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

Summary

EudraCT number	2013-002228-18
Trial protocol	ES
Global end of trial date	05 December 2016

Results information

Result version number	v1 (current)
This version publication date	11 June 2022
First version publication date	11 June 2022
Summary attachment (see zip file)	Perez 2017 PMID 28705252 (NFG - Perez et al (2017) BMC Psychiatry, Randomized clinical trial in MDD patients.pdf) AB-GEN-2013 Summary (AB-GEN-2013 Summary acc ICH E3.pdf) AB-GEN-2013 Clinical Study Report (5NEURO~2.PDF) AB-GEN-2013 Statistical Report (4NEURO~1.PDF)

Trial information

Trial identification

Sponsor protocol code	AB-GEN-2013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02529462
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AB-BIOTICS S.A.
Sponsor organisation address	Av. De la Torre Blanca, 57, Sant Cugat del Vallès, Spain, 08172
Public contact	Ariana Salavert, AB-BIOTICS, 0034 935946024, salavert@ab-biotics.com
Scientific contact	Ariana Salavert, AB-BIOTICS, 0034 935946024, salavert@ab-biotics.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2015
Global end of trial reached?	Yes
Global end of trial date	05 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess NEUROFARMAGEN test effectiveness in selecting drug treatments for mental disorders (major depressive disorder, bipolar disorder, schizophrenia and obsessive-compulsive disorder) by the proportion of patients achieving sustained response over a period of six months. Sustained response is considered when the patient gets a PGI-I of 2 points or less in two consecutive assessments after the last change in treatment.

Protection of trial subjects:

The study was assessed by the IRB of Hospital Clínic de Barcelona as the centralized reference IRB, as well as the IRB of each participating hospital. The study was conducted in compliance with Good Clinical Practice requirements and the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment.

An electronic case report form (eCRF) with remote access was designed with security protocols. This system met general and specific good clinical practice guidelines and the highest possible computerised system validation requirements with restricted and personalised access for each user (data manager, monitor, investigators, etc.). All data was collected and managed in strict compliance with Organic Law 15/1999 of 13 December, on Personal data protection.
The eCRF did not identify subjects by their name or initials or any other variable that may lead to their identification, such as their date of birth. The only acceptable identification that appeared on the eCRF or other documents was the unique subject identification number.
Patients were informed Tthat his/her participation in the study is completely free and voluntary and that he/she can withdraw from the study at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 316
Worldwide total number of subjects	316
EEA total number of subjects	316

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	272
From 65 to 84 years	42
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Five hundred and twenty patients (both outpatients and inpatients) were enrolled from 18 hospitals and associated mental health centers in Spain from July 29, 2014 to June 15, 2015.

Pre-assignment

Screening details:

Screening visit (week -4): fulfillment of eligibility criteria, collection of saliva sample to obtain the pharmacogenetic data. N = 520.
Randomization visit (week 0): fulfillment of the entry criteria. N = 316

Pre-assignment period milestones

Number of subjects started	520[1]
Number of subjects completed	316

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Incorrectly randomized: 105
Reason: Number of subjects	Not meeting eligibility criteria: 99

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: This trial had a screening visit (pre-baseline, week -4) to recruit patient meeting eligibility criteria and willing to participate, who needed to provide a saliva sample to genotype them so that those falling in the intervention group at the baseline (randomization, week 0) could have their pharamcogenetic information available. That is why 520 entered the study at the screening visit but only 316 still met eligibility criteria and were randomized at baseline.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[2]
Roles blinded	Subject, Monitor

Blinding implementation details:

Both patients and telephone interviewers who assessed the main variable were blind to the patient allocation (intervention or control group). The treating psychiatrists had access to the results of NEUROFARMAGEN at baseline for the patients in the study group, and at the final visit for the control patient group.

Arms

Are arms mutually exclusive?	Yes
Arm title	NEUROFARMAGEN-guided treatment (intervention group)

Arm description:

In the intervention group, the treating psychiatrists had the results of the NEUROFARMAGEN genetic test as supporting information to help them select the treatment for the patient.

Arm type	Experimental
Investigational medicinal product name	NEUROFARMAGEN (pharmacogenetic test)
Investigational medicinal product code	
Other name	NEUROPHARMAGEN
Pharmaceutical forms	Mouthwash
Routes of administration	Other use

Dosage and administration details:

The product under investigation (NEUROFARMAGEN) is a pharmacogenetic test developed by AB-BIOTICS that enables the analysis of genetic polymorphisms related to the pharmacokinetics and

pharmacodynamics of multiple psychoactive drugs. A saliva sample of the patients, obtained by means of a liquid saliva collector, was needed to genotype them and obtain a pharmacogenetic report. In the intervention arm, treating psychiatrists had access to the pharmacogenetic results to guide the choice the the patient's pharmacological treatment.

Arm title	Treatment as Usual (Control group)

Arm description:

In the control patient group, patients were selected and prescribed pharmacological treatment to treat major depression in accordance with routine clinical practice.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[2] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Both patients and phone interviewers who assessed the main variable were blind to the patient allocation (intervention or control group). The treating psychiatrists/investigators, who assessed patients' clinical status in this trial, had access to the results of NEUROFARMAGEN at baseline for the patients in the study group so that they could prescribe a treatment according to NEUROFARMAGEN. Thus, it is a single blinded trial with a second evaluators for the main variable who is also blind.

Number of subjects in period 1	NEUROFARMAGEN-guided treatment (intervention group)	Treatment as Usual (Control group)
Started	155	161
Completed	147	143
Not completed	8	18
Consent withdrawn by subject	2	4
Others	2	4
Lost to follow-up	4	10

Baseline characteristics

Reporting groups	
Reporting group title	NEUROFARMAGEN-guided treatment (intervention group)
Reporting group description:	
In the intervention group, the treating psychiatrists had the results of the NEUROFARMAGEN genetic test as supporting information to help them select the treatment for the patient.	
Reporting group title	Treatment as Usual (Control group)
Reporting group description:	
In the control patient group, patients were selected and prescribed pharmacological treatment to treat major depression in accordance with routine clinical practice.	

Reporting group values	NEUROFARMAGEN-guided treatment (intervention group)	Treatment as Usual (Control group)	Total
Number of subjects	155	161	316
Age categorical			
All subjects included in the study were 18 years and over (as per inclusion criterium).			
Units: Subjects			
18 years and over	155	161	316
Age continuous			
The age of patients was analysed as a continuous variable as part of the demographic characteristics of the sample population. The intervention and control groups were balanced for this variable.			
Units: years			
arithmetic mean	51.74	50.74	
standard deviation	± 12.05	± 13.12	-
Gender categorical			
Units: Subjects			
Female	99	102	201
Male	56	59	115
Ethnicity			
Self-reported.			
Units: Subjects			
Caucasian	145	147	292
Hispanic	7	10	17
Asian	0	1	1
Middle East	1	0	1
Others	2	3	5
Previous treatment			
Patients with previous antidepressant treatment for the current episode of major depression.			
Units: Subjects			
Yes	130	136	266
No	25	25	50
Patient Global Impression of Improvement (PGI-I)			
The PGI-I scale reports the patient's own assessment of improvement after the therapeutic interventions. It is a single-item questionnaire that assesses the change experienced using a 7-point Likert scale that runs from 1 (very much better) to 7 (very much worse). A patient will be considered a responder when reporting a PGI-I score of 2 or less (i.e. "much better"/"very much better").			
Units: Subjects			
Very much better	0	0	0
Much better	0	0	0

A little better	0	0	0
No change	108	123	231
A little worse	26	20	46
Much worse	16	16	32
Very much worse	5	2	7
Time since diagnosis			
Units: months			
arithmetic mean	58.89	61.52	
standard deviation	± 93.29	± 95.80	-
Previous treatment lines			
Number of previous failed antidepressant treatments for the current epidose of major depression.			
Units: Number of failed antidepressants			
arithmetic mean	2.55	2.57	
standard deviation	± 2.35	± 2.10	-
Clinical Global Impression-Severity (CGI-S) scale, clinician rated			
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.			
Units: Points			
arithmetic mean	4.50	4.40	
standard deviation	± 0.62	± 0.57	-
Hamilton Depression Rating Scale, 17-items (HDRS)			
HDRS-17 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.			
Units: Points			
arithmetic mean	19.47	19.01	
standard deviation	± 5.96	± 5.71	-
Burden of Side Effects			
Burden of side effects was evaluated using the Burden domain of the Frequency, Intensity and Burden of Side Effects Rating (FIBSER) scale. The Burden domain scores range from 0 (no side effects / no impairment) to 6 (intolerable / unable to function / present all of the time).			
Units: Points			
arithmetic mean	1.99	1.50	
standard deviation	± 1.83	± 1.66	-

Subject analysis sets

Subject analysis set title	Intention-to-Treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-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.

Reporting group values	Intention-to-Treat (ITT)		
Number of subjects	316		

Age categorical			
All subjects included in the study were 18 years and over (as per inclusion criterium).			
Units: Subjects			
18 years and over	316		
Age continuous			
The age of patients was analysed as a continuous variable as part of the demographic characteristics of the sample population. The intervention and control groups were balanced for this variable.			
Units: years			
arithmetic mean	51.23		
standard deviation	± 12.60		
Gender categorical			
Units: Subjects			
Female	201		
Male	115		
Ethnicity			
Self-reported.			
Units: Subjects			
Caucasian	292		
Hispanic	17		
Asian	1		
Middle East	1		
Others	5		
Previous treatment			
Patients with previous antidepressant treatment for the current episode of major depression.			
Units: Subjects			
Yes	266		
No	50		
Patient Global Impression of Improvement (PGI-I)			
The PGI-I scale reports the patient's own assessment of improvement after the therapeutic interventions. It is a single-item questionnaire that assesses the change experienced using a 7-point Likert scale that runs from 1 (very much better) to 7 (very much worse). A patient will be considered a responder when reporting a PGI-I score of 2 or less (i.e. "much better"/"very much better").			
Units: Subjects			
Very much better	0		
Much better	0		
A little better	0		
No change	231		
A little worse	46		
Much worse	32		
Very much worse	7		
Time since diagnosis			
Units: months			
arithmetic mean	60.23		
standard deviation	± 94.44		
Previous treatment lines			
Number of previous failed antidepressant treatments for the current epidose of major depression.			
Units: Number of failed antidepressants			
arithmetic mean	2.56		
standard deviation	± 2.22		
Clinical Global Impression-Severity (CGI-S) scale, clinician rated			
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.			
Units: Points			
arithmetic mean	4.45		
standard deviation	± 0.60		
Hamilton Depression Rating Scale, 17-items (HDRS)			
HDRS-17 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.			
Units: Points			
arithmetic mean	19.24		
standard deviation	± 5.83		
Burden of Side Effects			
Burden of side effects was evaluated using the Burden domain of the Frequency, Intensity and Burden of Side Effects Rating (FIBSER) scale. The Burden domain scores range from 0 (no side effects / no impairment) to 6 (intolerable / unable to function / present all of the time).			
Units: Points			
arithmetic mean	1.74		
standard deviation	± 1.76		

End points

End points reporting groups

Reporting group title	NEUROFARMAGEN-guided treatment (intervention group)

Reporting group description:

In the intervention group, the treating psychiatrists had the results of the NEUROFARMAGEN genetic test as supporting information to help them select the treatment for the patient.

Reporting group title	Treatment as Usual (Control group)

Reporting group description:

In the control patient group, patients were selected and prescribed pharmacological treatment to treat major depression in accordance with routine clinical practice.

Subject analysis set title	Intention-to-Treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-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.

Primary: Sustained response to treatment (accordig to PGI-I)

End point title	Sustained response to treatment (accordig to PGI-I)

End point description:

The PGI-I scale (Patient Global Impression of Improvement) reports the patient's own assessment of improvement after the therapeutic interventions. It is a single-item questionnaire that assesses the change experienced using a 7-point Likert scale that runs from 1 (very much better) to 7 (very much worse). A sustained response will be considered when the patient reports a PGI-I score of 2 or less, on at least two consecutive assessments, maintained until the end of the follow-up.

End point type	Primary

End point timeframe:

12 weeks

End point values	NEUROFARMAGEN-guided treatment (intervention group)	Treatment as Usual (Control group)	Intention-to-Treat (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	143	151	294	
Units: Patients				
number (not applicable)				
Yes	55	52	107	
No	88	99	187	

Statistical analyses

Statistical analysis title	Sustained Response at 12 weeks

Statistical analysis description:

Differences between the intervention and control groups with regards to the number of patients with at

least two consecutive evaluations by phone interview with a PGI-I score of 2 or less after the last change of treatment.

Comparison groups	Treatment as Usual (Control group) v NEUROFARMAGEN-guided treatment (intervention group)
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

Secondary: Response to treatment (according to PGI-I)

End point title	Response to treatment (according to PGI-I)

End point description:

The PGI-I scale (Patient Global Impression of Improvement) reports the patient's own assessment of improvement after the therapeutic interventions. It is a single-item questionnaire that assesses the change experienced using a 7-point Likert scale that runs from 1 (very much better) to 7 (very much worse). A patient was considered a responder when reporting a PGI-I score of 2 or less (i.e. "much better"/"very much better").

End point type	Secondary

End point timeframe:

12 weeks

End point values	NEUROFARMAGEN-guided treatment (intervention group)	Treatment as Usual (Control group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	144		
Units: Patients				
number (not applicable)				
Yes	65	52		
No	71	92		

Statistical analyses

Statistical analysis title	Response at 12 weeks
Comparison groups	NEUROFARMAGEN-guided treatment (intervention group) v Treatment as Usual (Control group)
Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.61

Secondary: Response to treatment (according to HDRS-17)

End point title	Response to treatment (according to HDRS-17)

End point description:

HDRS-17 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. The analysis of the response to treatment according the the HDRS-17 sought to find statystical differences between study groups in terms of score change in this scale from baseline to the end of the study.

End point type	Secondary

End point timeframe:

12 weeks

End point values	NEUROFARMAGEN-guided treatment (intervention group)	Treatment as Usual (Control group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	139		
Units: Points				
arithmetic mean (standard deviation)	-8.04 (± 7.72)	-6.47 (± 7.12)		

Statistical analyses

Statistical analysis title	Response at 12 weeks
Comparison groups	NEUROFARMAGEN-guided treatment (intervention group) v Treatment as Usual (Control group)
Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.1
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	3.32

Variability estimate	Standard error of the mean
Dispersion value	0.89

Secondary: Burden of Side Effects

End point title	Burden of Side Effects

End point description:

The Burden domain consists of 1 questions with scores ranging from 0 (no side effects / no impairment) to 6 (intolerable / unable to function / present all of the time). The aim was to compare the number of subjects in the study and control groups with a score equal or lower than 2 (i.e., tolerated pharmacological treatment).

End point type	Secondary

End point timeframe:

12 weeks

End point values	NEUROFARMAGEN-guided treatment (intervention group)	Treatment as Usual (Control group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	140		
Units: Points				
arithmetic mean (standard deviation)	-0.57 (± 2.00)	-0.01 (± 1.72)		

Statistical analyses

Statistical analysis title	Response at 12 weeks
Comparison groups	NEUROFARMAGEN-guided treatment (intervention group) v Treatment as Usual (Control group)
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.22

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events regardless of causality were collected for all patients from the time of signature of informed consent (screening visit, week -4) throughout the follow-up period (end of the study, week 12).

Adverse event reporting additional description:

All Adverse Events (AEs) starting after baseline were recorded on the case report form by the investigators, and included: start date, severity, causality with the drug, actions taken with regards to treatment, date and resolution of AE, unexpected and/or serious AE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Frequency threshold for reporting non-serious adverse events: 5 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Adverse events are reported in table 25 and table 26 of the Clinical Trial Report (attached document)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Main limitations:
- majority of patients of Caucasian origin
- primary variable measured with a simple patient-rated scale (PGI-I)

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/2870525

http://www.ncbi.nlm.nih.gov/pubmed/29728861

http://www.ncbi.nlm.nih.gov/pubmed/31480800