Clinical trial results:
PEntoxifylline in Anaemia Resistant to erythropoietin (PEAR)

Summary

EudraCT number	2011-006168-30
Trial protocol	GB
Global end of trial date	20 September 2017

Results information

Result version number	v1 (current)
This version publication date	21 April 2019
First version publication date	21 April 2019

Trial information

Trial identification

Sponsor protocol code	RLH_Pentoxifylline_Dec2011

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Barts Health NHS Trust
Sponsor organisation address	Whitechapel, London, United Kingdom, E1 1BB
Public contact	Dr Stanley FAN, Barts and The London NHS Trust, 44 2073777480, s.fan@qmul.ac.uk
Scientific contact	Dr Stanley FAN, Barts and The London NHS Trust, 44 2073777480, s.fan@qmul.ac.uk

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	20 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 September 2017
Global end of trial reached?	Yes
Global end of trial date	20 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study the effects Pentoxifylline in ESA resistant ESRD patients on haemodialysis.

The primary study endpoints is the ESA requirement relative to the Hb level (is there a difference in a randomised placebo controlled cross-over study)?

Protection of trial subjects:

But we had a safety committee comprised of other renal consultants who were not involved with the study

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2012
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	United Kingdom: 84
Worldwide total number of subjects	84
EEA total number of subjects	84

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)	55
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

2 week screening run-in period.
Subjects will attend their Dialysis Unit (run by BHT)for their standard hemodialysis on Day 1 (visit 1).Subjects will be entered in a run-in period for 2 weeks where biochemistry and haematology will be measure weekly (+/-3 days) to establish baseline. All blood tests will be taken prior to a dialysis session.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pentoxy

Arm description:

Trental 400

Arm type	Experimental
Investigational medicinal product name	Pentoxyphylline
Investigational medicinal product code	Pentoxyphylline
Other name	Trental 400
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule per day (overencapsulated Trental 400)

Arm title	Placebo

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Pentoxy	Placebo
Started	30	39
Completed	28	39
Not completed	2	0
Consent withdrawn by subject	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: 84 patients consented to the study. However, this study included a run-in period (before randomisation) and during this time, some patients withdrew. Hence the baseline numbers total 69 and

not the initial "full" 84

Baseline characteristics

Reporting groups	
Reporting group title	Pentoxy
Reporting group description: Trental 400	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Pentoxy	Placebo	Total
Number of subjects	30	39	69
Age categorical Units: Subjects			
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	56.5	56.1	
standard deviation	± 13.2	± 14.1	-
Gender categorical Units: Subjects			
Female	5	10	15
Male	25	29	54
Not recorded	0	0	0
Baseline Hb Units: g/dl			
arithmetic mean	11.3	10.7	
standard deviation	± 0.9	± 0.9	-

End points

End points reporting groups

Reporting group title	Pentoxy
Reporting group description: Trental 400	
Reporting group title	Placebo
Reporting group description: -	

Primary: ESA dose in iu / Hb in g/dl

End point title	ESA dose in iu / Hb in g/dl
End point description:	
End point type	Primary
End point timeframe: 6 months with last result carried forward	

End point values	Pentoxy	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	38		
Units: iu/g/dl				
arithmetic mean (standard deviation)	3.98 (± 3.09)	4.91 (± 3.49)		

Attachments (see zip file)	Outcome_ESA-Hb_1.pdf

Statistical analyses

Statistical analysis title	Primary ESA/Hb analysis

Statistical analysis description:

Primary end point was compared as difference in mean of ESA dose relative to haemoglobin between first two readings during run in period and last two readings during follow up period in experimental and placebo groups using unpaired student t-test. P values of < 0.05 will be considered statistically significant

Comparison groups	Pentoxy v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 6 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	Own specified list
Dictionary version	1

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	IMP arm
Reporting group description: -	

Serious adverse events	Placebo	IMP arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 39 (30.77%)	5 / 30 (16.67%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
cvs excluding fluid overload			
subjects affected / exposed	2 / 39 (5.13%)	3 / 30 (10.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
overload			
subjects affected / exposed	1 / 39 (2.56%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
stroke			
subjects affected / exposed	0 / 39 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
bleed			

subjects affected / exposed	1 / 39 (2.56%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdo Pain			
subjects affected / exposed	1 / 39 (2.56%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Elective bariatric surgery			
subjects affected / exposed	1 / 39 (2.56%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
elective surgery			
subjects affected / exposed	0 / 39 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
pychosomatic muscle weakness			
subjects affected / exposed	1 / 39 (2.56%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
glucose abnormalities			
subjects affected / exposed	1 / 39 (2.56%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	1 / 39 (2.56%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 39 (2.56%)	0 / 30 (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			
Dialysis Access infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 39 (7.69%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
foot infection			
subjects affected / exposed	0 / 39 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	IMP arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 39 (100.00%)	29 / 30 (96.67%)	
Investigations			
medication changes			
subjects affected / exposed	26 / 39 (66.67%)	15 / 30 (50.00%)	
occurrences (all)	65	40	
Vascular disorders			
Dialysis access- non infective			
subjects affected / exposed	32 / 39 (82.05%)	19 / 30 (63.33%)	
occurrences (all)	63	58	
Dialysis Access infections			
subjects affected / exposed	7 / 39 (17.95%)	2 / 30 (6.67%)	
occurrences (all)	10	5	
Cardiac disorders			

cvs excluding fluid overload subjects affected / exposed occurrences (all) fluid overload subjects affected / exposed occurrences (all)	30 / 39 (76.92%) 83 26 / 39 (66.67%) 44	17 / 30 (56.67%) 55 14 / 30 (46.67%) 29	
Nervous system disorders Neuro or eye issues subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	5 / 30 (16.67%) 11	
Gastrointestinal disorders GI disturbance subjects affected / exposed occurrences (all)	16 / 39 (41.03%) 20	7 / 30 (23.33%) 8	
Respiratory, thoracic and mediastinal disorders respiratory disorders subjects affected / exposed occurrences (all)	12 / 39 (30.77%) 20	8 / 30 (26.67%) 11	
Skin and subcutaneous tissue disorders Skin disorder subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	4 / 30 (13.33%) 4	
Renal and urinary disorders Genitourinary symptom subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 8	3 / 30 (10.00%) 3	
Endocrine disorders Endocrine disorder subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 5	8 / 30 (26.67%) 10	
Musculoskeletal and connective tissue disorders Bone Mineral Metabolism subjects affected / exposed occurrences (all)	20 / 39 (51.28%) 29	8 / 30 (26.67%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2013	We applying for the substantial amendment because in the original application the Active IMP, pentoxifylline 400mg prolonged release tablets (Trental), was to be sourced from Germany. Since then, our IMP supplier has informed us that the German product has become unavailable for export, so the IMP is now to be sourced from Portugal. Trental as marketed in Portugal has the Marketing Authorisation (registration) number 4600284 (packs of 60)
20 March 2013	After careful consideration of the recent literature and the funding situation, we should like to remove the "experimental end-points" in the protocol. However, we shall still be consenting patients to have bloods stored for future research. For this reason, we will not change the number, volume or the frequency of the blood tests. As per original protocol, blood will be stored in a HTA approved tissue bank. If we decide to analysis of these stored blood samples at a future date, we shall submit a new study protocol and seek ethical approval prior to any analysis. We believe that there would be potential ethical issues if we were performed tests on patients that are no longer relevant given the current literature. We believe the scientific validity of the study will not be compromised as we are seeking consent for blood to be stored. These can be analysed for experimental end-points at a future date (subject to a different study protocol/ethic submission). Because the frequency and the amount of blood / intervention is unchanged, we have not felt it necessary to amend the Patient Information Sheet (remaining version 4-1 27th Nov 2012).
01 November 2013	1. Changes to the inclusion crieteria: a. Removal of CRP > 5 as one of the inclusion crieteria b. Erythropoietin stimulating agent (ESA) dose has been changed to erythropoietin dose greater than or equal to 6000 iu equivalent of EPO (erythropoietin) per week or if ESA resistance index is greater than or equal to 6.5 iu /kg/wk/g Hb for equivalent EPO dose to maintain stable haemoglobin levels. This dose is similar to median ESA requirement for haemodialysis patients with arterio venous fistula as dialysis access in our unit. 2. Changes to FDG - PET / CT scan protocol : Following the review of initial 5 scans research team has changed the FDG-PET / CT protocol. The new protocol will provide sufficient data for secondary end point analysis. The duration of dynamic imaging for the PET scan has been changed from 0 to 50 minutes to 0 to 60 minutes. The initial protocol of whole body imaging at 60 min and 160 min has now been changed to single whole body imaging at 90 min. The number of venous blood samples during the dynamic imaging has also been reduced to total 11 samples (total blood volume 33 mls per scan) from total 21 blood samples (total blood volume 63mls per scan). This change in imaging protocol had to be implemented before formal approval because there is better patient experience during the scan visit and reduced radiation exposure to patients with no compromise to the quality of data obtained. 3. Patient information sheet has also been modified based in view of change in FDG-PET/CT protocol. Total imaging time for FDG-PET/CT scan has been reduced to 2 hrs compared to 4 hrs previously.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported