiazepine) - 1 patient from the group CD-008-0045 40 mg (2.4%) and 3 patients from Placebo (7.0%);
• «AE or SAE that could affect negatively safety of patient » - 2 patients from the group CD-008-0045 60 mg (4.5%) (development of AE: Anxiety disorder, Dizziness, Nausea, Somnolence).

observed in the placebo group: the mean VAS score was 15•2 ± 19•4, the change from the baseline level was −9•8 ± 17•6 ($p = 0$•010).

The treatment response rate in CGI-I at week 8 in MITT population is presented in Table 5.

3.2. Safety of aviandr

During the study, the total of 152 AEs were reported in 44/129 (34•1%) patients in cohorts 1, 2 and 3 (Table 6). Similar numbers of AEs were reported in cohorts 1 and 3: 12/42 (28•6%) and 12/43 (27•9%) patients, respectively. In cohort 2, AEs were recorded in 20/44 (45•5%) patients and this is significantly higher than number of AEs observed in cohorts 1 and 3. Thus, the number of patients who have AEs in cohort 2 differed significantly ($p = 0$•018) from placebo, while these numbers in cohort 1 did not differ from placebo. All the AEs were either mild or moderate in intensity in all cohorts. Severe AEs or SAEs related to aviandr therapy were not reported. One patient in cohort 2 had a total of 2 AEs that led to an interruption of aviandr. The following AEs: dysgeusia and abdominal upper pain were considered by the investigator to be related to aviandr therapy. Three patients (6•8%) in cohort 2 had a total of 5 AEs that led to a permanent discontinuation of aviandr. The following AEs (anxiety disorder, dizziness, nausea, somnolence and anxiety) were considered by the investigator to be related to aviandr therapy. One patient (2•3%) in cohort 3 had a total of 4 AEs that led to a permanent discontinuation of placebo administration. The following AEs (tearfulness, tremor, anxiety and insomnia) were not considered by the investigator to be related to aviandr administration. The nervous system was the most affected by adverse events related to aviandr in cohort 2. Somnolence, headache and dizziness were the most common adverse events in cohorts 1 and 2 or cohort 3 (Table 5). No clinically important changes in vital signs (blood pressure, sitting heart rate or respiratory rate) or laboratory values were noted in any treatment group during this study.

3.3. Pharmacokinetics assessment

Concentrations of aviandr and its metabolite M1 before the next drug administration ($C_{through}$) at weeks 4 and 8, and 1 h after drug

Table 2
Baseline demographic and clinical characteristics of patients with GAD in MITT population.

Characteristics	Aviandr		Placebo	*p*
	Cohort 1	Cohort 2	Cohort 3	
	40 mg (N = 41)	60 mg (N = 44)	(N = 43)	
Mean age, years (SD)	44•5 (12•7)	42•0 (13•1)	41•0 (13•5)	0•395[a]
Gender				
Male, n (%)	12 (29•3)	8 (18•2)	12 (27•9)	0•443[b]
Female, n (%)	29 (70•7)	36 (81•8)	31 (72•1)	
White race, n (%)	41 (100)	44 (100)	43 (100)	–
BMI, kg/m^2, mean (SD)	25•6 (4•4)	25•3 (6•3)	24•9 (5•7)	0•445[a]
HAM-A				
Total score, mean (SD)	26•5 (4•1)	26•8 (5•4)	26•9 (4•6)	0•890[b]
Mental anxiety subscale total score, mean (SD)	12•3 (2•0)	11•8 (2.3)	12•0 (2•0)	0•561[b]
Somatic anxiety subscale total score, mean (SD)	14•2 (3•3)	14•9 (3•6)	14•9 (3•8)	0•498[b]
HAM-D, total score, mean (SD)	10•9 (1•6)	10•9 (1•3)	10•7 (1•4)	0•558[b]
CGI-S, total score, mean (SD)	4•3 (0•5)	4•2 (0•5)	4•3 (0•5)	0•988[b]
CGI-I, total score, mean (SD)	4•0 (0•4)	4•0 (0•2)	4•0 (0•3)	0•901[b]

[a] *p* values are intergroup comparisons to aviandr at baseline and each assessment point using Kruskal-Wallis test. [b] *p* values are intergroup comparisons to aviandr at baseline and each assessment point using criterion χ^2. N = number in the total sample, n = number with characteristics, BMI = body-mass index, HAM-A = Hamilton Anxiety Scale, HAM-D = Hamilton Depression Scale, CGI-S = Clinical General Impression Scale, SD = standard deviation. – denotes data not applicable.

Table 3
Treatment response rate in HAM-A at week 8 in MITT population.

Treatment response rate	Aviandr		Placebo
	Cohort 1	Cohort 2	Cohort 3
	40 mg (N = 41)	60 mg (N = 44)	(N = 43)
No. of responders[b], n (%)	22 (53•7)	21 (47•7)	7 (16•3)
p[a]	<0•001	0•002	–

– denotes data not applicable.
[a] *p* values are intergroup comparisons between aviandr cohorts and placebo cohort using criterion χ2. N = number in the total sample, n = number with characteristics.
[b] Responders are the patients achieved a 50% decrease of the total score in the HAM-A from baseline.

administration (C_{max}) at week 4 are presented in Table 7. Concentrations of Aviandr and its metabolite M1 are not growing with the dose, median $C_{through}$ are 194 pg/ml and 162 pg/ml at the week 4 in cohorts 1 and 2 respectively. Similar results are observed at the week 8. Taking into account similar efficacy of aviandr demonstrated in both cohorts, we conclude that 40 mg/day and 60 mg/day dosage regimens are on the plateau of the dose/effect relationship curve.

4. Discussion

SSRIs remain the most commonly used group of drugs for the treatment of anxiety disorders (Baldwin et al., 2012). Despite their obvious advantages (adequate efficacy, good safety profile), they have a number of use restrictions related to tolerability – the side effects that are significant for some patient groups. The common side effects of SSRIs are: nausea, diarrhea, increased anxiety at treatment initiation, sexual dysfunction (anorgasmia, genital sensitivity decreased, ejaculation delayed), sleep disturbances. The specifics of the therapeutic action of this class of drugs also determine some difficulties at the treatment onset

Table 4
Changes in HAM-A, HAMD, CGI-S and CGI-I from baseline to week 8 in MITT population.

Outcome	Aviandr		Placebo
	Cohort 1	Cohort 2	Cohort 3
	40 mg (N = 41)	60 mg (N = 44)	(N = 43)
HAM-A total score, mean (SE)[a]	−11•97 (1•32)	−11•66 (1•31)	−6•58 (1•29)
Difference from placebo	−5•38	−5•08	–
95% CI	−8•98; −1•79	−8•56; −1•59	–
P	0•002	0•002	–
HAM-A Psychic anxiety subscale, mean (SE)[a]	−5•33 (0•63)	−5•59 (0•62)	−2•92 (0•62)
Difference from placebo	−2•41	−2•67	–
95% CI	−4•18; −0•64	−4•39; −0•96	–
P	0•005	0•001	–
HAM-A Somatic anxiety subscale, mean (SE)[a]	−6•57 (0•75)	−6•11 (0•74)	−3•63 (0•73)
Difference from placebo	−2•94	−2•67	–
95% CI	−4•95; −0•93	−4•42; −0•54	–
P	0•002	0•008	–
Improvement on the HAMD, mean (SE)[a]	−4•06 (0•60)	−4•52 (0•59)	−1•97 (0•58)
Difference from placebo	−2•09	−2.55	–
95% CI	−3•71; −0•46	−4•13; −0•97	–
P	0•008	0•001	–
CGI-S, mean (SE)[a]	−1•09 (0•17)	−1•.10 (0•17)	−0•68 (0•17)
Difference from placebo	−0•41	−0•42	–
95% CI	−0•89; 0•05	−0•88; 0•03	–
P	0•030	0•020	–
CGI-I, mean (SE)[a]	−1•53 (0•16)	−1•35 (0•16)	−0•71 (0•16)
Difference from placebo	−0•82	−0•64	–
95% CI	−1•34; −0•30	−1•14; −0•13	–
P	0•001	0•009	–

[a] Difference in least-squares means based on ANOVA model with treatment and center in the model and HAM-A baseline score as a covariate. *p* values are intergroup comparisons between aviandr cohorts and placebo cohort using LME. N = number in the total sample, n = number with characteristics, HAM-A = Hamilton Anxiety Scale, HAM-D = Hamilton Depression Scale, CGI-S = Clinical General Impression Scale, SE = standard error. – denotes data not applicable.

in patients with anxiety disorders: the therapeutic effect does not occur earlier than 2 weeks from the start of SSRIs administration, and many of the above-mentioned side effects remain and may even increase throughout the treatment: sexual dysfunction, SSRIs-induced apathy, sleep disturbances[17]. Another disadvantage of SSRIs and SSNRIs is reinforcement of anxiety symptoms at the start of treatment, that often needs concomitant therapy with benzodiazepines or anxiolytics of another groups (Ferguson, 2001).

Here we are reporting results of the first successful phase II randomized clinical trial of the novel NaSSA - aviandr ([3,4-dihydro-1H-pyrido [4,3-b] indoles row) for the treatment of GAD patients. This is one of the first studies to evaluate a non-benzodiazepine intervention in GAD and is specifically the first study to assess the efficacy and safety of aviandr and to select the dosing regimen of the study drug in patients with GAD. Aviandr is the first representative in more than 20 recent years of the new generation anxiolytic agents which has a high affinity for adrenergic α1A and serotonin 5-HT7, 5-HT2A and 5-HT2C receptors, and a very low activity toward SERT, NET and DAT Transporters and Dopamine Receptors.

In this study we demonstrated that the daily dosages of 40 mg and 60 mg of aviandr were effective in reducing anxiety in GAD patients as measured by primary and secondary outcomes. The preservation of the

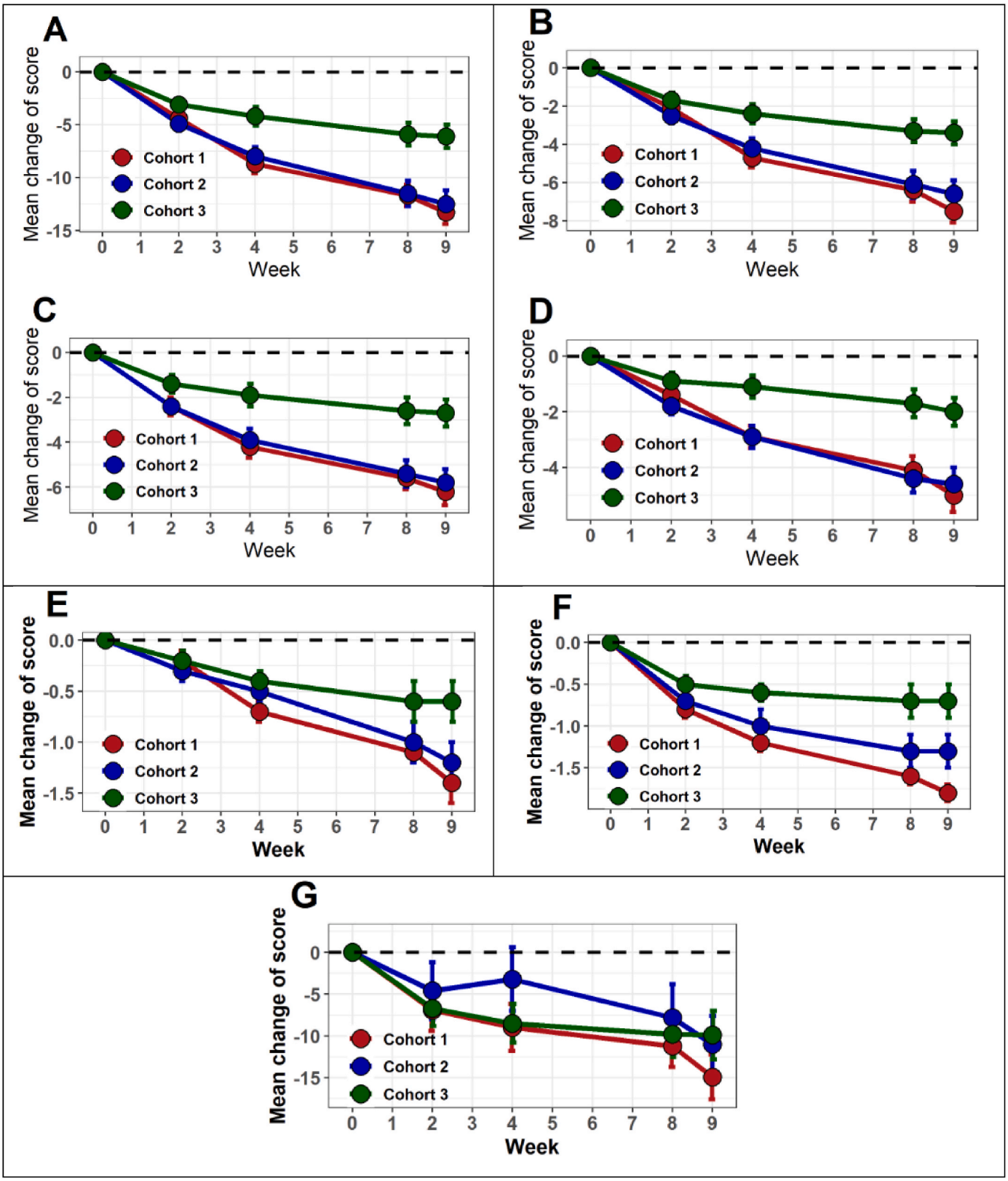

Fig. 2. Changes in HAM-A, HAMD, CGI-S, CGI-I and VAS from baseline to week 9 in MITT population. The values are mean changes in HAM-A total score (units) (A), HAM-A somatic subscale total score (units) (B), HAM-A psychic subscale total score (units) (C), HAMD total score (units) (D), CGI-S total score (units) (E), CGI-I total score (units) (F), and VAS total score (units) (G).

Table 5
Treatment response rate in CGI-I at week 8 in MITT population.

Response rate	Aviandr		Placebo	p[a]
	Cohort 1	Cohort 2	Cohort 3	
	40 mg (N = 41)	60 mg (N = 44)	(N = 43)	
Improvement, n (%)	34 (82•9)	36 (81•8)	23 (53•5)	<0•001
No change, n (%)	7 (17•1)	2 (4•5)	3 (7•0)	0•016
Worsening, n (%)	0	6 (13•6)	17 (39•5)	–

[a] *p* values are intergroup comparisons between aviandr cohorts and placebo cohort using criterion $\chi 2$. N = number in the total sample, n = number with response rate. – denotes data not applicable.

Table 6
Adverse events related to aviandr administration.

Adverse events[a]	Aviandr		Placebo
	Cohort 1	Cohort 2	Cohort 3
	40 mg (N = 42)	60 mg (N = 44)	(N = 43)
Gastrointestinal disorders, n (%)	0	3 (6•8)	2 (4•7)
Abdominal pain upper, n (%)	0	1 (2•3)	1 (2•3)
Constipation, n (%)	0	1 (2•3)	0
Dyspepsia, n (%)	0	0	1 (2•3)
Nausea, n (%)	0	2 (4•5)	0
General disorders and administration site conditions, n (%)	0	3 (6•8)	1 (2•3)
Asthenia, n (%)	0	3 (6•8)	1 (2•3)
Nervous system disorders, n (%)	2 (4•8)	12 (27•3)	3 (7•0)
Disturbance in attention, n (%)	0	1 (2•3)	0
Dizziness, n (%)	0	4 (9•1)	0
Dysgeusia, n (%)	0	1 (2•3)	0
Headache, n (%)	2 (4•8)	6 (13•6)	3 (7•0)
Paraesthesia, n (%)	0	1 (2•3)	0
Somnolence, n (%)	1 (2•4)	7 (15•9)	1 (2•3)
Psychiatric disorders, n (%)	1 (2•4)	3 (6•8)	0
Anxiety, n (%)	0	1 (2•3)	0
Anxiety disorder, n (%)	0	1 (2•3)	0
Insomnia, n (%)	1 (2•4)	0	0
Middle insomnia, n (%)	0	1 (2•3)	0

N = number in the total sample, n = number with response rate.
[a] AEs experienced by ≥ 5% of patients in any treatment group.

Table 7
$C_{through}$ (pg/ml) and C_{max} (pg/ml) concentrations of aviandr and its metabolite M1 in plasma of patients.

	Aviandr			Metabolite M1		
	Visit 4 (Week 4)		Visit 5 (Week 8)	Visit 4 (Week 4)		Visit 5 (Week 8)
	$C_{through}$	C_{max}	$C_{through}$	$C_{through}$	C_{max}	$C_{through}$
Cohort 1 (40 mg)						
Mean	545	1575	558	74•6	215	89•3
SD	905	3629	952	155	458	219
CV	166	230	171	208	213	246
Median	194	345	174	0	65•3	0
N	35	35	35	35	35	35
Cohort 2 (60 mg)						
Mean	344	861	289	58.6	228	41•6
SD	420	1217	352	156	338	112
CV	122	141	122	266	148	269
Median	162	371	152	0	107	0
N	37	37	37	37	37	37

positive dynamics of the state was noted in the groups of therapy even after discontinuation of the study drug. 4 cases of GAD symptoms aggravation required prescription of benzodiazepines were reported in this study, and only 1 of them was in the aviandr group. We consider this advantage of aviandr is related to its favorable receptor profile (blockade of H1-receptor and presynaptic alpha-adrenoreceptors). Another important parameter for an anti-anxiety drug is the timing of the onset of the therapeutic effect. It is known that the most common drugs for the treatment of GAD, antidepressants, show their clinical activity after a fairly long exposure: 4–6 weeks. Aviandr has been shown to be effective within the first two weeks of treatment at both low and high doses.

Aviandr has shown a favorable safety profile - all the AEs were mild or moderate in intensity, severe AEs and SAEs related to aviandr administration were not reported. Drowsiness, headache, and dizziness were the most common AEs in cohorts 1 and 2 or cohort 3. However, the safety profile of cohort 2 was slightly different from the placebo in the number of patients who developed AEs. This supports the choice of a daily dose of 40 mg for further study in phase III. The greatest attention was paid to its ability to induce drowsiness since this side effect most significantly limits the functioning of patients with GAD when prescribing anxiolytic drugs. It turned out that aviandr reduced drowsiness compared to baseline in the group of 40 mg. After discontinuation of the study drug and transfer of patients to placebo, there was no withdrawal syndrome in any of the groups of therapy.

While no comparator drug was used in this study we can compare efficacy of aviandr with available literature date for other anti-anxiety drugs. The efficacy of Aviandr measured by mean decrease of anxiety level in HAM-A scale is similar to that demonstrated in prior studies of commonly used anxiolytics. For example, the difference with Placebo in the group of aviandr 40 mg was −5•38 units (p = 0•002). This is comparable to the results of Pregabalin in the treatment of GAD where the difference with Placebo was from −2•50 to −3•10 units (Baldwin et al., 2015). Also the number of responders achieved a remission in the HAM-A scale (response defined as of 50% reduction in HAM-A score) was similar to results for Pregabalin (Baldwin et al., 2011). And in the study of Paroxetine approved its efficacy for treatment of GAD, the treatment response rate in HAM-A was 62% (Pollack et al., 2001).

In conclusion, the study results justified a significant improvement in aviandr treated groups compared to placebo as per the data of primary and secondary endpoints. Although the study did not include patients with comorbid depression, there was an improvement in the aviandr treatment groups, according to the HAM-D scale. This fact along with the receptor profile of the drug makes it possible to consider the further development of the drug aviandr, particularly for the treatment of major depressive disorder. The phase III study (NCT04598867) will take place in 15 clinics of the Russian Federation and will begin in 2021. The study will include 200 patients (120 patients will receive aviandr at a dose of 20 mg twice a day; 40 patients will receive a placebo capsule twice a day; 40 patients will receive a comparative drug afobazole 10 mg once a day). Also the total duration of therapy with aviandr will be increased to 32 weeks, that is in agreement with most part of clinical guidelines (Bandelow et al., 2008; De Lijster et al., 2017).

Data sharing

We are unable to share data because participants did not provide consent for data sharing.

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Declaration of competing interest

All authors declare no competing interests.

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References

A'hern, R.P., 2001. Sample size tables for exact single-stage phase II designs. In: STATISTICS IN MEDICINE Statist. Med, vol. 20.

Anttila, S.A.K., Leinonen, E.V.J., Anttila, S., 2001. NEW drugs A review of the pharmacological and clinical profile of Mirtazapine. In: CNS Drug Reviews, vol. 7. Issue 3.

Baldwin, D.S., Allgulander, C., Bandelow, B., Ferre, F., Pallanti, S., 2012. An international survey of reported prescribing practice in the treatment of patients with generalised anxiety disorder. World J. Biol. Psychiatr. 13 (7), 510–516. https://doi.org/10.3109/15622975.2011.624548.

Baldwin, D.S., Den Boer, J.A., Lyndon, G., Emir, B., Schweizer, E., Haswell, H., 2015. Efficacy and safety of pregabalin in generalised anxiety disorder: a critical review of the literature. In: Journal of Psychopharmacology, vol. 29. SAGE Publications Ltd, pp. 1047–1060. https://doi.org/10.1177/0269881115598411. Issue 10.

Baldwin, D.S., Waldman, S., Allgulander, C., 2011. Evidence-based pharmacological treatment of generalized anxiety disorder. In: International Journal of Neuropsychopharmacology, vol. 14, pp. 697–710. https://doi.org/10.1017/S1461145710001434, 5.

Bandelow, B., Zohar, J., Hollander, E., Kasper, S., Möller, H.J., Allgulander, C., Ayuso-Gutierrez, J., Baldwin, D.S., Bunevicius, R., Cassano, G., Fineberg, N., Gabriels, L., Hindmarch, I., Kaiya, H., Klein, D.F., Lader, M., Lecrubier, Y., Lépine, J.P., Liebowitz, M.R., et al., 2008. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. World J. Biol. Psychiatr. 9 (4), 248–312. https://doi.org/10.1080/15622970802465807.

Cénat, J.M., Dalexis, R.D., Guerrier, M., Noorishad, P.G., Derivois, D., Bukaka, J., Birangui, J.P., Adansikou, K., Clorméus, L.A., Kokou-Kpolou, C.K., Ndengeyingoma, A., Sezibera, V., Auguste, R.E., Rousseau, C., 2021. Frequency and correlates of anxiety symptoms during the COVID-19 pandemic in low- and middle-income countries: a multinational study. J. Psychiatr. Res. 132, 13–17. https://doi.org/10.1016/j.jpsychires.2020.09.031.

Czeisler, M.É., Ma, R.I.L., Petrosky, E., Wiley, J.F., Christensen, A., Njai, Rashid, Weaver, M.D., Robbins, R., Facer-Childs, E.R., Barger, L.K., Czeisler, C.A., Howard, M.E., Rajaratnam, S.M.W., 2015. Hospitalization rates and characteristics of children aged <18 Years hospitalized with laboratory-confirmed COVID-19-COVID-NET, 14 states. https://doi.org/10.1101/2020.04.22.20076141v1.

De Lijster, J.M., Dierckx, B., Utens, E.M.W.J., Verhulst, F.C., Zieldorff, C., Dieleman, G.C., Legerstee, J.S., 2017. The age of onset of anxiety disorders: a meta-analysis. In: Canadian Journal of Psychiatry, vol. 62. SAGE Publications Inc, pp. 237–246. https://doi.org/10.1177/0706743716640757. Issue 4.

Ferguson, J.M., 2001. SSRI antidepressant medications: adverse effects and tolerability. Prim. Care Companion J. Clin. Psychiatry 3 (1), 22–27. https://doi:10.4088/pcc.v03n0105.

Goularte, J.F., Serafim, S.D., Colombo, R., Hogg, B., Caldieraro, M.A., Rosa, A.R., 2021. COVID-19 and mental health in Brazil: psychiatric symptoms in the general population. J. Psychiatr. Res. 132, 32–37. https://doi.org/10.1016/j.jpsychires.2020.09.021.

Hamilton, M., 1959. The assessment of anxiety states by rating. Br. J. Med. Psychol. 32 (1), 50–55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x.

Ivachtchenko, A.V., Lavrovsky, Y., Okun, I., 2016. AVN-101: a multi-target drug candidate for the treatment of CNS disorders. J. Alzheim. Dis. 53 (2), 583–620. https://doi.org/10.3233/JAD-151146.

Matza, L.S., Morlock, R., Sexton, C., Malley, K., Feltner, D., 2010. Identifying HAM-A cutoffs for mild, moderate, and severe generalized anxiety disorder. Int. J. Methods Psychiatr. Res. 19 (4), 223–232. https://doi.org/10.1002/mpr.323.

Maust, D., Cristancho, M., Gray, L., Rushing, S., Tjoa, C., Thase, M.E., 2012. Psychiatric rating scales. In: Handbook of Clinical Neurology, vol. 106. Elsevier B.V, pp. 227–237. https://doi.org/10.1016/B978-0-444-52002-9.00013-9.

Pedrosa, A.L., Bitencourt, L., Fróes, A.C.F., Cazumbá, M.L.B., Campos, R.G.B., de Brito, S. B.C.S., Simões e Silva, A.C., 2020. Emotional, behavioral, and psychological impact of the COVID-19 pandemic. In: Frontiers in Psychology, vol. 11. Frontiers Media S.A. https://doi.org/10.3389/fpsyg.2020.566212.

Pollack, M.H., Zaninelli, R., Goddard, A., McCafferty, J.P., et al., 2001. Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial. J. *Clin. Psychiatr.* 62, 350–357. https://www.psychiatrist.com/jcp/depression/paroxetine-treatment-generalized-anxiety-disorder/.

Rickels, K., Zaninelli, R., McCafferty, J., Kevin Bellew, B., Malini Iyengar, M., Sheehan, D., 2003. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. In: Am J Psychiatry, vol. 160. http://ajp.psychiatryonline.org.

Ruscio, A.M., Hallion, L.S., Lim, C.C.W., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Andrade, L.H., Borges, G., Bromet, E.J., Bunting, B., De Almeida, J.M.C., Demyttenaere, K., Florescu, S., De Girolamo, G., Gureje, O., Haro, J.M., He, Y., Hinkov, H., Hu, C., et al., 2017. Cross-sectional comparison of the epidemiology of DSM-5 generalized anxiety disorder across the globe. JAMA Psychiatr. 74 (5), 465–475. https://doi.org/10.1001/jamapsychiatry.2017.0056.

Sartori, S.B., Singewald, N., 2019. Novel pharmacological targets in drug development for the treatment of anxiety and anxiety-related disorders. In: Pharmacology and Therapeutics, vol. 204. Elsevier Inc. https://doi.org/10.1016/j.pharmthera.2019.107402.

Terlizzi, E.P., Villarroel, M.A., 2020. Symptoms of Generalized Anxiety Disorder Among adults:United States, 2019. *Key Findings Data From the National Health Interview Survey, NCHS Data Brief*, N№378. https://www.cdc.gov/nchs/products/index.htm.

Glossary

GAD: Generalized anxiety disorder
HAM-A: Hamilton anxiety scale
HARS: Hamilton Anxiety Rating Scale
HAM-D: Hamilton Depression Scale
CGI-S: Clinical Global Impression Scale
VAS: Visual Analogue Scale
NCHS: National Center for Health Statistics
SSRI: selective serotonin reuptake inhibitors
SNRIs: serotonin-norepinephrine reuptake inhibitors
TCAs: tricyclic antidepressants
MAOIs: monoamine oxidase inhibitors
NaSSA: noradrenergic and specific serotonergic antidepressants
IECs: Independent Ethics Committees
DSM-V: Diagnosis and Statistics of Mental Disorders
IWRS: Interactive Web Response System
AE –: adverse event
SAE –: serious adverse event
TEAE: treatment-emergent adverse event
MITT: Modified Intention to Treat
LME: Linear Mixed Effect Model
LOCF: last observation carried forward,
SD: standard deviation
SE: standard error
BMI: body-mass index