Clinical trial results:
International Study to Predict Optimized Treatment - in Attention-Deficit and Hyperactivity Disorder

Summary

EudraCT number	2009-013272-47
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-A

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	21 December 2017
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 primary objectives of the iSPOT-A trial are to use Brain Resource's standardized 'Integrative Neuroscience' test batteries to 1) Identify objective markers of ADHD compared with healthy controls, using cognitive, brain and genetic markers
2) Identify objective markers that best predict treatment response (defined by active symptom remission) to methylphenidate (immediate release formulation) using cognitive, brain and genetic markers.

Protection of trial subjects:

Site/ Data monitoring completed intermittently.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Ethical reason, Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 174
Country: Number of subjects enrolled	United States: 354
Country: Number of subjects enrolled	Netherlands: 194
Worldwide total number of subjects	722
EEA total number of subjects	194

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)	376
Adolescents (12-17 years)	346
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

ADHD Subjects: To be eligible for screening, subjects must be 6-17 years of age, must have been provided written informed consent to participate from a parent and/or legally recognized guardian, must meet the DSM-IV criteria for ADHD and must be a candidate for treatment with methylphenidate (immediate or extended release).

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	Methylphenidate

Arm description:

Short acting- Dosage: 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended.
Long acting - Dosage: 9 to 20 mg once daily in the morning (with or without food) with gradual increments of 9 to 20 mg weekly. Daily dosage above 60 mg is not recommended.

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

Dosage and administration details:

Short Acting Methylphenidate
Dosage: 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended.

Drug: Long Acting Methylphenidate
Dosage: 9 to 20 mg once daily in the morning (with or without food) with gradual increments of 9 to 20 mg weekly. Daily dosage above 60 mg is not recommended.

Arm title	Healthy Control

Arm description:

Healthy Controls

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Methylphenidate	Healthy Control
Started	336	158
Completed	185	100
Not completed	151	58
Physician decision	2	1
Consent withdrawn by subject	16	6
Safety, tolerability or efficacy reasons	4	-
Subject randomized but never dosed with study drug	19	-
Lost to follow-up	108	49
Protocol deviation	2	2

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: 336 ADHD subjects and 158 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	494	494	
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	11.94		
standard deviation	± 3.25	-	
Gender categorical Units: Subjects			
Female	138	138	
Male	356	356	

End points

End points reporting groups

Reporting group title	Methylphenidate
Reporting group description:	
Short acting- Dosage: 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended. Long acting - Dosage: 9 to 20 mg once daily in the morning (with or without food) with gradual increments of 9 to 20 mg weekly. Daily dosage above 60 mg is not recommended.	
Reporting group title	Healthy Control
Reporting group description:	
Healthy Controls	

Primary: ADHD Rating Scale-IV

End point title	ADHD Rating Scale-IV[1][2]
End point description:	
The primary research outcome is treatment response, defined as a ≥25% decrease from the baseline on the 18 item ADHD Rating Scale-IV.	
End point type	Primary
End point timeframe:	
Baseline to week 6	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No comparison arms for primary endpoint.

[2] - 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	Methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	284			
Units: 18				
Responder	176			
Non-Responder	108			

Statistical analyses

No statistical analyses for this end point

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

Reporting groups	
Reporting group title	Methylphenidate
Reporting group description:	
Short acting- Dosage: 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended. Long acting - Dosage: 9 to 20 mg once daily in the morning (with or without food) with gradual increments of 9 to 20 mg weekly. Daily dosage above 60 mg is not recommended.	
Reporting group title	Healthy Control
Reporting group description:	
Healthy Controls	

Serious adverse events	Methylphenidate	Healthy Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 336 (1.49%)	0 / 158 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Orthodontic operation			
subjects affected / exposed	1 / 336 (0.30%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
his mother was seriously ill and hospitalized for the same			
subjects affected / exposed	1 / 336 (0.30%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
pharyngitis with abces, for which operation and two-day hospital stay was needed			

subjects affected / exposed	1 / 336 (0.30%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bruised tibia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
pyelonephritis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Methylphenidate	Healthy Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	213 / 336 (63.39%)	32 / 158 (20.25%)	
Nervous system disorders			
Headache			
subjects affected / exposed	50 / 336 (14.88%)	15 / 158 (9.49%)	
occurrences (all)	59	19	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	19 / 336 (5.65%)	1 / 158 (0.63%)	
occurrences (all)	19	5	
Nausea			
subjects affected / exposed	16 / 336 (4.76%)	2 / 158 (1.27%)	
occurrences (all)	17	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	32 / 336 (9.52%)	0 / 158 (0.00%)	
occurrences (all)	33	0	
Infections and infestations			

Influenza			
subjects affected / exposed	17 / 336 (5.06%)	8 / 158 (5.06%)	
occurrences (all)	19	9	
Nasopharyngitis			
subjects affected / exposed	25 / 336 (7.44%)	6 / 158 (3.80%)	
occurrences (all)	32	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	54 / 336 (16.07%)	0 / 158 (0.00%)	
occurrences (all)	55	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2009	1. Mini International Neuropsychiatric Interview (MINI Plus) replaced with Mini International Neuropsychiatric Interview for Children and Adolescents (MINI Kid) as this is more appropriate for the subject population. 2. Specific language to clarify the use of the MINI Kid to exclude subjects with pervasive developmental disorders and psychotic disorders. 3. Removal of the Clinical Global Impressions scale. 4. Conners Comprehensive Behaviour Rating Scales (CBRS) replaced with Conners Rating Scales- Revised (CRS-R). 5. Neuroticism, Extroversion and Openness Five Factor Inventory (NEO-FFI) for children replaced with Five Factor Personality Inventory – Children (FFPI-C). 6. 2nd blood draw added at week 6 visit
10 October 2010	1. Both short acting and extended release methylphenidate can be prescribed as treatment for the study as this is common practice. 2. Informed consent may be obtained more than 48hrs prior to screening procedures. 3. Development of an Early Termination Visit to obtain as much useful information from participants as possible. Patients who early terminate from the study can still complete follow up assessments. 4. Inclusion criteria – Subjects who score at least 6 Inattentive or Hyperactive/impulsive items >1 on the Attention Deficit / Hyperactivity Disorder Rating Scale. 5. Exclusion criteria – History of brain injury details to be standardized to match the Brain Resource International Database criteria. 6. Brain Resource must be notified of any Serious Adverse Events within 24hrs of site personnel being informed of the event. 7. The inclusion of a Publication Plan as Appendix F. 8. Definition of Study Deviation and description of standard procedure once one has occurred.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported