CLINICAL STUDY REPORT

NEUROFARMAGEN

A randomized controlled clinical trial for assessing the effectiveness of pharmacogenetic information obtained with NEUROFARMAGEN in the treatment of patients with mental disorders

Document type: Clinical Study Report

Development phase: III

1 Study information

Study title: A randomized controlled clinical trial for assessing the effectiveness of pharmacogenetic information with NEUROFARMAGEN in the treatment of patients with mental disorders.

Test drug/investigational product: NEUROFARMAGEN, personalized medicine test

Indication studied: Major depressive disorder.

Study design: A 3-month, multi-centre, randomised, controlled and parallel group clinical trial.

Sponsor: AB Biotics

Protocol identification: Protocol no. AB-GEN-2013, EudraCT no. 2013-002228-18

Development phase of study: III

Study initiation date: FPFV 29-JUL-2014

Study completion date: LPLV 16-OCT-2015

Reference Clinical Research Ethics Committee: Hospital Clínic i Provincial de Barcelona

Principal or Coordinating Investigators:

Principal Investigator: José Manuel Menchón, MD; Hospital Universitari de Bellvitge

Principal Investigator: Víctor Pérez, MD; Hospital del Mar in Barcelona

Company/Sponsor signatory:

Ariana Salavert, PhD; AB Biotics, Bellatera, Barcelona, Spain.

Statement: This study was conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

Report date(s): 16-JUL-2021

Version: Final 2.0

Earlier reports from the same study: NA

2 Synopsis

Name of the Sponsor/Company: AB Biotics S.A.	**Individual Study Table Referring to Module 5 of the Dossier** **Volume:** **Page:** **Study No.:**	**(For National Authority Use only)**
Name of Finished Product: NEUROFARMAGEN®		
Name of Active Ingredient: Personalized medicine test		
STUDY CODE: AB-GEN-2013		
TITLE OF STUDY: A randomized controlled clinical trial for assessing the effectiveness of pharmacogenetic information with NEUROFARMAGEN in the treatment of patients with mental disorders		
INVESTIGATORS: Dr. José Manuel Menchón, Dr. Víctor Pérez, Dr Eduard Vieta, Dr. Enric Alvarez, Dr. Diejo J. Palao, Dr. Josep Gascón, Dr. Josep Cañete, Dr. Jerónimo Saiz, Dr. José Manuel Montes, Dr. Roberto Rodríguez-Jiménez, Dr. Fco. Javier Quintero, Dr. Julio Bobes, Dr. José Manuel Olivares, Dr. Rafael Navarro, Dr. José María Villagrán, Dr. Xavier Labad and Dr. Fermin Mayoral		
STUDY CENTRES: H. U. Bellvitge, Barcelona; H. del Mar, Barcelona; H. Clinic Barcelona; H. Sant Pau, Barcelona; C. S. Parc Taulí, Sabadell, Barcelona; H. Mutua Terrasa, Terrassa, Barcelona; C. S. Maresme, Mataró, Barcelona; H. Ramón y Cajal, Madrid; H. U. Sureste, Madrid; H. 12 Octubre, Madrid; H. U. Infanta Leonor, Madrid; H. U. Central Asturias, Oviedo; C. Hosp. U. Vigo; H. U.San Cecilio, Granada; H. Jerez; Dr. J. M. Villagrán; Institut Pere Mata; Reus, Tarragona; H. U. Carlos Haya, Málaga		
STUDY PERIOD (YEARS): Date of first enrolment/first subject first visit: 29-JUL-2014 Date of last completed/last subject last visit: 16-OCT-2015		
PHASE OF DEVELOPMENT: III		

Name of the Sponsor/Company: AB Biotics S.A.	**Individual Study Table Referring to Module 5 of the Dossier**	**(For National Authority Use only)**
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OBJECTIVE:

To assess the NEUROFARMAGEN test effectiveness in selecting drug treatments for major depressive disorder by the proportion of patients achieving sustained response over a period of 12 weeks. Sustained response was considered when the patient gets a PGI-I of 2 points or less (i.e. “much improved” or “very much improved”) in two consecutive assessments after the last change in treatment.

METHODOLOGY:

This was a randomised, controlled and parallel multi-centre 3-month clinical trial. This study assessed the effectiveness of NEUROFARMAGEN test in selecting drug treatments for major depressive disorder.

NEUROFARMAGEN is a personalized medicine test developed by AB Biotics that enables the specific analysis of Single-Nucleotide Polymorphisms (SNPs) related to the pharmacokinetics and pharmacodynamics of different psychoactive drugs. The test also allows psychiatrists to specify concomitant medications and clinical conditions, and searches for potential drug-drug and drug-clinical condition interactions. The aim of the test is to provide the psychiatrist with information that can help him/her identify the most suitable medication for each patient.

In the study group, the psychiatrist had the results of the NEUROFARMAGEN test as supporting information to help him/her select the best treatment for the patient. In the control patient group, the treatment was selected and prescribed in accordance with routine clinical practice.

NUMBER OF SUBJECTS (planned and analysed):

No. planned:	518
No. included:	520
No. randomised:	316
No. ITT population:	316
No. PP population:	237

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Patients eligible for inclusion in this study had to fulfil all of the following criteria:

1. Patients of either sex over 18 years.
2. Patients with any of the following psychiatric diagnoses according to DSM-IV-TR: bipolar disorder, schizophrenia, major depressive disorder or obsessive-compulsive disorder.
3. Patients who have given their written informed consent to participate in the study. In the case of disabled patients, informed consent of the legal representative of family member.

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4. Patients with a value on the physician-rated clinical global impression scale of severity (CGI-S) equal or higher than 4.

5. Patients who are newly diagnosed and that require antidepressant medication or that are undergoing treatment and require a substitution or addition of medication.

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

NEURFARMAGEN is a personalized medicine test that assesses drug response. It is no an IMP. This trial had been considered a clinical trial since the test results can modify doctor's intention to treat.

DURATION OF TREATMENT:

A 3-month treatment period.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

NA

STATISTICAL METHODS:

The assessment of the primary variable was performed by determining the difference between two patient groups in the proportion of patients who obtained sustained response over a period of three month. It was considered that a patient has a sustained response when submitting a PGI-I score of 2 or less for two consecutive points. Assessment of PGI-I were conducted by monthly telephone interviews. The interviewer did not know the group assigned to the patient, so that the evaluation of the primary endpoint was a double-blind evaluation.

To compare the two patient groups, we contrasted them with a bilateral significance level of 0.05.

SUMMARY AND CONCLUSION(S):

No statistically significant differences were observed between patient groups in the proportion of subjects achieving sustained response. However, the number of patients with positive response to treatment at 12 weeks (end of follow-up) was significantly higher in the study group than in the control group.

Significant differences between study groups were observed for the frequency, intensity and burden of side effects items scores from visit 1 to visit 2, with patients in the study group presenting a better improvement in tolerance. Additionally, patients in the study group experienced a greater improvement in social disability subscale of SDI, in disease severity according CGI-S (both physician-rated during visits and patient-rated during phone interviews), in severity of depression with HAM-D, and a higher treatment satisfaction with the SATMED-Q.

Nevertheless, investigator evaluated the usefulness of the NEUROFARMAGEN test with a mean score of 4.01 through a Likert scale of five points (corresponding to useful).

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The safety profile was similar in the study and control groups.		

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4 List of abbreviations and definition of terms

AE	Adverse event
CDI	Children Depression Inventory
CI	Confidence interval
CGI	Clinical Global Impression
CRF	Case report form
EMA	European Medicines Agency
FDA	Food and Drug Administration
GWAS	Genome Wide Association Study
HAM-D	Hamilton Depression Rating Scale
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ITT	Intention-to-treat population
NA	Not applicable
PGI-I	Patient Global Impression of Improvement
PP	Per-protocol population
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDI	Sheehan Disability Inventory
VAS	Visual analogic scale

5 Ethics

5.1 Independent ethics committee or institutional review board

The study protocol and all amendments were reviewed by the Independent Ethics Committee (IEC) of Hospital Clínic I Provincial de Barcelona.

5.2 Ethical conduct of the study

The study was conducted according to the ethical principles of the Declaration of Helsinki.

5.3 Patient information and consent

Informed consent was obtained from each patient in writing at screening, before conducting any study-related procedures. All subjects received written and verbal information regarding the study. The given information emphasised that participation in the study was voluntary and that the subject could withdraw from the study at any time and for any reason. All subjects were given the opportunity to ask questions about the study and were given sufficient time to decide whether to participate in the study.

6 Introduction

Mental disorders are very common and represent a major health problem worldwide, with a great impact on social and economic level. The World Health Organization (WHO) estimated in 2002 that 154 million people globally suffer from depression, 25 million people from schizophrenia; 91 million people are affected by alcohol use disorders and 15 million by drug use disorders (1).

An important part of the patient treatment with neuropsychiatric disorders is based on the use of pharmacological drugs; however, patients do not always achieved a complete response[2]. For example, up to 60-70% of patients with depressive disorders do not respond fully to antidepressant drugs and 40% do not get any response (2, 3). In addition, adverse effects of antidepressant treatment are common (40-90%) and can not be previously predicted (4, 5).

It has been described that the genetic profile can alter the pharmacokinetics of many antidepressants, affecting the therapeutic response and facilitating the occurrence of adverse effects (6). Certain genetic factors can contribute to the response of antidepressants in approximately 50% of cases (4). It has also been reported that there are significant interindividual differences in clinical response and adverse effects of antipsychotic drugs (7).

NEUROPHARMAGEN is a personalized medicine test developed by AB Biotics that enables the specific analysis of Single-Nucleotide Polymorphisms (SNP) related to the pharmacokinetics and pharmacodynamics of different psychoactive drugs (8). This information is translated into drug-specific actionable recommendations, and can be combined with drug-drug and drug-medical condition interactions and alerts in the test reporting platform. The aim of the test is to provide the psychiatrist with information that can help him/her identify the most suitable medication for each patient.

NEUROFARMAGEN analyses the patient's saliva for genetic variations that indicate responses to different drugs. The test identifies SNPs in a set of 41 genes for which there is genetic information related to psychoactive drugs.

Because of the high prevalence of mental disorders worldwide (1, 9) and the limited response that these patients have to pharmacological treatments, application of pharmacogenetics in clinical practice could represent a step forward to improve efficiency in the selection of the best treatment to each patient (10-12). The use of pharmacogenetics in clinical practice is still widespread and only few clinical trials analysed its application. In this context, the present study will help to evaluate the effectiveness of NEUROFARMAGEN personalized medicine test in the selection of pharmacological treatments within the framework of psychiatric consultation. Thus, the main objective was to evaluate the efficacy of this test in the selection of the pharmacological treatments for patients with major depression, by the sustained response to treatment.

The selection of the follow-up period was made considering the pharmacogenetic analysis with NEUROFARMAGEN could present a clear advantage of the time needed for patients to achieved stabilization.

7 Study objectives

7.1 Primary objective(s)

The primary objective was to assess NEUROFARMAGEN test effectiveness in selecting drug treatments for major depressive disorder by the proportion of patients achieving sustained response over a period of 12 weeks. Sustained response was considered when the patient gets a PGI-I of 2 points or less (i.e. "much improved" or "very much improved") in two consecutive assessments after the last change in treatment.

7.2 Secondary objectives

- To describe the differences in the proportion of patients who discontinued treatment between groups.
- To describe differences in tolerability between treatment groups.
- To describe changes in patient-perceived disability between groups.
- To describe differences in changes in severity of the patient's disease by patient and investigator between groups.
- To describe differences in time to file a PGI-I of 2 or less points between groups.
- To describe differences in the clinical course of the patient according to specific scales of each of the diseases among groups.
- To describe differences in satisfaction with treatment by patients.
- Population subgroup analysis of the primary and secondary objective listed above
- Cost-effectiveness of NEUROFARMAGEN

8 Investigational plan

8.1 Study design

This was a randomised, controlled and parallel multi-centre 3-month clinical trial. This study assessed the effectiveness of NEUROFARMAGEN test in selecting drug treatments for major depressive disorder.

NEUROFARMAGEN is a personalized medicine test developed by AB Biotics that enables the specific analysis of Single-Nucleotide Polymorphisms related to the pharmacokinetics and pharmacodynamics of different psychoactive drugs. The aim of the test is to provide the psychiatrist with information that can help him/her identify the most suitable medication for each patient.

In the study group, the psychiatrist had the results of the NEUROFARMAGEN test as supporting information to help him/her select the best treatment for the patient. In the control patient group, the treatment was selected and prescribed in accordance with routine clinical practice.

A total of 520 patients with major depressive disorder were expected to be included.

Patients participated in the study for 12 weeks. The study consisted of 3 face-to-face visits (baseline visits, visit 2 at 6 weeks, visit 3 at 12 weeks), and 3 telephone contacts (at 4, 8 and 12 weeks of study).

8.2 Population

Patients over 18 years with a diagnosed psychiatric disorder that required medication were included in the study.

8.2.1 Inclusion criteria

6. Patients of either sex over 18 years.
7. Patients with any of the following psychiatric diagnoses according to DSM-IV-TR: bipolar disorder, schizophrenia, major depressive disorder or obsessive-compulsive disorder.
8. Patients who had given their written informed consent to participate in the study. In the case of disabled patients, informed consent of the legal representative of family member.
9. Patients with a value on the clinical global impression scale of severity (CGI-S) according to the doctor equal or more than 4.
10. Patients who were newly diagnosed and required medication or were undergoing treatment and required a substitution or addition of medication with an antidepressant.

8.2.2 Exclusion criteria

1. Patients who are expected no to be able to complete the study.
2. Patients who are actively participating or have participated in the last three months in another clinical trial.
3. Patients who are pregnant or breastfeeding, or patients who intend to become pregnant in the next 12 months.
4. Patients who are or require treatment with quinidine, cinacalcet and/or terbinafine (potent CYP2D6 inhibitors).

8.3 Treatment

8.3.1 Investigational and control treatment

NEURFARMAGEN is a personalized medicine test that assesses drug response. It is not an IMP. This study had been considered a clinical trial since the test results can modify doctor's intention to treat.

Study group: In the study patient group, the psychiatrist had the results of the NEUROPHARMAGEN personalized medicine test as supporting information to help him/her select the best treatment for the patient.

Control group: In the control patient group, the treatment was selected and prescribed in accordance with routine clinical practice

8.3.2 Treating the patient

8.3.2.1 Description of blinding methods

In the present study, both patients and telephone interviewer were blind to the patient allocation (in the intervention group or the control group). Saliva samples were collected from all participants at pre-randomization visit for pharmacogenetic analysis with NEUROFARMAGEN test. The psychiatrist had the results of the NEUROPHARMAGEN at baseline for the patients in the study group, and at the final visit for the control patient group. Thus, the psychiatrist knew whether patient belong to the study group or the control group, but patients did not have this information.

At the final visit genetic analysis results were given to all patients.

8.3.2.2 Method of assigning patients to treatment group

Randomization of patients was done centrally by the statistics department of the CRO and was completely independent and blind to the patients and to the responsibles for telephone follow-up, but not to investigators responsible for visiting to the patients.

A balanced list by centre was performed. Patients were included in one of the two groups with a probability of 0.5.

8.3.3 Withdrawal of patients from assessment

Patients were free to withdraw from the study at any time without giving a reason. Patients were advised that if they requested to withdraw from the study, at any time during the trial,

then this would have no negative consequences.

The investigator could also withdraw patients from the trial if they deemed it appropriate for safety or ethical reasons or if it was considered to be to be detrimental to the well-being of the patient. Patients who withdrew or were withdrawn underwent a final evaluation at [visit]. Patients who did not complete the study could not have been replaced.

Full documentation was made of any withdrawals that occurred during the study in the CRF. The Investigator documented the date and time of the withdrawal and results of any assessments made at this time.

8.3.4 Treatment exposure and compliance

Investigators were asked to describe whether or not the patient complied with the prescribed medication for the major depressive disorder.

8.4 Efficacy, safety and other assessments

8.4.1 Visit schedule

The study visits and procedures are presented in Table 1 which lists all of the assessments and indicates with an “X” the visits at which they were performed.

Table 1. Evaluation and visit schedule

Visit number	Pre-randomisation	Visit 1 (baseline)	Visit 2	Visit 3 (Final)	Telephone con.
Days	-2 to 4 weeks		6 weeks (± 1 week)	12 weeks (± 1 week)	4,8,12 weeks*
Eligibility criteria	X				
Informed consent	X				
Socio-demographic history	X				
Treatment history	X				
Saliva sample	X	X			
Treatment for major depressive disorder	X	X	Only if medication changed		
Concomitant medication	X		Only if medication changed		
Inclusion/exclusion criteria		X			
Randomisation		X			
Delivery of NEUROFARMAGEN results		Study group		Rest of patients	
PGI-I		X	X	X	X
SDI		X	X	X	X
CGI-S, doctor and patient	X	X	X	X	X**
STAMED-Q		X	X	X	
FIBSER		X	X	X	
HAM-D		X	X	X	
Liker scale				X	
Adverse events			If applicable		
Additional visits			If applicable		
Study completion		Only if interrupted		X	

* Telephone contact at 12 weeks were performed 2-3 days before final visit with investigator.** Only patient-rated CGI

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8.4.2 Efficacy assessments

8.4.2.1 Primary efficacy assessment

The primary endpoint of the study was to test the effectiveness of NEUROFARMAGEN in the selection of pharmacological treatments for major depression by the proportion of patients who obtained sustained response over a period of 12 weeks. The study was performed by comparing the group of patients with access to test information at baseline and patients without access to this information until the end of follow up period.

Sustained response was evaluated over the 12-week follow-up study by the score on the PGI-I scale. It was considered that a patient has a sustained response when submitting a PGI-I score of 2 or less (i.e. “much improved” or “very much improved”) for two consecutive points. Assessments were conducted monthly telephone. The interviewer will not know the group assigned to the patient, so that the evaluation of the primary endpoint was a double-blind evaluation.

8.4.2.2 Secondary efficacy assessments

- Tolerability through FIBSER (Frequency, Intensity and Burden of Side Effects Rating) scale. The scale consists of 3 questions with scores ranging from 0 (no side effects / no impairment) to 6 (intolerable / unable to function / present all of the time).
- Study of disability under the SDI (Sheehan Disability Inventory) scale. SDI is a questionnaire that can be self-administered to measure the disability of patients with mental disorders. It has 3 sub-scales that are scored independently (disability - 3 items, stress - 1 item and perceived social support - 1 item). As each item is scored using a Likert scale from 0 to 10, the maximum possible score is 30.
- Disease severity by the CGI-S (Clinical Global Impression-Severity) scale. The Clinical Global Impression scale (CGI-S, Clinical Global Impression-Severity). CGI-S is a descriptive scale that provides qualitative information on the severity of the patient's illness. It assesses the severity of the illness using a 7-point Likert scale that runs from 1 (not at all ill) to 7 (among the most extremely ill patients). In this study, both the self-rated (whereby the patient rates his/her own situation) and the doctor-rated versions will be administered so that the doctor can assess the severity of the condition.

- Depression through HAM-D (Hamilton Rating Scale for Depression). HAM-D rates the clinical severity of depression. It has 17 questions, each with three to five possible answers, with scores ranging from 0 to 2 or from 0 to 4, respectively. The total score ranges from 0 to 52 and cut-off scores can be used to classify the depressive disorder.
- Satisfaction with treatment as SATMED-Q (Treatment Satisfaction with Medicines Questionnaire). It is a 17-item questionnaire and is a valid scale for any chronic or long-term condition. It is a self-administered questionnaire on treatment satisfaction and it assesses the following areas or dimensions: side effects; effectiveness of the medication; convenience of the medication; impact of the medication on everyday life; medical follow-up of the disease; and the patient's general opinion regarding his/her condition and the medication. All items are assessed using a 5-point Likert scale that runs from "no, not at all" with a value of 0 to "yes, very much" with a value of 4.

All these variables were purely descriptive. We described the total score and analysed the comparison of the evolution of the two patient groups during the study.

8.4.3 Safety assessments

Safety assessments consisted on the control and collection of all adverse events (AEs) and serious adverse events (SAEs).

Full information about the definition of AEs and SAEs, the procedures for reporting them and the assessment of other safety variables is given in the study protocol.

8.5 Data quality assurance

8.5.1 Data collection

An on-line electronic CRF (e-CRF) was created in which the investigators recorded all the data directly via a web page. The data was entered in the e-CRF by the investigator or person authorized by him/her.

Source documents were those that provide evidence of the patient’s existence and ensure the integrity of the data collected in the CRF.

All the data on the patient’s participation in the study and clinical condition during the study period was recorded / filed in the patient’s medical record. These data were defined as source

data. Medical information relevant for the assessment of efficacy and safety was transcribed in the e-CRF specifically designed for the study and was also recorded in the medical record.

e-CRF data from source documents had to be consistent with these; any discrepancy had to be justified.

8.6 Statistical methods

8.6.1 Data analysis

Descriptive statistics including "n", range, and median for continuous variables and frequencies and percentages for categorical variables were provided unless otherwise specified.

Further technical details and discussion of the following statistical considerations was documented in the Statistical Analysis Plan, which was finalized prior to database lock and the analysis.

The assessment of the primary variable was performed by determining the proportion of patients who obtained sustained response over a period of 12 weeks. The analysis was conducted by comparing the group of patients with access to test information at baseline and patients without access to this information until the end of follow-up period.

Assessments were conducted monthly telephone. The interviewer did not know the group assigned to the patient, so that the evaluation of the primary endpoint was a single-blind evaluation by blinded.

8.6.2 Analysis sets

Intention-to-treat population (ITT): included all randomised patients.

Per-protocol population (PP): all patients in the ITT population who have at least two efficacy assessments during the study and have no major protocol deviations.

8.6.3 Sample size calculation

A simple size of 180 patients in each group were needed to detect a difference of 15% in the proportion of patients with sustained response, with a statistical power of 80%, and a significance level of 5%. Estimating a 20% loss to follow-up and a 20% not randomised

(because of not fulfilling randomisation criteria), a total of 259 patients were needed to be included in each study group (518 patients in total).

9 Study patients

9.1 Disposition of patients

Of the 520 patients included in the study, a total of 316 were randomized.

Table 2. Patient disposition

Variable		Total
Included patients	Total	520 (100.0%)
Randomized patients	Total	520 (100.0%)
	Randomized	316 (60.8%)
	Not randomized	204 (39.2%)

10 Efficacy evaluation

10.1 Data sets analysed

The intent-to-treat (ITT) population analysed 316 patients and the per protocol (PP) population analysed 237 patients. The percentage of participants not randomised and lost to follow-up was higher than expected. For this reason, the low number of patients included in PP population did not ensure that the test had high statistical power. Thus, the results reported herein are based on the ITT population.

The data sets analysed are presented in Table 3.

Table 3. Analysis patient sets

Analysis population	Total N=56	Study group N=67	Control group N=76
Intent-to-treat (ITT)	316	155 (95.52%)	161 (0.00%)
Per protocol (PP)	237 (75.0%)	120 (77.4%)	117 (72.7%)

The numbers of patients who meet the eligibility and inclusion criteria are described in Section 13, Tables 26 and 27. Figure 1 show a flow chart of patient disposition (Section 13).

10.2 Demographic and other baseline characteristics

Overall, demographic characteristics collected at baseline were similar between patient groups. The majority of evaluated patients (n = 316) were women (n = 201, 63.6%) and Caucasian (n = 292, 92.4%), with a mean age of 51.2 years (± 12.6).

Table 4 – Demographic data - ITT set

Variable		Total	Study group	Control group	p-value (1)
Age (years)	N	316	155	161	0.4801
	Mean (SD)	51.23 (12.60)	51.74 (12.05)	50.74 (13.12)	
	Median	51.0	52.0	51.0	
	(P25; P75)	(42.0; 60.0)	(43.0; 60.0)	(41.0; 59.0)	
	(Min; Max)	(18.0; 88.0)	(19.0; 83.0)	(18.0; 88.0)	
	N missing	0	0	0	
Gender	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.9239
	Male	115 (36.4%)	56 (36.1%)	59 (36.6%)	
	Female	201 (63.6%)	99 (63.9%)	102 (63.4%)	
Menopause	Total	201 (100.0%)	99 (100.0%)	102 (100.0%)	0.9113
	Yes	119 (59.2%)	59 (59.6%)	60 (58.8%)	
	No	82 (40.8%)	40 (40.4%)	42 (41.2%)	
Ethnicity	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.6215
	Caucasian	292 (92.4%)	145 (93.5%)	147 (91.3%)	
	Hispanic	17 (5.4%)	7 (4.5%)	10 (6.2%)	
	Asian	1 (0.3%)		1 (0.6%)	
	Middle East	1 (0.3%)	1 (0.6%)		
	Others	5 (1.6%)	2 (1.3%)	3 (1.9%)	

(1) Chi-squared test o ANOVA according data type

No statistically significant differences were noted in the other socio-demographic characteristics (eg, weight, education, living situation, or job activity). The majority of patients were married and employed. Data are available in Section 13, Tables 27-29.

The main disease characteristics were also compared by patient group. All analysed patients reported a major depressive disorder with a mean duration period from diagnosis of 60.2 months (± 94.4) and a median of 14.1 months. A total of 266 patients received previous treatment for the current episode, while 50 patients were antidepressant-naïve. On average, patients had received mean of 2.6 previous treatment lines (Table 5).

Table 5 – Main psychiatric diagnosis- ITT set

Variable		Total	Study group	Control group	p-value (1)
Major depressive disorder	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	
	Yes	316 (100.0%)	155 (100.0%)	161 (100.0%)	
Time since diagnosis	N	316	155	161	0.8050
	Mean (DE)	60.23 (94.44)	58.89 (93.29)	61.52 (95.80)	
	Median	14.1	10.8	16.0	
	(P25; P75)	(2.3; 77.3)	(2.3; 72.5)	(2.5; 78.1)	
	(Min; Max)	(0.5; 505.1)	(0.5; 460.3)	(0.5; 505.1)	
	N missing	0	0	0	
Depressive disorder	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.7035
	Major depressive disorder	294 (93.0%)	146 (94.2%)	148 (91.9%)	
	Dysthymic disorder	13 (4.1%)	5 (3.2%)	8 (5.0%)	
	Not specified depressive disorder	9 (2.8%)	4 (2.6%)	5 (3.1%)	
Previous treatment	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.8836
	Yes	266 (84.2%)	130 (83.9%)	136 (84.5%)	
	No	50 (15.8%)	25 (16.1%)	25 (15.5%)	
Previous treatment lines	N	315	154	161	0.9175
	Mean (DE)	2.56 (2.22)	2.55 (2.35)	2.57 (2.10)	
	Median	2.0	2.0	2.0	
	(P25; P75)	(1.0; 3.0)	(1.0; 3.0)	(1.0; 4.0)	
	(Min; Max)	(0.0; 15.0)	(0.0; 15.0)	(0.0; 10.0)	

Table 5 – Main psychiatric diagnosis- ITT set

Variable		Total	Study group	Control group	p-value (1)
	N missing	1	1	0	
(1) Chi-squared test o ANOVA according data type					

Approximately one third of patients had toxic habits. Smoking was reported in 80.8%; alcohol in 33.7%, and other drug use in 5.1% of them. Table 6 summarizes the toxic habits information by patient group.

Table 6 – Toxic habits - ITT set

Variable		Total	Study group	Control group	p-value (1)
Toxic habits	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.0558
	Yes	104 (32.9%)	59 (38.1%)	45 (28.0%)	
	No	212 (67.1%)	96 (61.9%)	116 (72.0%)	
Smoke	Total	104 (100.0%)	59 (100.0%)	45 (100.0%)	0.1826
	Yes	84 (80.8%)	45 (76.3%)	39 (86.7%)	
	No	20 (19.2%)	14 (23.7%)	6 (13.3%)	
Alcohol	Total	104 (100.0%)	59 (100.0%)	45 (100.0%)	0.9518
	Yes	35 (33.7%)	20 (33.9%)	15 (33.3%)	
	No	69 (66.3%)	39 (66.1%)	30 (66.7%)	
Other drugs regularly	Total	315 (100.0%)	154 (100.0%)	161 (100.0%)	0.5455
	Yes	16 (5.1%)	9 (5.8%)	7 (4.3%)	
	No	299 (94.9%)	145 (94.2%)	154 (95.7%)	
	N missing	1	1	0	
(1) Chi-squared test					

10.3 Measures of treatment compliance

Treatment compliance was also similar between patient groups. The majority of patients complied with their psychiatric medication according study investigator (n=249, 87.1%).

Table 7 – Therapeutic compliance- ITT set

Variable		Total	Study group	Control group	p-value (1)
Compliance – Whole study	Total	286 (100.0%)	145 (100.0%)	141 (100.0%)	0.9322
	Yes	249 (87.1%)	126 (86.9%)	123 (87.2%)	
	No	37 (12.9%)	19 (13.1%)	18 (12.8%)	
	N missing	30	10	20	
Compliance - Visit 1	Total	315 (100.0%)	155 (100.0%)	160 (100.0%)	0.7340
	Yes	308 (97.8%)	152 (98.1%)	156 (97.5%)	
	No	7 (2.2%)	3 (1.9%)	4 (2.5%)	
	N missing	1	0	1	
Compliance - Visit 2	Total	296 (100.0%)	148 (100.0%)	148 (100.0%)	0.8209
	Yes	275 (92.9%)	137 (92.6%)	138 (93.2%)	
	No	21 (7.1%)	11 (7.4%)	10 (6.8%)	
	N missing	20	7	13	
Compliance - Visit 3	Total	291 (100.0%)	146 (100.0%)	145 (100.0%)	0.3229
	Yes	273 (93.8%)	139 (95.2%)	134 (92.4%)	
	No	18 (6.2%)	7 (4.8%)	11 (7.6%)	
	N missing	25	9	16	

(1) Chi-squared test

10.4 Efficacy results and tabulations of individual patient data

10.4.1 Analysis of efficacy

The primary efficacy variable was the sustained response to treatment, considered when the patient had a PGI-I score of 2 or less on two consecutive assessments after the last change of treatment.

10.4.1.1 Primary efficacy results

No statistically significant differences were observed between patient groups in the proportion of subjects achieving sustained response at 12 weeks (Table 8).

The number of patients with positive response to treatment at 12 weeks was significantly higher in the study group than in the control group (47.8% vs 36.1%, p = 0.0476, OR = 1.62 [95%CI 1.00-2.61]) (Table 8).

There were no significant differences between groups in the proportion of subjects achieving sustained response at 12-week face-to-face visit, nor in the proportion of patients with a positive response at 6 weeks (Table 9).

Table 8 – Response at 12 weeks - ITT set

Variable		Total	Study group	Control group	p-value (1)
Sustained response at 12 weeks - Telephone contact	Total	294 (100.0%)	143 (100.0%)	151 (100.0%)	0.4735
	Yes	107 (36.4%)	55 (38.5%)	52 (34.4%)	
	No	187 (63.6%)	88 (61.5%)	99 (65.6%)	
	N missing	22	12	10	
Response at 12 weeks - Telephone contact	Total	280 (100.0%)	136 (100.0%)	144 (100.0%)	**0.0476**
	Yes	117 (41.8%)	65 (47.8%)	52 (36.1%)	
	No	163 (58.2%)	71 (52.2%)	92 (63.9%)	
	N missing	36	19	17	

(1) Chi-squared test

Table 9 - Response at 6 weeks - ITT set

Variable		Total	Study group	Control group	p-value (1)
Response at 6 weeks - Telephone contact	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.5830
	Yes	113 (39.0%)	58 (40.6%)	55 (37.4%)	
	No	177 (61.0%)	85 (59.4%)	92 (62.6%)	
	N missing	26	12	14	

(1) Chi-squared test

10.4.1.2 Secondary efficacy results

Secondary efficacy outcomes included changes in FIBSER scale (tolerability), SDI scale (disability), CGI-S (severity of illness), HAM-D scale (depression), SATMED-Q scale (treatment satisfaction) and cost-effectiveness analysis of NEUROFARMAGEN.

FIBSER Scale - Frecuency, Intensity and Burden of Side Effects Rating

The scale consists of 3 questions with scores ranging from 0 (no side effects / no impairment) to 6 (intolerable / unable to function / present all of the time).

Significant differences between study groups were observed for the frequency, intensity and burden of side effects items scores from visit 1 to visit 2. Additionally, there were significant differences between patient groups in intensity and burden of side effects from visit 1 to 3 (Table 10). In all cases, patients in the study group showed a better tolerance (score decrease), particularly at 6 weeks of treatment: reported fewer side effects, experienced side effects at lower intensities and at lower levels of impairment compared with their baseline scores.

Table 10 – Change in FIBSER from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
FIBSER Frequency - Visit 1 to 2	N	290	145	145	**0.0316**
	Mean (DE)	-0.20 (2.60)	-0.52 (2.55)	0.13 (2.62)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-2.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-6.0; 6.0)	(-6.0; 6.0)	(-6.0; 6.0)	
	N missing	26	10	16	
FIBSER Frequency - Visit 1 to 3	N	281	141	140	0.1280
	Mean (DE)	-0.47 (2.37)	-0.68 (2.35)	-0.25 (2.38)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-2.0; 0.0)	(-2.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-6.0; 6.0)	(-6.0; 6.0)	(-6.0; 6.0)	
	N missing	35	14	21	
	N	280	141	139	0.1306
	Mean (DE)	-0.33 (2.12)	-0.14 (2.12)	-0.53 (2.11)	

Table 10 – Change in FIBSER from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
FIBSER Frequency - Visit 2 to 3	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-1.0; 1.0)	(-1.0; 0.0)	
	(Min; Max)	(-6.0; 6.0)	(-6.0; 6.0)	(-6.0; 6.0)	
	N missing	36	14	22	
FIBSER Intensity - Visit 1 to 2	N	290	145	145	**0.0244**
	Mean (DE)	-0.14 (2.17)	-0.43 (2.12)	0.14 (2.19)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-1.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-6.0; 6.0)	(-6.0; 6.0)	(-5.0; 6.0)	
	N missing	26	10	16	
FIBSER Intensity - Visit 1 to 3	N	281	141	140	**0.0303**
	Mean (DE)	-0.34 (1.98)	-0.60 (2.01)	-0.09 (1.92)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-2.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-6.0; 6.0)	(-6.0; 5.0)	(-5.0; 6.0)	
	N missing	35	14	21	
FIBSER Intensity - Visit 2 to 3	N	280	141	139	0.4200
	Mean (DE)	-0.26 (1.67)	-0.18 (1.73)	-0.34 (1.60)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-1.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-6.0; 5.0)	(-6.0; 5.0)	(-6.0; 4.0)	
	N missing	36	14	22	
FIBSER Burden of side effects - Visit 1 to 2	N	290	145	145	**0.0105**
	Mean (DE)	-0.16 (2.00)	-0.46 (2.03)	0.14 (1.93)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-1.0; 0.0)	(0.0; 1.0)	
	(Min; Max)	(-5.0; 6.0)	(-5.0; 6.0)	(-4.0; 6.0)	
	N missing	26	10	16	
	N	281	141	140	**0.0125**
	Mean (DE)	-0.30 (1.88)	-0.57 (2.00)	-0.01 (1.72)	

Table 10 – Change in FIBSER from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
FIBSER Burden of side effects - Visit 1 to 3	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-2.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-6.0; 5.0)	(-6.0; 5.0)	(-4.0; 5.0)	
	N missing	35	14	21	
FIBSER Burden of side effects - Visit 2 to 3	N	280	141	139	0.6685
	Mean (DE)	-0.18 (1.58)	-0.13 (1.71)	-0.22 (1.44)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-1.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-6.0; 5.0)	(-6.0; 5.0)	(-6.0; 4.0)	
	N missing	36	14	22	

(1) ANOVA

SDI - Sheehan Disability Inventory

SDI is a questionnaire that can be self-administered to measure the disability of patients with mental disorders. It has 3 sub-scales that are scored independently (disability - 3 items, stress - 1 item and perceived social support - 1 item). As each item is scored using a Likert scale from 0 to 10, the maximum possible score is 30.

There were no significant differences between the two patient groups regarding the mean change in SDI scale, except for the change in social support perceived from visit 1 to 3 (p=0.0479). Patients in the study group experienced a greater increase from baseline compared with patients in control group (0.76 ± 2.96 vs 0.06 ± 2.94) (Table 11).

Table 11 – Change in SDI from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
SDI Disability - Visit 1 to 2	N	290	144	146	0.8606
	Mean (DE)	-2.99 (7.35)	-2.91 (7.04)	-3.06 (7.66)	
	Median	-2.0	-2.0	-1.0	

Table 11 – Change in SDI from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
	(P25; P75)	(-6.0; 1.0)	(-6.0; 0.0)	(-6.0; 1.0)	
	(Min; Max)	(-30.0; 27.0)	(-25.0; 27.0)	(-30.0; 24.0)	
	N missing	26	11	15	
SDI Disability - Visit 1 to 3	N	282	141	141	0.4721
	Mean (DE)	-4.31 (8.10)	-4.66 (8.32)	-3.96 (7.89)	
	Median	-3.0	-3.0	-2.0	
	(P25; P75)	(-9.0; 0.0)	(-9.0; 0.0)	(-8.0; 0.0)	
	(Min; Max)	(-30.0; 21.0)	(-30.0; 20.0)	(-26.0; 21.0)	
	N missing	34	14	20	
SDI Disability - Visit 2 to 3	N	279	140	139	0.6387
	Mean (DE)	-0.99 (7.12)	-1.19 (7.09)	-0.79 (7.17)	
	Median	0.0	-1.0	0.0	
	(P25; P75)	(-5.0; 3.0)	(-5.0; 2.0)	(-4.0; 3.0)	
	(Min; Max)	(-27.0; 24.0)	(-27.0; 20.0)	(-23.0; 24.0)	
	N missing	37	15	22	
SDI Stress - Visit 1 to 2	N	291	145	146	0.9698
	Mean (DE)	-1.27 (2.68)	-1.26 (2.63)	-1.27 (2.73)	
	Median	-1.0	-1.0	-1.0	
	(P25; P75)	(-3.0; 0.0)	(-2.0; 0.0)	(-3.0; 0.0)	
	(Min; Max)	(-10.0; 10.0)	(-10.0; 10.0)	(-10.0; 7.0)	
	N missing	25	10	15	
SDI Stress - Visit 1 to 3	N	283	142	141	0.2862
	Mean (DE)	-1.47 (3.09)	-1.67 (3.30)	-1.28 (2.86)	
	Median	-1.0	-1.0	-1.0	
	(P25; P75)	(-3.0; 0.0)	(-3.0; 0.0)	(-3.0; 0.0)	
	(Min; Max)	(-10.0; 10.0)	(-10.0; 10.0)	(-10.0; 6.0)	
	N missing	33	13	20	
SDI Stress - Visit 2 to 3	N	279	140	139	0.5233
	Mean (DE)	-0.22 (2.97)	-0.33 (2.93)	-0.10 (3.02)	
	Median	0.0	0.0	0.0	

Table 11 – Change in SDI from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
	(P25; P75)	(-2.0; 1.0)	(-2.0; 1.0)	(-2.0; 1.0)	
	(Min; Max)	(-10.0; 10.0)	(-9.0; 10.0)	(-10.0; 10.0)	
	N missing	37	15	22	
SDI Social support perceived - Visit 1 to 2	N	291	145	146	0.1979
	Mean (DE)	0.22 (2.60)	0.41 (2.43)	0.02 (2.75)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 1.0)	(-1.0; 2.0)	(-1.0; 1.0)	
	(Min; Max)	(-10.0; 9.0)	(-5.0; 8.0)	(-10.0; 9.0)	
	N missing	25	10	15	
SDI Social support perceived - Visit 1 to 3	N	283	142	141	**0.0479**
	Mean (DE)	0.41 (2.96)	0.76 (2.96)	0.06 (2.94)	
	Median	0.0	1.0	0.0	
	(P25; P75)	(-1.0; 2.0)	(-1.0; 2.0)	(-1.0; 1.0)	
	(Min; Max)	(-10.0; 9.0)	(-10.0; 9.0)	(-10.0; 8.0)	
	N missing	33	13	20	
SDI Social support perceived - Visit 2 to 3	N	279	140	139	0.3682
	Mean (DE)	0.12 (2.58)	0.26 (2.60)	-0.02 (2.56)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 1.0)	(-0.5; 1.0)	(-1.0; 1.0)	
	(Min; Max)	(-10.0; 10.0)	(-10.0; 10.0)	(-9.0; 8.0)	
	N missing	37	15	22	

(1) ANOVA

CGI-S scale - Clinical Global Impression-Severity

CGI-S is a descriptive scale that provides qualitative information on the severity of the patient's illness. It assesses the severity of the illness using a 7-point Likert scale that runs from 1 (not at all ill) to 7 (among the most extremely ill patients).

There were significant differences in the CGI-S mean changes between visit 1 to visit 3 (p=0.0425). Patients in the study group experienced a greater improvement (score decrease) in severity compared to patients in the control group (Table 12), as assessed by the physician (-1.14 ± 1.13 and -0.87 ± 1.13, in the study and control groups, respectively). (Table 12).

Table 12 – Change in CGI-S from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
Doctor-rated CGI-S- Visit 1 to 2	N	295	147	148	0.1433
	Mean (DE)	-0.60 (0.86)	-0.67 (0.85)	-0.53 (0.86)	
	Median	-1.0	-1.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-1.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-4.0; 2.0)	(-4.0; 1.0)	(-3.0; 2.0)	
	N missing	21	8	13	
Doctor-rated CGI-S- Visit 1 to 3	N	287	144	143	**0.0425**
	Mean (DE)	-1.00 (1.14)	-1.14 (1.13)	-0.87 (1.13)	
	Median	-1.0	-1.0	-1.0	
	(P25; P75)	(-2.0; 0.0)	(-2.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-5.0; 1.0)	(-5.0; 1.0)	(-4.0; 1.0)	
	N missing	29	11	18	
Doctor-rated CGI-S- Visit 2 to 3	N	281	142	139	0.2116
	Mean (DE)	-0.37 (0.95)	-0.44 (0.93)	-0.30 (0.96)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-1.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-4.0; 2.0)	(-4.0; 2.0)	(-4.0; 2.0)	
	N missing	35	13	22	
Self-rated CGI-S- Visit 1 to 2	N	295	147	148	0.3595
	Mean (DE)	-0.71 (1.12)	-0.77 (1.09)	-0.65 (1.16)	
	Median	0.0	-1.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-1.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-4.0; 2.0)	(-4.0; 2.0)	(-4.0; 2.0)	
	N missing	21	8	13	

Table 12 – Change in CGI-S from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
Self-rated CGI-S-Visit 1 to 3	N	287	144	143	0.1844
	Mean (DE)	-0.98 (1.38)	-1.09 (1.37)	-0.87 (1.38)	
	Median	-1.0	-1.0	-1.0	
	(P25; P75)	(-2.0; 0.0)	(-2.0; 0.0)	(-2.0; 0.0)	
	(Min; Max)	(-5.0; 2.0)	(-5.0; 1.0)	(-5.0; 2.0)	
	N missing	29	11	18	
Self-rated CGI-S-Visit 2 to 3	N	281	142	139	0.5365
	Mean (DE)	-0.24 (1.28)	-0.29 (1.28)	-0.19 (1.28)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-1.0; 0.0)	(-1.0; 0.0)	(-1.0; 0.0)	
	(Min; Max)	(-5.0; 4.0)	(-5.0; 4.0)	(-4.0; 4.0)	
	N missing	35	13	22	

(1) ANOVA

HAM-D scale – Hamilton Rating Scale for Depression

HAM-D rates the clinical severity of depression. It has 17 questions, each with three to five possible answers, with scores ranging from 0 to 2 or from 0 to 4, respectively. The total score ranges from 0 to 52 and cut-off scores can be used to classify the depressive disorder.

Significant differences were observed between patient groups in the change from baseline to 6 weeks (visit 2) on HAM-D score (p=0.0364). In this case, patients in the study group presented a greater improvement of depression (greater decrease in HAM-D scale) than control patients (-6.53 ± 6.54 vs -4.97 ± 6.12) (Table 13).

Table 13 – Change in HAM-D from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
HAM-D - Visit 1 to 2	N	288	144	144	**0.0364**
	Mean (DE)	-5.75 (6.37)	-6.53 (6.54)	-4.97 (6.12)	

Table 13 – Change in HAM-D from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
	Median	-5.0	-6.0	-5.0	
	(P25; P75)	(-9.0; -1.0)	(-10.0; -2.0)	(-8.5; -1.0)	
	(Min; Max)	(-25.0; 11.0)	(-25.0; 11.0)	(-24.0; 8.0)	
	N missing	28	11	17	
HAM-D - Visit 1 to 3	N	280	141	139	0.0771
	Mean (DE)	-7.26 (7.45)	-8.04 (7.72)	-6.47 (7.12)	
	Median	-6.0	-7.0	-6.0	
	(P25; P75)	(-12.0; -2.0)	(-13.0; -3.0)	(-11.0; -2.0)	
	(Min; Max)	(-30.0; 10.0)	(-30.0; 10.0)	(-24.0; 9.0)	
	N missing	36	14	22	
HAM-D - Visit 2 to 3	N	278	141	137	0.8360
	Mean (DE)	-1.42 (6.16)	-1.50 (6.16)	-1.34 (6.18)	
	Median	-2.0	-2.0	-1.0	
	(P25; P75)	(-5.0; 2.0)	(-5.0; 1.0)	(-5.0; 2.0)	
	(Min; Max)	(-21.0; 16.0)	(-21.0; 16.0)	(-21.0; 16.0)	
	N missing	38	14	24	

(1) Chi-squared test or ANOVA according data type

SATMED-Q – Treatment Satisfaction with Medicines Questionnaire

SATMED-Q is a 17-item questionnaire and is a valid scale for any chronic or long-term condition. It is a self-administered questionnaire on treatment satisfaction and it assesses the following areas or dimensions: side effects; effectiveness of the medication; convenience of the medication; impact of the medication on everyday life; medical follow-up of the disease; and the patient's general opinion regarding his/her condition and the medication. All items are assessed using a 5-point Likert scale that runs from "no, not at all" with a value of 0 to "yes, very much" with a value of 4, with a total score ranging from 0 (not satisfied at all) to 100 (totally satisfied).

Patients in the study group showed a higher increase in SATMED-Q total at 6 weeks from baseline (10.06 ±18.66 vs 4.45 ±18.69, p=0.0117), treatment effectiveness (14.22 ±30.43 vs 6.37 ±32.31, p=0.0349), impact on daily activities (12.73 ±27.61 vs 5.46 ±29.84, p=0.0324) and general satisfaction (15.39 ±32.39 vs 4.98 ±31.56, p=0.0061) domain scores than patients in the control group (Table 14).

Table 14 – Change in SATMED-Q from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
SATMED-Q - Visit 1 to 2	N	286	142	144	**0.0117**
	Mean (DE)	7.23 (18.86)	10.06 (18.66)	4.45 (18.69)	
	Median	6.6	8.8	3.7	
	(P25; P75)	(-2.9; 17.6)	(-1.5; 20.6)	(-5.1; 14.7)	
	(Min; Max)	(-41.2; 61.8)	(-41.2; 61.8)	(-41.2; 52.9)	
	N missing	30	13	17	
SATMED-Q - Visit 1 to 3	N	280	141	139	0.0844
	Mean (DE)	10.90 (20.58)	13.01 (21.34)	8.76 (19.63)	
	Median	10.3	11.8	7.4	
	(P25; P75)	(-2.2; 24.3)	(0.0; 27.9)	(-5.9; 20.6)	
	(Min; Max)	(-45.6; 69.1)	(-39.7; 69.1)	(-45.6; 61.8)	
	N missing	36	14	22	
SATMED-Q - Visit 2 to 3	N	277	138	139	0.5930
	Mean (DE)	3.79 (17.39)	3.23 (19.34)	4.35 (15.25)	
	Median	2.9	2.9	2.9	
	(P25; P75)	(-2.9; 11.8)	(-4.4; 11.8)	(-2.9; 10.3)	
	(Min; Max)	(-70.6; 63.2)	(-70.6; 63.2)	(-39.7; 55.9)	
	N missing	39	17	22	
SATMED Side effects - Visit 1 to 2	N	288	143	145	0.2636
	Mean (DE)	5.27 (37.39)	7.75 (35.68)	2.82 (38.98)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(0.0; 25.0)	(0.0; 25.0)	(-8.3; 16.7)	
	(Min; Max)	(-100.0; 100.0)	(-100.0; 100.0)	(-100.0; 100.0)	

Table 14 – Change in SATMED-Q from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
	N missing	28	12	16	
SATMED Side effects - Visit 1 to 3	N	281	141	140	0.4977
	Mean (DE)	6.79 (38.17)	8.33 (38.60)	5.24 (37.80)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(0.0; 25.0)	(0.0; 25.0)	(-8.3; 25.0)	
	(Min; Max)	(-100.0; 100.0)	(-100.0; 100.0)	(-100.0; 100.0)	
	N missing	35	14	21	
SATMED Side effects - Visit 2 to 3	N	278	139	139	0.5332
	Mean (DE)	3.69 (31.21)	2.52 (31.73)	4.86 (30.74)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(0.0; 16.7)	(0.0; 8.3)	(0.0; 16.7)	
	(Min; Max)	(-100.0; 100.0)	(-100.0; 100.0)	(-83.3; 100.0)	
	N missing	38	16	22	
SATMED Treatment effectiveness - Visit 1 to 2	N	287	143	144	**0.0349**
	Mean (DE)	10.28 (31.58)	14.22 (30.43)	6.37 (32.31)	
	Median	8.3	8.3	0.0	
	(P25; P75)	(-8.3; 25.0)	(-8.3; 33.3)	(-16.7; 25.0)	
	(Min; Max)	(-83.3; 100.0)	(-66.7; 100.0)	(-83.3; 75.0)	
	N missing	29	12	17	
SATMED Treatment effectiveness - Visit 1 to 3	N	280	141	139	**0.0205**
	Mean (DE)	17.59 (32.90)	22.10 (32.78)	13.01 (32.49)	
	Median	16.7	16.7	8.3	
	(P25; P75)	(0.0; 41.7)	(0.0; 50.0)	(-8.3; 33.3)	
	(Min; Max)	(-66.7; 100.0)	(-66.7; 100.0)	(-66.7; 100.0)	
	N missing	36	14	22	
SATMED Treatment effectiveness - Visit 2 to 3	N	278	139	139	0.7448
	Mean (DE)	6.47 (27.57)	7.01 (30.32)	5.94 (24.62)	
	Median	8.3	8.3	0.0	
	(P25; P75)	(-8.3; 16.7)	(-8.3; 16.7)	(-8.3; 16.7)	
	(Min; Max)	(-83.3; 100.0)	(-83.3; 100.0)	(-75.0; 100.0)	

Table 14 – Change in SATMED-Q from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
	N missing	38	16	22	
SATMED Convenience of use - Visit 1 to 2	N	289	144	145	0.8724
	Mean (DE)	3.98 (25.82)	4.22 (26.06)	3.74 (25.66)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(0.0; 16.7)	(-4.2; 16.7)	(0.0; 16.7)	
	(Min; Max)	(-75.0; 100.0)	(-75.0; 100.0)	(-75.0; 75.0)	
	N missing	27	11	16	
SATMED Convenience of use - Visit 1 to 3	N	281	141	140	0.3959
	Mean (DE)	6.41 (27.60)	7.80 (26.39)	5.00 (28.79)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(0.0; 25.0)	(0.0; 25.0)	(-8.3; 25.0)	
	(Min; Max)	(-75.0; 100.0)	(-66.7; 100.0)	(-75.0; 100.0)	
	N missing	35	14	21	
SATMED Convenience of use - Visit 2 to 3	N	279	140	139	0.6138
	Mean (DE)	2.84 (22.34)	3.51 (21.97)	2.16 (22.77)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(0.0; 16.7)	(0.0; 16.7)	(0.0; 16.7)	
	(Min; Max)	(-75.0; 100.0)	(-75.0; 75.0)	(-75.0; 100.0)	
	N missing	37	15	22	
SATMED Impact on activities of daily living - Visit 1 to 2	N	289	144	145	**0.0324**
	Mean (DE)	9.08 (28.93)	12.73 (27.61)	5.46 (29.84)	
	Median	0.0	8.3	0.0	
	(P25; P75)	(-8.3; 25.0)	(0.0; 29.2)	(-8.3; 25.0)	
	(Min; Max)	(-75.0; 100.0)	(-75.0; 75.0)	(-75.0; 100.0)	
	N missing	27	11	16	
SATMED Impact on activities of daily living - Visit 1 to 3	N	281	141	140	0.3871
	Mean (DE)	15.90 (35.62)	17.73 (37.41)	14.05 (33.75)	
	Median	8.3	16.7	8.3	
	(P25; P75)	(0.0; 41.7)	(0.0; 41.7)	(-8.3; 41.7)	
	(Min; Max)	(-75.0; 100.0)	(-75.0; 100.0)	(-50.0; 100.0)	

Table 14 – Change in SATMED-Q from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
	N missing	35	14	21	
SATMED Impact on activities of daily living - Visit 2 to 3	N	279	140	139	0.3964
	Mean (DE)	6.45 (30.98)	4.88 (34.50)	8.03 (27.02)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-8.3; 25.0)	(-8.3; 25.0)	(0.0; 25.0)	
	(Min; Max)	(-100.0; 100.0)	(-100.0; 100.0)	(-50.0; 100.0)	
	N missing	37	15	22	
SATMED Medical care - Visit 1 to 2	N	288	143	145	0.8158
	Mean (DE)	3.65 (20.76)	3.93 (20.58)	3.36 (21.00)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(0.0; 12.5)	(0.0; 12.5)	(0.0; 12.5)	
	(Min; Max)	(-50.0; 75.0)	(-50.0; 75.0)	(-50.0; 75.0)	
	N missing	28	12	16	
SATMED Medical care - Visit 1 to 3	N	281	141	140	0.4630
	Mean (DE)	2.94 (22.54)	1.95 (21.77)	3.93 (23.33)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(0.0; 12.5)	(0.0; 12.5)	(0.0; 18.8)	
	(Min; Max)	(-87.5; 75.0)	(-87.5; 75.0)	(-50.0; 75.0)	
	N missing	35	14	21	
SATMED Medical care - Visit 2 to 3	N	278	139	139	0.4948
	Mean (DE)	-0.31 (16.43)	-0.99 (17.81)	0.36 (14.97)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)	
	(Min; Max)	(-62.5; 50.0)	(-62.5; 50.0)	(-50.0; 37.5)	
	N missing	38	16	22	
SATMED General satisfaction - Visit 1 to 2	N	288	144	144	**0.0061**
	Mean (DE)	10.19 (32.35)	15.39 (32.39)	4.98 (31.56)	
	Median	8.3	16.7	0.0	
	(P25; P75)	(0.0; 25.0)	(0.0; 33.3)	(-8.3; 25.0)	
	(Min; Max)	(-83.3; 100.0)	(-66.7; 100.0)	(-83.3; 100.0)	

Table 14 – Change in SATMED-Q from baseline - ITT set

Variable		Total	Study group	Control group	p-value (1)
	N missing	28	11	17	
SATMED General satisfaction - Visit 1 to 3	N	280	141	139	0.0741
	Mean (DE)	12.80 (34.28)	16.43 (35.61)	9.11 (32.60)	
	Median	8.3	16.7	0.0	
	(P25; P75)	(0.0; 33.3)	(0.0; 33.3)	(-8.3; 33.3)	
	(Min; Max)	(-100.0; 100.0)	(-100.0; 100.0)	(-75.0; 100.0)	
	N missing	36	14	22	
SATMED General satisfaction - Visit 2 to 3	N	279	140	139	0.4601
	Mean (DE)	2.18 (27.81)	0.95 (28.89)	3.42 (26.73)	
	Median	0.0	0.0	0.0	
	(P25; P75)	(-8.3; 16.7)	(-8.3; 16.7)	(-16.7; 16.7)	
	(Min; Max)	(-100.0; 100.0)	(-100.0; 83.3)	(-58.3; 100.0)	
	N missing	37	15	22	

(1) ANOVA

Cost-effectiveness study

We analysed the differences in mental health-related hospitalizations (number of admissions and length of stay per admission), emergency department presentation for mental disorder, sick leave due to mental disorder and its duration, visits to the psychiatrist, non-mental health-related hospitalizations, emergency department presentation for non-mental disorder, sick leave not due to mental disorder, specialist visits for any reason and visits to the Primary Care centre for any reason).

There were no significant differences with regard the cost-effectiveness analysis between the two study groups (Section 13, Tables 44 and 45).

Other assessments

Only 8.2% of patients discontinued the study, particularly due to loss of follow-up. No statistical differences were observed between the two patient groups (Table 15).

Table 15 – Study discontinuation- ITT set

Variable		Total	Study group	Control group	p-value (1)
Study completed	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.0516
	Yes	290 (91.8%)	147 (94.8%)	143 (88.8%)	
	No	26 (8.2%)	8 (5.2%)	18 (11.2%)	
Reason for discontinuation	Total	26 (100.0%)	8 (100.0%)	18 (100.0%)	0.4623
	Eligibility / selection criteria mistakes	1 (3.8%)	1 (12.5%)		
	Voluntary withdrawal	6 (23.1%)	2 (25.0%)	4 (22.2%)	
	Loss of follow-up	14 (53.8%)	4 (50.0%)	10 (55.6%)	
	Others	5 (19.2%)	1 (12.5%)	4 (22.2%)	

(1) Chi-squared test

Investigator evaluated the usefulness of the NEUROFARMAGEN test in patient treatment through a Likert scale of five points (from not useful to very useful). The mean score was 4.01 ± 0.91 (Table 16).

Table 16 - NEUROFARMAGEN investigator satisfaction - ITT set

Variable		Total	Study group	Control group	p-value (1)
Likert scale– Visit 3	N	145	145	0	--
	Mean (DE)	4.01 (0.91)	4.01 (0.91)		
	Median	4.0	4.0		
	(P25; P75)	(4.0; 5.0)	(4.0; 5.0)		
	(Min; Max)	(1.0; 5.0)	(1.0; 5.0)		
	N missing	171	10	161	

(1) ANOVA

10.4.1.3 Additional analysis results

Because of a large heterogeneity regarding the number of previous treatments in the whole ITT population, a sub-analysis was undertaken to assess the effect of this factor.

The mean number of previous treatments was similar between groups (2.55 ± 2.35 for the study group and 2.57 ± 2.10 for the control group). There were also no significant differences between groups according the number of previous treatment categories (Section 13, Table 46).

Significant differences in PGI-I at 12 weeks (51.8% vs 31% in the study and control group, respectively, p = 0.0058, OR 2.39 [95%CI 1.28-4.44]), and in HAM-D change from baseline at 6 weeks and 12 weeks (p = 0.0237 and p = 0.0083, respectively) were observed in subjects having received up to 3 previous treatments (Table 21). Conversely, no differences were observed in subjects having received more than 3 previous treatments (Section 13, Tables 46 and 47).

Table 17 – Efficacy assessments – Patients with number of treatments = 0

Variable		Total	Study group	Control group	p-value (1)
PGI – Positive response at 12 weeks	Total	46 (100.0%)	24 (100.0%)	22 (100.0%)	0.8293
	Yes	16 (34.8%)	8 (33.3%)	8 (36.4%)	
	No	30 (65.2%)	16 (66.7%)	14 (63.6%)	
	N missing	4	1	3	
PGI – Positive response at 6 weeks	Total	44 (100.0%)	22 (100.0%)	22 (100.0%)	0.5465
	Yes	22 (50.0%)	10 (45.5%)	12 (54.5%)	
	No	22 (50.0%)	12 (54.5%)	10 (45.5%)	
	N missing	6	3	3	
HAM-D – Visit 1 to 2	N	48	23	25	0.6610
	Mean (SD)	-6.02 (6.83)	-6.48 (7.83)	-5.60 (5.89)	
	Median	-6.0	-7.0	-6.0	
	(P25; P75)	(-10.0; -1.0)	(-10.0; -2.0)	(-9.0; -1.0)	
	(Min; Max)	(-22.0; 11.0)	(-22.0; 11.0)	(-18.0; 5.0)	
	N missing	2	2	0	
HAM-D – Visit 1 to 3	N	44	21	23	0.9659
	Mean (SD)	-7.61 (7.73)	-7.67 (8.68)	-7.57 (6.96)	
	Median	-7.5	-8.0	-7.0	
	(P25; P75)	(-12.5; -3.0)	(-14.0; -3.0)	(-12.0; -4.0)	
	(Min; Max)	(-24.0; 8.0)	(-22.0; 7.0)	(-24.0; 8.0)	
	N missing	6	4	2	

(1) Chi-squared test or ANOVA according data type

Table 18 – Efficacy assessments – Patients with number of treatments = 1

Variable		Total	Study group	Control group	p-value (1)
PGI - Positive response at 12 weeks	Total	55 (100.0%)	27 (100.0%)	28 (100.0%)	**0.0019**
	Yes	25 (45.5%)	18 (66.7%)	7 (25.0%)	
	No	30 (54.5%)	9 (33.3%)	21 (75.0%)	

Table 18 – Efficacy assessments – Patients with number of treatments = 1

Variable		Total	Study group	Control group	p-value (1)
	N missing	5	3	2	
PGI - Positive response at 6 weeks	Total	56 (100.0%)	28 (100.0%)	28 (100.0%)	0.0612
	Yes	29 (51.8%)	18 (64.3%)	11 (39.3%)	
	No	27 (48.2%)	10 (35.7%)	17 (60.7%)	
	N missing	4	2	2	
HAM-D - Visit 1 to 2	N	55	26	29	**0.0288**
	Mean (DE)	-7.02 (7.04)	-9.19 (5.61)	-5.07 (7.70)	
	Median	-6.0	-10.0	-4.0	
	(P25; P75)	(-12.0; -1.0)	(-14.0; -5.0)	(-8.0; -0.0)	
	(Min; Max)	(-24.0; 8.0)	(-22.0; -1.0)	(-24.0; 8.0)	
	N missing	5	4	1	
HAM-D - Visit 1 to 3	N	55	27	28	0.0821
	Mean (DE)	-7.45 (7.25)	-9.19 (7.28)	-5.79 (6.95)	
	Median	-9.0	-9.0	-6.0	
	(P25; P75)	(-11.0; -2.0)	(-14.0; -3.0)	(-10.5; -0.5)	
	(Min; Max)	(-23.0; 6.0)	(-23.0; 3.0)	(-22.0; 6.0)	
	N missing	5	3	2	

(1) Chi-squared test or ANOVA according data type

Table 19 – Efficacy assessments – Patients with number of treatments = 1 or 2

Variable		Total	Study group	Control group	p-value (1)
PGI - Positive response at 12 weeks	Total	112 (100.0%)	55 (100.0%)	57 (100.0%)	**0.0238**
	Yes	51 (45.5%)	31 (56.4%)	20 (35.1%)	
	No	61 (54.5%)	24 (43.6%)	37 (64.9%)	
	N missing	13	8	5	
PGI - Positive response at 6 weeks	Total	116 (100.0%)	58 (100.0%)	58 (100.0%)	0.1920
	Yes	53 (45.7%)	30 (51.7%)	23 (39.7%)	
	No	63 (54.3%)	28 (48.3%)	35 (60.3%)	

Table 19 – Efficacy assessments – Patients with number of treatments = 1 or 2

Variable		Total	Study group	Control group	p-value (1)
	N missing	9	5	4	
HAM-D - Visit 1 to 2	N	114	58	56	**0.0398**
	Mean (DE)	-6.59 (6.57)	-7.83 (6.06)	-5.30 (6.88)	
	Median	-6.0	-7.0	-5.0	
	(P25; P75)	(-10.0; -2.0)	(-11.0; -3.0)	(-9.0; -0.0)	
	(Min; Max)	(-24.0; 8.0)	(-22.0; 2.0)	(-24.0; 8.0)	
	N missing	11	5	6	
HAM-D - Visit 1 to 3	N	114	59	55	**0.0248**
	Mean (DE)	-7.49 (7.55)	-9.02 (7.57)	-5.85 (7.25)	
	Median	-7.5	-9.0	-6.0	
	(P25; P75)	(-11.0; -2.0)	(-14.0; -3.0)	(-11.0; -1.0)	
	(Min; Max)	(-30.0; 10.0)	(-30.0; 10.0)	(-22.0; 9.0)	
	N missing	11	4	7	

(1) Chi-squared test or ANOVA according data type

Table 20 – Efficacy assessments – Patients with number of treatments = 1, 2 or 3

Variable		Total	Study group	Control group	p-value (1)
PGI - Positive response at 12 weeks	Total	172 (100.0%)	85 (100.0%)	87 (100.0%)	**0.0058**
	Yes	71 (41.3%)	44 (51.8%)	27 (31.0%)	
	No	101 (58.7%)	41 (48.2%)	60 (69.0%)	
	N missing	18	12	6	
PGI - Positive response at 6 weeks	Total	177 (100.0%)	89 (100.0%)	88 (100.0%)	0.3921
	Yes	72 (40.7%)	39 (43.8%)	33 (37.5%)	
	No	105 (59.3%)	50 (56.2%)	55 (62.5%)	
	N missing	13	8	5	
HAM-D - Visit 1 to 2	N	174	91	83	**0.0237**
	Mean (DE)	-6.17 (6.41)	-7.22 (6.14)	-5.02 (6.55)	
	Median	-5.0	-6.0	-5.0	

Table 20 – Efficacy assessments – Patients with number of treatments = 1, 2 or 3

Variable		Total	Study group	Control group	p-value (1)
	(P25; P75)	(-10.0; -1.0)	(-11.0; -3.0)	(-8.0; -0.0)	
	(Min; Max)	(-24.0; 8.0)	(-22.0; 8.0)	(-24.0; 8.0)	
	N missing	16	6	10	
HAM-D - Visit 1 to 3	N	173	90	83	**0.0083**
	Mean (DE)	-7.42 (7.52)	-8.86 (7.37)	-5.86 (7.40)	
	Median	-7.0	-9.0	-6.0	
	(P25; P75)	(-12.0; -2.0)	(-14.0; -3.0)	(-11.0; -1.0)	
	(Min; Max)	(-30.0; 10.0)	(-30.0; 10.0)	(-22.0; 9.0)	
	N missing	17	7	10	

(1) Chi-squared test or ANOVA according data type

Additionally, because 18% of the ITT population displayed a HAM-D score < 14 points on visit 1 (i.e. randomization visit), a sub-analysis was performed in the subpopulation displaying HAM-D ≥ 14 on visit 1. Significant differences were also observed in PGI-I at 12 weeks (46.9% vs. 33.3%, in the study and control group, respectively p = 0.0370, OR = 1.77 [95%CI 1.03-3.02]) and in HAM-D change from baseline at 6 weeks and 12 weeks (p = 0.0364, and p = 0.0372, respectively) (Table 21).

Table 21 – Efficacy assessments – Patients with HAM-D ≥ 14 in Visit 1

Variable		Total	Study group	Control group	p-value (1)
PGI – Positive response at 12 weeks	Total	227 (100.0%)	113 (100.0%)	114 (100.0%)	**0.0370**
	Yes	91 (40.1%)	53 (46.9%)	38 (33.3%)	
	No	136 (59.9%)	60 (53.1%)	76 (66.7%)	
	N missing	27	14	13	
PGI – Positive response at 6 weeks	Total	237 (100.0%)	118 (100.0%)	119 (100.0%)	0.4695
	Yes	87 (36.7%)	46 (39.0%)	41 (34.5%)	
	No	150 (63.3%)	72 (61.0%)	78 (65.5%)	
	N missing	17	9	8	
	N	234	120	114	**0.0364**

Table 21 – Efficacy assessments – Patients with HAM-D ≥ 14 in Visit 1

Variable		Total	Study group	Control group	p-value (1)
HAM-D - Visit 1 to 2	Mean (DE)	-6.45 (6.58)	-7.33 (6.66)	-5.53 (6.40)	
	Median	-6.0	-7.0	-5.0	
	(P25; P75)	(-10.0; -2.0)	(-11.0; -3.0)	(-9.0; -1.0)	
	(Min; Max)	(-25.0; 11.0)	(-25.0; 11.0)	(-24.0; 8.0)	
	N missing	20	7	13	
HAM-D - Visit 1 to 3	N	230	118	112	**0.0372**
	Mean (DE)	-7.98 (7.74)	-9.02 (7.78)	-6.89 (7.58)	
	Median	-7.5	-9.0	-6.0	
	(P25; P75)	(-13.0; -2.0)	(-14.0; -3.0)	(-12.0; -1.5)	
	(Min; Max)	(-30.0; 9.0)	(-30.0; 8.0)	(-24.0; 9.0)	
	N missing	24	9	15	

(1) Chi-squared test or ANOVA according data type

10.4.2 Summary of efficacy results

A total of 316 were randomized and included in the ITT population (155 patients in the study group and 161 patients in the control group).

Overall, socio-demographic and clinical characteristics collected at baseline were similar between patient groups. All analysed patients reported a major depressive disorder with a mean duration period from diagnosis of 60.2 months.

Regarding the primary endpoint, no statistically significant differences were observed between patient groups in the proportion of subjects achieving sustained response evaluated both through the telephone contacts as well as face-to-face visits. However, the number of patients with positive response to treatment at 12 weeks was significantly higher in the study group than in the control group (47.8% vs 36.1%, p = 0.0476, OR = 1.62 [95%CI 1.00-2.61]).

Significant differences between study groups were observed for the frequency, intensity and burden of side effects items scores from visit 1 to visit 2, with patients in the study group

presenting a better tolerance. Additionally, patients in the study group experienced a greater improvement in social disability subscale of SDI.

There were significant differences in the CGI-S (disease severity) mean changes between visit 1 to visit 3 for both the self-rated and the doctor-rated version. In both cases, patients in the study group experienced a greater improve compared to patients in the control group.

Regarding the assessment of severity of depression, patients in the study group presented a greater improvement of depression than control patients.

Overall, patients in the study group showed a higher satisfaction with the treatment by SATMED-Q at 6 weeks from baseline.

Additionally, in the subgroup of patients with HAM-D score ≥ 14 and the subgroup of patients with up to 3 previous treatments, we found a higher percentage of patients with positive response to treatment (PGI) at 12 weeks, and a better improvement of depression (HAM-D) at 6 and 12 weeks in study group than in control group.

There were no significant differences between the two study groups with regard the cost-effectiveness analysis.

Investigator evaluated the usefulness of the NEUROFARMAGEN test with a mean score of 4.01 through a Likert scale of five points (corresponding to useful).

11 Safety evaluation

11.1 Extent of exposure

A total of 316 patients received at least one psychiatric medication during the study (155 patients in the intervention group and 161 patients in the control group).

Table 22 – Psychiatric medication- Safety set

Variable		Total	Study group	Control group	p-value (1)
	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	

Table 22 – Psychiatric medication- Safety set

Variable		Total	Study group	Control group	p-value (1)
Non-randomised patients with at least one psychiatric medication	Yes	316 (100.0%)	155 (100.0%)	161 (100.0%)	

(1) Chi-squared test

11.1.1 Concomitant medication

More than half of patients were taking concomitant medication (63.6% in the study group and 61.0% in the control group).

Table 23 – Concomitant medication- Safety set

Variable		Total	Study group	Control group	p-value (1)
Patients with at least one concomitant treatment	Total	313 (100.0%)	154 (100.0%)	159 (100.0%)	0.6312
	Yes	195 (62.3%)	98 (63.6%)	97 (61.0%)	
	No	118 (37.7%)	56 (36.4%)	62 (39.0%)	
	N missing	3	1	2	

(1) Chi-squared test

11.2 Adverse events

11.2.1 Brief summary of adverse events

All safety analyses were performed on the safety analysis set, which included all randomly assigned patients (N=370). Adverse events regardless of causality were collected for all patients from the time of signature of informed consent throughout the follow-up period. An overall summary of the AEs observed in this study is presented in Table 24.

Table 24 – Adverse events – Safety set

Variable		Total	Study group	Control group	p-value (1)
Patients with at least one AE	Total	307 (100.0%)	151 (100.0%)	156 (100.0%)	0.5155
	Yes	72 (23.5%)	33 (21.9%)	39 (25.0%)	
	No	235 (76.5%)	118 (78.1%)	117 (75.0%)	
	N missing	9	4	5	

(1) Chi-squared test

11.2.2 Display of adverse events

Displays of AEs are presented in the following tables:

- Adverse Events by MedDRA System Organ Class (SOC). Total and by treatment group assignment. Table 25.
- Adverse Events by SOC and Preferred Term (PT). Total and by treatment group assignment. Table 26.

11.2.3 Analysis of adverse events

Overall, a total of 106 AEs were reported in 72 of the 307 (23.5%) patients enrolled in this study (54 in study group and 52 in control group). Very similar rates in each group were observed (Table 24, Table 25).

AE verbatim terms were converted to MedDRA Preferred Term. The SOCs with the highest incidence of AEs (>10%) included the nervous system disorders, psychiatric disorders and gastrointestinal disorders. The overall incidence was similar between the two treatment groups (Table 25).

Adverse events were reported in the nervous system disorders SOC in 20 (37.0%) patients in study group and in 14 (26.9%) in control group (Table 25). The AEs reported most often in this SOC were hepatic tremor (n=8, 7.5%), somnolence (n=6, 7.5%) and headache (n=4, 3.8%) (Table 26).

Adverse events were reported in the psychiatric disorders SOC in 16 (29,6%) patients in study group and in 10 (19,2%) patients in control group (Table 25). The AEs reported most often in this SOC were Restlessness (n=6, 5.7%) and depression (n=4, 3.8%) (Table 26).

Adverse events were reported in the gastrointestinal disorders SOC in 7 (13,0%) patients in study group and in 8 (15,4%) patients in control group (Table 25). The AEs reported most often in this SOC were dry mouth (n=5, 4.7%) and abdominal discomfort (n=4, 3.8%) (Table 26).

All AEs reported during the study are summarized by system organ class and preferred term in Table 26, along with their incidence rate in either group.

Table 25 – Adverse Events (SOC term)

SOC term	Total	Study group	Control group	p-value (1)
Total	106 (100,0%)	54 (100,0%)	52 (100,0%)	0,4785
Gastrointestinal disorders	15 (14,2%)	7 (13,0%)	8 (15,4%)	
General disorders and administration site conditions	4 (3,8%)	2 (3,7%)	2 (3,8%)	
Infections and infestations	9 (8,5%)	5 (9,3%)	4 (7,7%)	
Injury, poisoning and procedural complications	3 (2,8%)		3 (5,8%)	
Investigations	2 (1,9%)	1 (1,9%)	1 (1,9%)	
Metabolism and nutrition disorders	2 (1,9%)	1 (1,9%)	1 (1,9%)	
Nervous system disorders	34 (32,1%)	20 (37,0%)	14 (26,9%)	
Psychiatric disorders	26 (24,5%)	16 (29,6%)	10 (19,2%)	
Reproductive system and breast disorders	4 (3,8%)	1 (1,9%)	3 (5,8%)	
Skin and subcutaneous tissue disorders	4 (3,8%)	1 (1,9%)	3 (5,8%)	
Surgical and medical procedures	2 (1,9%)		2 (3,8%)	
Vascular disorders	1 (0,9%)		1 (1,9%)	

(1) Chi-square test

Table 26 – Adverse Events (PT term)					
Variable		**Total**	**Study group**	**Control group**	**p-value (1)**
PT term	Total	106 (100,0%)	54 (100,0%)	52 (100,0%)	0,5249
Gastrointestinal disorders					
	Abdominal discomfort	4 (3,8%)	3 (5,6%)	1 (1,9%)	
	Constipation	2 (1,9%)		2 (3,8%)	
	Dry mouth	5 (4,7%)	3 (5,6%)	2 (3,8%)	
	Glossodynia	1 (0,9%)		1 (1,9%)	
	Nausea	3 (2,8%)	1 (1,9%)	2 (3,8%)	
General disorders and administration site conditions					
	Condition aggravated	1 (0,9%)	1 (1,9%)		
	Malaise	1 (0,9%)		1 (1,9%)	
	Oedema	1 (0,9%)	1 (1,9%)		
	Pyrexia	1 (0,9%)		1 (1,9%)	
Infections and infestations					
	Adenoiditis	1 (0,9%)	1 (1,9%)		
	Gastroenteritis	3 (2,8%)		3 (5,8%)	
	Infection	1 (0,9%)	1 (1,9%)		
	Influenza	1 (0,9%)	1 (1,9%)		
	Pneumonia	2 (1,9%)	1 (1,9%)	1 (1,9%)	
	Urinary tract infection	1 (0,9%)	1 (1,9%)		
Injury, poisoning and procedural complications					
	Fracture	2 (1,9%)		2 (3,8%)	
	Humerus fracture	1 (0,9%)		1 (1,9%)	
Investigations					
	Investigation	1 (0,9%)	1 (1,9%)		
	Weight increased	1 (0,9%)		1 (1,9%)	
Metabolism and nutrition disorders					
	Food craving	1 (0,9%)		1 (1,9%)	
	Increased appetite	1 (0,9%)	1 (1,9%)		
Nervous system disorders					

Table 26 – Adverse Events (PT term)				
Variable	**Total**	**Study group**	**Control group**	**p-value (1)**
Central nervous system lesion	1 (0,9%)		1 (1,9%)	
Clumsiness	1 (0,9%)		1 (1,9%)	
Depressed level of consciousness	1 (0,9%)		1 (1,9%)	
Dizziness	3 (2,8%)	1 (1,9%)	2 (3,8%)	
Dysgeusia	1 (0,9%)	1 (1,9%)		
Headache	4 (3,8%)	2 (3,7%)	2 (3,8%)	
Intention tremor	1 (0,9%)		1 (1,9%)	
Migraine	3 (2,8%)	1 (1,9%)	2 (3,8%)	
Myoclonus	2 (1,9%)	2 (3,7%)		
Restless legs syndrome	1 (0,9%)	1 (1,9%)		
Sedation	2 (1,9%)	2 (3,7%)		
Somnolence	6 (5,7%)	3 (5,6%)	3 (5,8%)	
Tremor	8 (7,5%)	7 (13,0%)	1 (1,9%)	
Psychiatric disorders				
Aggression	1 (0,9%)	1 (1,9%)		
Anxiety	1 (0,9%)	1 (1,9%)		
Confusional state	1 (0,9%)		1 (1,9%)	
Depression	4 (3,8%)	2 (3,7%)	2 (3,8%)	
Dysphemia	1 (0,9%)	1 (1,9%)		
Irritability	1 (0,9%)	1 (1,9%)		
Libido decreased	1 (0,9%)		1 (1,9%)	
Loss of libido	1 (0,9%)	1 (1,9%)		
Middle insomnia	2 (1,9%)	1 (1,9%)	1 (1,9%)	
Mood altered	1 (0,9%)	1 (1,9%)		
Restlessness	6 (5,7%)	4 (7,4%)	2 (3,8%)	
Self injurious behaviour	3 (2,8%)	2 (3,7%)	1 (1,9%)	
Somnambulism	1 (0,9%)		1 (1,9%)	
Suicide attempt	2 (1,9%)	1 (1,9%)	1 (1,9%)	
Reproductive system and breast disorders				
Erectile dysfunction	1 (0,9%)		1 (1,9%)	

Table 26 – Adverse Events (PT term)				
Variable	**Total**	**Study group**	**Control group**	**p-value (1)**
Sexual dysfunction	2 (1,9%)	1 (1,9%)	1 (1,9%)	
Testicular pain	1 (0,9%)		1 (1,9%)	
Skin and subcutaneous tissue disorders				
Hyperhidrosis	2 (1,9%)	1 (1,9%)	1 (1,9%)	
Night sweats	1 (0,9%)		1 (1,9%)	
Pruritus	1 (0,9%)		1 (1,9%)	
Surgical and medical procedures				
Hospitalisation	1 (0,9%)		1 (1,9%)	
Skin operation	1 (0,9%)		1 (1,9%)	
Vascular disorders				
Orthostatic hypotension	1 (0,9%)		1 (1,9%)	
(1) Chi-square test				

11.2.4 Listing of adverse events by patient

The listing of AEs by patient will be presented in Appendix 15, List 15.1.7 in the final study report.

11.3 Summary of safety results

A total of 316 patients received at least one psychiatric medication during the study (155 patients in the intervention group and 161 patients in the control group). The overall incidence of AEs was similar in the study and control groups. Overall, 72 patients (23.5%) had at least one AE. No deaths were observed.

12 Overall conclusions

The current report displays the results from the study conducted in order to assess the NEUROFARMAGEN test effectiveness in selecting drug treatments for major depressive disorder by the proportion of patients achieving sustained response over a period of 12 weeks. Sustained response was considered when the patient gets a PGI-I of 2 points or less (i.e. “much

improved" or "very much improved") in two consecutive assessments after the last change in treatment.

No statistically significant differences were observed between patient groups in the proportion of subjects achieving sustained response evaluated both through the telephone contacts as well as face-to-face visits. However, the number of patients with positive response to treatment at 12 weeks was significantly higher in the study group than in the control group.

Significant differences between study groups were observed for the frequency, intensity and burden of side effects items scores from visit 1 to visit 2, with patients in the study group presenting a better tolerance. Additionally, patients in the study group experienced a greater improvement in social disability subscale of SDI, in disease severity according CGI-S, in severity of depression with Ham-D and a higher treatment satisfaction with the SATMED-Q.

In the subgroup of patients with HAM-D score ≥ 14 and the subgroup of patients with up to 3 previous treatments, we found a higher percentage of patients with positive response to treatment (PGI) at 12 weeks and a better improvement of depression (HAM-D) at 6 and 12 weeks in study group than in control group.

There were no significant differences between the two study groups with regard the cost-effectiveness analysis. Nevertheless, investigator evaluated the usefulness of the NEUROFARMAGEN test with a mean score of 4.01 through a Likert scale of five points (corresponding to useful).

The safety profile was similar in the study and control groups.

13 Tables, figures and graphs

13.1 Disposition of subjects

Table 27 – Eligibility criteria

Variable		Total	Study group	Control group
Selection criterion 1	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)
	Yes	316 (100.0%)	155 (100.0%)	161 (100.0%)
Selection criterion 2	Total	314 (100.0%)	154 (100.0%)	160 (100.0%)
	Yes	314 (100.0%)	154 (100.0%)	160 (100.0%)
	N missing	2	1	1
Selection criterion 3	Total	314 (100.0%)	154 (100.0%)	160 (100.0%)
	Yes	314 (100.0%)	154 (100.0%)	160 (100.0%)
	N missing	2	1	1
Selection criterion 4	Total	314 (100.0%)	154 (100.0%)	160 (100.0%)
	Yes	314 (100.0%)	154 (100.0%)	160 (100.0%)
	N missing	2	1	1
Selection criterion 5	Total	314 (100.0%)	154 (100.0%)	160 (100.0%)
	Yes	314 (100.0%)	154 (100.0%)	160 (100.0%)
	N missing	2	1	1
Non-eligibility criterion 1	Total	314 (100.0%)	154 (100.0%)	160 (100.0%)
	No	314 (100.0%)	154 (100.0%)	160 (100.0%)
	N missing	2	1	1
Non-eligibility criterion 2	Total	314 (100.0%)	154 (100.0%)	160 (100.0%)
	No	314 (100.0%)	154 (100.0%)	160 (100.0%)
	N missing	2	1	1
Non-eligibility criterion 3	Total	200 (100.0%)	98 (100.0%)	102 (100.0%)
	No	200 (100.0%)	98 (100.0%)	102 (100.0%)
	NA	115	56	59
	N missing	1	1	0
Non-eligibility criterion 4	Total	314 (100.0%)	154 (100.0%)	160 (100.0%)

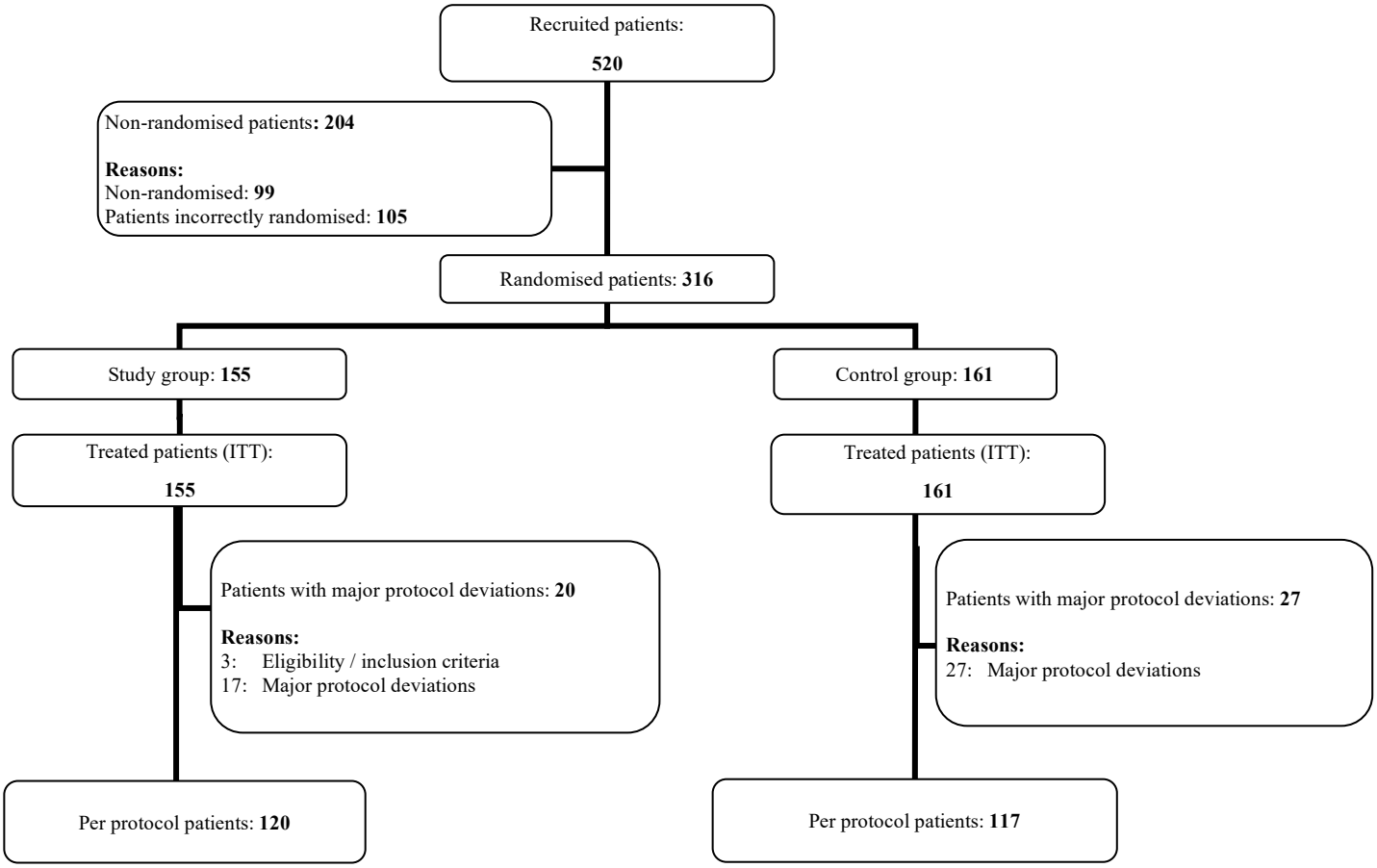
Table 27 – Eligibility criteria

Variable		Total	Study group	Control group
	No	314 (100.0%)	154 (100.0%)	160 (100.0%)
	N missing	2	1	1

Table 28 – Inclusion criteria

Variable		Total	Study group	Control group
Inclusion criterion 1	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)
	Yes	316 (100.0%)	155 (100.0%)	161 (100.0%)
Inclusion criterion 2	Total	314 (100.0%)	154 (100.0%)	160 (100.0%)
	Yes	314 (100.0%)	154 (100.0%)	160 (100.0%)
	N missing	2	1	1
Inclusion criterion 3	Total	314 (100.0%)	154 (100.0%)	160 (100.0%)
	Yes	311 (99.0%)	151 (98.1%)	160 (100.0%)
	No	3 (1.0%)	3 (1.9%)	
	N missing	2	1	1

Figure 1. Patient flow and disposition



13.2 Demographic data

Table 29 – Demographic data II - ITT set

Variable		Total	Study group	Control group	p-value (1)
Height (cm)	N	314	155	159	0.1681
	Mean (DE)	165.29 (9.55)	164.54 (9.90)	166.02 (9.16)	
	Median	165.0	162.0	165.0	
	(P25; P75)	(158.0; 172.0)	(158.0; 171.0)	(160.0; 172.0)	
	(Min; Max)	(139.0; 192.0)	(142.0; 191.0)	(139.0; 192.0)	
	N missing	2	0	2	
Weight (kg)	N	314	155	159	0.6333
	Mean (DE)	72.24 (14.67)	71.84 (14.01)	72.63 (15.31)	
	Median	71.8	71.0	73.0	
	(P25; P75)	(62.0; 81.0)	(62.0; 79.5)	(60.0; 82.0)	
	(Min; Max)	(41.9; 128.0)	(45.0; 115.0)	(41.9; 128.0)	
	N missing	2	0	2	
BMI (kg/m^2)	N	314	155	159	0.5760
	Mean (DE)	26.42 (4.84)	26.58 (4.96)	26.27 (4.73)	
	Median	25.7	26.0	25.7	
	(P25; P75)	(23.1; 29.3)	(23.6; 29.4)	(22.8; 29.3)	
	(Min; Max)	(16.1; 44.6)	(16.1; 44.6)	(16.6; 40.0)	
	N missing	2	0	2	

(1) ANOVA

Table 30 – Demographic data III - ITT set

Variable		Total	Study Group	Control group	p-value (1)
Job activity	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.9820
	Student	9 (2.8%)	5 (3.2%)	4 (2.5%)	
	Retired	68 (21.5%)	32 (20.6%)	36 (22.4%)	

Table 30 – Demographic data III - ITT set

Variable		Total	Study Group	Control group	p-value (1)
	Unemployed	119 (37.7%)	60 (38.7%)	59 (36.6%)	
	Employed	59 (18.7%)	29 (18.7%)	30 (18.6%)	
	Work leave	61 (19.3%)	29 (18.7%)	32 (19.9%)	
Disabled	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.7837
	Yes	30 (9.5%)	14 (9.0%)	16 (9.9%)	
	No	286 (90.5%)	141 (91.0%)	145 (90.1%)	
Under the care of a family member	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.6267
	Yes	32 (10.1%)	17 (11.0%)	15 (9.3%)	
	No	284 (89.9%)	138 (89.0%)	146 (90.7%)	
Disability pension	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.4556
	Yes	56 (17.7%)	30 (19.4%)	26 (16.1%)	
	No	260 (82.3%)	125 (80.6%)	135 (83.9%)	

(1) Chi-squared test

Table 31 – Demographic data IV - ITT set

Variable		Total	Study group	Control group	p-value (1)
Education	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.3022
	No education	17 (5.4%)	11 (7.1%)	6 (3.7%)	
	Primary education	112 (35.4%)	57 (36.8%)	55 (34.2%)	
	Secondary Education	112 (35.4%)	56 (36.1%)	56 (34.8%)	
	Higher education	75 (23.7%)	31 (20.0%)	44 (27.3%)	
Marital status	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.3680
	Single	70 (22.2%)	34 (21.9%)	36 (22.4%)	
	Married/ cohabiting	183 (57.9%)	96 (61.9%)	87 (54.0%)	
	Widowed	19 (6.0%)	7 (4.5%)	12 (7.5%)	

Table 31 – Demographic data IV - ITT set

Variable		Total	Study group	Control group	p-value (1)
	Divorced	44 (13.9%)	18 (11.6%)	26 (16.1%)	
		(1) Chi-squared test			

Table 32 – Psychiatric history- ITT set

Variable		Total	Study group	Control group	p-value (1)
Psychiatric history related to study disorder	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.2113
	Yes	254 (80.4%)	129 (83.2%)	125 (77.6%)	
	No	62 (19.6%)	26 (16.8%)	36 (22.4%)	
Mood disorder	Total	254 (100.0%)	129 (100.0%)	125 (100.0%)	0.6672
	Yes	217 (85.4%)	109 (84.5%)	108 (86.4%)	
	No	37 (14.6%)	20 (15.5%)	17 (13.6%)	
	N missing	62	26	36	
Type	Total	217 (100.0%)	109 (100.0%)	108 (100.0%)	0.7331
	Depressive disorders	189 (87.1%)	94 (86.2%)	95 (88.0%)	
	Bipolar disorders	11 (5.1%)	5 (4.6%)	6 (5.6%)	
	Others	17 (7.8%)	10 (9.2%)	7 (6.5%)	
Anxiety disorder	Total	254 (100.0%)	129 (100.0%)	125 (100.0%)	0.1037
	Yes	91 (35.8%)	40 (31.0%)	51 (40.8%)	
	No	163 (64.2%)	89 (69.0%)	74 (59.2%)	
	N missing	62	26	36	
Type	Total	91 (100.0%)	40 (100.0%)	51 (100.0%)	0.6574
	Anxiety disorder	33 (36.3%)	17 (42.5%)	16 (31.4%)	
	Generalized	32 (35.2%)	12 (30.0%)	20 (39.2%)	
	Obsessive-compulsive disorder	11 (12.1%)	4 (10.0%)	7 (13.7%)	
	Other	15 (16.5%)	7 (17.5%)	8 (15.7%)	
Schizophrenia	Total	254 (100.0%)	129 (100.0%)	125 (100.0%)	

Table 32 – Psychiatric history- ITT set

Variable		Total	Study group	Control group	p-value (1)
	No	254 (100.0%)	129 (100.0%)	125 (100.0%)	
	N missing	62	26	36	
Other psychotic disorders	Total	254 (100.0%)	129 (100.0%)	125 (100.0%)	0.6983
	Yes	9 (3.5%)	4 (3.1%)	5 (4.0%)	
	No	245 (96.5%)	125 (96.9%)	120 (96.0%)	
	N missing	62	26	36	
Substance abuse	Total	254 (100.0%)	129 (100.0%)	125 (100.0%)	0.3944
	Yes	32 (12.6%)	14 (10.9%)	18 (14.4%)	
	No	222 (87.4%)	115 (89.1%)	107 (85.6%)	
	N missing	62	26	36	
Type	Total	32 (100.0%)	14 (100.0%)	18 (100.0%)	0.5767
	Alcohol abuse	20 (62.5%)	9 (64.3%)	11 (61.1%)	
	Cannabis abuse	2 (6.3%)	1 (7.1%)	1 (5.6%)	
	Cocaine abuse	2 (6.3%)		2 (11.1%)	
	Opiate abuse	1 (3.1%)	1 (7.1%)		
	Others	7 (21.9%)	3 (21.4%)	4 (22.2%)	
Other psychiatric disorders	Total	254 (100.0%)	129 (100.0%)	125 (100.0%)	0.9188
	Yes	36 (14.2%)	18 (14.0%)	18 (14.4%)	
	No	218 (85.8%)	111 (86.0%)	107 (85.6%)	
	N missing	62	26	36	
Suicide of a family member	Total	254 (100.0%)	129 (100.0%)	125 (100.0%)	0.5608
	Yes	16 (6.3%)	7 (5.4%)	9 (7.2%)	
	No	238 (93.7%)	122 (94.6%)	116 (92.8%)	
	N missing	62	26	36	
Suicide attempt of a first degree relative	Total	254 (100.0%)	129 (100.0%)	125 (100.0%)	0.5194
	Yes	19 (7.5%)	11 (8.5%)	8 (6.4%)	
	No	235 (92.5%)	118 (91.5%)	117 (93.6%)	
	N missing	62	26	36	

(1) Chi-squared test

Table 33 – Non-psychiatric treatment - ITT set

Variable		Total	Study group	Control group	p-value (1)
Medical history not related to study disorder	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.1162
	Yes	245 (77.5%)	126 (81.3%)	119 (73.9%)	
	No	71 (22.5%)	29 (18.7%)	42 (26.1%)	

(1) Chi-squared test

13.3 Efficacy data

Table 34 - CGI - ITT set

Variable		Total	Study group	Control group	p-value (1)
Doctor-rated CGI-S- Visit 0	N	316	155	161	0.5807
	Mean (DE)	4.52 (0.62)	4.54 (0.64)	4.50 (0.60)	
	Median	4.0	4.0	4.0	
	(P25; P75)	(4.0; 5.0)	(4.0; 5.0)	(4.0; 5.0)	
	(Min; Max)	(4.0; 6.0)	(4.0; 6.0)	(4.0; 6.0)	
	N missing	0	0	0	
Doctor-rated CGI-S- Visit 0	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	
	≥ 4	316 (100.0%)	155 (100.0%)	161 (100.0%)	
Doctor-rated CGI-S- Visit 1	N	316	155	161	0.1663
	Mean (DE)	4.45 (0.60)	4.50 (0.62)	4.40 (0.57)	
	Median	4.0	4.0	4.0	
	(P25; P75)	(4.0; 5.0)	(4.0; 5.0)	(4.0; 5.0)	
	(Min; Max)	(4.0; 6.0)	(4.0; 6.0)	(4.0; 6.0)	
	N missing	0	0	0	
Doctor-rated CGI-S- Visit 1	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	
	≥ 4	316 (100.0%)	155 (100.0%)	161 (100.0%)	
Doctor-rated CGI-S- Visit 2	N	295	147	148	0.8464
	Mean (DE)	3.83 (0.95)	3.82 (0.93)	3.84 (0.97)	
	Median	4.0	4.0	4.0	
	(P25; P75)	(3.0; 4.0)	(3.0; 4.0)	(3.0; 4.0)	
	(Min; Max)	(1.0; 6.0)	(1.0; 6.0)	(1.0; 6.0)	
	N missing	21	8	13	
Doctor-rated CGI-S- Visit 2	Total	295 (100.0%)	147 (100.0%)	148 (100.0%)	0.5909
	< 4	96 (32.5%)	50 (34.0%)	46 (31.1%)	
	≥ 4	199 (67.5%)	97 (66.0%)	102 (68.9%)	
	N missing	21	8	13	
	N	287	144	143	0.3368

Table 34 - CGI - ITT set

Variable		Total	Study group	Control group	p-value (1)
Doctor-rated CGI-S- Visit 3	Mean (DE)	3.43 (1.19)	3.36 (1.20)	3.50 (1.19)	
	Median	4.0	3.0	4.0	
	(P25; P75)	(3.0; 4.0)	(3.0; 4.0)	(3.0; 4.0)	
	(Min; Max)	(1.0; 6.0)	(1.0; 6.0)	(1.0; 6.0)	
	N missing	29	11	18	
Doctor-rated CGI-S- Visit 3	Total	287 (100.0%)	144 (100.0%)	143 (100.0%)	**0.0205**
	< 4	130 (45.3%)	75 (52.1%)	55 (38.5%)	
	≥ 4	157 (54.7%)	69 (47.9%)	88 (61.5%)	
	N missing	29	11	18	
Self-rated CGI-S- Visit 0	N	315	155	160	0.3200
	Mean (DE)	4.75 (0.89)	4.80 (0.99)	4.70 (0.78)	
	Median	5.0	5.0	5.0	
	(P25; P75)	(4.0; 5.0)	(4.0; 5.0)	(4.0; 5.0)	
	(Min; Max)	(1.0; 7.0)	(1.0; 7.0)	(1.0; 7.0)	
	N missing	1	0	1	
Self-rated CGI-S- Visit 0	Total	315 (100.0%)	155 (100.0%)	160 (100.0%)	0.6991
	< 4	9 (2.9%)	5 (3.2%)	4 (2.5%)	
	≥ 4	306 (97.1%)	150 (96.8%)	156 (97.5%)	
	N missing	1	0	1	
Self-rated CGI-S- Visit 1	N	316	155	161	0.7535
	Mean (DE)	4.74 (0.79)	4.75 (0.81)	4.73 (0.78)	
	Median	5.0	5.0	5.0	
	(P25; P75)	(4.0; 5.0)	(4.0; 5.0)	(4.0; 5.0)	
	(Min; Max)	(3.0; 7.0)	(3.0; 7.0)	(3.0; 7.0)	
	N missing	0	0	0	
Self-rated CGI-S- Visit 1	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.2961
	< 4	4 (1.3%)	3 (1.9%)	1 (0.6%)	
	≥ 4	312 (98.7%)	152 (98.1%)	160 (99.4%)	
	N	295	147	148	0.6617

Table 34 - CGI - ITT set

Variable		Total	Study group	Control group	p-value (1)
Self-rated CGI-S-Visit 2	Mean (DE)	4.03 (1.19)	4.00 (1.14)	4.06 (1.24)	
	Median	4.0	4.0	4.0	
	(P25; P75)	(3.0; 5.0)	(3.0; 5.0)	(3.0; 5.0)	
	(Min; Max)	(1.0; 6.0)	(1.0; 6.0)	(1.0; 6.0)	
	N missing	21	8	13	
Self-rated CGI-S-Visit 2	Total	295 (100.0%)	147 (100.0%)	148 (100.0%)	0.8685
	< 4	85 (28.8%)	43 (29.3%)	42 (28.4%)	
	≥ 4	210 (71.2%)	104 (70.7%)	106 (71.6%)	
	N missing	21	8	13	
Self-rated CGI-S-Visit 3	N	287	144	143	0.3482
	Mean (DE)	3.74 (1.43)	3.66 (1.44)	3.82 (1.42)	
	Median	4.0	4.0	4.0	
	(P25; P75)	(3.0; 5.0)	(3.0; 5.0)	(3.0; 5.0)	
	(Min; Max)	(1.0; 7.0)	(1.0; 6.0)	(1.0; 7.0)	
	N missing	29	11	18	
Self-rated CGI-S-Visit 3	Total	287 (100.0%)	144 (100.0%)	143 (100.0%)	0.3529
	< 4	108 (37.6%)	58 (40.3%)	50 (35.0%)	
	≥ 4	179 (62.4%)	86 (59.7%)	93 (65.0%)	
	N missing	29	11	18	

(1) Chi-squared test or ANOVA according data type

Table 35 - PGI-I - ITT set

Variable		Total	Study group	Control group	p-value (1)
PGI - Visit 1	Total	316 (100.0%)	155 (100.0%)	161 (100.0%)	0.4026
	No change	231 (73.1%)	108 (69.7%)	123 (76.4%)	
	A little worse	46 (14.6%)	26 (16.8%)	20 (12.4%)	
	Much worse	32 (10.1%)	16 (10.3%)	16 (9.9%)	

Table 35 - PGI-I - ITT set

Variable		Total	Study group	Control group	p-value (1)
	Very much worse	7 (2.2%)	5 (3.2%)	2 (1.2%)	
PGI - Visit 2	Total	295 (100.0%)	147 (100.0%)	148 (100.0%)	0.3025
	Very much better	36 (12.2%)	23 (15.6%)	13 (8.8%)	
	Much better	53 (18.0%)	24 (16.3%)	29 (19.6%)	
	A little better	85 (28.8%)	44 (29.9%)	41 (27.7%)	
	No change	74 (25.1%)	35 (23.8%)	39 (26.4%)	
	A little worse	29 (9.8%)	15 (10.2%)	14 (9.5%)	
	Much worse	10 (3.4%)	2 (1.4%)	8 (5.4%)	
	Very much worse	8 (2.7%)	4 (2.7%)	4 (2.7%)	
	N missing	21	8	13	
PGI - Visit 3	Total	287 (100.0%)	144 (100.0%)	143 (100.0%)	0.4406
	Very much better	52 (18.1%)	30 (20.8%)	22 (15.4%)	
	Much better	62 (21.6%)	32 (22.2%)	30 (21.0%)	
	A little better	65 (22.6%)	36 (25.0%)	29 (20.3%)	
	No change	56 (19.5%)	23 (16.0%)	33 (23.1%)	
	A little worse	21 (7.3%)	9 (6.3%)	12 (8.4%)	
	Much worse	23 (8.0%)	9 (6.3%)	14 (9.8%)	
	Very much worse	8 (2.8%)	5 (3.5%)	3 (2.1%)	
	N missing	29	11	18	

(1) Chi-squared test

Table 36 - SDI - ITT set

Variable		Total	Study group	Control group	p-value (1)
SDI Disability - Visit 1	N	310	152	158	0.2223
	Mean (DE)	22.53 (6.04)	22.10 (6.34)	22.94 (5.71)	
	Median	24.0	23.0	24.0	
	(P25; P75)	(20.0; 27.0)	(19.5; 27.0)	(20.0; 27.0)	

Table 36 - SDI - ITT set

Variable		Total	Study group	Control group	p-value (1)
	(Min; Max)	(0.0; 30.0)	(0.0; 30.0)	(0.0; 30.0)	
	N missing	6	3	3	
SDI Disability - Visit 2	N	294	146	148	0.3563
	Mean (DE)	19.46 (7.83)	19.03 (7.32)	19.88 (8.31)	
	Median	21.0	21.0	23.0	
	(P25; P75)	(15.0; 25.0)	(15.0; 25.0)	(16.0; 26.0)	
	(Min; Max)	(0.0; 30.0)	(0.0; 30.0)	(0.0; 30.0)	
	N missing	22	9	13	
SDI Disability - Visit 3	N	286	143	143	0.2008
	Mean (DE)	18.24 (9.05)	17.56 (8.87)	18.93 (9.20)	
	Median	20.0	19.0	22.0	
	(P25; P75)	(12.0; 25.0)	(11.0; 25.0)	(13.0; 26.0)	
	(Min; Max)	(0.0; 30.0)	(0.0; 30.0)	(0.0; 30.0)	
	N missing	30	12	18	
SDI Stress - Visit 1	N	311	153	158	0.7709
	Mean (DE)	7.46 (2.27)	7.42 (2.27)	7.50 (2.27)	
	Median	8.0	8.0	8.0	
	(P25; P75)	(6.0; 9.0)	(6.0; 9.0)	(6.0; 9.0)	
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	5	2	3	
SDI Stress - Visit 2	N	294	146	148	0.7142
	Mean (DE)	6.20 (2.95)	6.14 (2.74)	6.26 (3.16)	
	Median	7.0	7.0	7.0	
	(P25; P75)	(4.0; 9.0)	(4.0; 8.0)	(4.5; 9.0)	
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	22	9	13	
SDI Stress - Visit 3	N	286	143	143	0.2072
	Mean (DE)	5.98 (3.18)	5.74 (3.13)	6.22 (3.23)	
	Median	7.0	7.0	7.0	

Table 36 - SDI - ITT set

Variable		Total	Study group	Control group	p-value (1)
	(P25; P75)	(4.0; 9.0)	(3.0; 8.0)	(4.0; 9.0)	
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	30	12	18	
SDI Social support perceived - Visit 1	N	311	153	158	0.1449
	Mean (DE)	5.79 (2.92)	5.55 (2.91)	6.03 (2.91)	
	Median	6.0	6.0	7.0	
	(P25; P75)	(4.0; 8.0)	(3.0; 8.0)	(4.0; 8.0)	
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	5	2	3	
SDI Social support perceived - Visit 2	N	294	146	148	0.9511
	Mean (DE)	5.97 (2.90)	5.96 (2.87)	5.98 (2.94)	
	Median	6.0	6.0	7.0	
	(P25; P75)	(4.0; 8.0)	(4.0; 8.0)	(4.0; 8.0)	
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	22	9	13	
SDI Social support perceived - Visit 3	N	286	143	143	0.4486
	Mean (DE)	6.20 (2.96)	6.33 (2.99)	6.06 (2.93)	
	Median	7.0	7.0	7.0	
	(P25; P75)	(4.0; 9.0)	(4.0; 9.0)	(4.0; 8.0)	
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	30	12	18	

(1) ANOVA

Table 37 - FIBSER - ITT set

Variable		Total	Study group	Control group	p-value (1)
FIBSER Frequency - Visit 1	N	308	151	157	0.0791
	Mean (DE)	2.10 (2.23)	2.32 (2.23)	1.88 (2.21)	
	Median	2.0	2.0	0.0	

Table 37 - FIBSER - ITT set

Variable		Total	Study group	Control group	p-value (1)
	(P25; P75)	(0.0; 4.0)	(0.0; 4.0)	(0.0; 4.0)	
	(Min; Max)	(0.0; 6.0)	(0.0; 6.0)	(0.0; 6.0)	
	N missing	8	4	4	
FIBSER Frequency - Visit 2	N	295	147	148	0.5218
	Mean (DE)	1.92 (2.09)	1.84 (1.98)	1.99 (2.21)	
	Median	1.0	2.0	1.0	
	(P25; P75)	(0.0; 3.0)	(0.0; 3.0)	(0.0; 4.0)	
	(Min; Max)	(0.0; 6.0)	(0.0; 6.0)	(0.0; 6.0)	
	N missing	21	8	13	
FIBSER Frequency - Visit 3	N	286	143	143	0.8791
	Mean (DE)	1.63 (1.94)	1.65 (1.95)	1.62 (1.94)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(0.0; 3.0)	(0.0; 3.0)	(0.0; 3.0)	
	(Min; Max)	(0.0; 6.0)	(0.0; 6.0)	(0.0; 6.0)	
	N missing	30	12	18	
FIBSER Intensity - Visit 1	N	308	151	157	0.0272
	Mean (DE)	1.94 (1.88)	2.18 (1.86)	1.71 (1.87)	
	Median	2.0	2.0	1.0	
	(P25; P75)	(0.0; 4.0)	(0.0; 4.0)	(0.0; 3.0)	
	(Min; Max)	(0.0; 6.0)	(0.0; 6.0)	(0.0; 6.0)	
	N missing	8	4	4	
FIBSER Intensity - Visit 2	N	295	147	148	0.9169
	Mean (DE)	1.79 (1.78)	1.78 (1.71)	1.80 (1.86)	
	Median	2.0	2.0	1.0	
	(P25; P75)	(0.0; 3.0)	(0.0; 3.0)	(0.0; 3.0)	
	(Min; Max)	(0.0; 6.0)	(0.0; 6.0)	(0.0; 6.0)	
	N missing	21	8	13	
	N	286	143	143	0.9167
	Mean (DE)	1.57 (1.69)	1.56 (1.64)	1.58 (1.75)	

Table 37 - FIBSER - ITT set

Variable		Total	Study group	Control group	p-value (1)
FIBSER Intensity - Visit 3	Median	1.0	2.0	1.0	
	(P25; P75)	(0.0; 3.0)	(0.0; 3.0)	(0.0; 3.0)	
	(Min; Max)	(0.0; 6.0)	(0.0; 6.0)	(0.0; 6.0)	
	N missing	30	12	18	
FIBSER Burden of side effects - Visit 1	N	308	151	157	**0.0157**
	Mean (DE)	1.74 (1.76)	1.99 (1.83)	1.50 (1.66)	
	Median	2.0	2.0	1.0	
	(P25; P75)	(0.0; 3.0)	(0.0; 4.0)	(0.0; 3.0)	
	(Min; Max)	(0.0; 6.0)	(0.0; 6.0)	(0.0; 6.0)	
	N missing	8	4	4	
FIBSER Burden of side effects - Visit 2	N	295	147	148	0.9572
	Mean (DE)	1.59 (1.73)	1.60 (1.71)	1.59 (1.75)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(0.0; 3.0)	(0.0; 3.0)	(0.0; 3.0)	
	(Min; Max)	(0.0; 6.0)	(0.0; 6.0)	(0.0; 6.0)	
	N missing	21	8	13	
FIBSER Burden of side effects - Visit 3	N	286	143	143	0.8267
	Mean (DE)	1.45 (1.62)	1.43 (1.60)	1.47 (1.64)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(0.0; 3.0)	(0.0; 2.0)	(0.0; 3.0)	
	(Min; Max)	(0.0; 6.0)	(0.0; 5.0)	(0.0; 6.0)	
	N missing	30	12	18	

(1) ANOVA

Table 38 - SATMED-Q - ITT set

Variable	Total	Study group	Control group	p-value (1)
N	306	151	155	0.4333

Table 38 - SATMED-Q - ITT set

Variable		Total	Study group	Control group	p-value (1)
SATMED-Q - Visit 1	Mean (DE)	54.16 (15.82)	53.44 (16.07)	54.86 (15.59)	
	Median	54.4	55.9	52.9	
	(P25; P75)	(44.1; 66.2)	(41.2; 64.7)	(44.1; 66.2)	
	(Min; Max)	(8.8; 94.1)	(8.8; 86.8)	(13.2; 94.1)	
	N missing	10	4	6	
SATMED-Q - Visit 2	N	292	144	148	0.1930
	Mean (DE)	61.26 (19.06)	62.73 (18.34)	59.83 (19.70)	
	Median	61.8	63.2	61.8	
	(P25; P75)	(48.5; 76.5)	(51.5; 77.9)	(44.1; 75.0)	
	(Min; Max)	(11.8; 100.0)	(16.2; 100.0)	(11.8; 97.1)	
	N missing	24	11	13	
SATMED-Q - Visit 3	N	286	143	143	0.3195
	Mean (DE)	65.44 (19.45)	66.59 (19.80)	64.29 (19.09)	
	Median	67.6	69.1	66.2	
	(P25; P75)	(52.9; 79.4)	(52.9; 80.9)	(51.5; 77.9)	
	(Min; Max)	(13.2; 100.0)	(16.2; 100.0)	(13.2; 100.0)	
	N missing	30	12	18	
SATMED Side effects - Visit 1	N	308	151	157	0.5015
	Mean (DE)	67.72 (35.43)	66.34 (35.13)	69.06 (35.77)	
	Median	75.0	75.0	83.3	
	(P25; P75)	(25.0; 100.0)	(33.3; 100.0)	(25.0; 100.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	8	4	4	
SATMED Side effects - Visit 2	N	293	145	148	0.9999
	Mean (DE)	72.24 (31.69)	72.24 (30.76)	72.24 (32.68)	
	Median	75.0	75.0	79.2	
	(P25; P75)	(50.0; 100.0)	(50.0; 100.0)	(50.0; 100.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	23	10	13	

Table 38 - SATMED-Q - ITT set

Variable		Total	Study group	Control group	p-value (1)
SATMED Side effects - Visit 3	N	286	143	143	0.8256
	Mean (DE)	75.00 (31.23)	75.41 (31.54)	74.59 (31.01)	
	Median	91.7	91.7	83.3	
	(P25; P75)	(58.3; 100.0)	(58.3; 100.0)	(58.3; 100.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	30	12	18	
SATMED Treatment effectiveness - Visit 1	N	307	151	156	0.6464
	Mean (DE)	34.04 (24.39)	33.39 (25.27)	34.67 (23.58)	
	Median	33.3	33.3	33.3	
	(P25; P75)	(16.7; 50.0)	(16.7; 50.0)	(16.7; 50.0)	
	(Min; Max)	(0.0; 91.7)	(0.0; 91.7)	(0.0; 83.3)	
	N missing	9	4	5	
SATMED Treatment effectiveness - Visit 2	N	293	145	148	0.0993
	Mean (DE)	44.45 (29.24)	47.30 (28.10)	41.67 (30.15)	
	Median	50.0	50.0	37.5	
	(P25; P75)	(25.0; 66.7)	(25.0; 75.0)	(16.7; 66.7)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	23	10	13	
SATMED Treatment effectiveness - Visit 3	N	286	143	143	0.0332
	Mean (DE)	51.84 (28.96)	55.48 (28.03)	48.19 (29.51)	
	Median	50.0	66.7	50.0	
	(P25; P75)	(25.0; 75.0)	(33.3; 75.0)	(25.0; 75.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	30	12	18	
SATMED Convenience of use - Visit 1	N	307	151	156	0.7773
	Mean (DE)	68.81 (26.36)	68.38 (26.74)	69.23 (26.07)	
	Median	75.0	75.0	75.0	
	(P25; P75)	(50.0; 100.0)	(50.0; 100.0)	(50.0; 100.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	

Table 38 - SATMED-Q - ITT set

Variable		Total	Study group	Control group	p-value (1)
	N missing	9	4	5	
SATMED Convenience of use - Visit 2	N	294	146	148	0.5789
	Mean (DE)	72.45 (25.00)	71.63 (25.31)	73.25 (24.75)	
	Median	75.0	75.0	75.0	
	(P25; P75)	(50.0; 100.0)	(50.0; 100.0)	(50.0; 100.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	22	9	13	
SATMED Convenience of use - Visit 3	N	286	143	143	0.8842
	Mean (DE)	75.44 (23.61)	75.64 (24.00)	75.23 (23.30)	
	Median	75.0	75.0	75.0	
	(P25; P75)	(58.3; 100.0)	(58.3; 100.0)	(58.3; 100.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	30	12	18	
SATMED Impact on activities of daily living - Visit 1	N	308	151	157	0.9737
	Mean (DE)	31.68 (26.03)	31.73 (26.08)	31.63 (26.06)	
	Median	25.0	25.0	25.0	
	(P25; P75)	(8.3; 50.0)	(8.3; 50.0)	(8.3; 50.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	8	4	4	
SATMED Impact on activities of daily living - Visit 2	N	294	146	148	0.0544
	Mean (DE)	40.70 (30.28)	44.12 (29.61)	37.33 (30.65)	
	Median	41.7	50.0	33.3	
	(P25; P75)	(16.7; 66.7)	(25.0; 75.0)	(0.0; 58.3)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	22	9	13	
SATMED Impact on activities of daily living - Visit 3	N	286	143	143	0.4824
	Mean (DE)	47.96 (32.20)	49.30 (32.27)	46.62 (32.19)	
	Median	50.0	50.0	50.0	
	(P25; P75)	(25.0; 75.0)	(25.0; 75.0)	(25.0; 75.0)	

Table 38 - SATMED-Q - ITT set

Variable		Total	Study group	Control group	p-value (1)
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	30	12	18	
SATMED Medical care - Visit 1	N	308	151	157	0.3555
	Mean (DE)	74.07 (25.05)	75.41 (23.69)	72.77 (26.31)	
	Median	75.0	75.0	75.0	
	(P25; P75)	(75.0; 100.0)	(75.0; 100.0)	(62.5; 100.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	8	4	4	
SATMED Medical care - Visit 2	N	293	145	148	0.4821
	Mean (DE)	78.46 (24.71)	79.48 (24.99)	77.45 (24.47)	
	Median	75.0	75.0	75.0	
	(P25; P75)	(75.0; 100.0)	(75.0; 100.0)	(75.0; 100.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	23	10	13	
SATMED Medical care - Visit 3	N	286	143	143	0.9088
	Mean (DE)	78.50 (25.73)	78.67 (26.20)	78.32 (25.35)	
	Median	75.0	75.0	75.0	
	(P25; P75)	(75.0; 100.0)	(75.0; 100.0)	(75.0; 100.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	30	12	18	
SATMED General satisfaction - Visit 1	N	307	151	156	0.1309
	Mean (DE)	55.10 (27.36)	52.70 (27.31)	57.43 (27.30)	
	Median	58.3	58.3	58.3	
	(P25; P75)	(33.3; 75.0)	(33.3; 75.0)	(41.7; 75.0)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	9	4	5	
SATMED General satisfaction - Visit 2	N	294	146	148	0.1389
	Mean (DE)	65.36 (28.78)	67.87 (26.32)	62.89 (30.91)	
	Median	66.7	66.7	66.7	

Table 38 - SATMED-Q - ITT set

Variable		Total	Study group	Control group	p-value (1)
	(P25; P75)	(50.0; 91.7)	(50.0; 91.7)	(41.7; 87.5)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	22	9	13	
SATMED General satisfaction - Visit 3	N	286	143	143	0.6386
	Mean (DE)	68.27 (28.26)	69.06 (29.35)	67.48 (27.20)	
	Median	75.0	75.0	75.0	
	(P25; P75)	(50.0; 91.7)	(50.0; 100.0)	(50.0; 83.3)	
	(Min; Max)	(0.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)	
	N missing	30	12	18	

(1) ANOVA

Table 39 - HAM-D - ITT set

Variable		Total	Study group	Control group	p-value (1)
HAM-D - Visit 1	N	309	152	157	0.4818
	Mean (DE)	19.24 (5.83)	19.47 (5.96)	19.01 (5.71)	
	Median	19.0	20.0	19.0	
	(P25; P75)	(15.0; 23.0)	(15.0; 24.0)	(15.0; 23.0)	
	(Min; Max)	(6.0; 37.0)	(7.0; 37.0)	(6.0; 34.0)	
	N missing	7	3	4	
HAM-D - Visit 2	N	292	146	146	0.2835
	Mean (DE)	13.48 (7.03)	13.04 (6.69)	13.92 (7.35)	
	Median	13.0	12.0	14.0	
	(P25; P75)	(9.0; 18.0)	(9.0; 18.0)	(9.0; 19.0)	
	(Min; Max)	(0.0; 33.0)	(0.0; 32.0)	(0.0; 33.0)	
	N missing	24	9	15	
HAM-D - Visit 3	N	285	143	142	0.2655
	Mean (DE)	11.84 (7.38)	11.36 (7.12)	12.33 (7.61)	
	Median	11.0	10.0	12.5	

Table 39 - HAM-D - ITT set

Variable		Total	Study group	Control group	p-value (1)
	(P25; P75)	(6.0; 18.0)	(6.0; 17.0)	(6.0; 19.0)	
	(Min; Max)	(0.0; 37.0)	(0.0; 37.0)	(0.0; 32.0)	
	N missing	31	12	19	

(1) Chi-squared test or ANOVA according data type

Table 40 - PGI-I - ITT set

Variable		Total	Study group	Control group	p-value (1)
PGI - Telephone contact 1	Total	291 (100.0%)	144 (100.0%)	147 (100.0%)	0.4169
	Very much better	25 (8.6%)	11 (7.6%)	14 (9.5%)	
	Much better	63 (21.6%)	30 (20.8%)	33 (22.4%)	
	A little better	77 (26.5%)	44 (30.6%)	33 (22.4%)	
	No change	83 (28.5%)	41 (28.5%)	42 (28.6%)	
	A little worse	18 (6.2%)	10 (6.9%)	8 (5.4%)	
	Much worse	16 (5.5%)	6 (4.2%)	10 (6.8%)	
	Very much worse	9 (3.1%)	2 (1.4%)	7 (4.8%)	
	N missing	25	11	14	
PGI - Telephone contact 2	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.7779
	Very much better	37 (12.8%)	20 (14.0%)	17 (11.6%)	
	Much better	76 (26.2%)	38 (26.6%)	38 (25.9%)	
	A little better	71 (24.5%)	38 (26.6%)	33 (22.4%)	
	No change	68 (23.4%)	28 (19.6%)	40 (27.2%)	
	A little worse	16 (5.5%)	9 (6.3%)	7 (4.8%)	
	Much worse	12 (4.1%)	5 (3.5%)	7 (4.8%)	
	Very much worse	10 (3.4%)	5 (3.5%)	5 (3.4%)	
	N missing	26	12	14	
PGI - Telephone contact 3	Total	280 (100.0%)	136 (100.0%)	144 (100.0%)	0.4036
	Very much better	49 (17.5%)	24 (17.6%)	25 (17.4%)	
	Much better	68 (24.3%)	41 (30.1%)	27 (18.8%)	

Table 40 - PGI-I - ITT set

Variable		Total	Study group	Control group	p-value (1)
	A little better	69 (24.6%)	29 (21.3%)	40 (27.8%)	
	No change	48 (17.1%)	20 (14.7%)	28 (19.4%)	
	A little worse	14 (5.0%)	6 (4.4%)	8 (5.6%)	
	Much worse	15 (5.4%)	8 (5.9%)	7 (4.9%)	
	Very much worse	17 (6.1%)	8 (5.9%)	9 (6.3%)	
	N missing	36	19	17	
(1) Chi-squared test					

Table 41 - CGI-I - ITT set

Variable		Total	Study group	Control group	p-value (1)
Self-rated CGI-S-Telephone contact 1	N	291	144	147	0.7203
	Mean (DE)	4.18 (1.23)	4.20 (1.21)	4.15 (1.25)	
	Median	4.0	4.0	4.0	
	(P25; P75)	(4.0; 5.0)	(4.0; 5.0)	(4.0; 5.0)	
	(Min; Max)	(1.0; 7.0)	(1.0; 7.0)	(1.0; 7.0)	
	N missing	25	11	14	
Self-rated CGI-S-Telephone contact 1	Total	291 (100.0%)	144 (100.0%)	147 (100.0%)	0.5484
	< 4	67 (23.0%)	31 (21.5%)	36 (24.5%)	
	≥ 4	224 (77.0%)	113 (78.5%)	111 (75.5%)	
	N missing	25	11	14	
Self-rated CGI-S-Telephone contact 2	N	290	143	147	0.3922
	Mean (DE)	4.04 (1.29)	3.98 (1.24)	4.11 (1.34)	
	Median	4.0	4.0	4.0	
	(P25; P75)	(3.0; 5.0)	(3.0; 5.0)	(3.0; 5.0)	
	(Min; Max)	(1.0; 7.0)	(1.0; 6.0)	(1.0; 7.0)	
	N missing	26	12	14	
	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.9850

Table 41 - CGI-I - ITT set

Variable		Total	Study group	Control group	p-value (1)
Self-rated CGI-S-Telephone contact 2	< 4	83 (28.6%)	41 (28.7%)	42 (28.6%)	
	≥ 4	207 (71.4%)	102 (71.3%)	105 (71.4%)	
	N missing	26	12	14	
Self-rated CGI-S-Telephone contact 3	N	280	136	144	0.1153
	Mean (DE)	3.85 (1.34)	3.72 (1.33)	3.97 (1.33)	
	Median	4.0	4.0	4.0	
	(P25; P75)	(3.0; 5.0)	(3.0; 5.0)	(3.0; 5.0)	
	(Min; Max)	(1.0; 7.0)	(1.0; 6.0)	(1.0; 7.0)	
	N missing	36	19	17	
Self-rated CGI-S-Telephone contact 3	Total	280 (100.0%)	136 (100.0%)	144 (100.0%)	0.3311
	< 4	93 (33.2%)	49 (36.0%)	44 (30.6%)	
	≥ 4	187 (66.8%)	87 (64.0%)	100 (69.4%)	
	N missing	36	19	17	

(1) Chi-squared test or ANOVA according data type

Table 42 - SDI - ITT set

Variable		Total	Study group	Control group	p-value (1)
SDI Disability - Telephone contact 1	N	290	143	147	0.9811
	Mean (DE)	21.02 (7.59)	21.03 (7.42)	21.01 (7.77)	
	Median	23.0	22.0	24.0	
	(P25; P75)	(17.0; 27.0)	(16.0; 27.0)	(17.0; 27.0)	
	(Min; Max)	(0.0; 30.0)	(0.0; 30.0)	(0.0; 30.0)	
	N missing	26	12	14	
SDI Disability - Telephone contact 2	N	285	142	143	0.6548
	Mean (DE)	19.43 (8.53)	19.20 (8.43)	19.66 (8.66)	
	Median	21.0	20.0	22.0	
	(P25; P75)	(15.0; 26.0)	(14.0; 26.0)	(15.0; 26.0)	
	(Min; Max)	(0.0; 30.0)	(0.0; 30.0)	(0.0; 30.0)	

Table 42 - SDI - ITT set

Variable		Total	Study group	Control group	p-value (1)
	N missing	31	13	18	
SDI Disability - Telephone contact 3	N	278	134	144	0.7216
	Mean (DE)	19.23 (8.51)	19.04 (8.42)	19.41 (8.62)	
	Median	21.0	21.0	22.0	
	(P25; P75)	(14.0; 26.0)	(13.0; 26.0)	(15.5; 26.0)	
	(Min; Max)	(0.0; 30.0)	(0.0; 30.0)	(0.0; 30.0)	
	N missing	38	21	17	
SDI Stress - Telephone contact 1	N	288	142	146	0.5988
	Mean (DE)	6.89 (2.63)	6.97 (2.40)	6.81 (2.85)	
	Median	7.0	7.0	7.0	
	(P25; P75)	(5.0; 9.0)	(5.0; 9.0)	(5.0; 9.0)	
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	28	13	15	
SDI Stress - Telephone contact 2	N	285	141	144	0.9083
	Mean (DE)	6.49 (2.83)	6.48 (2.63)	6.51 (3.02)	
	Median	7.0	7.0	7.0	
	(P25; P75)	(5.0; 9.0)	(5.0; 9.0)	(5.0; 9.0)	
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	31	14	17	
SDI Stress - Telephone contact 3	N	276	133	143	0.4539
	Mean (DE)	6.45 (2.85)	6.32 (2.80)	6.57 (2.90)	
	Median	7.0	7.0	7.0	
	(P25; P75)	(5.0; 8.0)	(5.0; 8.0)	(5.0; 8.0)	
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	40	22	18	
SDI Social support perceived - Telephone contact 1	N	289	142	147	0.5817
	Mean (DE)	5.89 (3.46)	6.01 (3.46)	5.78 (3.47)	
	Median	7.0	7.0	6.0	
	(P25; P75)	(3.0; 9.0)	(3.0; 9.0)	(3.0; 9.0)	

Table 42 - SDI - ITT set

Variable		Total	Study group	Control group	p-value (1)
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	27	13	14	
SDI Social support perceived - Telephone contact 2	N	285	141	144	0.6628
	Mean (DE)	6.20 (3.33)	6.29 (3.38)	6.12 (3.30)	
	Median	7.0	7.0	7.0	
	(P25; P75)	(4.0; 9.0)	(4.0; 9.0)	(4.0; 9.0)	
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	31	14	17	
SDI Social support perceived - Telephone contact 3	N	275	133	142	0.1731
	Mean (DE)	6.02 (3.41)	6.31 (3.40)	5.75 (3.41)	
	Median	7.0	7.0	7.0	
	(P25; P75)	(3.0; 9.0)	(5.0; 10.0)	(3.0; 9.0)	
	(Min; Max)	(0.0; 10.0)	(0.0; 10.0)	(0.0; 10.0)	
	N missing	41	22	19	

(1) ANOVA

Table 43 – Sustained response at 12 weeks - PP set

Variable		Total	Study group	Control group	p-value (1)
Sustained response during 12 weeks - Telephone contact	Total	237 (100.0%)	120 (100.0%)	117 (100.0%)	0.9083
	Yes	90 (38.0%)	46 (38.3%)	44 (37.6%)	
	No	147 (62.0%)	74 (61.7%)	73 (62.4%)	
Response at 12 weeks - Telephone contact	Total	237 (100.0%)	120 (100.0%)	117 (100.0%)	0.1992
	Yes	99 (41.8%)	55 (45.8%)	44 (37.6%)	
	No	138 (58.2%)	65 (54.2%)	73 (62.4%)	
Sustained response during 12 weeks - Face-to-face visits	Total	237 (100.0%)	120 (100.0%)	117 (100.0%)	0.9762
	Yes	63 (26.6%)	32 (26.7%)	31 (26.5%)	
	No	174 (73.4%)	88 (73.3%)	86 (73.5%)	

Table 43 – Sustained response at 12 weeks - PP set

Variable		Total	Study group	Control group	p-value (1)
Response at 12 weeks - Face-to-face visits	Total	237 (100.0%)	120 (100.0%)	117 (100.0%)	0.2980
	Yes	93 (39.2%)	51 (42.5%)	42 (35.9%)	
	No	144 (60.8%)	69 (57.5%)	75 (64.1%)	

(1) Chi-squared test

Table 44 - Response at 6 weeks - PP set

Variable		Total	Study group	Control group	p-value (1)
Response at 6 weeks - Telephone contact	Total	237 (100.0%)	120 (100.0%)	117 (100.0%)	0.7055
	Yes	92 (38.8%)	48 (40.0%)	44 (37.6%)	
	No	145 (61.2%)	72 (60.0%)	73 (62.4%)	
Response at 6 weeks - Face-to-face visits	Total	237 (100.0%)	120 (100.0%)	117 (100.0%)	0.7657
	Yes	71 (30.0%)	37 (30.8%)	34 (29.1%)	
	No	166 (70.0%)	83 (69.2%)	83 (70.9%)	

(1) Chi-squared test

Table 45 – Cost comparison between groups – ITT set

Variable		Total	Study group	Control group	p-value (1)
Mental health-related hospitalizations - During the study	Total	300 (100.0%)	147 (100.0%)	153 (100.0%)	0.7379
	Yes	17 (5.7%)	9 (6.1%)	8 (5.2%)	
	No	283 (94.3%)	138 (93.9%)	145 (94.8%)	
	N missing	16	8	8	
Number of admissions - During the study	N	17	9	8	0.8484
	Mean (DE)	1.41 (0.71)	1.44 (0.73)	1.38 (0.74)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 1.5)	
	(Min; Max)	(1.0; 3.0)	(1.0; 3.0)	(1.0; 3.0)	
	N missing	0	0	0	
	N	17	9	8	0.8176

Table 45 – Cost comparison between groups – ITT set

Variable		Total	Study group	Control group	p-value (1)
Length of stay per admission (days) - During the study	Mean (DE)	13.59 (16.65)	12.67 (18.83)	14.63 (15.03)	
	Median	7.0	5.0	9.5	
	(P25; P75)	(3.0; 12.0)	(3.0; 12.0)	(5.5; 20.5)	
	(Min; Max)	(1.0; 60.0)	(1.0; 60.0)	(1.0; 45.0)	
	N missing	0	0	0	
Emergency department presentation for mental disorder - During the study	Total	300 (100.0%)	147 (100.0%)	153 (100.0%)	0.4148
	Yes	40 (13.3%)	22 (15.0%)	18 (11.8%)	
	No	260 (86.7%)	125 (85.0%)	135 (88.2%)	
	N missing	16	8	8	
Number of admissions - During the study	N	39	21	18	0.4292
	Mean (DE)	2.03 (1.78)	2.24 (2.00)	1.78 (1.52)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 3.0)	(1.0; 3.0)	(1.0; 2.0)	
	(Min; Max)	(1.0; 8.0)	(1.0; 8.0)	(1.0; 6.0)	
	N missing	1	1	1	
Sick leave due to mental disorder - During the study	Total	299 (100.0%)	147 (100.0%)	152 (100.0%)	0.4128
	Yes	90 (30.1%)	41 (27.9%)	49 (32.2%)	
	No	209 (69.9%)	106 (72.1%)	103 (67.8%)	
	N missing	17	8	9	
Length of sick leave (days) - During the study	N	90	41	49	0.9487
	Mean (DE)	71.48 (27.42)	71.68 (25.95)	93.68 (22.92)	
	Median	90.0	90.0	90.0	
	(P25; P75)	(60.0; 92.0)	(60.0; 91.0)	(60.0; 92.0)	
	(Min; Max)	(1.0; 120.0)	(15.0; 93.0)	(1.0; 120.0)	
	N missing	0	0	0	
Visits to the psychiatrist - During the study	Total	300 (100.0%)	147 (100.0%)	153 (100.0%)	0.4537
	Yes	276 (92.0%)	137 (93.2%)	139 (90.8%)	
	No	24 (8.0%)	10 (6.8%)	14 (9.2%)	
	N missing	16	8	8	

Table 45 – Cost comparison between groups – ITT set

Variable		Total	Study group	Control group	p-value (1)
Number of visits - During the study	N	276	137	139	0.0342
	Mean (DE)	3.10 (3.08)	3.50 (3.56)	2.71 (2.46)	
	Median	3.0	3.0	2.0	
	(P25; P75)	(2.0; 3.0)	(2.0; 4.0)	(2.0; 3.0)	
	(Min; Max)	(1.0; 30.0)	(1.0; 30.0)	(1.0; 24.0)	
	N missing	0	0	0	
Non-mental health-related hospitalizations - During the study	Total	300 (100.0%)	147 (100.0%)	153 (100.0%)	0.8691
	Yes	17 (5.7%)	8 (5.4%)	9 (5.9%)	
	No	283 (94.3%)	139 (94.6%)	144 (94.1%)	
	N missing	16	8	8	
Number of admissions - During the study	N	17	8	9	0.8683
	Mean (DE)	1.35 (0.49)	1.38 (0.52)	1.33 (0.50)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 2.0)	
	(Min; Max)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 2.0)	
	N missing	0	0	0	
Length of stay per admission (days) - During the study	N	15	7	8	0.5161
	Mean (DE)	5.07 (4.96)	6.00 (5.74)	4.25 (4.40)	
	Median	3.0	5.0	2.5	
	(P25; P75)	(1.0; 7.0)	(1.0; 10.0)	(1.5; 5.5)	
	(Min; Max)	(1.0; 17.0)	(1.0; 17.0)	(1.0; 14.0)	
	N missing	2	1	1	
Emergency department presentation for non-mental disorder - During the study	Total	300 (100.0%)	147 (100.0%)	153 (100.0%)	0.6425
	Yes	70 (23.3%)	36 (24.5%)	34 (22.2%)	
	No	230 (76.7%)	111 (75.5%)	119 (77.8%)	
	N missing	16	8	8	
Number of admissions - During the study	N	70	36	34	0.0839
	Mean (DE)	2.09 (1.65)	2.42 (1.95)	1.74 (1.19)	
	Median	1.0	2.0	1.0	

Table 45 – Cost comparison between groups – ITT set

Variable		Total	Study group	Control group	p-value (1)
	(P25; P75)	(1.0; 3.0)	(1.0; 3.0)	(1.0; 2.0)	
	(Min; Max)	(1.0; 10.0)	(1.0; 10.0)	(1.0; 6.0)	
	N missing	0	0	0	
Sick leave not due to mental disorder - During the study	Total	299 (100.0%)	147 (100.0%)	152 (100.0%)	0.2074
	Yes	19 (6.4%)	12 (8.2%)	7 (4.6%)	
	No	280 (93.6%)	135 (91.8%)	145 (95.4%)	
	N missing	17	8	9	
Length of sick leave (days) - During the study	N	19	12	7	0.5894
	Mean (DE)	60.16 (33.82)	56.83 (37.10)	65.86 (29.11)	
	Median	60.0	60.0	60.0	
	(P25; P75)	(30.0; 90.0)	(28.5; 91.5)	(59.0; 90.0)	
	(Min; Max)	(1.0; 93.0)	(1.0; 93.0)	(10.0; 92.0)	
	N missing	0	0	0	
Specialist visit for any reason - During the study	Total	300 (100.0%)	147 (100.0%)	153 (100.0%)	0.6581
	Yes	186 (62.0%)	93 (63.3%)	93 (60.8%)	
	No	114 (38.0%)	54 (36.7%)	60 (39.2%)	
	N missing	16	8	8	
Number of visits - During the study	N	186	93	93	0.0381
	Mean (DE)	3.15 (2.83)	2.72 (2.10)	3.58 (3.37)	
	Median	2.0	2.0	2.0	
	(P25; P75)	(1.0; 4.0)	(1.0; 4.0)	(1.0; 4.0)	
	(Min; Max)	(1.0; 18.0)	(1.0; 10.0)	(1.0; 18.0)	
	N missing	0	0	0	
Visits to the Primary Care centre for any reason - During the study	Total	300 (100.0%)	147 (100.0%)	153 (100.0%)	0.8401
	Yes	224 (74.7%)	109 (74.1%)	115 (75.2%)	
	No	76 (25.3%)	38 (25.9%)	38 (24.8%)	
	N missing	16	8	8	
	N	223	109	114	0.2180
	Mean (DE)	3.57 (2.92)	3.82 (3.11)	3.33 (2.72)	

Table 45 – Cost comparison between groups – ITT set

Variable		Total	Study group	Control group	p-value (1)
Number of visits - During the study	Median	3.0	3.0	2.0	
	(P25; P75)	(1.0; 5.0)	(2.0; 5.0)	(1.0; 5.0)	
	(Min; Max)	(1.0; 14.0)	(1.0; 14.0)	(1.0; 12.0)	
	N missing	1	0	1	

(1) Chi-squared test or ANOVA according data type

Table 46 – Cost-effectiveness of NEUROFARMAGEN - ITT set

Variable		Total	Study group	Control group	p-value (1)
Mental health-related hospitalizations - Telephone contact 1	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.4914
	Yes	10 (3.4%)	6 (4.2%)	4 (2.7%)	
	No	280 (96.6%)	137 (95.8%)	143 (97.3%)	
	N missing	26	12	14	
Number of admissions - Telephone contact 1	N	10	6	4	0.4468
	Mean (SD)	1.20 (0.63)	1.33 (0.82)	1.00 (0.00)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 1.0)	(1.0; 1.0)	(1.0; 1.0)	
	(Min; Max)	(1.0; 3.0)	(1.0; 3.0)	(1.0; 1.0)	
	N missing	0	0	0	
Length of stay per admission (days) - Telephone contact 1	N	10	6	4	0.4191
	Mean (SD)	10.20 (8.80)	12.17 (11.09)	7.25 (2.87)	
	Median	7.5	9.5	6.5	
	(P25; P75)	(5.0; 12.0)	(3.0; 20.0)	(5.0; 9.5)	
	(Min; Max)	(1.0; 30.0)	(1.0; 30.0)	(5.0; 11.0)	
	N missing	0	0	0	
Mental health-related hospitalizations - Telephone contact 2	Total	287 (100.0%)	143 (100.0%)	144 (100.0%)	0.9944
	Yes	4 (1.4%)	2 (1.4%)	2 (1.4%)	
	No	283 (98.6%)	141 (98.6%)	142 (98.6%)	
	N missing	29	12	17	
	N	4	2	2	0.4226

Table 46 – Cost-effectiveness of NEUROFARMAGEN - ITT set

Variable		Total	Study group	Control group	p-value (1)
Number of admissions - Telephone contact 2	Mean (SD)	1.25 (0.50)	1.00 (0.00)	1.50 (0.71)	
	Median	1.0	1.0	1.5	
	(P25; P75)	(1.0; 1.5)	(1.0; 1.0)	(1.0; 2.0)	
	(Min; Max)	(1.0; 2.0)	(1.0; 1.0)	(1.0; 2.0)	
	N missing	0	0	0	
Length of stay per admission (days) - Telephone contact 2	N	4	2	2	0.9235
	Mean (SD)	17.00 (15.10)	16.00 (19.80)	18.00 (16.97)	
	Median	18.0	16.0	18.0	
	(P25; P75)	(4.0; 30.0)	(2.0; 30.0)	(6.0; 30.0)	
	(Min; Max)	(2.0; 30.0)	(2.0; 30.0)	(6.0; 30.0)	
	N missing	0	0	0	
Mental health-related hospitalizations - Telephone contact 3	Total	280 (100.0%)	136 (100.0%)	144 (100.0%)	0.9346
	Yes	8 (2.9%)	4 (2.9%)	4 (2.8%)	
	No	272 (97.1%)	132 (97.1%)	140 (97.2%)	
	N missing	36	19	17	
Number of admissions - Telephone contact 3	N	7	3	4	<0.0001
	Mean (SD)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 1.0)	(1.0; 1.0)	(1.0; 1.0)	
	(Min; Max)	(1.0; 1.0)	(1.0; 1.0)	(1.0; 1.0)	
	N missing	1	1	0	
Length of stay per admission (days) - Telephone contact 3	N	7	3	4	0.2449
	Mean (SD)	8.71 (10.53)	3.00 (2.00)	13.00 (12.73)	
	Median	5.0	3.0	10.5	
	(P25; P75)	(1.0; 15.0)	(1.0; 5.0)	(3.5; 22.5)	
	(Min; Max)	(1.0; 30.0)	(1.0; 5.0)	(1.0; 30.0)	
	N missing	1	1	0	
Emergency department presentation for	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.4388
	Yes	19 (6.6%)	11 (7.7%)	8 (5.4%)	

Table 46 – Cost-effectiveness of NEUROFARMAGEN - ITT set

Variable		Total	Study group	Control group	p-value (1)
mental disorder - Telephone contact 1	No	271 (93.4%)	132 (92.3%)	139 (94.6%)	
	N missing	26	12	14	
Number of admissions - Telephone contact 1	N	19	11	8	0.5796
	Mean (SD)	2.11 (1.49)	2.27 (1.42)	1.88 (1.64)	
	Median	1.0	2.0	1.0	
	(P25; P75)	(1.0; 3.0)	(1.0; 3.0)	(1.0; 2.5)	
	(Min; Max)	(1.0; 5.0)	(1.0; 5.0)	(1.0; 5.0)	
	N missing	0	0	0	
Emergency department presentation for non-mental disorder - Telephone contact 2	Total	287 (100.0%)	143 (100.0%)	144 (100.0%)	0.7802
	Yes	15 (5.2%)	8 (5.6%)	7 (4.9%)	
	No	272 (94.8%)	135 (94.4%)	137 (95.1%)	
	N missing	29	12	17	
Number of admissions - Telephone contact 2	N	15	8	7	0.2115
	Mean (SD)	1.47 (0.92)	1.75 (1.16)	1.14 (0.38)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.5)	(1.0; 1.0)	
	(Min; Max)	(1.0; 4.0)	(1.0; 4.0)	(1.0; 2.0)	
	N missing	0	0	0	
Emergency department presentation for mental disorder - Telephone contact 3	Total	280 (100.0%)	136 (100.0%)	144 (100.0%)	0.2274
	Yes	14 (5.0%)	9 (6.6%)	5 (3.5%)	
	No	266 (95.0%)	127 (93.4%)	139 (96.5%)	
	N missing	36	19	17	
Number of admissions - Telephone contact 3	N	13	8	5	0.0179
	Mean (SD)	1.31 (0.63)	1.00 (0.00)	1.80 (0.84)	
	Median	1.0	1.0	2.0	
	(P25; P75)	(1.0; 1.0)	(1.0; 1.0)	(1.0; 2.0)	
	(Min; Max)	(1.0; 3.0)	(1.0; 1.0)	(1.0; 3.0)	
	N missing	1	1	0	
	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.5948

Table 46 – Cost-effectiveness of NEUROFARMAGEN - ITT set

Variable		Total	Study group	Control group	p-value (1)
Sick leave due to mental disorder - Telephone contact 1	Yes	75 (25.9%)	35 (24.5%)	40 (27.2%)	
	No	215 (74.1%)	108 (75.5%)	107 (72.8%)	
	N missing	26	12	14	
Length of sick leave (days) - Telephone contact 1	N	75	35	40	0.6721
	Mean (SD)	30.79 (7.33)	30.40 (0.50)	31.13 (10.07)	
	Median	30.0	30.0	30.0	
	(P25; P75)	(30.0; 31.0)	(30.0; 31.0)	(30.0; 31.0)	
	(Min; Max)	(15.0; 90.0)	(30.0; 31.0)	(15.0; 90.0)	
	N missing	0	0	0	
Sick leave due to mental disorder - Telephone contact 2	Total	287 (100.0%)	143 (100.0%)	144 (100.0%)	0.3556
	Yes	71 (24.7%)	32 (22.4%)	39 (27.1%)	
	No	216 (75.3%)	111 (77.6%)	105 (72.9%)	
	N missing	29	12	17	
Length of sick leave (days) - Telephone contact 2	N	71	32	39	0.2840
	Mean (SD)	29.11 (5.39)	29.88 (2.76)	28.49 (6.82)	
	Median	30.0	30.0	30.0	
	(P25; P75)	(30.0; 31.0)	(30.0; 31.0)	(30.0; 31.0)	
	(Min; Max)	(2.0; 31.0)	(15.0; 31.0)	(2.0; 31.0)	
	N missing	0	0	0	
Sick leave due to mental disorder - Telephone contact 3	Total	279 (100.0%)	136 (100.0%)	143 (100.0%)	0.4731
	Yes	71 (25.4%)	32 (23.5%)	39 (27.3%)	
	No	208 (74.6%)	104 (76.5%)	104 (72.7%)	
	N missing	37	19	18	
Length of sick leave (days) - Telephone contact 3	N	71	32	39	0.7424
	Mean (SD)	28.97 (5.82)	28.72 (6.51)	29.18 (5.26)	
	Median	30.0	30.0	30.0	
	(P25; P75)	(30.0; 31.0)	(30.0; 31.0)	(30.0; 31.0)	
	(Min; Max)	(1.0; 31.0)	(3.0; 31.0)	(1.0; 31.0)	
	N missing	0	0	0	

Table 46 – Cost-effectiveness of NEUROFARMAGEN - ITT set

Variable		Total	Study group	Control group	p-value (1)
Visits to the psychiatrist - Telephone contact 1	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.0114
	Yes	214 (73.8%)	115 (80.4%)	99 (67.3%)	
	No	76 (26.2%)	28 (19.6%)	48 (32.7%)	
	N missing	26	12	14	
Number of visits - Telephone contact 1	N	214	115	99	0.0930
	Mean (SD)	1.50 (1.15)	1.62 (1.29)	1.35 (0.93)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 1.0)	
	(Min; Max)	(1.0; 10.0)	(1.0; 10.0)	(1.0; 8.0)	
	N missing	0	0	0	
Visits to the psychiatrist - Telephone contact 2	Total	287 (100.0%)	143 (100.0%)	144 (100.0%)	0.1164
	Yes	211 (73.5%)	111 (77.6%)	100 (69.4%)	
	No	76 (26.5%)	32 (22.4%)	44 (30.6%)	
	N missing	29	12	17	
Number of visits - Telephone contact 2	N	210	110	100	0.2195
	Mean (SD)	1.43 (1.16)	1.53 (1.36)	1.33 (0.89)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 1.0)	(1.0; 2.0)	(1.0; 1.0)	
	(Min; Max)	(1.0; 10.0)	(1.0; 10.0)	(1.0; 8.0)	
	N missing	1	1	0	
Visits to the psychiatrist - Telephone contact 3	Total	280 (100.0%)	136 (100.0%)	144 (100.0%)	0.2829
	Yes	168 (60.0%)	86 (63.2%)	82 (56.9%)	
	No	112 (40.0%)	50 (36.8%)	62 (43.1%)	
	N missing	36	19	17	
Number of visits - Telephone contact 3	N	167	85	82	0.4951
	Mean (SD)	1.41 (1.22)	1.47 (1.37)	1.34 (1.04)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 1.0)	(1.0; 1.0)	(1.0; 1.0)	
	(Min; Max)	(0.0; 10.0)	(1.0; 10.0)	(0.0; 8.0)	

Table 46 – Cost-effectiveness of NEUROFARMAGEN - ITT set

Variable		Total	Study group	Control group	p-value (1)
	N missing	1	1	0	
Non-mental health-related hospitalizations - Telephone contact 1	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.4980
	Yes	8 (2.8%)	3 (2.1%)	5 (3.4%)	
	No	282 (97.2%)	140 (97.9%)	142 (96.6%)	
	N missing	26	12	14	
Number of admissions - Telephone contact 1	N	8	3	5	<0.0001
	Mean (SD)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 1.0)	(1.0; 1.0)	(1.0; 1.0)	
	(Min; Max)	(1.0; 1.0)	(1.0; 1.0)	(1.0; 1.0)	
	N missing	0	0	0	
Length of stay per admission (days) - Telephone contact 1	N	8	3	5	0.6123
	Mean (SD)	4.13 (3.40)	5.00 (4.36)	3.60 (3.13)	
	Median	2.5	3.0	2.0	
	(P25; P75)	(1.5; 7.0)	(2.0; 10.0)	(1.0; 7.0)	
	(Min; Max)	(1.0; 10.0)	(2.0; 10.0)	(1.0; 7.0)	
	N missing	0	0	0	
Non-mental health-related hospitalizations - Telephone contact 2	Total	287 (100.0%)	143 (100.0%)	144 (100.0%)	0.4671
	Yes	8 (2.8%)	5 (3.5%)	3 (2.1%)	
	No	279 (97.2%)	138 (96.5%)	141 (97.9%)	
	N missing	29	12	17	
Number of admissions - Telephone contact 2	N	8	5	3	<0.0001
	Mean (SD)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 1.0)	(1.0; 1.0)	(1.0; 1.0)	
	(Min; Max)	(1.0; 1.0)	(1.0; 1.0)	(1.0; 1.0)	
	N missing	0	0	0	
Length of stay per admission (days) -	N	7	4	3	0.8748
	Mean (SD)	3.14 (2.41)	3.00 (2.16)	3.33 (3.21)	

Table 46 – Cost-effectiveness of NEUROFARMAGEN - ITT set

Variable		Total	Study group	Control group	p-value (1)
Telephone contact 2	Median	2.0	2.5	2.0	
	(P25; P75)	(1.0; 6.0)	(1.5; 4.5)	(1.0; 7.0)	
	(Min; Max)	(1.0; 7.0)	(1.0; 6.0)	(1.0; 7.0)	
	N missing	1	1	0	
Non-mental health-related hospitalizations - Telephone contact 3	Total	280 (100.0%)	136 (100.0%)	144 (100.0%)	0.9346
	Yes	8 (2.9%)	4 (2.9%)	4 (2.8%)	
	No	272 (97.1%)	132 (97.1%)	140 (97.2%)	
	N missing	36	19	17	
Number of admissions - Telephone contact 3	N	7	3	4	<0.0001
	Mean (SD)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 1.0)	(1.0; 1.0)	(1.0; 1.0)	
	(Min; Max)	(1.0; 1.0)	(1.0; 1.0)	(1.0; 1.0)	
	N missing	1	1	0	
Length of stay per admission (days) - Telephone contact 3	N	6	3	3	0.4035
	Mean (SD)	3.50 (3.89)	5.00 (5.29)	2.00 (1.73)	
	Median	2.0	3.0	1.0	
	(P25; P75)	(1.0; 4.0)	(1.0; 11.0)	(1.0; 4.0)	
	(Min; Max)	(1.0; 11.0)	(1.0; 11.0)	(1.0; 4.0)	
	N missing	2	1	1	
Emergency department presentation for non-mental disorder - Telephone contact 1	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.8262
	Yes	46 (15.9%)	22 (15.4%)	24 (16.3%)	
	No	244 (84.1%)	121 (84.6%)	123 (83.7%)	
	N missing	26	12	14	
Number of admissions - Telephone contact 1	N	46	22	24	0.1676
	Mean (SD)	1.41 (0.83)	1.59 (1.05)	1.25 (0.53)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 1.0)	
	(Min; Max)	(1.0; 5.0)	(1.0; 5.0)	(1.0; 3.0)	

Table 46 – Cost-effectiveness of NEUROFARMAGEN - ITT set

Variable		Total	Study group	Control group	p-value (1)
	N missing	0	0	0	
Emergency department presentation for non-mental disorder - Telephone contact 2	Total	287 (100.0%)	143 (100.0%)	144 (100.0%)	0.0917
	Yes	33 (11.5%)	21 (14.7%)	12 (8.3%)	
	No	254 (88.5%)	122 (85.3%)	132 (91.7%)	
	N missing	29	12	17	
Number of admissions - Telephone contact 2	N	33	21	12	0.3031
	Mean (SD)	1.33 (0.69)	1.43 (0.81)	1.17 (0.39)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 1.0)	(1.0; 2.0)	(1.0; 1.0)	
	(Min; Max)	(1.0; 4.0)	(1.0; 4.0)	(1.0; 2.0)	
	N missing	0	0	0	
Emergency department presentation for non-mental disorder - Telephone contact 3	Total	280 (100.0%)	136 (100.0%)	144 (100.0%)	0.3286
	Yes	26 (9.3%)	15 (11.0%)	11 (7.6%)	
	No	254 (90.7%)	121 (89.0%)	133 (92.4%)	
	N missing	36	19	17	
Number of admissions - Telephone contact 3	N	26	15	11	0.7394
	Mean (SD)	1.42 (0.76)	1.47 (0.83)	1.36 (0.67)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 2.0)	
	(Min; Max)	(1.0; 4.0)	(1.0; 4.0)	(1.0; 3.0)	
	N missing	0	0	0	
Sick leave not due to mental disorder - Telephone contact 1	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.5679
	Yes	16 (5.5%)	9 (6.3%)	7 (4.8%)	
	No	274 (94.5%)	134 (93.7%)	140 (95.2%)	
	N missing	26	12	14	
Length of sick leave (days) - Telephone contact 1	N	16	9	7	0.1994
	Mean (SD)	26.88 (8.11)	29.22 (3.49)	23.86 (11.38)	
	Median	30.0	30.0	30.0	

Table 46 – Cost-effectiveness of NEUROFARMAGEN - ITT set

Variable		Total	Study group	Control group	p-value (1)
	(P25; P75)	(30.0; 30.5)	(30.0; 31.0)	(14.0; 30.0)	
	(Min; Max)	(2.0; 31.0)	(20.0; 31.0)	(2.0; 31.0)	
	N missing	0	0	0	
Sick leave not due to mental disorder - Telephone contact 2	Total	287 (100.0%)	143 (100.0%)	144 (100.0%)	0.5969
	Yes	16 (5.6%)	9 (6.3%)	7 (4.9%)	
	No	271 (94.4%)	134 (93.7%)	137 (95.1%)	
	N missing	29	12	17	
Length of sick leave (days) - Telephone contact 2	N	16	9	7	0.7538
	Mean (SD)	26.13 (9.36)	25.44 (10.50)	27.00 (8.39)	
	Median	30.0	30.0	30.0	
	(P25; P75)	(30.0; 30.5)	(30.0; 31.0)	(30.0; 30.0)	
	(Min; Max)	(1.0; 31.0)	(1.0; 31.0)	(8.0; 31.0)	
	N missing	0	0	0	
Sick leave not due to mental disorder - Telephone contact 3	Total	279 (100.0%)	136 (100.0%)	143 (100.0%)	0.3134
	Yes	11 (3.9%)	7 (5.1%)	4 (2.8%)	
	No	268 (96.1%)	129 (94.9%)	139 (97.2%)	
	N missing	37	19	18	
Length of sick leave (days) - Telephone contact 3	N	11	7	4	0.8700
	Mean (SD)	26.82 (8.04)	27.14 (8.90)	26.25 (7.50)	
	Median	30.0	30.0	30.0	
	(P25; P75)	(30.0; 31.0)	(30.0; 31.0)	(22.5; 30.0)	
	(Min; Max)	(7.0; 31.0)	(7.0; 31.0)	(15.0; 30.0)	
	N missing	0	0	0	
Specialist visit for any reason - Telephone contact 1	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.6675
	Yes	114 (39.3%)	58 (40.6%)	56 (38.1%)	
	No	176 (60.7%)	85 (59.4%)	91 (61.9%)	
	N missing	26	12	14	
	N	114	58	56	0.0628
	Mean (SD)	1.82 (1.09)	1.64 (1.00)	2.02 (1.15)	

Table 46 – Cost-effectiveness of NEUROFARMAGEN - ITT set

Variable		Total	Study group	Control group	p-value (1)
Number of visits - Telephone contact 1	Median	1.0	1.0	2.0	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 3.0)	
	(Min; Max)	(1.0; 6.0)	(1.0; 4.0)	(1.0; 6.0)	
	N missing	0	0	0	
Specialist visit for any reason - Telephone contact 2	Total	287 (100.0%)	143 (100.0%)	144 (100.0%)	0.6588
	Yes	108 (37.6%)	52 (36.4%)	56 (38.9%)	
	No	179 (62.4%)	91 (63.6%)	88 (61.1%)	
	N missing	29	12	17	
Number of visits - Telephone contact 2	N	108	52	56	0.1225
	Mean (SD)	1.86 (1.59)	1.62 (1.37)	2.09 (1.75)	
	Median	1.0	1.0	1.5	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 2.0)	
	(Min; Max)	(1.0; 10.0)	(1.0; 10.0)	(1.0; 9.0)	
	N missing	0	0	0	
Specialist visit for any reason - Telephone contact 3	Total	280 (100.0%)	136 (100.0%)	144 (100.0%)	0.1644
	Yes	100 (35.7%)	43 (31.6%)	57 (39.6%)	
	No	180 (64.3%)	93 (68.4%)	87 (60.4%)	
	N missing	36	19	17	
Number of visits - Telephone contact 3	N	99	43	56	0.6355
	Mean (SD)	1.79 (1.22)	1.72 (1.12)	1.84 (1.30)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 2.0)	
	(Min; Max)	(1.0; 8.0)	(1.0; 6.0)	(1.0; 8.0)	
	N missing	1	0	1	
Visits to the Primary Care centre for any reason - Telephone contact 1	Total	290 (100.0%)	143 (100.0%)	147 (100.0%)	0.9217
	Yes	157 (54.1%)	77 (53.8%)	80 (54.4%)	
	No	133 (45.9%)	66 (46.2%)	67 (45.6%)	
	N missing	26	12	14	
	N	157	77	80	0.6308

Table 46 – Cost-effectiveness of NEUROFARMAGEN - ITT set

Variable		Total	Study group	Control group	p-value (1)
Number of visits - Telephone contact 1	Mean (SD)	1.78 (1.10)	1.74 (0.99)	1.83 (1.20)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 2.0)	
	(Min; Max)	(1.0; 6.0)	(1.0; 5.0)	(1.0; 6.0)	
	N missing	0	0	0	
Visits to the Primary Care centre for any reason - Telephone contact 2	Total	287 (100.0%)	143 (100.0%)	144 (100.0%)	0.6776
	Yes	149 (51.9%)	76 (53.1%)	73 (50.7%)	
	No	138 (48.1%)	67 (46.9%)	71 (49.3%)	
	N missing	29	12	17	
Number of visits - Telephone contact 2	N	149	76	73	0.3585
	Mean (SD)	1.83 (1.11)	1.91 (1.19)	1.74 (1.03)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 2.0)	
	(Min; Max)	(1.0; 5.0)	(1.0; 5.0)	(1.0; 4.0)	
	N missing	0	0	0	
Visits to the Primary Care centre for any reason - Telephone contact 3	Total	278 (100.0%)	135 (100.0%)	143 (100.0%)	0.4694
	Yes	140 (50.4%)	71 (52.6%)	69 (48.3%)	
	No	138 (49.6%)	64 (47.4%)	74 (51.7%)	
	N missing	38	20	18	
Number of visits - Telephone contact 3	N	138	71	67	0.1671
	Mean (SD)	1.77 (1.41)	1.93 (1.69)	1.60 (1.02)	
	Median	1.0	1.0	1.0	
	(P25; P75)	(1.0; 2.0)	(1.0; 2.0)	(1.0; 2.0)	
	(Min; Max)	(1.0; 12.0)	(1.0; 12.0)	(1.0; 5.0)	
	N missing	2	0	2	

(1) Chi-squared test or ANOVA according data type

13.4 Additional analysis

Table 47 – Number of treatments - ITT set

Variable		Total	Study group	Control group	p-value (1)
Number of treatments	N	315	154	161	0.9175
	Mean (DE)	2.56 (2.22)	2.55 (2.35)	2.57 (2.10)	
	Median	2.0	2.0	2.0	
	(P25; P75)	(1.0; 3.0)	(1.0; 3.0)	(1.0; 4.0)	
	(Min; Max)	(0.0; 15.0)	(0.0; 15.0)	(0.0; 10.0)	
	N missing	1	1	0	
Number of treatments	Total	315 (100.0%)	154 (100.0%)	161 (100.0%)	0.8364
	0	50 (15.9%)	25 (16.2%)	25 (15.5%)	
	1	60 (19.0%)	30 (19.5%)	30 (18.6%)	
	2	65 (20.6%)	33 (21.4%)	32 (19.9%)	
	3	65 (20.6%)	34 (22.1%)	31 (19.3%)	
	4	32 (10.2%)	10 (6.5%)	22 (13.7%)	
	5	16 (5.1%)	8 (5.2%)	8 (5.0%)	
	6	8 (2.5%)	4 (2.6%)	4 (2.5%)	
	7	7 (2.2%)	4 (2.6%)	3 (1.9%)	
	8	3 (1.0%)	1 (0.6%)	2 (1.2%)	
	9	4 (1.3%)	2 (1.3%)	2 (1.2%)	
	10	3 (1.0%)	1 (0.6%)	2 (1.2%)	
	11	1 (0.3%)	1 (0.6%)		
	15	1 (0.3%)	1 (0.6%)		
	N missing	1	1	0	

(1) Chi-squared test o ANOVA according data type

Table 48 – Efficacy assessments – Patients with number of treatments = 3 or 4

Variable		Total	Study group	Control group	p-value (1)
	Total	89 (100.0%)	40 (100.0%)	49 (100.0%)	0.6384

Table 48 – Efficacy assessments – Patients with number of treatments = 3 or 4

Variable		Total	Study group	Control group	p-value (1)
PGI – Positive response at 6 weeks	Yes	29 (32.6%)	12 (30.0%)	17 (34.7%)	
	No	60 (67.4%)	28 (70.0%)	32 (65.3%)	
	N missing	8	4	4	
PGI – Positive response at 12 weeks	Total	88 (100.0%)	39 (100.0%)	49 (100.0%)	0.3097
	Yes	31 (35.2%)	16 (41.0%)	15 (30.6%)	
	No	57 (64.8%)	23 (59.0%)	34 (69.4%)	
	N missing	9	5	4	
HAM-D - Visit 1 to 2	N	86	42	44	0.3594
	Mean (DE)	-5.24 (6.02)	-5.86 (6.86)	-4.66 (5.11)	
	Median	-5.0	-5.0	-4.5	
	(P25; P75)	(-8.0; -1.0)	(-10.0; -1.0)	(-8.0; -1.0)	
	(Min; Max)	(-25.0; 8.0)	(-25.0; 8.0)	(-19.0; 7.0)	
	N missing	11	2	9	
HAM-D - Visit 1 to 3	N	86	41	45	0.1497
	Mean (DE)	-7.10 (7.58)	-8.34 (7.89)	-5.98 (7.18)	
	Median	-6.0	-7.0	-4.0	
	(P25; P75)	(-12.0; -2.0)	(-13.0; -3.0)	(-11.0; -1.0)	
	(Min; Max)	(-25.0; 9.0)	(-25.0; 8.0)	(-20.0; 9.0)	
	N missing	11	3	8	

(1) Chi-squared test or ANOVA according data type

Table 49 – Efficacy assessments – Patients with number of treatments > 3

Variable		Total	Study group	Control group	p-value (1)
PGI – Positive response at 12 weeks	Total	63 (100.0%)	28 (100.0%)	35 (100.0%)	0.9068
	Yes	23 (36.5%)	10 (35.7%)	13 (37.1%)	
	No	40 (63.5%)	18 (64.3%)	22 (62.9%)	

Table 49 – Efficacy assessments – Patients with number of treatments > 3

Variable		Total	Study group	Control group	p-value (1)
	N missing	12	4	8	
PGI – Positive response at 6 weeks	Total	66 (100.0%)	29 (100.0%)	37 (100.0%)	0.7785
	Yes	24 (36.4%)	10 (34.5%)	14 (37.8%)	
	No	42 (63.6%)	19 (65.5%)	23 (62.2%)	
	N missing	9	3	6	
HAM-D - Visit 1 to 2	N	65	29	36	0.9194
	Mean (DE)	-4.32 (5.77)	-4.24 (6.42)	-4.39 (5.29)	
	Median	-4.0	-3.0	-4.5	
	(P25; P75)	(-8.0; -1.0)	(-7.0; -0.0)	(-8.0; -1.0)	
	(Min; Max)	(-25.0; 7.0)	(-25.0; 6.0)	(-17.0; 7.0)	
	N missing	10	3	7	
HAM-D - Visit 1 to 3	N	63	30	33	0.4509
	Mean (DE)	-6.59 (7.16)	-5.87 (7.86)	-7.24 (6.51)	
	Median	-5.0	-5.0	-5.0	
	(P25; P75)	(-10.0; -1.0)	(-8.0; -0.0)	(-11.0; -3.0)	
	(Min; Max)	(-25.0; 8.0)	(-25.0; 8.0)	(-22.0; 2.0)	
	N missing	12	2	10	

(1) Chi-squared test or ANOVA according data type

14 Reference List

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15 Appendices

15.1 Subject Data Listings

15.1.1 **Subject allocation to each patient group**

15.1.2 **Eligibility / selection criteria**

15.1.3 **Demographic data**

15.1.4 **Psychiatric treatments during the study**

15.1.5 **Previous psychiatric treatments**

15.1.6 **Concomitant treatments**

15.1.7 **Adverse events**

16 Signatures

I have read this Clinical Study Report and I confirm that it, to the best of my knowledge, accurately describes the conduct and results of the study.

SPONSOR'S REPRESENTATIVE:

DATE: _____

Name, title
Affiliation

COORDINATING/PRINCIPAL INVESTIGATOR:

DATE: _____

Name, title
Affiliation

OTHER:

DATE: _____

Name, title
Affiliation