Short report: "Effekt af erythropoietin på depressive symptomer og neurokognitive deficit ved behandlingsresistent depression og ved bipolar lidelse i remitteret fase", (protokol code: 1, EudraCT: 2008-004857-14)

Background

Depression and bipolar disorder are associated with reduced neural plasticity and deficits in memory, attention and executive function. Pharmacological treatments for these affective disorders have insufficient clinical effects in a large group and fail to reverse their cognitive deficits. There is thus a need for more effective treatments which aid cognitive function.

Erythropoietin (EPO) is involved in neuroplasticity and is a candidate for future treatment of affective disorders. The investigators have demonstrated that a single dose of EPO improves cognitive function and reduces neurocognitive processing of negative emotional information in healthy and depressed individuals similar to effects seen with conventional antidepressants. The current study therefore investigated whether repeated EPO administration has antidepressant effects in patients with treatment resistant depression (TRD) and reverses cognitive impairments in these patients and in patients with bipolar disorder (BD) in remission.

Methods/design

The trial had a double-blind, placebo-controlled, parallel-group design. Patients with an ICD-10 diagnosis of TRD (sub-study 1) or BD in remission (sub-study 2) were recruited and randomised, with stratification for age and gender, to receive weekly infusions of EPO (Eprex; 40,000 IU) or saline (NaCl 0.9%) for 8 weeks. Patients were assessed at baseline, and weeks 5, 9, and 14. Clinical trial registration: clinicaltrials.gov: NCT00916552.

For sub-study 1, the primary outcome was reduction in depression severity measured with the Hamilton Depression Rating Scale 17 items (HDRS-17) from baseline to week 9. Global Assessment of Function (GAF) was reported in addition. The secondary outcome was remission rate, and tertiary outcomes were changes verbal memory measured with the Rey Auditory Verbal Learning Test (RAVLT), self-rated depression symptoms measured with Beck Depression Inventory 21-items (BDI-21), and WHO Quality of life-BREF (WHOQOL-BREF). Exploratory outcomes in this sub-study were depression and cognition composite scores.

For sub-study 2, the primary outcome was verbal memory indexed by the total words recalled across RAVLT learning trials (I-V) from baseline to week 9. Secondary

outcomes were sustained attention measured with the Rapid Visual Processing (RVP) test from the CANTAB test battery (Cambridge Cognition A/S) and facial expression recognition measured with the facial expression recognition test from the Emotional Test Battery (P1Vital, University of Oxford), and tertiary outcomes were additional measures of attention and executive function, as well as subjective cognitive function and mood symptoms. Analysis was intention-to-treat using repeated-measures analysis of covariance adjusted for stratification variables and mood symptoms. The statistical threshold for which results were considered significant was $p \leq 0.05$ (2-tailed).

Results

A total of 40 patients with TRD and 44 patients with BD were included in the trial. The first patient was randomized in September 2009 and last assessment completed in October 2012. For patient flow throughout the two sub-studies see figures 1 and 2.

Sub-study 1 demonstrated no effects of EPO over saline in HDRS-17, GAF, or remission rates at week 9 (p-values$\geq$0.09). However, EPO improved self-rated depression symptoms (p=0.02) and quality of life (P=0.01), and this was maintained at follow-up week 14 after normalization of red blood cells (p-values$\leq$0.04). EPO also enhanced verbal recall (p=0.02) and recognition (p=0.03), which was sustained at follow-up (p-values$\leq$0.04) (see figure 3). Exploratory analysis in patients fulfilling depression severity criteria at trial start revealed ameliorated HDRS-17 in EPO (N=14) versus saline groups (N=17) which was sustained at week 14 (p-values$\leq$0.05).[1] Exploratory analysis in the complete cohort showed that EPO reduced depression composite at weeks 9 and 14 (p-values=0.02) (see figure 3).

Sub-study 2 revealed no significant improvement of verbal memory in EPO versus saline treated bipolar patients (p=0.10). However, EPO enhanced sustained attention (p=0.001), recognition of happy faces (p=0.03), and speed of complex information processing across learning, attention, and executive function (p=0.01) (see figure 4). These effects occurred in absence of changes in simple reaction times or mood (p-values>0.16) and were maintained after red blood cell normalization.

[1] Analyses excluding eight patients who had displayed marked mood improvement in the two weeks between screening and trial start (baseline) (HDRS-17: mean reduction (SD): 5 (2)) and no longer fulfilled depression severity criteria at baseline.

Conclusion

This is the first trial investigating EPO to treat mood symptoms and cognitive dysfunction in patients with affective disorders. The primary outcomes of the trial were negative. However, sub-study 1 provides some indication for antidepressant efficacy of EPO in TRD as well as robust mood-independent enhancement of verbal memory, which was maintained six weeks after treatment completion. Further, the findings in sub-study 2 indicate that EPO may be a valuable adjunct treatment in patients with BD to enhance sustained attention, executive function, and overall speed of complex cognitive processing. The results of the trial therefore warrant further clinical trials of EPO or its non-hematopoietic analogues as new treatments for mood symptoms and cognitive dysfunction in patients with affective disorders.

Publications

The results of the trial have been published in full in Neuropsychopharmacology (sub-study 1) (doi: 10.1038/npp.2013.335.) and in Journal of Clinical Psychiatry (sub-study 2) (in press) (attached).

Figure 1. CONSORT flow-chart sub-study 1.

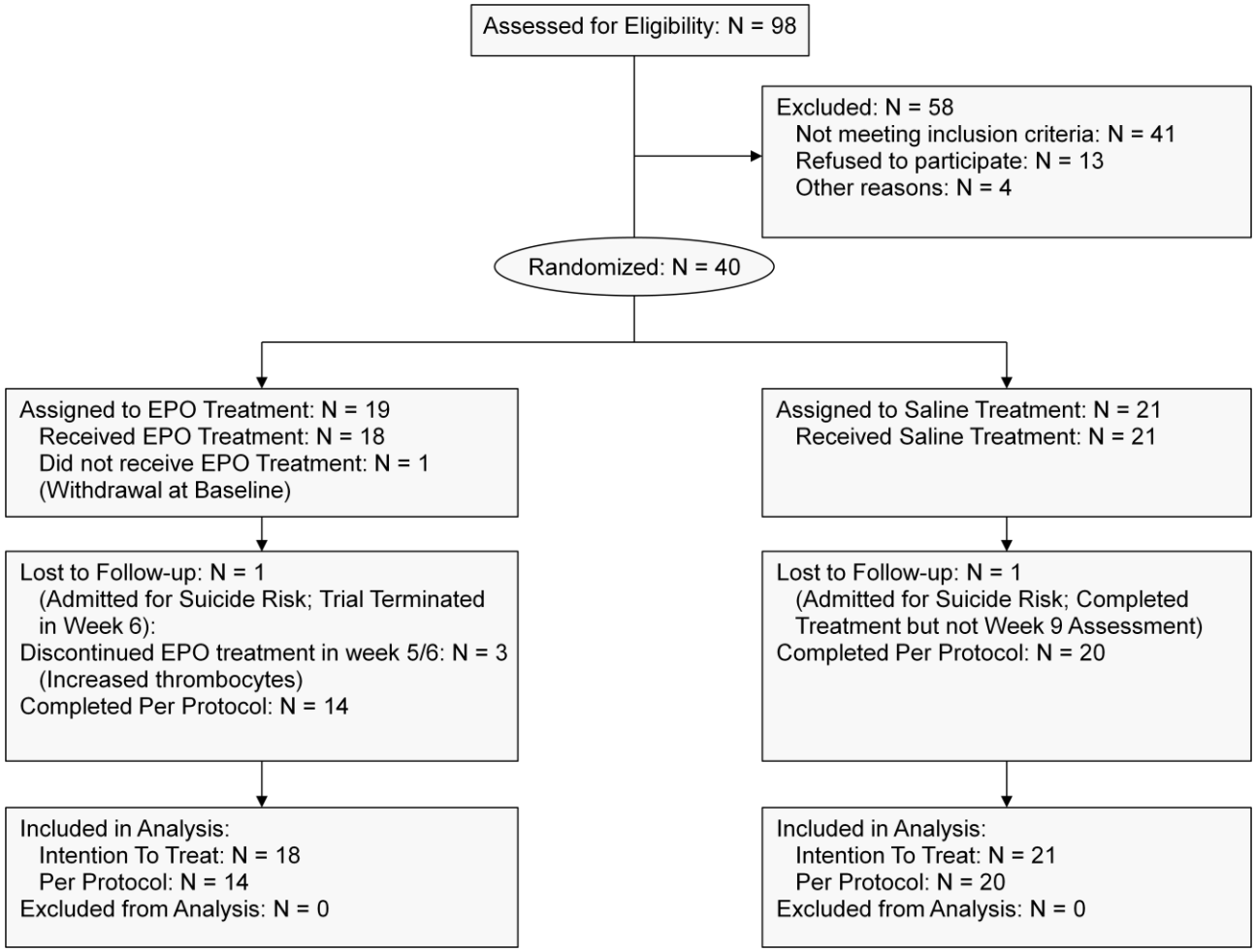

Figure 2. CONSORT flow-chart sub-study 2. *One patient (EPO) was admitted to hospital due to physical illness unrelated to EPO in week 10, i.e. *after* the primary outcome assessment time (week 9), and LOCF was thus performed from weeks 9 to 14. **For the patient (saline) who dropped out in week 5, cognition was only assessed at baseline and the patient was thus excluded from the analyses of cognitive outcomes; however, since the patient's mood symptoms were assessed at week 5, LOCF was performed for analyses of mood symptoms.

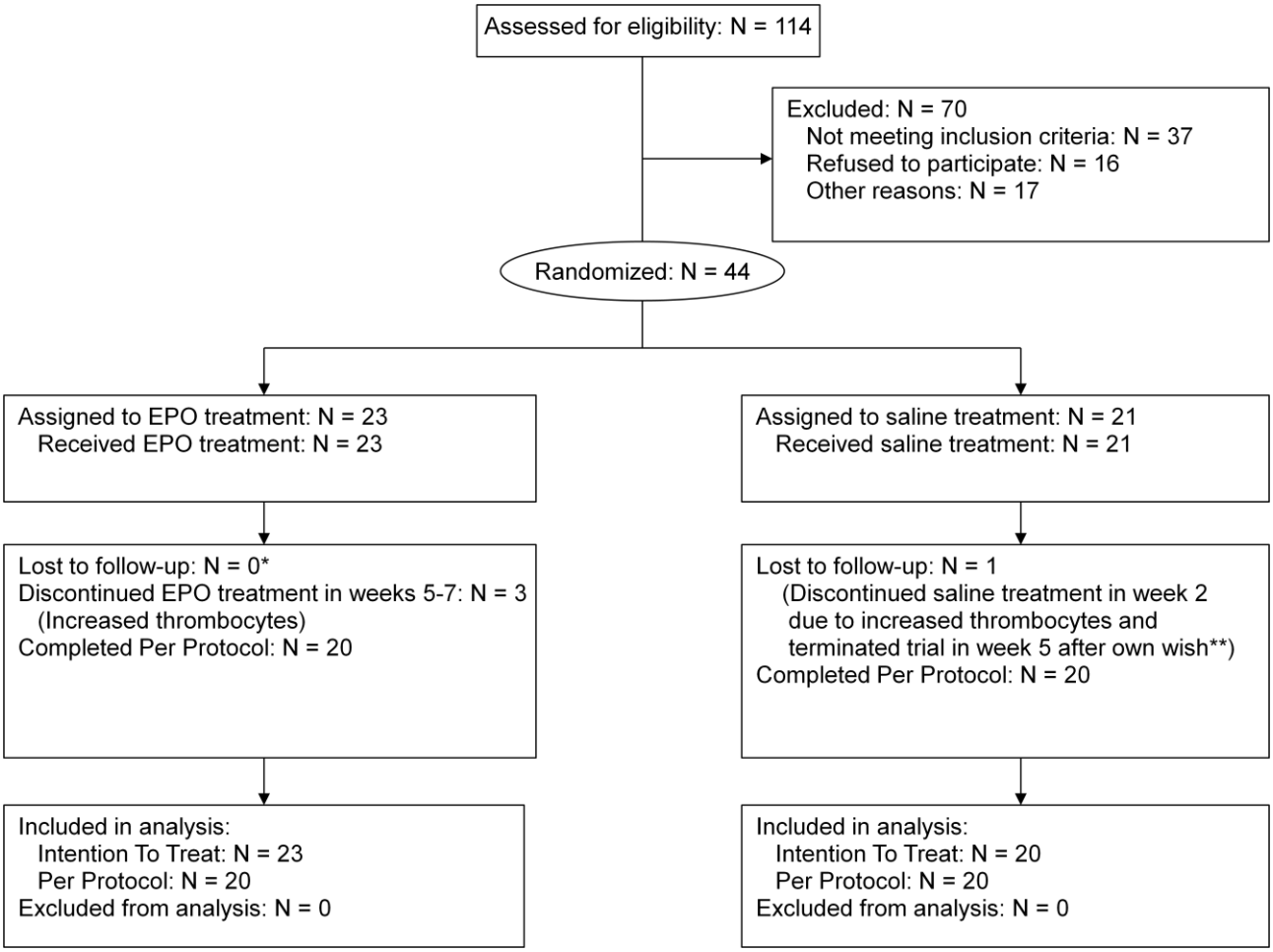

Figure 3. **Explorative depression and memory composite scores sub-study 1.** Percent improvement of explorative depression and cognition composite scores from individual baseline. .**A** Explorative depression composite. The dotted line denotes the estimated depression composite of healthy individuals within the lower normal range calculated by z-transformation and averaging the cut-offs HDRS-17=7, BDI-21=7,GAF=70 and the mean WHOQOL-BREF score in the Danish population (Noerholm *et al,* 2004). **B.** Explorative RAVLT composite. This was obtained by summation of the four z-transformed RAVLT measures, addition of 10 to these summed score to obtain overall positive values and calculation of percent change from individual baseline. P-values indicate the results of the ANCOVA of the mean change from the individual baseline between the drug groups. The dotted line denotes the estimated RAVLT memory composite of healthy, age-matched individuals of average intelligence. Mean and s.e.m are presented.

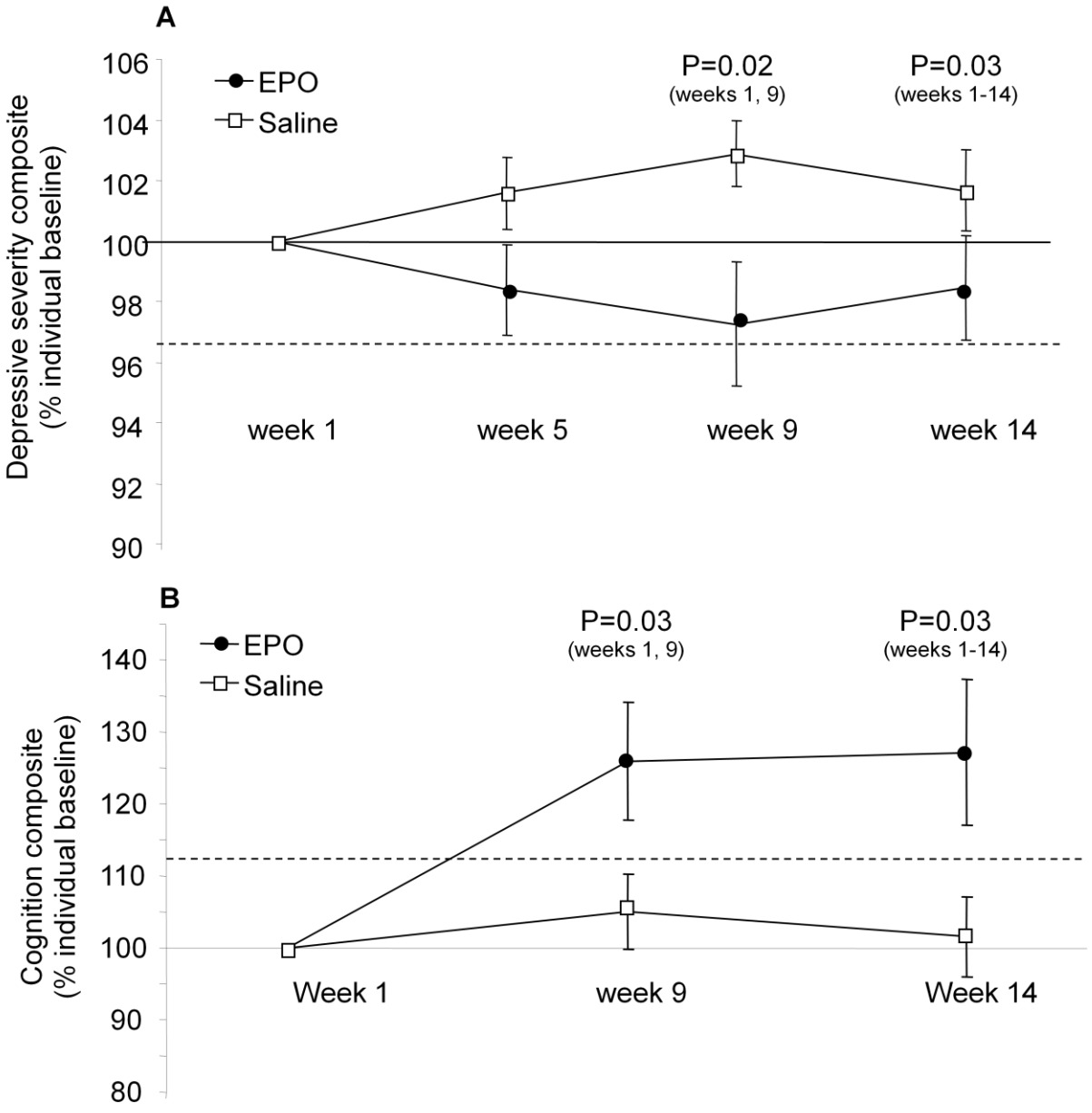

Figure 4. Exploratory cognitive composite sub-study 2. Percent improvement from individual baseline in the cognition composite score of 'overall speed of complex cognitive processing. This was obtained by: 1) summation of the z-transformed scores from tests probing the different cognitive domains: RAVLT total recall trials I-V (verbal memory), RVP speed for correct responses and RBANS coding (attention), WAIS letter-number sequencing, Trail Making B, and verbal fluency letter D (executive function), 2) addition of 15 to these summed scores to obtain overall positive values, and 3) calculation of percent change from individual baseline. Error bars denote standard errors of the mean. P-values denote the results of the ANCOVA of the raw composite scores. The dotted line denotes the estimated mean cognitive composite score of healthy, age-matched individuals calculated by z-transformation and summation of the average norms for healthy individuals on these tests: RAVLT total recall trials I-V: meta-norms in healthy individuals aged 40-49 years (32) RVP speed for correct responses: norms from 47 healthy British individuals aged 40-49 years (CANTAB norms provided by Cambridge Cognition); WAIS letter-number sequencing: norms from a large group of Danish healthy individuals aged 39-41 years (WAIS-III administration booklet); RBANS coding: norms from a large group of healthy American individuals; Verbal fluency letter D: norms from group of 37 healthy Danish individuals aged 39-50 years with or without genetic predisposition for dementia with normal IQ and no clinical symptoms (provided by Danish Dementia Research Centre, July 2013); Trail Making B: norms from a large group of Danish healthy individuals aged 40-40 years.