Clinical trial results:
A randomised, double-blind, placebo controlled, parallel group comparison study to evaluate the efficacy and safety of Paxil® Tablets in children and adolescents with Major Depressive Disorder- MRP

Summary

EudraCT number	2015-004905-17
Trial protocol	Outside EU/EEA
Global end of trial date	21 February 2011

Results information

Result version number	v1 (current)
This version publication date	01 December 2016
First version publication date	01 December 2016

Trial information

Trial identification

Sponsor protocol code	112487

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 April 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 February 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

TBD

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 March 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 56
Worldwide total number of subjects	56
EEA total number of subjects	0

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)	5
Adolescents (12-17 years)	51
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:

This study consisted of 3 phases: a 2-week placebo run-in phase, an 8-week treatment phase, and a 0- to 3-week taper phase. In the run-in phase, placebo was administered once daily for 2 weeks. In the treatment phase, paroxetine or placebo was orally administered once daily for 8 weeks. In the taper phase, the dose was gradually reduced.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants took placebo once daily in the treatment phase (8 weeks) and the taper phase (0 to 3 weeks).

Arm type	Placebo
Investigational medicinal product name	Matched placebo to Paroxetine 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet once a day after evening meal

Investigational medicinal product name	Matched placebo to Paroxetine 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 tablets once a day after evening meal

Arm title	Paroxetine

Arm description:

Paroxetine at the initial dose of 10 milligrams (mg) was orally administered once daily for the first 2 weeks of the treatment phase (total of 8 weeks). During the next 6 weeks, paroxetine 10 to 20 mg for participants aged 7 to 11 years or 10 to 40 mg for participants aged 12 to 17 years was orally administered. The dose was up-titrated by one level at a time (an increment of 10 mg/day) at intervals of at least 2 weeks based on clinical judgment. During the taper phase, (0 to 3 weeks), the last dose level in the treatment phase was reduced by 10 mg/day at intervals of 1 week to the final dose level of 10 mg/day.

Arm type	Experimental

Investigational medicinal product name	Paroxetine 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 or 2 tablets once daily after evening meal

Investigational medicinal product name	Paroxetine 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet once a day after evening meal

Number of subjects in period 1	Placebo	Paroxetine
Started	27	29
Completed	24	25
Not completed	3	4
Consent withdrawn by subject	-	2
Adverse event, non-fatal	2	1
Lost to follow-up	-	1
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants took placebo once daily in the treatment phase (8 weeks) and the taper phase (0 to 3 weeks).	
Reporting group title	Paroxetine
Reporting group description:	
Paroxetine at the initial dose of 10 milligrams (mg) was orally administered once daily for the first 2 weeks of the treatment phase (total of 8 weeks). During the next 6 weeks, paroxetine 10 to 20 mg for participants aged 7 to 11 years or 10 to 40 mg for participants aged 12 to 17 years was orally administered. The dose was up-titrated by one level at a time (an increment of 10 mg/day) at intervals of at least 2 weeks based on clinical judgment. During the taper phase, (0 to 3 weeks), the last dose level in the treatment phase was reduced by 10 mg/day at intervals of 1 week to the final dose level of 10 mg/day.	

Reporting group values	Placebo	Paroxetine	Total
Number of subjects	27	29	56
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	14.8	14.4	
standard deviation	± 2.62	± 1.99	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	18	16	34
Male	9	13	22
Race/Ethnicity, Customized Units: Subjects			
Asian - Japanese Heritage	27	29	56

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants took placebo once daily in the treatment phase (8 weeks) and the taper phase (0 to 3 weeks).

Reporting group title	Paroxetine

Reporting group description:

Paroxetine at the initial dose of 10 milligrams (mg) was orally administered once daily for the first 2 weeks of the treatment phase (total of 8 weeks). During the next 6 weeks, paroxetine 10 to 20 mg for participants aged 7 to 11 years or 10 to 40 mg for participants aged 12 to 17 years was orally administered. The dose was up-titrated by one level at a time (an increment of 10 mg/day) at intervals of at least 2 weeks based on clinical judgment. During the taper phase, (0 to 3 weeks), the last dose level in the treatment phase was reduced by 10 mg/day at intervals of 1 week to the final dose level of 10 mg/day.

Primary: Change from Baseline in the Children's Depression Rating Scale -Revised (CDRS-R) Total Score at Week 8

End point title	Change from Baseline in the Children's Depression Rating Scale -Revised (CDRS-R) Total Score at Week 8

End point description:

The CDRS-R has been widely used for the evaluation of children and adolescents with major depressive disorder (MDD). The CDRS-R total score is the sum of the responses to 17 questions. Each question is graded on a 5- or 7-point scale. The highest possible score is 113 (the most severe measure of depression), and the lowest is 17 (not suffering from depression). CDRS-R scores were assessed by the investigator. The change from Baseline in the CDRS-R total score was calculated as the total score at Week 8 minus the total score at Baseline. The data were adjusted with the total score at Baseline. Full Analysis Set (FAS): all participants who entered the treatment phase, but excluding participants without the target indication, participants who received no tablet of the treatment phase medication, or participants who had no post-baseline CDRS-R data. The analysis was performed on the last observation carried forward (LOCF) dataset.

End point type	Primary

End point timeframe:

Baseline and Week 8

End point values	Placebo	Paroxetine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[1]	29[2]		
Units: scores on a scale				
least squares mean (standard error)	-11.9 (± 2.54)	-16.5 (± 2.45)		

Notes:

[1] - Full Analysis Set.

[2] - Full Analysis Set.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Mean difference was estimated as paroxetine minus placebo.

Comparison groups	Paroxetine v Placebo
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.198
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	2.5

Secondary: Change from Baseline in the CDRS-R Total Score at Weeks 1, 2, 3, 4, and 6

End point title	Change from Baseline in the CDRS-R Total Score at Weeks 1, 2, 3, 4, and 6

End point description:

The CDRS-R has been widely used for the evaluation of children and adolescents with major depressive disorder. The CDRS-R total score is the sum of the responses to 17 questions. Each question is graded on a 5- or 7-point scale. The highest possible score is 113 (the most severe measure of depression), and the lowest is 17 (not suffering from depression). CDRS-R scores were assessed by the investigator. The change from Baseline in the CDRS-R total score was calculated as the total score at Week 8 minus the total score at Baseline. The data were adjusted with the total score at Baseline.
The analysis was performed on the observed case dataset. Participants whose observation was missing at a particular visit were not included in the analysis for that week.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, and 6

End point values	Placebo	Paroxetine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[3]	29[4]		
Units: scores on a scale				
least squares mean (standard error)				
Week 1, n=27, 29	-4.6 (± 1.1)	-5.4 (± 1.06)		
Week 2, n=26, 29	-4.9 (± 1.56)	-8.8 (± 1.48)		
Week 3, n=24, 28	-10.6 (± 1.9)	-12 (± 1.76)		
Week 4, n=25, 27	-12.5 (± 2.24)	-14.6 (± 2.15)		
Week 6, n=24, 26	-14.2 (± 2.21)	-15.7 (± 2.12)		

Notes:

[3] - Full Analysis Set.

[4] - Full Analysis Set.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Clinical Global Impression - Global Improvement (CGI-GI) Responders at Weeks 1, 2, 3, 4, 6, and 8

End point title	Number of Clinical Global Impression - Global Improvement (CGI-GI) Responders at Weeks 1, 2, 3, 4, 6, and 8

End point description:

CGI-GI is assessed on an 8-grade scale: 0, not assessed; 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse. CGI-GI was assessed by the investigator. Participants who were rated as 1 (very much improved) or 2 (much improved) were categorized as CGI-GI responders.
The analysis was performed on the OC dataset. Participants whose observation was missing at a particular visit were not included in the analysis for that week. The analysis of data at Week 8 was also performed on the LOCF dataset

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3, 4, 6, and 8

End point values	Placebo	Paroxetine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[5]	29[6]		
Units: participants				
Week 1, n=27, 29	4	4		
Week 2, n=26, 29	4	7		
Week 3, n=24, 28	7	9		
Week 4, n=25, 27	13	12		
Week 6, n=24, 26	12	13		
Week 8 (OC), n=24, 25	11	14		
Week 8 (LOCF), n=27, 29	11	15		

Notes:

[5] - Full Analysis Set.

[6] - Full Analysis Set.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Clinical Global Impression - Severity of Illness (CGI-SI) Score at Weeks 1, 2, 3, 4, 6, and 8

End point title	Change from Baseline in the Clinical Global Impression - Severity of Illness (CGI-SI) Score at Weeks 1, 2, 3, 4, 6, and 8

End point description:

CGI-SI is assessed on an 8-grade scale: 0, not assessed; 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; and 7, among the most extremely ill. CGI-SI was assessed by the investigator. The change from Baseline in CGI-SI score was calculated as the score at Weeks 1, 2, 3, 4, 6, and 8 minus the score at Baseline.
The analysis was performed on the OC dataset. Participants whose observation was missing at a particular visit were not included in the analysis for
that week. The analysis of data at Week 8 was also performed on the LOCF dataset.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 6, and 8

End point values	Placebo	Paroxetine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[7]	29[8]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1, n=27, 29	-0.1 (± 0.32)	-0.2 (± 0.41)		
Week 2, n=26, 29	-0.1 (± 0.48)	-0.5 (± 0.69)		
Week 3, n=24, 28	-0.3 (± 0.62)	-0.6 (± 0.57)		
Week 4, n=25, 27	-0.5 (± 0.82)	-0.7 (± 0.76)		
Week 6, n=24, 26	-0.5 (± 0.66)	-0.8 (± 0.82)		
Week 8 (OC), n=24, 25	-0.5 (± 0.72)	-1 (± 0.89)		
Week 8 (LOCF), n=27, 29	-0.4 (± 0.75)	-0.9 (± 0.88)		

Notes:

[7] - Full Analysis Set.

[8] - Full Analysis Set.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma paroxetine concentrations at 12 hours and 24 hours after administration of study drug at Week 8 or Withdrawal

End point title	Plasma paroxetine concentrations at 12 hours and 24 hours after administration of study drug at Week 8 or Withdrawal[9]

End point description:

Summary statistics for the plasma paroxetine concentrations at each time point were calculated by the dosage just before blood sampling using data from participants in whom plasma samples were collected at either 12 hours (plus or minus 2 hours) or 24 hours (plus or minus 2 hours) after the last administration of the study drug at Week 8 or Withdrawal (up to Week 8).
All participants who received paroxetine and in whom plasma samples were collected at either 12 hours (plus or minus 2 hours) or 24 hours (plus or minus 2 hours) after the last administration of the study drug at Week 8 or Withdrawal (up to Week 8).

End point type	Secondary

End point timeframe:

Week 8 or Withdrawal (up to Week 8)

Notes:

[9] - 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: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Paroxetine			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
paroxetine 10 mg, 12 hours, n=4	4.4683 (± 2.16507)			
paroxetine 10 mg, 24 hours, n=3	8.9713 (± 7.81518)			
paroxetine 20 mg, 12 hours, n=1	49.582 (± 0)			

paroxetine 20 mg, 24 hours, n=3	18.2713 (± 9.78765)			
paroxetine 30 mg, 12 hours, n=2	64.4285 (± 23.34372)			
paroxetine 40 mg, 12 hours, n=3	108.9133 (± 9.01693)			
paroxetine 40 mg, 24 hours, n=2	67.9855 (± 4.08778)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected during the treatment (8 weeks at maximum) and taper phases (3 weeks at maximum). SAEs were also collected during the follow-up phase (2 weeks after the last dose of investigational product).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants took placebo once daily in the treatment phase (8 weeks) and the taper phase (0 to 3 weeks).

Reporting group title	Paroxetine

Reporting group description:

Paroxetine at the initial dose of 10 mg was orally administered once daily for the first 2 weeks of the treatment phase. In the next 6 weeks, paroxetine 10 to 20 mg for participants aged 7 to 11 years or 10 to 40 mg for participants aged 12 to 17 years was orally administered. The dose was up-titrated by one level at a time (an increment of 10 mg/day) at intervals of at least 2 weeks based on clinical judgment. During the taper phase (0 to 3 weeks), the last dose level in the treatment phase was reduced by 10 mg/day at intervals of 1 week to the final dose level of 10 mg/day.

Serious adverse events	Placebo	Paroxetine	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 29 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Placebo	Paroxetine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 27 (33.33%)	9 / 29 (31.03%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 27 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			

Dysmenorrhoea subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 29 (3.45%) 1	
Psychiatric disorders Suicidal ideation subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	0 / 29 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4 2 / 27 (7.41%) 2	6 / 29 (20.69%) 6 1 / 29 (3.45%) 1	

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

None reported