Clinical trial results:
Effect of erythropoietin (EPO) on cognitive function and frontal lobe activity in patients with bipolar disorder and unipolar depression in remission (PRETEC-EPO)

Summary

EudraCT number	2016-004023-24
Trial protocol	DK
Global end of trial date	27 July 2022

Results information

Result version number	v1 (current)
This version publication date	19 August 2023
First version publication date	19 August 2023

Trial information

Trial identification

Sponsor protocol code	PRETEC-EPO

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	Lars Vedel Kessing, Copenhagen Affective Disorder research Center (CADIC), Psychiatric Centre Copenhagen, Frederiksberg , +45 38647081, lars.vedel.kessing@regionh.dk
Scientific contact	Lars Vedel Kessing, Copenhagen Affective Disorder research Center (CADIC), Psychiatric Centre Copenhagen, Frederiksberg, +45 38647081, lars.vedel.kessing@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	27 July 2022
Global end of trial reached?	Yes
Global end of trial date	27 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to investigate the effect of 12 weeks of erythropoietin (EPO) treatment on cognitive impairments in patients with bipolar disorder or depression in remission with cognitive difficulties

Protection of trial subjects:

The Good Clinical Practice (GCP) Unit, Copenhagen, monitored the trial (https://gcp-enhed.dk/english/)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 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: 103
Worldwide total number of subjects	103
EEA total number of subjects	103

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)	103
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with bipolar disorder (BD; type I or II) or major depressive disorder (MDD) were recruited from psychiatric outpatient clinics in the Mental Health Services Capital Region of Denmark, consultant psychiatrists, as well as through online advertisements.

Pre-assignment

Screening details:

Eligible patients were diagnosed with ICD-10 BD or recurrent MDD (≥two previous depressive episodes) verified with Schedules for Clinical Assessment in Neuropsychiatry (SCAN) in full or partial remission but with cognitive impairments according to the SCIP (Screen for Cognitive Impairment in Psychiatry).

Period 1

Period 1 title	PRETEC-EPO 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:

To ensure blinding of outcome-assessors, sealed randomization envelopes are kept in a locked cabinet only accessible to study personnel responsible for preparing the study medication not involved in evaluation of the efficacy parameters or regular interaction with participants. Double-blinding is achieved during infusion through injection of 1 ml colourless recombinant human EPO (Eprex; 40,000 IU; Janssen-Cilag) or saline (NaCl 0.9%) was injected into a standard 100 ml saline infusion bag.

Arms

Are arms mutually exclusive?	Yes
Arm title	Erythropoietin

Arm description:

12 weeks of erythropoietin (EPO) infusions

Arm type	Experimental
Investigational medicinal product name	Erythropoietin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eprex 40,000 IU/ml solution for injection in pre-filled syringe. Firstly, according to the description of EPO treatment administration procedures in the Danish product resume for recombinant human EPO (revised 26th August 2016), it is instructed that "Eprex must not be administered as intravenous infusion or together with other medical solutions". However, in accordance with our previous administration approach and its documented safety profile, we chose to dilute the EPO in saline and administer infusions intravenously (1 ml Eprex of 40,000 IU dissolved in 100 ml isotonic saline) in the trial.

Arm title	Saline

Arm description:

12 weekly infusions of saline (NaCl 0.9%)

Arm type	Placebo
Investigational medicinal product name	Sodium Chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:
0.9% NaCl

Number of subjects in period 1	Erythropoietin	Saline
Started	58	45
Completed	49	36
Not completed	9	9
Adverse event, serious fatal	1	-
Consent withdrawn by subject	-	2
Adverse event, non-fatal	6	4
Started smoking	1	1
COVID	-	2
COVID vaccine	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Erythropoietin
Reporting group description:	
12 weeks of erythropoietin (EPO) infusions	
Reporting group title	Saline
Reporting group description:	
12 weekly infusions of saline (NaCl 0.9%)	

Reporting group values	Erythropoietin	Saline	Total
Number of subjects	58	45	103
Age categorical			
Adult participants 18-64 years of age were included.			
Units: Subjects			
Adults (18-64 years)	58	45	103
Age continuous			
Units: years			
arithmetic mean	37	36	
standard deviation	± 17	± 16	-
Gender categorical			
Units: Subjects			
Female	33	25	58
Male	25	20	45

Subject analysis sets	
Subject analysis set title	Primary outcome analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants were included in the intention-to-treat (ITT) analyses as described in the trial protocol (25). Accordingly, we analyzed behavioral data for a total of N=101 patients (EPO: n=58; saline, n=43). Here, we report the primary outcomes.

For details on secondary and tertiary outcomes, please refer to the outcome article that includes a detailed report of all outcomes.

Reporting group values	Primary outcome analysis		
Number of subjects	101		
Age categorical			
Adult participants 18-64 years of age were included.			
Units: Subjects			
Adults (18-64 years)	101		
Age continuous			
Units: years			
arithmetic mean	37		
standard deviation	± 17		

Gender categorical Units: Subjects			
Female	58		
Male	43		

End points

End points reporting groups

Reporting group title	Erythropoietin
Reporting group description:	
12 weeks of erythropoietin (EPO) infusions	
Reporting group title	Saline
Reporting group description:	
12 weekly infusions of saline (NaCl 0.9%)	
Subject analysis set title	Primary outcome analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants were included in the intention-to-treat (ITT) analyses as described in the trial protocol (25). Accordingly, we analyzed behavioral data for a total of N=101 patients (EPO: n=58; saline, n=43). Here, we report the primary outcomes.

For details on secondary and tertiary outcomes, please refer to the outcome article that includes a detailed report of all outcomes.

Primary: Speed of complex cognitive processing composite score

End point title	Speed of complex cognitive processing composite score

End point description:

The primary outcome measure was a cognitive composite score, 'speed of complex cognitive processing', covering domains of attention, verbal learning and memory, and executive functions. This composite was selected based on previously demonstrated improvement on this measure in our prior 8-week EPO trial and in accordance with the ISBD TF guidelines suggesting inclusion of a cognitive composite score as primary outcome measure. Measures included in this outcome were: Rey Auditory Verbal Learning Test (RAVLT) List I-V Total recall, The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Coding, Verbal Fluency (letter "D"), Wechsler Adult Intelligence Scale (WAIS)-III Letter-Number Sequencing, Trail Making Test Part B (TMT-B), and Rapid Visual Information Processing (RVP) from Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition Ltd.). The values provided here are the composite change scores from baseline to end of treatment (week 13).

End point type	Primary

End point timeframe:

Baseline (week 1), two weeks of treatment (week 3), end of treatment (week 13) (primary outcome assessment timeframe) and a 6-months follow-up after treatment completion.

End point values	Erythropoietin	Saline	Primary outcome analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	45	101	
Units: cognitive test z-scores				
arithmetic mean (standard deviation)	0.44 (± 0.47)	0.38 (± 0.47)	0.41 (± 0.47)	

Statistical analyses

Statistical analysis title	Linear mixed models analysis

Statistical analysis description:

To investigate effects of EPO vs. saline, the pre-defined primary, secondary, and tertiary outcomes were analyzed with linear mixed effect models. Model factors were time, stratum (classifying age and sex) and treatment (with placebo treatment as reference category for baseline correction). Fixed effects were time, stratum, time*stratum, and time*treatment. Statistical analyses were performed with IBM SPSS v28 applying a significance α-level<0.05 (two-tailed).

Comparison groups	Erythropoietin v Saline
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[1] - We applied a significance α-level=<0.05 (two-tailed).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 weeks

Adverse event reporting additional description:

Adverse events were reported throughout the active treatment period. Additional details are provided in the outcome article.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Erythropoietin

Reporting group description:

In the EPO arm, one patient died (unrelated to the intervention), two experienced serious adverse events (symptom recurrence, discovery of cyst in abdomen), and four experienced suspected non-serious adverse effects.

Reporting group title	Saline

Reporting group description: -

Serious adverse events	Erythropoietin	Saline	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Social circumstances			
Death	Additional description: Death due to other circumstances.		
subjects affected / exposed[1]	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	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: There were no deaths among participants in the saline arm.

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Erythropoietin	Saline	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	2 / 2 (100.00%)	
Infections and infestations			

COVID-19 subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	2 / 2 (100.00%) 2	

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