Clinical trial results:
International Study to Predict Optimised Treatment - in Depression (iSPOT-D)

Summary

EudraCT number	2008-004122-17
Trial protocol	NL
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	03 June 2020
First version publication date	03 June 2020

Trial information

Trial identification

Sponsor protocol code	iSPOT-D

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Total Brain
Sponsor organisation address	268 Bush Street, #2633, San Francisco, United States,
Public contact	Donna Palmer, Total Brain, +614 0404 861 295, donna.palmer@totalbrain.com
Scientific contact	Donna Palmer, Total Brain, +614 0404 861 295, donna.palmer@totalbrain.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	Interim
Date of interim/final analysis	01 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objectives of the iSPOT-D trial are to use standardised genetic-brain-cognition protocols to:
1. Identify markers of MDD as a diagnostic group and its subtypes
2. Identify markers which change with acute (8 weeks) drug treatment in MDD
3. Identify predictors of treatment response in MDD, and types of response
4. To determine whether distinct individual characteristics in MDD subjects predict degree of response to different treatment with different medications
Secondary questions will also be explored systematically within each of the above objectives:
1. Whether the markers of MDD and its sub-types also distinguish clusters of comorbid conditions in MDD.
2. Whether the extent of change in markers with treatment is associated with other subject's characteristics, such as age and sex.
3. If markers which predict severity and response to treatment, also predict other aspects of drug response, such as number of side effects.

Protection of trial subjects:

Site/ Data monitoring completed intermittently.
Data Safety Management Board (DSMB) convened intermittently.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Ethical reason
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 659
Country: Number of subjects enrolled	United States: 1318
Country: Number of subjects enrolled	New Zealand: 65
Country: Number of subjects enrolled	Netherlands: 112
Country: Number of subjects enrolled	South Africa: 9
Worldwide total number of subjects	2163
EEA total number of subjects	112

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)	2163
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At screening, clinic trial coordinators gather participant eligibility and sociodemographic data. The Mini-International Neuropsychiatric Interview (MINI-Plus) is used to confirm DSM-IV criteria for nonpsychotic MDD, and assess for psychiatric and substance abuse disorders and other potential exclusion criteria.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Escitalopram

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Escitalopram
Investigational medicinal product code	
Other name	Lexapro
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg/day as a single dose, increased to max 20 mg/day

Arm title	Sertraline

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Zoloft
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg/day as a single dose, increased to max of 200 mg/day

Arm title	Venlafaxine-XR

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Effexor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

75 mg/day given once daily; increased to 150-225 mg/day

Arm title	Healthy Control

Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1[1]	Escitalopram	Sertraline	Venlafaxine-XR
Started	336	336	336
Completed	172	164	176
Not completed	164	172	160
Physician decision	2	1	1
Consent withdrawn by subject	20	-	21
Withdrew Consent	-	26	-
Other	2	-	-
Safety, tolerability or efficacy reasons	20	14	17
Subject randomized but never dosed with study drug	29	20	31
Lost to follow-up	84	104	87
Study discontinued by sponsor	-	-	-
Protocol deviation	7	7	3

Number of subjects in period 1[1]	Healthy Control
Started	336
Completed	250
Not completed	86
Physician decision	2
Consent withdrawn by subject	12
Withdrew Consent	-
Other	-
Safety, tolerability or efficacy reasons	-
Subject randomized but never dosed with study drug	-
Lost to follow-up	70
Study discontinued by sponsor	2
Protocol deviation	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1008 MDD subjects and 336 matched healthy controls have been used in primary analyses. Remaining subjects have been withheld as validation cohort in line with dialogue with the FDA.

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	1344	1344	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	37.6		
standard deviation	± 12.7	-	
Gender categorical Units: Subjects			
Female	762	762	
Male	582	582	

End points

End points reporting groups

Reporting group title	Escitalopram
Reporting group description: -	
Reporting group title	Sertraline
Reporting group description: -	
Reporting group title	Venlafaxine-XR
Reporting group description: -	
Reporting group title	Healthy Control
Reporting group description: -	

Primary: Hamilton Rating Scale for Depression

End point title	Hamilton Rating Scale for Depression[1]

End point description:

The primary research outcome is treatment response, defined as a ≥50% decrease from the baseline on the 17 item Hamilton Rating Scale for Depression.

End point type	Primary

End point timeframe:

Baseline to week 8

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint not required for Healthy Controls

End point values	Escitalopram	Sertraline	Venlafaxine-XR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	246	233	
Units: 17				
Responder	141	163	139	
Non-Responder	92	83	94	

Statistical analyses

Statistical analysis title	Mixed-linear models
Comparison groups	Escitalopram v Sertraline v Venlafaxine-XR
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	> 0.05
Method	Mixed models analysis

Notes:

[2] - See https://www.ncbi.nlm.nih.gov/pubmed/25586212 for full details

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline through to Week 52 (if completed) for each participant in first cohort.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Escitalopram
Reporting group description: -	
Reporting group title	Sertraline
Reporting group description: -	
Reporting group title	Venlafaxine-XR
Reporting group description: -	
Reporting group title	Healthy Controls

Reporting group description: -

Serious adverse events	Escitalopram	Sertraline	Venlafaxine-XR
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 336 (1.49%)	4 / 336 (1.19%)	5 / 336 (1.49%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung cancer developed			
subjects affected / exposed	0 / 336 (0.00%)	1 / 336 (0.30%)	0 / 336 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
blood too thin			
subjects affected / exposed	0 / 336 (0.00%)	0 / 336 (0.00%)	1 / 336 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Placentia previa, bleeding problems			
subjects affected / exposed	0 / 336 (0.00%)	0 / 336 (0.00%)	1 / 336 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

blood clot			
subjects affected / exposed	0 / 336 (0.00%)	0 / 336 (0.00%)	0 / 336 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 336 (0.00%)	1 / 336 (0.30%)	0 / 336 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
oesophageal spasm requiring hospitalisation			
subjects affected / exposed	1 / 336 (0.30%)	0 / 336 (0.00%)	0 / 336 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Miscarriage			
subjects affected / exposed	0 / 336 (0.00%)	0 / 336 (0.00%)	1 / 336 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Depression (with melancholic features associated with bereavement)			
subjects affected / exposed	1 / 336 (0.30%)	0 / 336 (0.00%)	0 / 336 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 336 (0.30%)	0 / 336 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchitis and Viral Infection			

subjects affected / exposed	1 / 336 (0.30%)	0 / 336 (0.00%)	0 / 336 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 336 (0.30%)	1 / 336 (0.30%)	2 / 336 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fractured Vertebra (Prolonged Hospitalization)			
subjects affected / exposed	1 / 336 (0.30%)	0 / 336 (0.00%)	0 / 336 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Healthy Controls		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 336 (0.30%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung cancer developed			
subjects affected / exposed	0 / 336 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
blood too thin			
subjects affected / exposed	0 / 336 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Placentia previa, bleeding problems			
subjects affected / exposed	0 / 336 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
blood clot			

subjects affected / exposed	1 / 336 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 336 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
oesophageal spasm requiring hospitalisation			
subjects affected / exposed	0 / 336 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Miscarriage			
subjects affected / exposed	0 / 336 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Depression (with melancholic features associated with bereavement)			
subjects affected / exposed	0 / 336 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 336 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchitis and Viral Infection			
subjects affected / exposed	0 / 336 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 336 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fractured Vertebra (Prolonged Hospitalization)			
subjects affected / exposed	0 / 336 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Escitalopram	Sertraline	Venlafaxine-XR
Total subjects affected by non-serious adverse events			
subjects affected / exposed	193 / 336 (57.44%)	185 / 336 (55.06%)	231 / 336 (68.75%)
Vascular disorders			
Diziness			
subjects affected / exposed	15 / 336 (4.46%)	10 / 336 (2.98%)	16 / 336 (4.76%)
occurrences (all)	17	10	16
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 336 (9.82%)	35 / 336 (10.42%)	36 / 336 (10.71%)
occurrences (all)	40	41	41
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	24 / 336 (7.14%)	20 / 336 (5.95%)	15 / 336 (4.46%)
occurrences (all)	27	21	16
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	11 / 336 (3.27%)	15 / 336 (4.46%)	19 / 336 (5.65%)
occurrences (all)	11	16	19
Nausea			
subjects affected / exposed	35 / 336 (10.42%)	30 / 336 (8.93%)	50 / 336 (14.88%)
occurrences (all)	42	31	59
Psychiatric disorders			

Anxiety			
subjects affected / exposed	12 / 336 (3.57%)	17 / 336 (5.06%)	12 / 336 (3.57%)
occurrences (all)	12	19	12
Insomnia			
subjects affected / exposed	19 / 336 (5.65%)	22 / 336 (6.55%)	29 / 336 (8.63%)
occurrences (all)	20	22	29
Poor quality sleep			
subjects affected / exposed	14 / 336 (4.17%)	10 / 336 (2.98%)	21 / 336 (6.25%)
occurrences (all)	16	12	26
Infections and infestations			
Influenza			
subjects affected / exposed	9 / 336 (2.68%)	7 / 336 (2.08%)	12 / 336 (3.57%)
occurrences (all)	13	8	13
Nasopharyngitis			
subjects affected / exposed	10 / 336 (2.98%)	11 / 336 (3.27%)	6 / 336 (1.79%)
occurrences (all)	10	11	6
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	11 / 336 (3.27%)	8 / 336 (2.38%)	15 / 336 (4.46%)
occurrences (all)	11	8	17

Non-serious adverse events	Healthy Controls		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 336 (20.54%)		
Vascular disorders			
Diziness			
subjects affected / exposed	1 / 336 (0.30%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 336 (5.06%)		
occurrences (all)	21		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 336 (2.68%)		
occurrences (all)	12		
Gastrointestinal disorders			

Dry mouth subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 0 / 336 (0.00%) 0 2 / 336 (0.60%) 2		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Poor quality sleep subjects affected / exposed occurrences (all)	 0 / 336 (0.00%) 0 2 / 336 (0.60%) 2 2 / 336 (0.60%) 2		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 19 / 336 (5.65%) 20 17 / 336 (5.06%) 18		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	 0 / 336 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2008	Herein is a summary of the major changes made to the original protocol dated 07 March 2008 and reflected in Amendment 1 dated 03 June 2008. Deleted text is struck through and additional text is underlined. 1. More specific and robust language added to exclude subjects with suicidal ideologies and/or tendencies. 2. Change from the Quick Inventory of Depressive Symptomatology – Clinician (QIDS-C) rated scale to the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR). At the completion of the Pretreatment visit, subjects will be given a login ID and password to complete computerized assessment on Day 4 and Weeks 2, 4, 6, 8, 12, 16, 24 and 52 post treatment initiation. A member of the research staff will contact the subjects to confirm current medication use and to record adverse events. During this call, the subjects will be reminded to login to the internet system to complete the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR) as well as the Self-Rated Global Measure of the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER). 3. The specific use of a "saliva" drug screen for illicit drug has been removed as none of the commercially available saliva drug kits have been neither FDA approved nor CLIA-waived for use. 4. Typographical error in exclusion number 4 has been corrected to exclude subjects with a known contra-indication to the use of any of the intended medications.
19 January 2009	Herein is a summary of the major changes made to the first amended protocol dated 12 June 2008 and reflected in Amendment 2 dated 19 January 2009. 1. The intent of Section 1.2 Objective 3B is to identify markers that predict a "potential placebo response" based on subject reported early symptom reduction. The current analysis includes use of the HAM-D results however the HAM-D is a clinician rated severity of depression and not done at Day 4. Therefore, the HAM-D results have been removed as an indicator for "potential placebo response" at Day 4. 2. In an effort to clarify the prohibited psychological co-morbid conditions, a list of Axis II disorders has been added to the exclusion criteria for both Depressed and Control Subjects. 3. Ongoing discussions with general practitioners and other treating physicians indicate that thyroid stimulating hormone (TSH) assays are not routinely ordered or reviewed in the initial work-up for depression. Therefore, in an effort to follow standard of care practices, the presence of known hyper- or hypothyroidism as an exclusionary criteria has been removed for both study groups. 4. Reference to the Australian Bureau of Statistics for alcohol consumption has been removed in the exclusion criteria for both study groups. 5. More robust and specific language has been added to Section 4 of the protocol in an effort to better clarify the methods (clinician interview versus on-line self reported questionnaire) used to capture psychological and cognitive data. In addition, to lesson the burden and time required by the subject during the Pretreatment and Week 8 clinic visits, a number of questionnaires and interviews have been deleted, combined, reorganized or shortened. Specifically, all interviews and scales completed by a clinician have been grouped as "Psychological and clinical work-up" and all subject completed questionnaires and scales have been grouped and are now in the "BRC Web Questionnaire". The follow

17 May 2011	Herein is a summary of the major changes made to the second amended protocol dated 19 January 2009 and reflected in Amendment 3 dated 17 May 2011. 1. To ensure that the informed consent is always collected, even in cases where further explorative questions are asked on the telephone screening call, informed consent can be completed any time prior to screening and prior to the baseline directed 48hour window. 2. To reduce potential missing data, saliva may be collected in exceptional cases for DNA analysis where blood cannot be collected. To reduce the likelihood of this method being used as a standard as it is a limited option of DNA collection, sites are directed to only collect saliva instead of blood at a 1:15 ratio and document the reasoning in the source. If it is possible, blood should be collected at the week 8 visit as the optimal form of genetic and Metabolomic variables. 3. More robust and specific language has been used in section 4 of the protocol in an effort to better clarify the study procedures. These include: • Participants must start taking the medication by the Day 4 follow-up call. If they have not started by week 2, they are to be excluded from the study. • During the first 8 weeks, patients are to receive the study medication as their only form of treatment. After Week 8, the patient may receive alternate forms of treatment and these should be recorded under concomitant medications. • Early Termination of Medication Visit is to be conducted when patient stops medication before Week 8. The patient should not be washed out of medication at the time of this visit. 4. The following changes to the exclusion criteria were made for MDD subjects: • In an effort to standardise the data with the Brain Resource Databse (used to confirm data), the head injury item has been altered from 15minutes to 10minutes of "loss of consciousness". • In enhance the ability to enrolled appropriate participants the presence of suicidal ideations and/or

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported