Clinical trial results:
A Pilot Randomised Controlled Trial of Drug Treatment for Depression in Patients undergoing Haemodialysis

Summary

EudraCT number	2012-000547-27
Trial protocol	GB
Global end of trial date	13 October 2015

Results information

Result version number	v1 (current)
This version publication date	29 March 2019
First version publication date	29 March 2019
Summary attachment (see zip file)	EudraCT 2012-000547-27 Summary of results (EudraCT 2012-000547-27 Summary of results - Friedli et al CJASN 2017.pdf)

Trial information

Trial identification

Sponsor protocol code	CTIMPMCRENAL12

Additional study identifiers

ISRCTN number	ISRCTN06146268
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ASSERTID: RD2012-37

Notes:

Sponsors

Sponsor organisation name	The University of Hertfordshire
Sponsor organisation address	College Lane, Hatfield, United Kingdom, AL10 9AB
Public contact	Dr Karin Friedli, University of Hertfordshire, 01707 286472, k.friedli1@herts.ac.uk
Scientific contact	Dr Karin Friedli, University of Hertfordshire, 01707 286472, k.friedli1@herts.ac.uk
Sponsor organisation name	East and North Hertfordshire NHS Trust
Sponsor organisation address	Coreys Mill Lane, Stevenage, United Kingdom, SG14AB
Public contact	Professor Phillip Smith, East and North Hertfordshire NHS Trust, 0203 826 2075, phillip.smith5@nhs.net
Scientific contact	Professor Ken Farrington, East and North Hertfordshire NHS Trust, 01438 284346, ken.farrington@nhs.net

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	13 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main research question is to evaluate the feasibility of conducting a randomised, double blind, placebo pilot trial in patients with end stage renal disease (ESRD) and depression. The treatment under investigation is Sertraline, a licensed anti-depressant. The study is split into four phases. Phase one will evaluate the number of ESRD patients eligible for this clinical trial. Phase two will assess the feasibility of conducting a randomised drug trial in this group of patients, by measuring the number who take part. Phase three will look at the safety and drug exposure of Sertraline in ESRD patients and phase four will explore the patient experience of participating in this trial.

Protection of trial subjects:

Patients were afforded the opportunity to talk to a psychiatrist and were monitored carefully and frequently for their low mood.

Research staff conducted close monitoring of patients for serious adverse events/reactions of study IMP, particularly for signs of worsening depression and suicide ideation.

Background therapy:

N/A

Evidence for comparator:

Intervention: Sertraline hydrochloride, starting with 50 mgs orally per day for 2 months, with the option of stepping up to 100 orally mgs for remainder of the trial, if clinically indicated. Control: matched placebo.

Actual start date of recruitment	01 August 2012
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	United Kingdom: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	19
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 709 patients were screened and enrolled between April of 2013 and October of 2014. 37 were diagnosed with major depressive disorder, and 30 were randomised (15 patients to the intervention arm, 15 patients to the control arm)

Pre-assignment

Screening details:

Inclusion: 1. Patients with ESRD and receiving HD. They will have started dialysis at least 3 months ago and have continued to receive dialysis in the past 3 months prior to the invitation to take part in this study. 2. Adults aged 18 or over. 3. Patients who speak and read English sufficiently well to complete questionnaires.

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	Investigator, Monitor, Data analyst, Subject

Blinding implementation details:

The study randomisation codes were only to be broken for medical and safety reasons. In addition blinding could be broken if:
1. requested by the Data Monitoring and Ethics Committee
2. a patient in the study is withdrawn due to the offer of a transplant

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention arm

Arm description:

Sertraline hydrochloride, starting with 50 mgs orally per day for 2 months, with the option of stepping up to 100 orally mgs for remainder of the trial

Arm type	Experimental
Investigational medicinal product name	Sertraline hydrochloride
Investigational medicinal product code	MIA(IMP)11149
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

50 mgs orally per day for 2 months, with the option of stepping up to 100 orally mgs for remainder of the trial

Arm title	Control arm

Arm description:

Control: matched placebo

Arm type	Placebo
Investigational medicinal product name	Matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

50mg orally once a day for one month

Number of subjects in period 1	Intervention arm	Control arm
Started	15	15
Completed	8	13
Not completed	7	2
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	2
Adverse event, non-fatal	4	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	30	30	
Age categorical			
Patients over the age of 18 years old who had been receiving treatment by hemodialysis for 3 months or more were approached. Baseline characteristics were similar in the sertraline and placebo groups. The sertraline group was, on average, 5 years older. For the whole study sample,mean age was 59.06 +/- 13.8 years old.			
Units: Subjects			
30-40 years old	3	3	
41-50 years old	3	3	
51-60 years old	9	9	
61-70 years old	8	8	
71-80 years old	7	7	
Gender categorical			
11 men, 4 women were randomised to the intervention arm, 12 men and 3 women were randomised to the control arm			
Units: Subjects			
Female	7	7	
Male	23	23	

Subject analysis sets

Subject analysis set title	n/a
Subject analysis set type	Full analysis

Subject analysis set description:

Randomised patients

Reporting group values	n/a		
Number of subjects	30		
Age categorical			
Patients over the age of 18 years old who had been receiving treatment by hemodialysis for 3 months or more were approached. Baseline characteristics were similar in the sertraline and placebo groups. The sertraline group was, on average, 5 years older. For the whole study sample,mean age was 59.06 +/- 13.8 years old.			
Units: Subjects			
30-40 years old	3		
41-50 years old	3		
51-60 years old	9		
61-70 years old	8		
71-80 years old	7		
Gender categorical			
11 men, 4 women were randomised to the intervention arm, 12 men and 3 women were randomised to the control arm			
Units: Subjects			
Female	7		

Male	23		

End points

End points reporting groups

Reporting group title	Intervention arm
Reporting group description:	
Sertraline hydrochloride, starting with 50 mgs orally per day for 2 months, with the option of stepping up to 100 orally mgs for remainder of the trial	
Reporting group title	Control arm
Reporting group description:	
Control: matched placebo	
Subject analysis set title	n/a
Subject analysis set type	Full analysis
Subject analysis set description:	
Randomised patients	

Primary: Primary

End point title	Primary[1]
End point description:	
The primary aim was to assess the feasibility of undertaking a large RCT to evaluate the acceptability and effectiveness of sertraline to treat depression in patients on hemodialysis.	
End point type	Primary
End point timeframe:	
from first patient first visit to last patient last visit.	

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: Detailed statistical analyses available in attached publication.

End point values	Intervention arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Number of subjects	15	15		

Attachments (see zip file)	Results summary/EudraCT 2012-000547-27 Summary of

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoints

End point title	Secondary endpoints
End point description:	
Secondary outcomes included the number of patients not meeting the eligibility criteria, the number who refused to take part in the trial, the number who withdrew from the trial, the reasons given, and the number and nature of adverse events reported. Changes in MADRS and BDI-II scores over the course of the study were also evaluated. To estimate medication adherence, we also analysed information on the number of returned tablets and pre-and post-dialysis sertraline levels.	
End point type	Secondary

End point timeframe:
Duration of the trial

End point values	Intervention arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Number of subjects	15	15		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 months following randomisation

Adverse event reporting additional description:

Patients were reassessed by the psychiatrist at 2 weeks and 2, 4, and 6 months and assessed monthly by the research nurse.

Assessment type	Systematic

Dictionary used

Dictionary name	MADRS
Dictionary version	n/a

Reporting groups

Reporting group title	All randomised patients

Reporting group description:

Intervention arm = 15 patients, control arm = 15 patients.

Serious adverse events	All randomised patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 30 (33.33%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Chest pain			

subjects affected / exposed	3 / 30 (10.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Carotid artery stenosis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aneurysm repair	Additional description: Elective Abdominal Aortic Aneurysm repair		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Fluid overload			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fistula repair			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transplant			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All randomised patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 30 (26.67%)		
Injury, poisoning and procedural complications			
Fracture	Additional description: Stress fracture in the right shin		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vascular disorders			
Fistula repair	Additional description: Planned admission for fistulaplasty and aneurysm repair		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Influenza	Additional description: cold/flu-like symptoms with facial pain. General infection.		
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Fatigue	Additional description: Post-dialysis weakness		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Constipation			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis	Additional description: Classification of sweating and palpitation		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Suicidal ideation			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Renal and urinary disorders			
Catheter site infection	Additional description: Haemodialysis exit site infection and High CRP / line infection		
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Bone pain	Additional description: Leg and hip pain		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Infections and infestations			
Nail infection	Additional description: Infected toe from ingrown nail		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Infection	Additional description: Chest infection		
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2013	Substantial Amendment 2 contained a number of protocol (V4.0) changes including the addition of two questionnaires, the Multidimensional Fatigue Inventory (MFI) and Short Form 36 (SF36) energy/fatigue subscale. These questionnaires were used to estimate the prevalence of fatigue and tiredness in ESRD patients as it is believed that Identification and management of fatigue improves the quality of life and might prevent patient from becoming depressed. Patients to be assessed for fatigue as well as depression, QoL, demographic and clinical measures during the prevalence and screening phase of the trial as well as at baseline, during and at the end of the trial. The protocol (V4.0) was changed so that in some trusts patients may initially be approached by letter with the PIS and a short version of the PIS attached. Once the patient has received this information, the research nurse to approach the patients in the same way as the other recruiting trusts. In protocol V4.0 it was assumed that all patients randomised to Arm A received Sertraline hydrochloride and arm B received placebo. This is not the case. In protocol V5.0 Patients to be randomised to Sertraline hydrochloride (Arm A or B) or a placebo (Arm A or B). The way in which SAE's are reported was modified. In protocol V5.0 the CI, PIs or their deputies to complete the sponsor's SAE form on the electronic CRF within 24 hours of his/her becoming aware of the event instead of completing a paper SAE form. The PI to produce a full written report within 5 days once the SAE has been fully managed and send it to the CI and the sponsors (as per GCP guidelines). Minor protocol changes were also made including the addition of new members to the study team at East and North Herts NHS Trust, the alteration of contact details and minor grammatical changes. The ASSERTID drug label (V5.0) was modified to reflect protocol changes.
09 January 2014	Key changes included: amendment objectives were amended to explore views of eligible patients on their willingness to enter a treatment trial, regardless of whether they had consented to take part or not. Inclusion criteria and study procedures were amended to explore reasons why patients choose to enter the trial or not be interviewing eligible patients who have declined to take part in the trial. The sample size estimation was amended in-line with recruitment rates. Patients were invited to take part in phase 2 regardless of whether they had originally consented to take part. An additional site and PI were added.
23 April 2015	Collection of additional data from the patients to estimate impact on depression and survival of patients in this high risk cohort. Added C-Reactive Protein (CRP) as another data variable to collect at screening and at the nurse baseline assessment. The archiving section was clarified in the protocol. A study guidance document was produced. New study document: AssertID Trial Patient Study Card

Notes:

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.

Small sample size : RCT recruitment was difficult and constrained by exclusion of a high number of patients, a large proportion of whom were already receiving treatment for depression, and reluctance of chronically ill patients to participate.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28126706