Clinical trial results:
Effects of erythropoietin (EPO) on cognitive side-effects of electroconvulsive therapy (ECT) (EPO-T)

Summary

EudraCT number	2016-002326-36
Trial protocol	DK
Global end of trial date	10 January 2023

Results information

Result version number	v1 (current)
This version publication date	23 July 2023
First version publication date	23 July 2023

Trial information

Trial identification

Sponsor protocol code	2016-858

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Mental Health Services, Capital Region of Denmark
Sponsor organisation address	Hovedvejen 13, Nordre Fasanvej 57, Frederiksberg, Denmark, 2000
Public contact	Psychiatric Centre Copenhagen, Frederiksberg Hospital, Hovedvejen 13, Nordre Fasanvej 57, Mental Health Services, Capital Region of Denmark, 3864 7087, martin.balslev.joergensen@regionh.dk
Scientific contact	Psychiatric Centre Copenhagen, Frederiksberg Hospital, Hovedvejen 13, Nordre Fasanvej 57, Mental Health Services, Capital Region of Denmark, 3864 7087, martin.balslev.joergensen@regionh.dk

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	04 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2023
Global end of trial reached?	Yes
Global end of trial date	10 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective is to investigate whether short-term add-on treatment with high dose erythropoietin (EPO) can counteract the cognitive sideeffects of ECT and if such beneficial effects are long-lasting.

Protection of trial subjects:

Good Clinical Practice (GCP) Unit, Copenhagen, Denmark

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 2017
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	Denmark: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	60
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

We recruited in-patients from the Mental Health Services, Capital Region of Denmark.

Pre-assignment

Screening details:

Eligible participants were 18-70 years of age, had a diagnosis of UD or BD with current moderate to severe depressive symptoms, as reflected by a HDRS-17 total score≥17. Exclusion criteria were involuntary ECT, previous ECT within the last three months, other neuropsychiatric conditions, alcohol or substance use disorder, or acute suicide risk.

Period 1

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

Blinding implementation details:

The randomization list was kept in a locked filing cabinet. Preparation of study medication to ensure double-blinding: 1 ml recombinant human EPO (Eprex; 40,000 IU; Janssen-Cilag) or saline (NaCl 0.9%) was injected into a standard 100 ml saline (NaCl 0.9%) infusion bag, which is then given to the study nurse or physician administering the medication. Double-blinding was further ensured by EPO being a colorless liquid undistinguishable from saline.

Arms

Are arms mutually exclusive?	Yes
Arm title	Erythropoietin

Arm description:

Four intravenous infusions of high-dose recombinant human EPO (Epoetin alpha; Eprex; 40.000 IU/ml) diluted with 100 ml saline (0.9% NaCl) during a 2.5-week add-on treatment period.

Arm type	Experimental
Investigational medicinal product name	Epoetin alpha; Eprex; 40.000 IU/ml
Investigational medicinal product code	B03XA01
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Epoetin alpha; Eprex; 40.000 IU/ml diluted with 100 ml saline (0.9% NaCl) and administered intravenously over 15 minutes.

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Saline (1 ml sodium chloride (NaCl) 0.9%); placebo) diluted with 100 ml saline (0.9% NaCl) and administered intervenously over 15 minutes.

Arm title	Saline

Arm description:

Saline (1 ml NaCl 0.9%) injected into a saline solution (100 ml NaCl, 0.9%) and administered intravenously over 15 min.

Arm type	Placebo

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	NaCl 0.9%
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

0.9% NaCl isotonic saline

Number of subjects in period 1	Erythropoietin	Saline
Started	34	26
Completed	28	26
Not completed	6	0
Consent withdrawn by subject	1	-
Lost to follow-up	5	-

Baseline characteristics

Reporting groups	
Reporting group title	Erythropoietin
Reporting group description:	
Four intravenous infusions of high-dose recombinant human EPO (Epoetin alpha; Eprex; 40.000 IU/ml) diluted with 100 ml saline (0.9% NaCl) during a 2.5-week add-on treatment period.	
Reporting group title	Saline
Reporting group description:	
Saline (1 ml NaCl 0.9%) injected into a saline solution (100 ml NaCl, 0.9%) and administered intravenously over 15 min.	

Reporting group values	Erythropoietin	Saline	Total
Number of subjects	34	26	60
Age categorical Units: Subjects			
Adults (18-64 years)	34	26	60
Age continuous Units: years			
arithmetic mean	40	38	
standard deviation	± 14	± 12	-
Gender categorical Units: Subjects			
Female	24	18	42
Male	10	8	18

End points

End points reporting groups

Reporting group title	Erythropoietin
Reporting group description:	
Four intravenous infusions of high-dose recombinant human EPO (Epoetin alpha; Eprex; 40.000 IU/ml) diluted with 100 ml saline (0.9% NaCl) during a 2.5-week add-on treatment period.	
Reporting group title	Saline
Reporting group description:	
Saline (1 ml NaCl 0.9%) injected into a saline solution (100 ml NaCl, 0.9%) and administered intravenously over 15 min.	

Primary: Speed of complex cognitive processing composite score

End point title	Speed of complex cognitive processing composite score
End point description:	
End point type	Primary
End point timeframe:	
Baseline (pre-ECT) to after the 8th ECT session (2.5 weeks), corresponding to 4 EPO/saline infusions given over 2.5 weeks	

End point values	Erythropoietin	Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[1]	26		
Units: z-scores				
arithmetic mean (standard deviation)	-0.10 (± 1.11)	-0.28 (± 1.07)		

Notes:

[1] - One subject withdrew before the baseline assessment and therefore had no data that could be included

Statistical analyses

Statistical analysis title	Linear mixed-effects models
Comparison groups	Erythropoietin v Saline
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Autobiographical memory

End point title	Autobiographical memory

End point description:

End point type	Secondary

End point timeframe:

Cross-sectional assessment after 8th ECT (2.5 weeks of EPO/saline treatment).

End point values	Erythropoietin	Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[2]	12[3]		
Units: z-scores				
arithmetic mean (standard deviation)	7 (± 2)	10 (± 4)		

Notes:

[2] - Autobiographical memory was assessed during fMRI, which was conducted for a subgroup of patients

[3] - Autobiographical memory was assessed during fMRI, which was conducted for a subgroup of patients

Statistical analyses

Statistical analysis title	Independent samples t¬test

Statistical analysis description:

Cross-sectional comparison between EPO and saline groups after 8th ECT.

Comparison groups	Erythropoietin v Saline
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.025 [4]
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[4] - Given we had 2 secondary outcomes, we conducted Bonferroni correction for multiple comparisons (i.e., p<=0.025).

Secondary: Verbal memory

End point title	Verbal memory

End point description:

End point type	Secondary

End point timeframe:

Baseline (pre-ECT) to week 4 (after 8th ECT/ 2.5 weeks of weekly EPO/saline infusions)

End point values	Erythropoietin	Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	26		
Units: z-scores				
arithmetic mean (standard deviation)	-0.25 (± 1.09)	-0.62 (± 0.97)		

Statistical analyses

Statistical analysis title	Linear mixed-effects models
Comparison groups	Saline v Erythropoietin
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.025 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[5] - There were two secondary outcomes and the threshold for statistical significance was therefore Bonferroni corrected and set tp P<=0.025.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Active treatment phase, from baseline (pre-ECT) to week 4 (completion of EPO/saline treatment)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	Erythropoietin
Reporting group description: Active treatment arm.	
Reporting group title	Saline
Reporting group description: Placebo arm.	

Serious adverse events	Erythropoietin	Saline	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Deep vein thrombosis	Additional description: Deep vein thrombosis		
subjects affected / exposed[1]	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Only one subject experienced a deep vein thrombosis. This was a participant in the EPO arm. None of the patients in the saline arm experienced such a serious adverse event.

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

Non-serious adverse events	Erythropoietin	Saline	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	3 / 3 (100.00%)	
Psychiatric disorders			
Symptom deterioration	Additional description: Symptoms of depression and mania are common in patients with mood disorders.		
subjects affected / exposed[2]	2 / 2 (100.00%)	3 / 3 (100.00%)	
occurrences (all)	2	3	

Notes:

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: There were 2 participants in the EPO arm and 3 participants in the saline arm who experienced a symptom deterioration during the active treatment period. This is specified in the form.

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