2. SYNOPSIS

Protocol code:	Protocol AB/PD/21
Title:	A multicenter, parallel-group, double-blind, randomized, placebo-controlled, increasing-dose study, to evaluate preliminarily the clinical effects, the safety and tolerability of ABIO 08/01, in patients suffering from panic disorder.
Clinical Design:	Phase IIa, multicenter, parallel-group, double-blind, randomized, placebo-controlled, increasing dose, proof of concept study to assess the preliminary clinical effects, safety and tolerability of ABIO 08/01 in patients suffering from panic disorder. The study plan entailed the involvement of two Italian study centres (then extended to 12) and, by means of a competitive enrolment, aimed to reach a total of 110 treated patients (55 per arm who took at least one dose of treatment). Patients referring to each centre with diagnosis of panic disorder as per Structured Clinical Interview –Clinician Version (SCID-CV) were offered to take part in the study. Upon the release of the consent to participate, the patient entered a screening period to evaluate patient's fulfilment to entry criteria. Following a screening period lasting a maximum of 7 days, those patients deemed eligible to treatment were randomly assigned to ABIO 08/01 or placebo to be started in the morning of the following day. Treated patients should return each week to the site for clinical assessments up to a total of 9 weeks (8 weeks of treatment and one follow up week). During the treatment period the treatment dose could be doubled every two weeks in patients not responding to the therapy. The planned duration of individual patient participation in the study was a minimum of 71 days including the screening period. The enrolment period started on February 2008 and ended on December 2010.
Clinical Phase	IIa
Trial period	February 8th, 2008 - February, 28th 2011
Centres involved	12 Italian sites
Objectives and outcome variables	**<u>Primary objective</u>** To evaluate the effects on PDSS item score after 8 weeks of double-blind treatment. **<u>Secondary objectives</u>** The study secondary objectives are: - to evaluate the effects on PDSS item score during the 8 week double-blind treatment period and at the end of the 1 week follow-up period; - to evaluate the proportion of patients who respond to treatment (response is defined as ≥ 50% decrease in PDSS item score) during the 8 week double-blind treatment period and at the end of the 1 week follow-up period; - to evaluate the effects on CGI, HAM-A, PAS-SR, PAS (Bandelow) during the 8 week double-blind treatment period and at the end of the 1 week follow-up period; - to evaluate the safety and tolerability of ABIO 08/01 over the whole study period; - to assess the compliance of the patient to the treatment.

Subjects Enrolment	One hundred and twenty-two (122) outpatient subjects signed the informed consent and were enrolled into the study entering the screening period between February 2008 and December 2010. Seventeen (17) patients did not pass the screening assessments or withdrew the consent and had no access to the treatment. One hundred and five (105) out of the 122 enrolled patients were randomised and treated; data analysed and results presented are referred to treated patients.
Diagnosis and main criteria for inclusion	**Patients suffering from panic disorder** **Inclusion criteria** • Caucasian male or female between 18 and 60 years of age on the day of the screening visit; • Patient affected by panic disorders (including naïve patients) according to DSM-IV, evaluated with SCID-CV; • PDSS (Panic Disease Severity Scale) total score > 12; • Patient presenting at the screening and baseline visit a total score of at least 20 on the Hamilton Rating Scale for Anxiety (HAM-A) and scores of at least 2 on items 1 (anxious mood) and 2 (tension). However, the patient who had a reduction of at least 20% in the HAM-A total score between the screening visit and the baseline visit was not eligible; • Patient willing and able to understand and sign an Informed Consent form. **Exclusion criteria** • History of alcohol or drug abuse in the last year; • Positive toxicological urinary screening; • Smoker of more than 20 cigarettes/day; • Pregnant or lactating women; • Women of childbearing potential, except for those using appropriate contraceptive methods; • History of allergic response to drugs; • Participation to a previous clinical trial within the past 3 months; • Patient with coexisting primary MDD (major depressive disorder), evaluated by means of HAM-D; • History or presence of any psychotic illness, bipolar disorder, antisocial personality or other severe Axis II disorder, or presenting a clinically significant psychiatric disturbances other than panic disorder; • Patient at immediate risk of committing harm to self or others; • Use of any investigational drug or procedure, any antipsychotic, antiepileptic antihistaminic drug, or the regular use of benzodiazepines or hypnotics within 30 days from baseline; or any use of antidepressants (including TCAs) within 14 days (fluoxetine within 30 days) or any episodic use of an anxiolytic within 7 days before baseline visit; • Electroconvulsive therapy in the year prior to entry; • Treatment with any known enzyme inhibiting or inducing agents (barbiturates, phenothiazines, etc.) within the past 4 weeks; • Patient with treatment resistant panic disorder (defined as lack of response to two different effective drugs both used over six weeks at therapeutic dosages); • Patient positive to HIV test and/or Hepatitis B or C tests; • Patient unwilling to give written informed consent; • Patient drinking excessive amounts of tea, cacao, coffee and/or beverages containing caffeine (> 5 cups/day) or wine (> 0,5 l/day or equivalents for spirits); • In the judgment of the Clinical Investigator subject likely to be not compliant or uncooperative during the study;

	• Lack of an appropriate family support; • Patient with clinically significant diseases other than the disease under study. A significant disease is defined as a disease which in the opinion of the investigator may either put the patient at risk because of participation in the study or may influence the results of the trial or the patient's ability to participate in the study; • Patient with a history of clinically significant liver disease (defined as SGOT or SGPT> 3 times UNL), renal disease (defined as a serum creatinine >2.0 mg/dl) or clinical history of major cardiovascular disease. Severe neurological disease which may impair the results. The only patients with known prior malignant disease who are eligible are those with cured skin cancer (excluding melanoma); • Patient who do not wish to discontinue current, ineffective treatment for panic disorder; • Patient who have undergone psychotherapy during the previous 6 months from the study entry.
Study populations	Two populations were identified to conduct the data analysis: the Safety Analysis and the Full Analysis sets defined as follows: Safety Analysis Set (SAS): it includes all patients who received at least one dose of study product. Full Analysis Set (FAS): it is a subset of the Safety Analysis Set excluding all patients for whom no data on the primary efficacy variable (PDSS score) is available and analysing patients up to their discontinuation from the study. Missing data were not replaced.
Efficacy results	The primary analysis conducted on the FAS population did not demonstrate the ABIO 08/01 is statistically more effective than placebo in improving the PDSS score of patients suffering from panic disorder. Similarly, in none of the other secondary objectives the superiority of ABIO 08/01 was statistically demonstrated, however, efficacy results seems to suggest that ABIO08/01, when administered up to the highest dose of 40 mg, may have an impact on the PDSS and HAM-A scores resulting in an improvement of patient conditions.
Safety results	The total number of patients experiencing an adverse event was 22 (41%) and 31 (61%) in patients receiving ABIO 08/01 or Placebo respectively. Only 30% of patients receiving ABIO 08/01 reported adverse drug reactions (against 35% of patients allocated to the Placebo group). The most recurrent event considered related to the use of ABIO 08/01 were insomnia, headache, dry mouth and dyspepsia. Two serious adverse events were reported. Major depressive disorder and anxious/depressive syndrome, both occurred to patients treated by ABIO 08/01 and considered not related to the treatment but caused by the underlying patient's conditions.

Conclusions	Results of this proof of concept study to preliminarily assess clinical effects, safety and tolerability of ABIO 08/01 in patients suffering from panic disorder are encouraging regarding the safety profile of the drug and stimulating as far as clinical effects are concerned. The analysis on the PDSS, the primary endpoint of this study, did not show any significant difference in patients undergoing 8 weeks of treatment with ABIO 08/01 against patient receiving placebo, however, ABIO 08/01 when administered up to the highest dose of 40 mg daily, showed some trends to clinical effects in PDSS and HAM-A. The strong effect of Placebo could also be evinced from the efficacy results. The safety data collected in this study showed that ABIO 08/01 is well tolerated in patients suffering from panic disorder. No difference in frequency was observed in patients treated with ABIO 08/01 and Placebo and events considered related to the study drug are limited to insomnia, dry mouth, dyspepsia and headache. The safety profile could be considered satisfying.