



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 (\geq 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 |

| 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

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 22 |
|--------------------|----|

Reporting groups

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|-----------------------|----------------|
| 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