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(71) Applicant and

(72) Inventor: EHRENREICH, Hannelore [DE/DE]; Cal-
sowstr. 17, 37085 Göttingen (DE).

(74) Agent: PFENNING, MEINIG & PARTNER GbR;
Patent- und Rechtsanwälte, Theresienhöhe 13, 80339
München (DE).

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(54) Title: USE OF EPO RECEPTOR ACTIVATION OR STIMULATION FOR THE IMPROVEMENT OF THE EDSS SCORE
IN PATIENTS WITH MULTIPLE SCLEROSIS

(57) Abstract: The present invention concerns a Method for the improvement of the expanded disability status scale (EDSS) score
achieved by mammals affected by multiple sclerosis, wherein a substance effecting increased and/or prolonged activation and/or
stimulation of the erythropoietin receptor is applied to the mammal.

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Use of EPO receptor activation or stimulation for the
10 improvement of the EDSS score in patients with multiple
sclerosis

The present invention relates to a method for the improvement
of the EDSS score achieved by mammals which are affected by
15 multiple sclerosis and also the use of substances effecting
increased and/or prolonged activation and/or stimulation of the
erythropoietin receptor for this purpose and also for the
production of a drug for this purpose.

20 With approx. 80 to 110 cases of multiple sclerosis (MS) per
100,000 persons, multiple sclerosis is the most frequent
chronic disease of the central nervous system. A third of
patients thereby shows a primary or secondary progressive
course of the multiple sclerosis, for which no therapy has been
25 available to date. Understanding and treatment of the
progressive phase of multiple sclerosis (MS), which is
characterized by the steady accumulation of neurological
disability, is far from being satisfactory. Progression is most
likely driven by the high prevalence of neurodegenerative
30 compared with inflammatory pathological changes, explaining the
limited long-term efficacy of current anti-inflammatory and
immunosuppressive treatment strategies. It seems that once the

cascade of events leading to neuronal and axonal loss is established, even an effective suppression of inflammation fails to protect from clinical disease progression. The development of *add-on* treatments targeting axonal repair and remyelination and / or the slowing of disease progression through neuroprotection / neuroregeneration remains therefore the most important challenge and goal in clinical management of chronic progressive MS.

- 10 Disability of patients affected by multiple sclerosis can be determined based on different parameters. One of the parameters - mainly determining motoric ability - is the Expanded Disability Status Scale (EDSS). This parameter is described in Kurtzke J.F., Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS), Neurology 1983; 33: 1444-52. At present, no therapy is available which would improve the EDSS score achieved by patients.
- 20 In the following and throughout this application, the term "achieved by patients" shall have the same or corresponding meaning as "achievable by patients".

- 25 Erythropoietin (EPO) is a glycoprotein produced naturally in the body, having a molecular weight of 34,000 D. It is an essential growth factor for the production of erythrocytes and was isolated for the first time in 1977. It binds to and stimulates the endogenous erythropoietin receptor.
- 30 Erythropoietin has been in frequent clinical use for many years in patients with renal anaemia, in the case of nephrodialysis, in order to obtain fairly large quantities of autologous blood

before planned operations, and it also appeared in press headlines as a doping agent.

Erythropoietin thereby proved to be exceptionally well

5 tolerated with only minor or no side effects at all.

Intolerance reactions or anaphylactic reactions are rarities with erythropoietin.

There are a plethora of substances, known and produced, which
10 all are considered to increase or prolong the activation and/or increase or prolong stimulation of the erythropoietin receptor (e.g. as shown in the following paragraph). Besides erythropoietin itself, whether native or recombinant, whether in native sequence or even after sequence changes or sequence
15 shortening, erythropoietin analogues, erythropoietin fragments or erythropoietin agonists were developed. As examples for recombinant erythropoietins, Epoetin α (Epogen by Amgen Inc., Procrit by OrthoBiotech Inc., Johnson and Johnson Inc.), Epoetin β (NeorecormonTM by F. Hoffmann-La Roche AG) and Epoetin
20 ω (EpomaxTM), Epoetin δ (DynEpoTM, Shire Pharmaceuticals Group PLC) with varying glycosilation and sialysation are known. Genetically modified EPO are known as Darbepoetin α TM (by Amgen Inc.) and CERATM (by F. Hoffmann-La Roche AG). Further, erythropoietin receptor activating antibody (e.g. by Abbott),
25 fusion proteins like Epo-Fc and carbamylated EPO (CEPOTM, by H. Lundbeck A/S) are known. Endogenous erythropoietin stimulating substances, substances increasing the release and/or activity of endogenous erythropoietin (e.g. HIF-stabilisers, e.g. by FibroGen Inc. or Torrent Pharmaceuticals Ltd.) are also known.
30 Furthermore, erythropoietin analogues or mimetics are known, e.g. SEP (Synthetic Erythropoiese Protein, by Gryphon Therapeutics), HematideTM (by Affymax Inc.) and others known as

EPO-analogues or EPO-mimetics by AplaGen. It is even known to transfer the gene coding for erythropoietin into a patient in order to express erythropoietin.

- 5 All of these substances are known to increase and/or prolong the activation and/or stimulation of the erythropoietin receptor besides their antiapoptotic, tissueprotective effect. Some useable EPO variants are published for example in the following publications:

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Leist et al., Science 2004, Vol. 305, pp. 239 - 242, WO 86/03520, WO 85/02610, WO 90/11354, WO 91/06667, WO 91/09955, WO 93/09222, WO 94/12650, WO 95/31560, WO 95/05465. An overview of known EPO variants, analogues, mimetics and
15 equivalents which can also be used in their entirety in the present invention and also of known fields of use thereof appears in Brines and Cerami, Nature Reviews, Neuroscience, June 2005, Vol. 6, pages 484 - 494.

- 20 WO 00/61164 discloses the use of EPO for the protection of neuronal tissue, in particular also of the central nervous system. It is mentioned in passing in this document that multiple sclerosis might also be treated with EPO.

- 25 WO 00/61164 in fact discloses the use of EPO for the treatment of multiple sclerosis but indicates no experimental data or treatment regime at all. It is not disclosed therein, in what respect (cognitive, motoric function or others) patients suffering from multiple sclerosis might benefit from treatment
30 with EPO.

It is therefore the object of the present invention to develop a method for the safe improvement of the expanded disability status scale (EDSS) score achieved by mammals and the use of substances effecting increased and/or prolonged activation and/or stimulation of the erythropoietin receptor for the safe improvement of the expanded disability status scale (EDSS) score achieved by mammals affected by multiple sclerosis.

This object is achieved by the method according to claim 1 and also the use according to claim 14. Advantageous developments of the method according to the invention and of the use according to the invention are given in the respective dependent claims.

According to the invention, in the method of the present invention in mammals, in particular in humans, a substance effecting increased and/or prolonged activation and/or increased and/or prolonged stimulation of the erythropoietin receptor is administered to the mammal, e.g. to a human patient affected by multiple sclerosis.

As substance effecting increased and/or prolonged activation and/or stimulation of the erythropoietin receptor and substance as described above may be used, e.g. erythropoietin, native or recombinant, variants or derivatives of erythropoietin, analogues, mimetics, agonists of erythropoietin or substances for genetically altering the patient in order to achieve said activation/stimulation of the erythropoietin receptor.

The present invention for the first time shows, that a treatment or use according to the present invention improves not only cognitive parameters but effect a significant

improvement of the EDSS score in patients suffering from multiple sclerosis. This improvement has not been known before and could not have been foreseen considering the purely speculative nature of the above cited documents generally relating to the use of erythropoietin in treatment of multiple sclerosis. It is of great importance that the proposed method and proposed use is safe with no or only minor side effects.

The method can be used with patients suffering from any kind of multiple sclerosis, e.g. primary progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS), relapsing/remitting multiple sclerosis (RRMS) or progressive relapsing multiple sclerosis (PRMS).

In particular, an improvement in the symptoms was observed not only in the case of chronic-progressive multiple sclerosis but also in the case of relapsing-remitting multiple sclerosis. In particular in the case of (chronic) progressive multiple sclerosis, a deterioration in the symptoms would have been expected during the treatment-free interval. However stabilisation also occurred here.

Advantageously, the erythropoietin is applied intermittently. This means that, as an advantageous development of the present invention, an interval treatment is proposed. It is thereby particularly advantageous if the treatment comprises a sequence of periods of time with application of EPO (application period) and periods of time without application of EPO (application-free periods).

The individual periods of time thereby comprise several weeks. A sequence has emerged as particularly advantageous in which

each application period lasts 12 to 48 weeks, advantageously 18 to 36 weeks, advantageously 24 to 28 weeks, whilst the application-free periods last 8 to 53 weeks, advantageously 16 to 28 weeks. Within the application periods, the dosage can be varied, for example firstly a period of time with a weekly application and a subsequent period of time with a two-weekly application.

The dosage is thereby respectively in the values described in the claims, particularly advantageously in a dosage range of 5,000 IU to 100,000 IU (international units), advantageously in a dosage range of 30.000 IU to 60.000 IU, advantageously in a dosage range of 40000 IU to 50000 IU, per week or per administration, including or excluding the respective range limits. In the alternative, doses equivalent to said doses given in the preceding sentence, which lead to comparable erythropoietin levels or comparable erythropoietin receptor activating or stimulating biological activity may be used as dosage.

With the mentioned interval dosage schemes, the result surprisingly is a constant improvement in the clinical symptoms during treatment. The improved level is maintained astonishingly in the interval and the second cycle produces a further improvement.

The interval treatment according to the invention is an innovative improvement to the entire concept of neuroprotection which, in the case of EPO with multiple sclerosis, exploits in addition the fact that the result with half-yearly erythropoietin treatment is a latent, desired lack of iron. Since lack of iron can be advantageous in addition for the known neuroprotective EPO effect in chronic inflammatory diseases such as multiple sclerosis, advantageously iron is substituted neither in the treatment nor in the treatment-free phase. The treatment-free phase serves therefore also for slow replenishment of the depleted iron stores, as a result of balanced nutrition.

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In particular in the case of use of EPO with haematopoietic effect, the neuroprotective effect is consequently supplemented by the latent lack of iron produced by the EPO treatment.

5 The effect according to the invention is also achieved however already by using EPO derivatives or variants without haematopoietic effect. It turned out, that is not of particular relevance in the present invention whether the EPO analogues or erythropoietin fragments which are used have a
10 haematopoietic effect (e.g. Epogen™) or not (e.g. CEPO™).

The above explanation relates to the method but the invention is not only directed to the therapeutic method but also to the use of the above mentioned substances in a method of this type
15 and also the use of the above mentioned substances for the production/manufacturing of a drug for use in a method of this type.

In the following, an explanatory study is described which
20 provides experimental proof for the invention. This example contains four tables (table 1, supplementary table 1, supplementary table 2, supplementary table 3) as part of the description and is further explained on the basis of 5 figures. Therein

25

figure 1 shows the design of the EPO MS exploratory study. Low-dose EPO treatment was only performed until week 12;

figure 2 shows changes in blood cell counts and iron parameters
30 during and after EPO treatment. The mean of two baseline values of each patient was set to 100% for each of the laboratory parameters and used for calculating individual change over

time. Mean change of all patients within each group during follow-up upon treatment or during the treatment-free period is expressed in % baseline. Low-dose EPO MS patients and Parkinson patients were only followed until week 12. Filled circles: high-dose EPO MS patients (N=5); open circles: low-dose EPO MS patients (N=3); gray triangles: high-dose EPO Parkinson patients (N=2);

figure 3 shows changes in parameters of motor function upon EPO treatment. (a) The mean of all available baseline values of maximum walking distance of each patient obtained during the whole lead-in period was set to 100% and used for calculating individual change over time. Mean change of all patients within each group during follow-up upon treatment or during the treatment-free period is expressed in % baseline. (b) Follow-up of maximum walking distance of one high-dose EPO MS patient over a total of 60 weeks, including two EPO treatment periods, is presented as raw data for every test time-point. The trend line illustrates the improvement over time. (c) For presenting the course of EDSS scores during the study, mean individual baseline was set to 0 and subsequent values denote change of EDSS score during follow-up of individual MS patients (left panel) or of mean EDSS score of the groups (right panel). For determining individual EDSS change over time, the mean value of consecutive ratings over six week follow-up periods was used. (d) Intra-individual course of central motor conduction time (Tibialis MEP, original data; MS high-dose patients N=4, due to methodological problems in one patient during baseline measurement).

Low-dose EPO MS patients and Parkinson patients were only followed until week 12. Filled circles: high-dose EPO MS patients (N=5); open circles: low-dose EPO MS patients (N=3);

gray triangles: high-dose EPO Parkinson patients (N=2). Significance values refer to the high-dose EPO MS patients only and denote changes of the respective parameter from baseline to the end of each treatment period, including all testing time-points. Statistical analysis: Friedman test (SPSS 14.0 for Windows);

figure 4 shows changes in parameters of fine motor coordination upon EPO treatment. (a) Change of performance in MacQuarrie Tapping test (MacQuarrie TW. MacQuarrie Test for Mechanical Ability. Monterey, CA: CTB/McGraw-Hill, 1925, 1953), (b) MacQuarrie Dotting test (MacQuarrie TW. MacQuarrie Test for Mechanical Ability. Monterey, CA: CTB/McGraw-Hill, 1925, 1953), and (c) 9-hole peg test (Cutter GR, Baier ML, Rudick RA, Cookfair DL, Fischer JS, Petkau J, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999; 122 (Pt 5): 871-82), is expressed as % individual baseline. The mean of all available baseline values of each patient was set to 100% for each of these parameters and used for calculating individual change over time. Mean change of all patients within each group during follow-up upon treatment or during the treatment-free period is expressed in % baseline. Low-dose EPO MS patients and Parkinson patients were only followed until week 12. Filled circles: high-dose EPO MS patients (N=5); open circles: low-dose EPO MS patients (N=3); gray triangles: high-dose EPO Parkinson patients (N=2). Significance values refer to the high-dose EPO MS patients only and denote changes of the respective parameter from baseline to the end of each treatment period, including all testing time-points. Statistical analysis: Friedman test; and

figure 5 shows changes in cognitive function tests upon EPO treatment. (a) Decrease of reaction time in Trail Making - Part B. (b) Improvement of performance on WMS-R Letter Number Sequencing. (c-d) Reduction of reaction time in TAP subtests Visual Scanning - critical trials and Working Memory in the high-dose EPO MS group (N=5). Low-dose EPO MS and Parkinson patients fail to show improvement. The mean of two baseline values of each patient was set to 100% for each of the cognitive parameters and used for calculating individual change over time. Mean change of all patients within each group during follow-up upon treatment or during the treatment-free period is expressed in % baseline. Low-dose EPO MS patients and Parkinson patients were only followed until week 12. Filled circles: high-dose EPO MS patients (N=5); open circles: low-dose EPO MS patients (N=3); gray triangles: high-dose EPO Parkinson patients (N=2). Significance values refer to the high-dose EPO MS patients only and denote changes of the respective parameter from baseline to the end of each treatment period, including all testing time-points. Statistical analysis: Friedman test.

Detailed description of the present study and its results

The main objectives of the present study were: (1) to evaluate safety of long-term high-dose EPO treatment in chronic progressive MS, and (2) to collect first evidence of potential efficacy with respect to a variety of clinical parameters, in particular Expanded Disability Status Scale (EDSS), but also walking distance, fine motor function and cognition. A careful and comprehensive individual follow-up of a small number of patients during a 6-week lead-in phase, a 12-24 week treatment phase, and a 24-week post-treatment phase delivered information about dosing of EPO, necessary duration of treatment in order

to see improvement, and effect of EPO treatment-free periods on maintaining status. Finally, effects found in chronic progressive MS could be compared to effects observed in drug-naïve patients suffering from another degenerative disease,

5 Morbus Parkinson.

Materials and methods

Patients and procedures

5 Following announcement of the present exploratory study to the local ethical committee, a total of eight patients suffering from chronic progressive MS (primary or secondary), who had previously failed on disease-modifying drugs, and, as disease control, two patients with Morbus Parkinson were included into
10 this study (for overview see Table 1). Written informed consent was obtained after comprehensive and repeated information of the respective patient in the absence and in the presence of selected relatives or close advisors (mostly physicians). Patients were fully aware that they participated in an
15 experimental study, set up to evaluate safety and efficacy of EPO in chronic progressive MS with respect to EDSS score. The study was designed as an exploratory open-label study employing two different doses of recombinant human (rh) EPO. The high dose (48000 IU of EPO α , ERYPO^R, Janssen-Cilag,
20 Germany) was selected as presumably effective dose, based on previous trials in stroke and in schizophrenia patients, whereas the low dose (8000 IU of EPO α) lies in the upper dose range of anemia treatment (e.g. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-
25 stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. N Engl J Med 1987; 316: 73-8) and was explored for the first time in a neurological indication. Of the eight MS patients, five received high-dose rhEPO, whereas three received low-dose
30 rhEPO. Dosing was randomly assigned. Patients were unaware of the dose being "high" or "low". The two drug-naïve Parkinson patients received high-dose rhEPO (48000 IU of EPO α).

An overview of the study design including tests and follow-up parameters is presented in Figure 1. After baseline examination and confirmation of inclusion / exclusion criteria, patients entered a lead-in phase of six weeks duration, where they were asked to regularly score or test their performance in a number of items, either specifically reflecting their individual handicaps or important for general well-being and health. For that, every patient received an individually tailored questionnaire, which should provide insight into the longitudinally evaluated baseline performance as well as, later, the treatment and post-treatment follow-up period.

Following the lead-in period, the treatment period was initiated. It started with a one-week inpatient setting, which allowed a comprehensive examination of the patient including magnetic resonance tomography (MRI) of brain and spinal cord, neurological, neuropsychological, electrophysiological, urological, ophthalmological examination, and routine laboratory analyses (including EPO-antibody testing). Patients were then started on high-dose prednisolone (1000 mg / 100 ml over 30 min intravenously) in order to create a comparable immunosuppression as a starting point of neuroprotective therapy. One day later, a second infusion of prednisolone was given, followed by the first infusion of EPO (48000 or 8000 IU of EPO α , respectively, in 50 ml of 0.9% sodium chloride over 15 min intravenously). The third treatment day included prednisolone followed by EPO. Parkinson patients did not receive prednisolone, but were otherwise treated identically. One day later, patients were discharged and asked to return weekly to the clinic for application of the study drug, documentation of clinical state, performance rating, monitoring

of adverse events and safety, including measurement of blood pressure and routine laboratory workup. Blood letting (350-450 ml) was performed if the hematocrit exceeded 50% in male or 48% in female patients on two consecutive weeks. During the one-
5 week inpatient phase, the 12-24 week outpatient treatment phase, as well as the 24-week post-treatment phase, patients were asked to continue regular (daily / weekly) self-rating using their individually tailored questionnaire.

10 Neuropsychological baseline and follow-up testing of patients included the Mehrfachwahl-Wortschatz-Intelligenztest (Lehrl S. Mehrfachwahl-Wortschatz-Intelligenztest. MWT-B. Erlangen: Straube, 1999), four subtests (Information, Similarities, Picture Completion, Block Design) of the revised German version
15 of the Wechsler Adult Intelligence Scale (Tewes U. Hamburg-Wechsler Intelligenztest für Erwachsene. Revision 1991. Bern: Huber, 1991), the Repeatable Battery for the Assessment of Neuropsychological Status (Randolph C. RBANS Manual - Repeatable Battery for the Assessment of Neuropsychological
20 Status. Harcourt, Texas: Psychological Corporation, 1998), subtests Visual Scanning, Working Memory and Alertness of the computer-assisted battery for attention testing (Zimmermann P, Fimm B. Testbatterie zur Aufmerksamkeitsprüfung (TAP). Herzogenrath: PsyTest, 1995), subtest Letter Number Sequencing
25 of the Wechsler Memory Scale - Revised (Wechsler D. Wechsler Memory Scale - 3rd edition (WMS-III). Harcourt, Texas: Psychological Corporation, 1998), Wisconsin Card Sorting Test - 64 Card Version (Kongs SK, Thompson LL, Iverson GL, Heaton RK. WCST-64: Wisconsin Card Sorting Test - 64 Card Version. Odessa,
30 FL: Psychological Assessment Resources, 2000) and the Trail Making Test (Reitan RM. Validity of the Trail Making test as an

indicator of organic brain damage. Percept Motor Skills 1958; 8: 271-276).

MRI of brain and spinal cord was conducted on a Siemens 1.5T scanner (scans before and after gadolinium; for cranial imaging transverse, coronal and sagittal T1-weighted sequences, T2-weighted TSE- and TIRM-sequences; for spinal imaging sagittal and transverse T1-weighted TIRM- and TSE-sequences, T2-weighted TSE-sequences; slice thickness: 6mm (19 slices, cranial), 3mm (15 slices, cervical); 4mm (11 slices, thoracic); semi-automated volumetrical analyses carried out, in a blinded fashion, with Centricity Radiology RA 1000, General Electrics, in T2-weighted images). Electrophysiology wherever technically possible (motor-evoked potentials: MEP), maximum walking distance, fine motor assessment using the 9-hole peg test (Cutter GR, Baier ML, Rudick RA, Cookfair DL, Fischer JS, Petkau J, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999; 122 (Pt 5): 871-82; Rudick RA, Cutter G, Baier M, Fisher E, Dougherty D, Weinstock-Guttman B, et al. Use of the Multiple Sclerosis Functional Composite to predict disability in relapsing MS. Neurology 2001; 56: 1324-30), as well as MacQuarrie Tapping and Dotting tests (MacQuarrie TW. MacQuarrie Test for Mechanical Ability. Monterey, CA: CTB/McGraw-Hill, 1925, 1953) were performed.

Inclusion and exclusion criteria

An overview of all eight MS patients and the two Parkinson patients is provided in Table 1. MS patients were in a chronic progressive state (either primary or secondary) of their disease. They were free of other severe psychiatric or

neurological disorders. A minimum of measurable walking distance was required. Patients were not allowed to smoke or to take sex steroid hormones to avoid a potential additional vascular risk on top of their relative immobility. Two patients
5 quit smoking several weeks before the lead-in phase, another patient stopped taking sex steroid medication (in accordance with her gynecologist). All medication was documented. Start of any MS-related novel medication during the study was not allowed nor was any kind of iron substitution. Previous
10 medication in all MS patients included corticosteroids, intrathecal prednisolone, beta interferon, copaxone, mitoxantrone, cyclophosphamide, iv-immunoglobulins, deoxyspergualin and riluzole. Treatment was terminated at least half a year before EPO treatment due to lack of efficacy. All
15 patients had shown distinct progression of their disease in the past year.

"Consilium": Decision on study continuation after 12 weeks

20 After 12 weeks of weekly EPO treatment a so-called *consilium* took place, integrating all test results and observations of all participating parties, the patient, potential relatives or family members, an independent MS specialist, members of the clinical neuroscience team, a clinical neurophysiologist, a
25 neuroradiologist, and a physiotherapist. Continuation of treatment was only recommended if a patient had clearly improved performance in at least three independent items, previously identified to be affected in this particular individual, e.g. walking distance, cognition, and bladder
30 function.

Statistical analysis

All numerical results are presented as mean $\pm$ SD. For analysis, individual mean baseline performance in each of the items of interest was set to 100% in order to reach comparable baseline values among patients. Individual change during follow-up upon treatment or during the treatment-free period was expressed in % individual baseline. This way, patients can be compared and intra-group comparisons investigating the course of various variables in the high-dose EPO MS group, including all testing time-points from baseline on, can be performed using the Friedman test of SPSS 14.0 for Windows. This special nonparametric procedure for comparing repeated measures data with small sample sizes can be used for metric as well as ordered categorical data. Supplementary Tables 2 and 3 additionally provide significance values based on analyses of raw scores. Inter- and intragroup comparisons of MRI data were carried out using the nonparametric Mann-Whitney-U-test (independent and dependant). Statistical significance was set to 0.05 for all analyses.

Results

Study participation

25

All ten patients participated in the study until the *consilium* took place after 12 weeks of weekly EPO treatment. At that time-point, only the five high-dose MS patients met criteria for continuation, whereas all three low-dose EPO MS patients as well as the two high-dose EPO Parkinson patients did not show sufficient improvement that would have justified continuation according to our *consilium* criteria for beneficial treatment

response. This, however, does not prejudice effectiveness of EPO treatment with low-doses. The five high-dose EPO MS patients stayed on continuous treatment for another 12 weeks to receive intravenous high-dose EPO now once every other week.

5 After this second treatment period, there was a 24-week treatment-free follow-up period for all high-dose EPO MS patients. One of these patients could be followed over another EPO treatment cycle.

10 Safety

There were no adverse events reported or observed in any of the patients at any time. One Parkinson patient complained about being tired for approximately two to three days after each EPO
15 infusion. All other patients (high-dose as well as low-dose EPO MS and Parkinson) reported on feeling physically stronger, less tired, more optimistic, more enduring. They did not report that their sleep was in any way affected. Quality of life self-rating during that time stayed stable (data not shown). No
20 relapses were observed in any of the MS patients during the study period. Mean changes in blood cell counts and iron parameters during and after EPO treatment are illustrated in Figure 2. Original data (mean $\pm$ SD) of high-dose and low-dose MS patients and of Parkinson patients are presented in
25 Supplementary Table 1. The response of hemoglobin, hematocrit, and erythrocytes to EPO in MS patients was surprisingly low. Of the high-dose EPO MS group, a total of only five blood-lettings were necessary during the whole treatment phase (three times in one patient and once in two patients; see Supplementary Table
30 1). In the low-dose EPO group, no blood-letting had to be performed. The two Parkinson patients responded stronger to EPO and both required blood-letting. MCV and MCH declined similarly

strongly in all high-dose patients. The iron parameters showed the expected pattern, more pronounced upon high-dose and less upon low-dose EPO treatment: Distinct decrease in serum ferritin levels, paralleled by increases in serum transferrin and, particularly, in soluble transferrin receptor (Figure 2; Supplementary Table 1). Platelet counts increased in all patients at approximately the same rate but stayed essentially within the normal range. Whereas there was no measurable change in c-reactive protein (CRP), erythrocyte sedimentation rate tended to decrease in all patients over time of EPO treatment. All patients were EPO-antibody negative at baseline and none of the patients had developed EPO-antibodies by the end of the treatment period. No appreciable change in blood pressure upon EPO treatment was observed in any of the patients (data not shown).

Motor function

All patients in the high-dose EPO MS group showed a significant improvement in their maximum walking distance over time as compared to baseline, which became first apparent after three weeks, gradually improved during the treatment phase to reach a plateau at around eight weeks and still persisted after cessation of EPO treatment (Figure 3a,b; Supplementary Table 2). The increase in maximum walking distance in high-dose EPO MS patients resulted in a reduction of the EDSS (Figure 3c) and was paralleled in patients, who could be followed electrophysiologically, by a reduction in the central motor conduction time (left Tibialis MEP; Figure 3d, Supplementary Table 2). In contrast, neither low-dose EPO MS patients nor Parkinson patients, according to the Unified Parkinson's Disease Rating Score (Movement Disorder Society Task Force on

Rating Scales for Parkinson's Disease, 2003; Fahn S, Elton RL. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB and Goldstein M, editors. Recent Developments in Parkinson's Disease. Florham Park, NJ: Macmillan Health Care Information, 1987), displayed any measurable beneficial effect on walking distance/gait. Figure 3b illustrates the course of the maximum walking distance, both supervised and self-measurements, over more than one year in one of the high-dose EPO MS patients who underwent two EPO treatment periods. The trend-line from lead-in to the end of the observation period clearly directs upwards, with no change after switch to bi-weekly application. The EPO treatment break did not provoke any loss of the gained function, underlining that the effect of EPO is long lasting. Also, results of supervised ratings and self-ratings were quite consistent.

Fine motor performance in MacQuarrie Tapping and Dotting tests also showed improvement in high-dose EPO MS patients only (Figure 4a,b), whereas in the 9-hole peg test, there was no significant beneficial effect of EPO treatment in any group and no group difference (Figure 4c; Supplementary Table 2). Medianus MEP stayed stable over time (Supplementary Table 2). Bladder function was initially reported to be affected in three of the five high-dose and all three low-dose EPO MS patients. Subjective rating by the patients yielded distinct improvement only upon high-dose EPO treatment (data not shown). One MS patient with respiratory insufficiency due to muscle weakness showed improvement in lung function (vital capacity and forced vital capacity) upon high-dose EPO treatment.

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Cognitive functions

Premorbid intelligence as measured at baseline with the MWT-B was almost identical in all MS patients (Table 1). In contrast, estimation of the current intelligence using HAWIE-R showed a higher variability (high-dose EPO MS: 132.8 ± 15.4 ; low-dose EPO MS: 119.3 ± 14.7). High-dose EPO MS patients displayed a clear improvement in cognitive tests related to executive functioning, i.e. Trail Making - Part B, WMS-R Letter Number Sequencing, Visual Scanning, RBANS Coding and Working Memory, and psychomotor speed (Trail Making - Part A), which was absent both in low-dose MS and Parkinson patients (Figure 5, Supplementary Table 3). This improvement remained stable even during the EPO treatment break. In contrast, parameters of learning and memory (see Supplementary Table 3 for the most relevant items) remained essentially unchanged on a high performance level, consistent with a ceiling effect.

Other outcome and follow-up parameters

Analysis of MRI data did not uncover changes upon EPO treatment. Volumetrical analysis of total brain (excluding cerebellum, brain stem and ventricles) as well as of ventricles did not yield differences among high and low-dose MS patients upon study entry (1195.8 ± 65.6 ml versus 1013.6 ± 189.7 ml, $p=0.4$; and 48.3 ± 17.6 ml versus 46.4 ± 12.8 ml, $p=0.857$). Follow-up of the high-dose patients after three months (3.6 ± 1.1 months) showed no change in total brain or ventricle volume compared to baseline (baseline versus 3 months: 1195.8 ± 65.6 ml versus 1152.4 ± 47.7 ml, $p=0.317$; and 48.3 ± 17.6 ml versus 47.9 ± 17.8 ml, $p=1.0$). Serum levels of the glial damage marker S100B did not

reveal consistent changes in any of the patients upon treatment (Supplementary Table 1).

Conclusion

5

The results presented above demonstrate safety and potential beneficial effects of long-term EPO treatment in chronic progressive MS. In this study, there were no adverse events, no safety concerns, and an astonishingly low need of blood
10 lettings. Using an intra-individual follow-up design, a significant clinical and a tendency of electrophysiological improvement of motor function in chronic progressive MS at least upon high-dose EPO treatment was found as reflected by a reduction in EDSS. Improvement of this score has to our
15 knowledge not yet been observed in any chronic progressive MS trial.

The demonstrated beneficial effects on motor function and cognition cannot simply explained by improved mood since an
20 improvement in general well-being and mood was observed in all patients, independent of the dose, and became evident already after the first infusion of EPO. In contrast to mood and general well-being, no clear beneficial effect of low-dose EPO treatment in MS patients on any of the other parameters tested
25 could be demonstrated at present. Further, there was no measurable effect of high-dose EPO treatment in the two drug-naïve Parkinson patients. These latter findings may also exclude a pure placebo effect to explain the improvement found in EPO MS patients.

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The improvement was kept during EPO reduction and even after complete cessation of EPO treatment over a follow-up time of 24

weeks, pointing to a regenerative effect mediated by EPO rather than a temporary and short-lived action. These results may be tested using an interval treatment as described in DE 10 2006 004 008.2 and in PCT/EP2007/000640. The teaching of this document with respect to the beneficial effects of EPO in patients suffering from multiple sclerosis using an interval treatment is fully included into the present document by reference. It remains to be determined, however, whether continuation of EPO treatment in MS patients after a treatment-free interval will lead to further improvement, or at least contribute to maintaining the improved status and to slowing of progression. The observations in one of our patients who could be followed over more than one year and two EPO treatment cycles, supports the latter assumption.

Taken together, we were able to provide first evidence that EPO may show an effect on the clinical course, as demonstrated by the EDSS score, of chronic progressive MS, acting via as yet undetermined mechanisms that improve function, enhance regeneration and / or slow deterioration. Although there are reports of beneficial effects of EPO in rodent studies of EAE, EPO is the first compound that apparently demonstrated to effect an improvement in EDSS and a tendency of improvement in central motor conduction time in a cohort of chronic progressive MS patients.

Of note is the fact that all MS patients, high-dose as well as low-dose EPO received the same three-day high-dose corticosteroid infusion to create an immunologically comparable starting-point of longterm EPO therapy. Although no persisting beneficial effects of steroid treatment per se would be expected (but rather a potential rebound effect, i.e. a relapse

of the disease after discontinuation of therapy - Agnello D, Bigini P, Villa P, Mennini T, Cerami A, Brines ML, et al. Erythropoietin exerts an anti-inflammatory effect on the CNS in a model of experimental autoimmune encephalomyelitis. Brain Res 5 2002; 952: 128-34), the lasting clinical improvement in the high-dose EPO MS group makes a steroid effect explaining this improvement very unlikely.

Regarding the mechanism of action of EPO on motor and cognitive 10 performance in chronic progressive MS, the observed gradual improvement, first visible after a latency of several weeks, and, in particular, its stability over several months of EPO reduction and EPO treatment-free interval, suggests a morphological rather than a purely functional and transient 15 effect. This is further supported by the observed improvement of the central motor conduction time. This improvement is particularly striking and difficult to reconcile with the known spectrum of EPO functions, as remyelination by EPO has not yet been demonstrated.

Whereas the obvious failure of low-dose EPO to lead to an appreciable improvement in MS patients might be explained by an insufficient concentration of EPO achieved in the central nervous system, it is unclear why the Parkinson patients did 20 not have any measurable benefit. EPO penetrates through a blood-brain-barrier at least upon high-dose peripheral application (Banks et al., 2004; Brines et al., 2000; Ehrenreich et al., 2004b; Xenocostas et al., 2005) and should therefore have reached the brain also in the two Parkinson 25 patients in amounts sufficient to exert neurotrophic effects. In this disease, however, symptoms become usually overt when 70% of neurons in the substantia nigra are degenerated (Koller 30

WC. When does Parkinson's disease begin? Neurology 1992; 42: 27-31; discussion 41-8). Neurotrophic effects on the remaining neuronal population may not lead to rapid clinical improvement or require longer time periods of treatment and follow-up.

5

The infrequent requirement of blood lettings in MS patients, consistent with a relative hyporesponsiveness of the hematopoietic system to EPO (Kwack C, Balakrishnan VS. Managing erythropoietin hyporesponsiveness. Semin Dial 2006; 19: 146-10 51), might be due to a systemic latent inflammatory condition altering cytokine patterns that modulate the bone marrow response to EPO. This proposed latent inflammatory condition cannot be easily diagnosed with routine laboratory parameters of inflammation. Here, the response of the hematopoietic system to EPO might even serve in future studies of MS as an indicator 15 of occult inflammation, and thus requirement of additional immunosuppression. Moreover, the hyporesponsiveness of the hematopoietic system, in contrast to the nervous system, to EPO in MS supports the notion that the observed therapeutic efficacy in MS is not simply due to improved oxygen supply via 20 increased red blood cell mass.

EPO treatment leads to temporary shifts in iron stores as delineated here by several determinants of iron metabolism. 25 Accelerated and intensified integration of iron into new red blood cells and thereby withdrawal of iron from its stores, leads to a picture similar to that of true iron deficiency. This picture is corrected after termination of EPO treatment without extra iron substitution. In the absence of appreciable 30 blood loss and upon normal nutrition, iron deficiency will not occur. Binding more and more of the freely available iron, on the other hand, might additionally reduce inflammatory

processes in MS and thereby contribute to the beneficial effect of high-dose long-term EPO treatment. In fact, iron chelators have been proposed for treatment of MS (e.g. desferrioxamine; Lynch SG, Fonseca T, Levine SM. A multiple course trial of desferrioxamine in chronic progressive multiple sclerosis. Cell Mol Biol (Noisy-le-grand) 2000; 46: 865-9)). Interestingly, disturbed iron metabolism has been described in MS patients (Sfagos C, Makis AC, Chaidos A, Hatzimichael EC, Dalamaga A, Kosma K, et al. Serum ferritin, transferrin and soluble transferrin receptor levels in multiple sclerosis patients. Mult Scler 2005; 11: 272-5).

To summarize, in the presented example, eight MS patients, five randomly assigned to high-dose (48000 IU), three to low-dose (8000 IU) rhEPO treatment, and, as disease controls, two drug-naïve Parkinson patients (receiving 48000 IU) were followed over up to 48 weeks: A 6-week lead-in phase, a 12-week treatment phase with weekly EPO, another 12-week treatment phase with bi-weekly EPO, and a 24-week post-treatment phase. Not only an improvement of cognitive performance or the first time but also a reduction in EDSS was observed upon high-dose EPO treatment in MS patients, persisting for three to six months after cessation of EPO application. In contrast, low-dose EPO MS patients and drug-naïve Parkinson patients did not improve in any of the parameters tested in the present study. There were no adverse events, no safety concerns and a surprisingly low need of blood-lettings.

Table 1: Patient Characteristics

Treatment group	Patient ID	Age (years)	Sex	Education total (years)	Premorbid intelligence quotient ^a (years)	Disease duration (years)	Disease subtype	Optic nerve involvement ^b	Leading symptoms	EDSS upon inclusion	Walking distance upon inclusion
MS high-dose (N=5)	1	34	female	19.5	118	9.2	PPMS	none	tetraspastic (mainly legs/right side), slight ataxia	5.5	88m
	2	42	male	22	112	9.7	SPMS	none	ataxia, dysarthria, urinary dysfunction, mild cognitive deficits, fatigue, inadequate affect	6.0	140m (with crutch)
	3	53	male	20.5	136	19.3	PPMS	bilateral	tetraspastic (mainly legs/left side), urinary/bowel dysfunction, slight fatigue	6.5	25m (with walker)
	4	44	male	20.5	112	12.1	PPMS	bilateral	tetraspastic (mainly arms/right side), ataxia, respiratory insufficiency (muscle weakness)	5.5	110m
	5	45	female	20	143	14.8	SPMS	none	tetraspastic, ataxia of upper limbs, urinary/bowel dysfunction, fatigue, dysthymia	6.0	77m (intermittent assistance)
MS low-dose (N=3)	m/f: 43.6 (6.8) 3/2					20.5 (0.9)	124.2 (14.4)	13.0 (4.1)	3x PPMS 2x SPMS	5.9 (0.4)	88.0 (42.7)
	6	38	male	20	130	9.5	PPMS	unilateral	ataxia, paraparesis, severe sensory dysfunction, urinary dysfunction, slight dysarthria	4.5	381m
	7	42	male	23	107	18.3	SPMS	bilateral	tetraspastic (mainly legs), urinary dysfunction, cognitive deficits, INO, dysarthria	6.5	54m (with walker)
	8	63	female	23	136	10.4	SPMS	none	paresis (mainly legs/right side), muscle cramps, urinary dysfunction, dysarthria	6.0	118m (with cane)
m/f: 47.7 (13.4) 2/1					22.0 (1.7)	124.3 (15.3)	12.7 (4.8)	1x PPMS 2x SPMS	5.7 (1.0)	184.3 (173.3)	
Treatment group	Patient ID	Age (years)	Sex	Education total (years)	Premorbid intelligence quotient ^a (years)	Disease duration (years)	Disease subtype	Leading symptoms	UPDRS upon inclusion		
Parkinson high-dose (N=2)	9	43	male	24	145	1.8	idiopathic	-	tremor (mainly right side), rigidity, bradykinesia, micrographia, mild cognitive deficits, dysarthria	30	-
	10	73	female	18	118	0.7	idiopathic	-	tremor (mainly legs), bradykinesia, impaired fine motor function, fatigue, cognitive dysfunction	20	-

Means (SD) presented for treatment groups "MS high-dose" and "MS low-dose": PPMS: primary progressive multiple sclerosis. SPMS: secondary progressive multiple sclerosis. EDSS: Expanded Disability Status Scale; UPDRS: Unified Parkinson's Disease Rating Scale; INO: internuclear ophthalmoplegia. ^aPremorbid intelligence quotient based on results of the Mehrfachwahl-Intelligenztest (MMT B). ^bState of ophthalmological examination and VEPs (visual evoked potentials) upon study entry which remained unchanged during follow-up.

Supplementary Table 1: Routine Laboratory Data – Part 1

	Base- EPO weekly										EPO bi-weekly										EPO-free period		Ref. Rang																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8		Week 9		Week 10		Week 11			Week 12		Week 13		Week 14		Week 15		Week 16		Week 17		Week 18		Week 19		Week 20		Week 21		Week 22		Week 23		Week 24		Week 25		Week 26		Week 27		Week 28		Week 29		Week 30		Week 31		Week 32		Week 33		Week 34		Week 35		Week 36		Week 37		Week 38		Week 39		Week 40		Week 41		Week 42		Week 43		Week 44		Week 45		Week 46		Week 47		Week 48		Week 49		Week 50		Week 51		Week 52		Week 53		Week 54		Week 55		Week 56		Week 57		Week 58		Week 59		Week 60		Week 61		Week 62		Week 63		Week 64		Week 65		Week 66		Week 67		Week 68		Week 69		Week 70		Week 71		Week 72		Week 73		Week 74		Week 75		Week 76		Week 77		Week 78		Week 79		Week 80		Week 81		Week 82		Week 83		Week 84		Week 85		Week 86		Week 87		Week 88		Week 89		Week 90		Week 91		Week 92		Week 93		Week 94		Week 95		Week 96		Week 97		Week 98		Week 99		Week 100		Week 101		Week 102		Week 103		Week 104		Week 105		Week 106		Week 107		Week 108		Week 109		Week 110		Week 111		Week 112		Week 113		Week 114		Week 115		Week 116		Week 117		Week 118		Week 119		Week 120		Week 121		Week 122		Week 123		Week 124		Week 125		Week 126		Week 127		Week 128		Week 129		Week 130		Week 131		Week 132		Week 133		Week 134		Week 135		Week 136		Week 137		Week 138		Week 139		Week 140		Week 141		Week 142		Week 143		Week 144		Week 145		Week 146		Week 147		Week 148		Week 149		Week 150		Week 151		Week 152		Week 153		Week 154		Week 155		Week 156		Week 157		Week 158		Week 159		Week 160		Week 161		Week 162		Week 163		Week 164		Week 165		Week 166		Week 167		Week 168		Week 169		Week 170		Week 171		Week 172		Week 173		Week 174		Week 175		Week 176		Week 177		Week 178		Week 179		Week 180		Week 181		Week 182		Week 183		Week 184		Week 185		Week 186		Week 187		Week 188		Week 189		Week 190		Week 191		Week 192		Week 193		Week 194		Week 195		Week 196		Week 197		Week 198		Week 199		Week 200		Week 201		Week 202		Week 203		Week 204		Week 205		Week 206		Week 207		Week 208		Week 209		Week 210		Week 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911		Week 912		Week 913		Week 914		Week 915		Week 916		Week 917		Week 918		Week 919		Week 920		Week 921		Week 922		Week 923		Week 924		Week 925		Week 926		Week 927		Week 928		Week 929		Week 930		Week 931		Week 932		Week 933		Week 934		Week 935		Week 936		Week 937		Week 938		Week 939		Week 940		Week 941		Week 942		Week 943		Week 944		Week 945		Week 946		Week 947		Week 948		Week 949		Week 950		Week 951		Week 952		Week 953		Week 954		Week 955		Week 956</	

SD= standard deviation; ref. range= reference range of laboratory

^{1,2} denotes number of blood lettings necessary in the respective week (blood letting if hematocrit > 50% in male, > 48% in female patients).

Supplementary Table 1: Routine Laboratory Data – Part 2

		Base- EPO weekly										EPO bi-weekly										EPO-free																				
		line		Week		Week		Week		Week		Week		Week		Week		Week		Week		period																				
		baseline	Mean (SD)	1	Mean (SD)	2	Mean (SD)	3	Mean (SD)	4	Mean (SD)	5	Mean (SD)	6	Mean (SD)	7	Mean (SD)	8	Mean (SD)	9	Mean (SD)	10	Mean (SD)	11	Mean (SD)	12	Mean (SD)	14	Mean (SD)	16	Mean (SD)	18	Mean (SD)	20	Mean (SD)	22	Mean (SD)	24	Mean (SD)	26	Mean (SD)	36
MCH (pg)		30.14 (0.79)	30.14 (1.17)	29.52 (1.51)	29.52 (0.69)	29.23 (0.85)	29.22 (1.27)	28.54 (1.35)	28.68 (1.43)	27.80 (1.03)	27.42 (0.48)	27.32 (0.99)	26.94 (1.58)	26.30 (1.89)	25.88 (1.50)	25.30 (1.29)	25.40 (1.59)	25.04 (1.03)	25.58 (1.10)	25.75 (0.95)	28.34 (0.70)	26-																				
MS high-dose (N=5)																																										
MS low-dose (N=3)		29.70 (0.44)	29.60 (1.04)	30.17 (0.83)	30.20 (0.82)	30.20 (0.66)	30.17 (0.76)	30.47 (0.83)	30.00 (0.26)	30.10 (1.11)	29.87 (0.45)	29.87 (0.93)	29.83 (0.61)	29.40 (0.98)	-	-	-	-	-	-	-	-																				
Parkinson high-dose (N=2)		30.25 (0.92)	30.25 (1.34)	29.90 (1.56)	30.20 (1.56)	28.80 (0.85)	29.30 (0.71)	29.60 (0.28)	28.35 (2.19)	28.55 (0.07)	28.60 (0.99)	27.80 (0.42)	28.40 (0.99)	26.90 (1.27)	-	-	-	-	-	-	-	-																				
Thrombocytes(Tsd/ μ l)																																										
MS high-dose (N=5)		259.6 (19.0)	231.8 (55.8)	267.8 (25.7)	263.0 (51.8)	326.3 (75.6)	321.4 (43.6)	310.8 (41.3)	275.6 (15.7)	293.6 (42.1)	309.6 (61.8)	316.4 (23.1)	315.6 (33.3)	303.6 (40.3)	273.2 (40.6)	281.4 (33.5)	255.4 (52.9)	270.4 (34.9)	285.0 (51.3)	287.3 (21.3)	254.4 (42.8)	150-																				
MS low-dose (N=3)		282.8 (62.6)	307.7 (54.5)	301.7 (21.5)	324.0 (57.7)	322.7 (59.0)	381.0 (46.0)	331.7 (31.6)	328.7 (40.4)	307.7 (60.6)	341.7 (41.0)	338.0 (43.5)	322.7 (48.9)	323.3 (66.5)	-	-	-	-	-	-	-	-																				
Parkinson high-dose (N=2)		245.8 (58.3)	244.0 (73.5)	277.0 (75.0)	228.0 (25.5)	250.5 (61.5)	272.5 (72.8)	294.5 (78.5)	282.0 (21.2)	275.0 (50.9)	261.0 (43.8)	290.0 (93.3)	308.5 (74.2)	292.0 (87.7)	-	-	-	-	-	-	-	-																				
Iron (μ mol/l)																																										
MS high-dose (N=5)		23.93 (4.9)	8.60 (3.1)	8.94 (3.3)	-	29.88 (7.6)	-	12.82 (3.9)	-	10.86 (4.2)	-	10.60 (4.6)	-	9.50 (1.4)	30.08 (17.3)	25.92 (2.5)	30.38 (7.1)	34.74 (18.7)	24.90 (6.7)	28.63 (5.7)	21.92 (8.4)	ms 12-																				
MS low-dose (N=3)		14.70 (2.8)	-	19.53 (2.5)	-	14.10 (3.6)	-	17.20 (2.7)	-	17.43 (6.7)	-	19.50 (3.3)	-	17.97 (7.5)	-	-	-	-	-	-	-	ferm 9-;																				
Parkinson high-dose (N=2)		23.95 (8.9)	10.75 (0.9)	10.10 (0.6)	-	17.20 (3.0)	-	13.30 (9.8)	-	12.45 (6.2)	-	12.75 (5.0)	-	9.55 (2.5)	-	-	-	-	-	-	-	-																				
Transferrin (μ mol/l)																																										
MS high-dose (N=5)		269.6 (44.3)	246.0 (26.8)	264.4 (28.7)	-	299.0 (20.7)	-	301.4 (22.4)	-	325.4 (55.0)	-	337.0 (25.8)	-	339.2 (32.7)	333.2 (30.8)	327.4 (34.5)	310.8 (43.4)	321.8 (39.3)	310.6 (15.9)	305.3 (35.7)	292.6 (25.2)	168-																				
MS low-dose (N=3)		232.0 (21.8)	255.0 (4.2)	250.3 (21.4)	-	248.7 (3.5)	-	255.7 (4.7)	-	250.7 (8.5)	-	267.3 (6.5)	-	275.3 (30.0)	-	-	-	-	-	-	-	-																				
Parkinson high-dose (N=2)		262.0 (32.5)	251.0 (62.2)	260.5 (53.0)	-	285.0 (55.2)	-	301.0 (67.9)	-	319.0 (58.0)	-	314.5 (60.1)	-	312.5 (24.7)	-	-	-	-	-	-	-	-																				
Transferrin saturation (%)																																										
MS high-dose (N=5)		36.07 (8.1)	13.96 (4.9)	13.30 (4.2)	-	39.82 (10.4)	-	17.31 (6.5)	-	13.68 (5.9)	-	12.72 (5.6)	-	11.25 (2.0)	35.43 (19.9)	31.83 (4.9)	40.22 (13.2)	43.14 (23.9)	31.97 (8.6)	36.68 (3.3)	30.66 (14.8)	16-																				
MS low-dose (N=3)		25.03 (3.0)	30.48 (10.2)	31.28 (5.6)	-	22.72 (5.6)	-	26.82 (4.5)	-	27.61 (10.4)	-	26.94 (3.7)	-	25.43 (7.7)	-	-	-	-	-	-	-	-																				
Parkinson high-dose (N=2)		37.74 (18.5)	17.40 (2.9)	15.67 (2.3)	-	24.07 (0.5)	-	16.56 (9.2)	-	16.51 (10.7)	-	17.06 (9.6)	-	12.33 (4.1)	-	-	-	-	-	-	-	-																				

SD= standard deviation; ref. range= reference range of laboratory.

Supplementary Table 1: Routine Laboratory Data – Part 3

Base-line	EPO weekly										EPO bi-weekly										EPO free																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8		Week 9		Week 10		Week 11		Week 12		Week 14		Week 16		Week 18		Week 20		Week 22		Week 24		Week 26		Week 28		Week 30		Week 32		Week 34		Week 36																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)

SD= standard deviation, ref. range= reference range of laboratory

Supplementary Table 2: Motor Data (original) – Part 2

MEP CMCT (ms)	EPO weekly										EPO bi-weekly										EPO-free period			
	Mean baseline (SD)	Week 1 Mean (SD)	Week 2 Mean (SD)	Week 3 Mean (SD)	Week 4 Mean (SD)	Week 5 Mean (SD)	Week 6 Mean (SD)	Week 7 Mean (SD)	Week 8 Mean (SD)	Week 9 Mean (SD)	Week 10 Mean (SD)	Week 11 Mean (SD)	Week 12 Mean (SD)	Week 14 Mean (SD)	Week 16 Mean (SD)	Week 18 Mean (SD)	Week 20 Mean (SD)	Week 22 Mean (SD)	Week 24 Mean (SD)	Week 26 Mean (SD)	Week 36 Mean (SD)	Week 48 Mean (SD)		
<i>Medianus nerve right</i>	13.9 (3.7)	-	-	-	-	-	-	-	-	-	-	-	14.3 (3.5)	-	-	-	-	-	-	13.8 (3.2)	-	-		
MS high-dose (N=5)																								
MS low-dose (N=3)	20.6 (2.2)	-	-	-	-	-	-	-	-	-	-	-	16.8 (4.8)	-	-	-	-	-	-	-	-	-		
<i>Medianus nerve left</i>	13.6 (3.9)	-	-	-	-	-	-	-	-	-	-	-	13.8 (4.7)	-	-	-	-	-	-	14.3 (3.9)	-	-		
MS high-dose (N=5)																								
MS low-dose (N=3)	16.5 (6.1)	-	-	-	-	-	-	-	-	-	-	-	14.5 (1.0)	-	-	-	-	-	-	-	-	-		
<i>Tibialis nerve right</i>	36.6 (11.7)	-	-	-	-	-	-	-	-	-	-	-	38.7 (9.1)	-	-	-	-	-	-	30.6 (8.6)	-	-		
MS high-dose (N=4*)																								
MS low-dose (N=3)	34.7 (5.0)	-	-	-	-	-	-	-	-	-	-	-	32.1 (10.0)	-	-	-	-	-	-	-	-	-		
<i>Tibialis nerve left</i>	42.5 (9.6)	-	-	-	-	-	-	-	-	-	-	-	38.6 (10.1)	-	-	-	-	-	-	30.9 (10.9)	-	-		
MS high-dose (N=4*)																								
MS low-dose (N=3)	31.8 (10.1)	-	-	-	-	-	-	-	-	-	-	-	30.4 (16.5)	-	-	-	-	-	-	-	-	-		

SD: standard deviation; MEP CMCT: motor evoked potentials central motor conduction time. *Missing data of one patient due to methodological problems during baseline measurement.

P₁ denotes significance from baseline to week 24. Statistical analysis: Friedman test (performed in high-dose EPO MS patients only).

Supplementary Table 3: Neuropsychological Test Data (original) – Part 1

Cognitive domain	Cognitive parameter	Baseline		EPO weekly				EPO bi-weekly				EPO-free period	
		Baseline Mean (SD)	Day 6 Mean (SD)	Week 2 Mean (SD)	Week 6 Mean (SD)	Week 9 Mean (SD)	Week 12 Mean (SD)	Week 18 Mean (SD)	Week 24 Mean (SD)	P ₁		Week 36 Mean (SD)	Week 48 Mean (SD)

Visual scanning / attention	Visual Scanning – critical trials (median ms)																			0.007	1510.6 (534.4)	1515.2 (563.8)	1530.9 (402.0)	1531.0 (534.6)	1567.1 (524.8)	1641.3 (410.2)	1927.4 (432.9)	2162.4 (621.6)	2506.2 (834.6)	2533.8 (726.8)	2556.2 (34.0)	258.1 (47.2)	266.4 (51.9)	269.9 (38.8)	278.4 (60.3)	1605.8 (499.8)			
	MS high-dose (N=5)																																						
	MS low-dose (N=3)																																						
	Parkinson high-dose (N=2)																																						
	Visual Scanning – noncritical trials (median ms)																																						
	MS high-dose (N=5)																																						
	MS low-dose (N=3)																																						
	Parkinson high-dose (N=2)																																						
	Alertness – without cue sound (median ms)																																						
	MS high-dose (N=5)																																						
	MS low-dose (N=3)																																						
	Parkinson high-dose (N=2)																																						
	Alertness – with cue sound (median ms)																																						
	MS high-dose (N=5)																																						
MS low-dose (N=3)																																							
Parkinson high-dose (N=2)																																							
RBANS Coding (raw score)																																							
MS high-dose (N=5)																																							
MS low-dose (N=3)																																							
Parkinson high-dose (N=2)																																							
Trail Making Part A (reaction time in s)																																							
MS high-dose (N=5)																																							
MS low-dose (N=3)																																							
Parkinson high-dose (N=2)																																							
Trail Making Part B (reaction time in s)																																							
MS high-dose (N=5)																																							
MS low-dose (N=3)																																							
Parkinson high-dose (N=2)																																							

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.
 P_1 denotes significance from baseline to week 24; P_2 denotes significance from baseline to week 36; Statistical analysis: Friedman test (performed in high-dose EPO MS patients only).

Supplementary Table 3: Neuropsychological Test Data (original) – Part 2

Cognitive domain		Cognitive parameter	Baseline					EPO weekly					EPO bi-weekly			P ₁	EPO-free period	
			Baseline Mean (SD)	Day 6 Mean (SD)	Week 2 Mean (SD)	Week 6 Mean (SD)	Week 9 Mean (SD)	Week 12 Mean (SD)	Week 18 Mean (SD)	Week 24 Mean (SD)	Week 36 Mean (SD)							
Working memory / executive functions	Trail Making Part B (reaction time in s) (N=5) MS high-dose (N=5) MS low-dose (N=3) Parkinson high-dose (N=2) Working Memory (median ms) MS high-dose (N=5) MS low-dose (N=3) Parkinson high-dose (N=2) WMS-R Letter Number Sequencing (raw score) MS high-dose (N=5) MS low-dose (N=3) Parkinson high-dose (N=2) WCST-64 perseverative errors (raw score) (N=5) MS low-dose (N=3) Parkinson high-dose (N=2)	68.4 (26.6)	50.8 (18.7)	57.6 (23.0)	60.4 (29.2)	45.2 (14.5)	49.8 (13.9)	45.2 (11.3)	51.4 (18.4)			0.009	46.8 (17.5)					
		131.0 (46.4)	129.3 (59.4)	156.3 (118.4)	110.7 (66.3)	108.0 (35.6)	173.0 (167.2)	-	-				-					
		127.3 (102.9)	-	112.5 (79.9)	-	-	143.5 (130.8)	-	-				-					
		721.8 (261.5)	487.6 (142.5)	610.9 (222.2)	682.4 (275.3)	654.5 (325.1)	592.9 (260.5)	504.0 (83.3)	548.9 (170.2)			0.051	570.6 (212.4)					
		792.3 (94.2)	703.0 (67.3)	792.5 (339.3)	908.0 (207.3)	799.8 (108.7)	892.0 (105.9)	-	-				-					
		554.1 (63.5)	-	619.5 (215.7)	-	-	650.5 (252.4)	-	-				-					
		12.9 (2.8)	12.6 (2.6)	13.2 (3.1)	13.8 (3.6)	14.6 (2.6)	14.8 (2.2)	15.6 (3.2)	14.4 (2.9)			0.019	14.4 (2.9)					
		10.5 (1.0)	10.3 (0.6)	11.0 (1.0)	12.0 (0.0)	11.7 (1.2)	11.0 (2.6)	-	-				-					
		12.3 (5.3)	-	12.5 (3.5)	-	-	13.0 (5.7)	-	-				-					
		8.0 (7.3)	-	-	5.9 (4.0)	-	7.8 (7.3)	-	4.2 (1.6)			0.164	-					
Learning and memory	MS low-dose (N=3) Parkinson high-dose (N=2) RBANS list learning (raw score) MS high-dose (N=5) MS low-dose (N=3) Parkinson high-dose (N=2) RBANS list recall (raw score) MS high-dose (N=5) MS low-dose (N=3)	6.7 (2.5)	-	-	7.3 (4.9)	-	8.7 (7.2)	-	-				-					
		8.5 (6.4)	-	-	-	-	15.0 (14.1)	-	-				-					
		35.8 (3.3)	-	-	33.0 (4.4)	-	34.0 (5.0)	-	36.3 (3.4)			0.084	-					
		29.0 (5.6)	-	-	29.3 (4.0)	-	29.3 (5.7)	-	-				-					
		31.0 (8.5)	-	-	-	-	34.5 (6.4)	-	-				-					
		9.2 (0.4)	-	-	8.1 (2.0)	-	7.9 (2.8)	-	9.0 (1.7)			0.506	-					
		6.0 (4.6)	-	-	6.7 (2.5)	-	4.7 (3.2)	-	-				-					

	Parkinson high-dose (N=2)	7.5 (0.7)	-	-	-	-	9.5 (0.7)	-	-	-
	RBANS figure recall (raw score)									
	MS high-dose (N=5)	17.2 (1.8)	-	-	18.8 (1.8)	-	19.8 (0.4)	-	17.6 (2.3)	0.153
	MS low-dose (N=3)	15.7 (4.0)	-	-	15.0 (4.6)	-	16.7 (5.8)	-	-	-
	Parkinson high-dose (N=2)	19.5 (0.7)	-	-	-	-	19.0 (1.4)	-	-	-

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; WCST-64: Wisconsin Card Sorting Test – 64 Card Version.
P₁ denotes significance from baseline to week 24; P₂ denotes significance from baseline to week 36; Statistical analysis: Friedman test (performed in high-dose EPO MS patients only).

Patent Claims

1. Method for the improvement of the expanded disability status scale (EDSS) score achieved by mammals affected by multiple sclerosis, wherein a substance effecting increased and/or prolonged activation and/or stimulation of the erythropoietin receptor is applied to the mammal.
2. Method according to the preceding claim, characterized in that a erythropoietin receptor activator or stimulator with or without hematopoietic/erythropoietic activity is applied to the mammal as substance effecting increase and/or prolonged activation and/or stimulation of the erythropoietin-receptor.
3. Method according to one of the preceding claims, characterized in that at least one of the following substances: erythropoietin (e.g. a native erythropoietin or recombinant erythropoietin), a derivative thereof, a variant thereof, a fusion protein thereof, an analogue thereof, an effective fragment thereof, a mimetics thereof, an erythropoietin agonist, a synthetic erythropoiesis stimulating protein, an erythropoietin stabilizing substance, an erythropoietin receptor activating and/or stimulating antibody and a substance genetically modifying the

mammal in order to increase erythropoietin expression is applied to the mammal as substance effecting increase and/or prolonged activation and/or stimulation of the erythropoietin-receptor.

4. Method according to one of the preceding claims, characterised in that the substance is applied in intervals which are interrupted by application-free periods of time in which said substance is not applied.
5. Method according to the preceding claim, characterised in that the application of the substance is effected intermittently in at least two application periods with a duration of respectively at least two weeks, application-free periods with a duration of at least two weeks in which said substance is not applied being provided between two application periods.
6. Method according to one of claims 4 and 5, characterised in that an application period lasts 12 to 48 weeks, advantageously 18 to 36 weeks, advantageously 24 to 28 weeks.
7. Method according to one of claims 4 to 6, characterised in that an application-free period lasts 8 to 53 weeks, advantageously 16 to 28 weeks.
8. Method according to one of claims 4 to 7, characterised in that at least one of the application periods comprises two partial periods, said substance being applied weekly in a first partial period and

said substance being applied every two weeks in a subsequent second partial period.

9. Method according to one of the preceding claims, characterised in that said substance is given in a dose or an equivalent to a dose of 1,000 IU to 200,000 IU, advantageously 5,000 IU to 100,000 IU, advantageously 30000 IU to 60000 IU, advantageously 40000 IU to 50000 IU per week, per application and/or per application time or doses equivalent to said doses leading to comparable erythropoietin levels or comparable erythropoietin receptor activating biological activity, said international unit being international units of native or recombinant erythropoietin.
10. Method according to one of the preceding claims, characterised in that the application is effected parenterally/systemically.
11. Method according to one of the preceding claims, characterised in that the application is effected vascularly, intranasally and/or by inhalation.
12. Method according to one of the preceding claims, characterised in that the application is effected intravenously, subcutaneously and/or intramuscularly.
13. Method according to one of the preceding claims, characterised in that the mammal is a human.

14. Use of a substance effecting increased and/or prolonged activation and/or stimulation of the erythropoietin receptor for the production of a drug for the improvement of the expanded disability status scale (EDSS) score achieved by mammals affected by multiple sclerosis.
15. Use according to claim 14 of an erythropoietin receptor activator or stimulator with or without hematopoietic / erythropoietic activity as substance effecting increase and/or prolonged activation and/or stimulation of the erythropoietin-receptor.
16. Use according to one of claims 14 and 15 of at least one of the following substances: erythropoietin (e.g. a native erythropoietin or recombinant erythropoietin), a derivative thereof, a variant thereof, a fusion protein thereof, an analogue thereof, an effective fragment thereof, a mimetics thereof, an erythropoietin agonist, a synthetic erythropoiesis stimulating protein, an erythropoietin stabilizing substance, an erythropoietin receptor activating and/or stimulating antibody and a substance genetically modifying the mammal in order to increase erythropoietin expression as substance effecting increase and/or prolonged stimulation of the erythropoietin-receptor.
17. Use according to one of claims 14 to 16 for the production of a drug for intermittent treatment for improvement of the expanded disability status scale

(EDSS) score achieved by mammals affected by multiple sclerosis.

18. Use according to claim 17, characterised in that the substance effecting increase and/or prolonged activation and/or stimulation of the erythropoietin-receptor is applied in intervals for intermittent treatment, said intervals being interrupted by application-free periods of time in which said substance is not applied.
19. Use according to one of the claims 17 and 18, characterised in that the substance effecting increased and/or prolonged activation and/or stimulation of the erythropoietin-receptor is applied intermittently in at least two application periods with a duration of respectively at least two weeks, application-free periods with a duration of at least two weeks in which said substance effecting increased and/or prolonged activation and/or stimulation of the erythropoietin-receptor is not applied being provided between two application periods.
20. Use according to one of claims 18 and 19, characterised in that an application period lasts 12 to 48 weeks, advantageously 18 to 36 weeks, advantageously 24 to 28 weeks.
21. Use according to one of claims 18 to 20, characterised in that an application-free period lasts 8 to 53 weeks, advantageously 16 to 28 weeks.

22. Use according to one of claims 18 to 21, characterised in that at least one of the application periods comprises two partial periods, said substance being applied weekly in a first partial period and said substance being applied every two weeks in a subsequent second partial period.
23. Use according to one of the claims 14 to 22, characterised in that the said substance is given in a dose or an equivalent to a dose of 1,000 IU to 200,000 IU, advantageously 5,000 IU to 100,000 IU, advantageously 30000 IU to 60000 IU per week, per application and/or per application period, said international units being international units of native or recombinant erythropoietin.
24. Use according to one of the claims 14 to 23, characterised in that the application is effected parenterally/systemically.
25. Use according to one of the claims 14 to 24, characterised in that the application is effected vascularly, intranasally and/or by inhalation.
26. Use according to one of claims 14 to 25, characterised in that the application is effected intravenously, subcutaneously and/or intramuscularly.
27. Use according to one of the claims 14 to 26, characterised in that the mammal is a human.

Figure 1

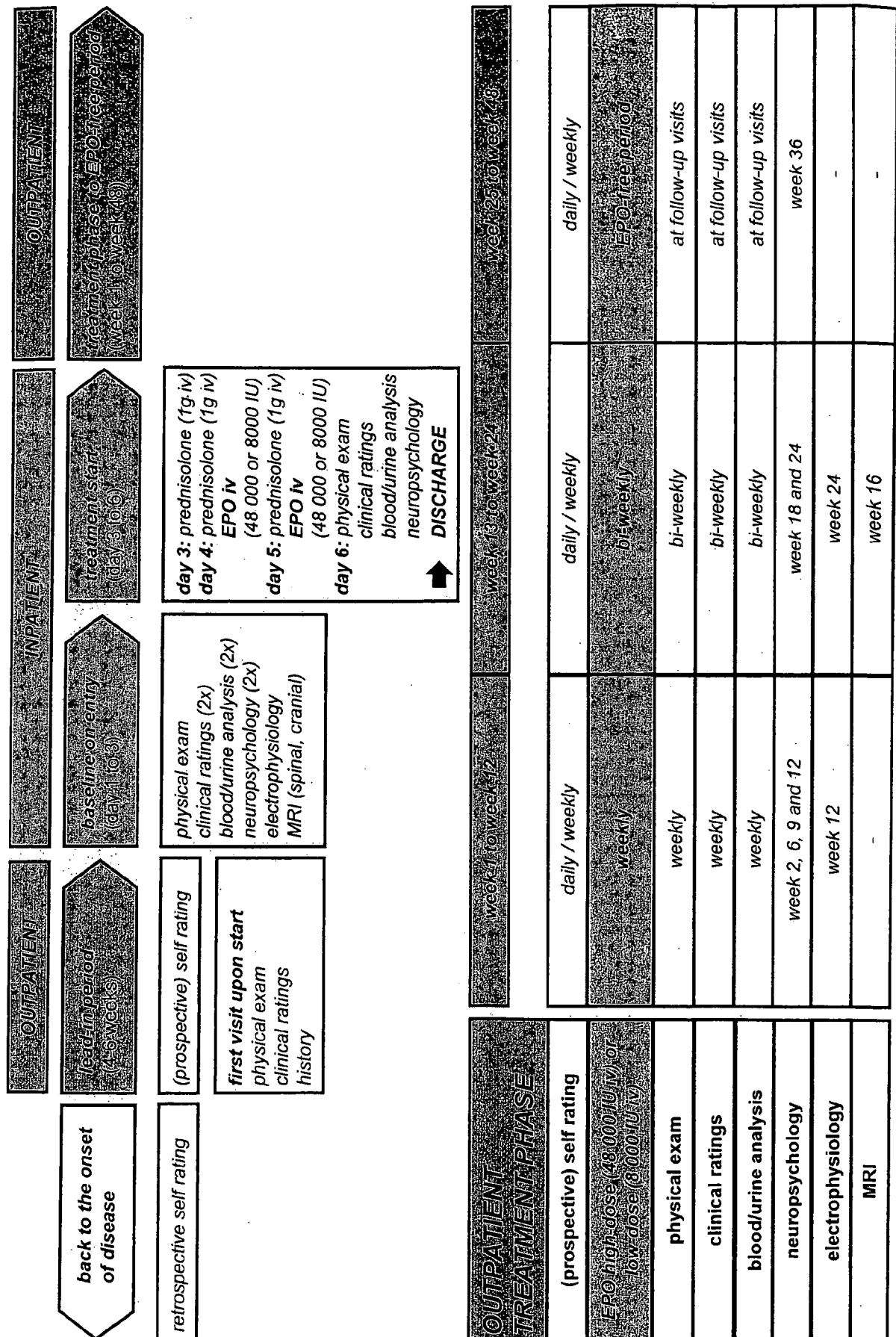


Figure 2

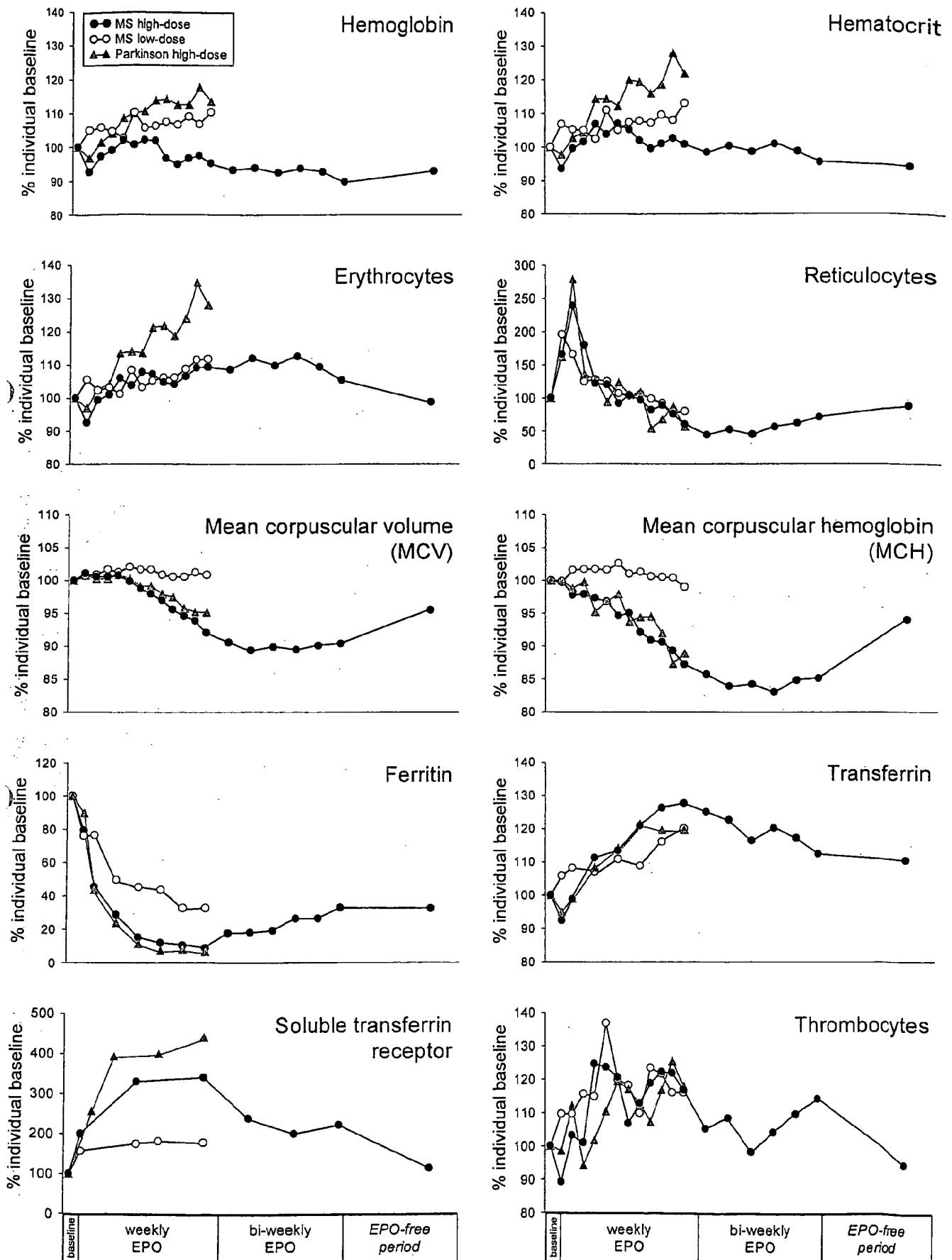


Figure 3

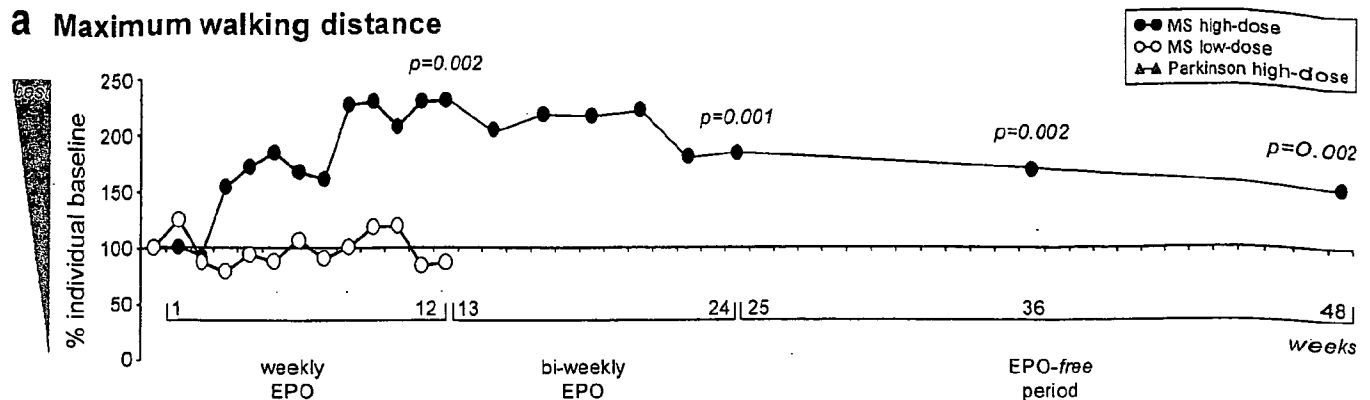
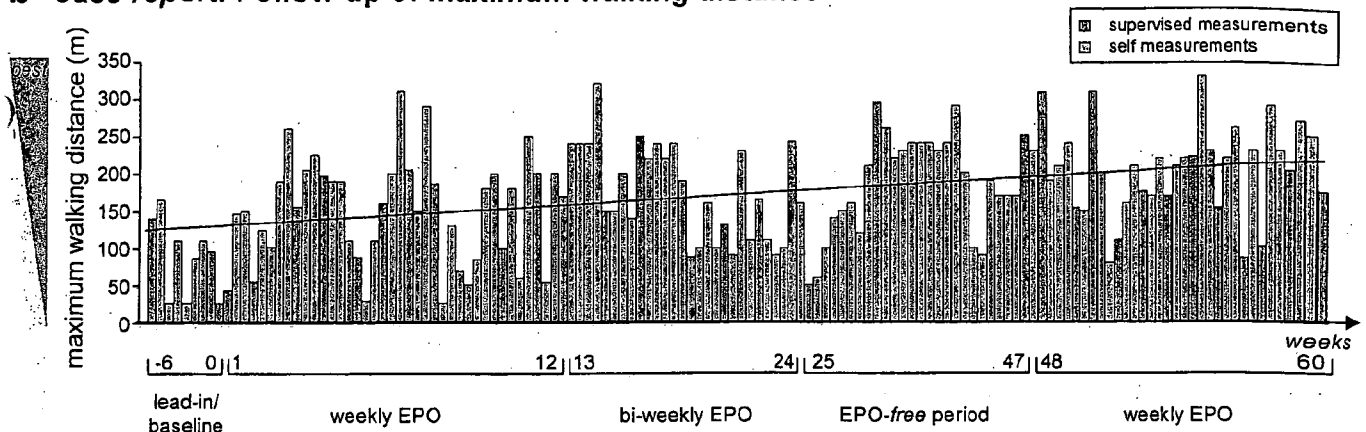
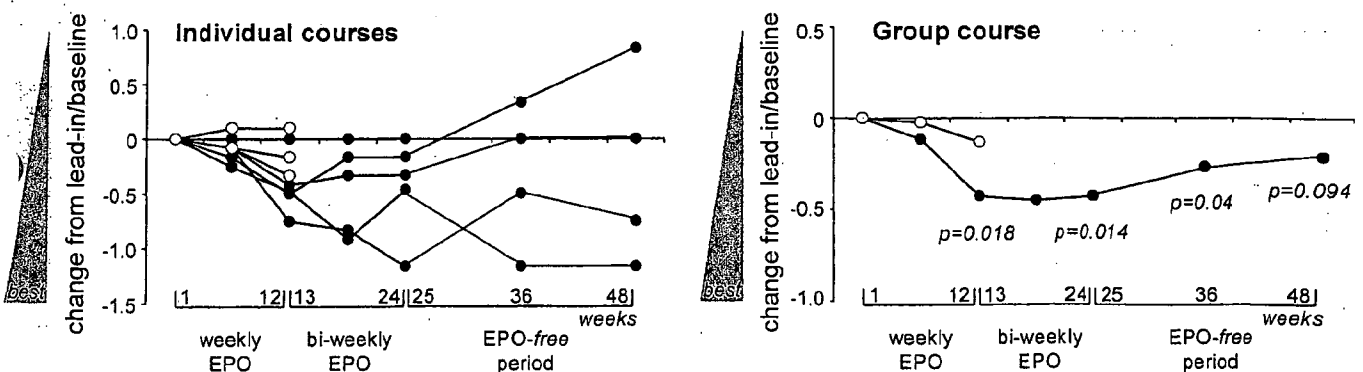
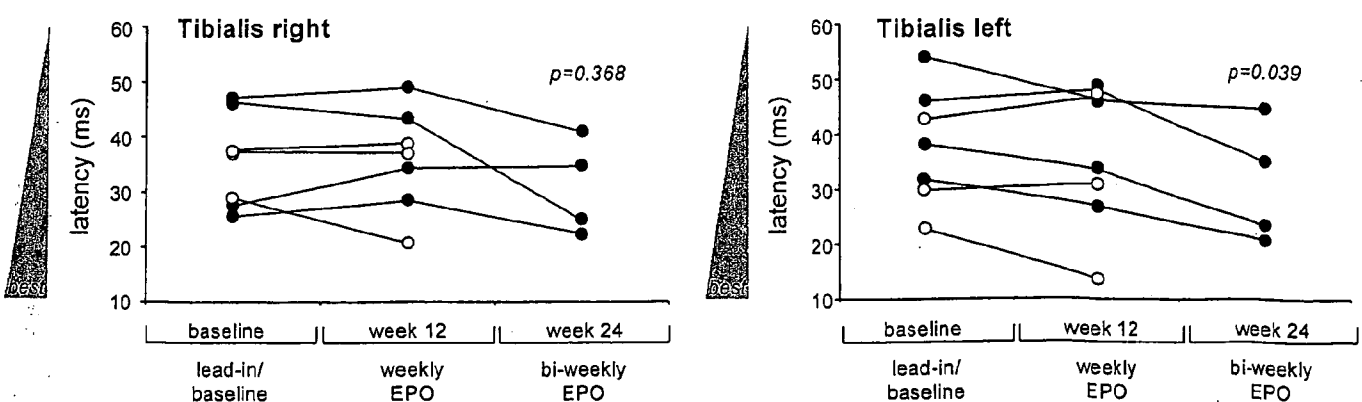
a Maximum walking distance**b Case report: Follow-up of maximum walking distance****c Expanded Disability Status Scale (EDSS)****d Motor Evoked Potentials (MEPs)**

Figure 4

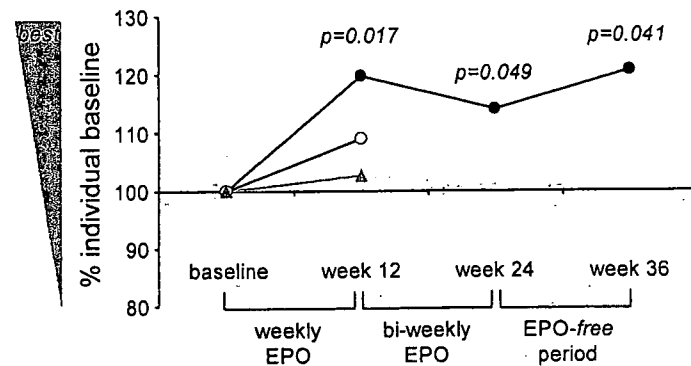
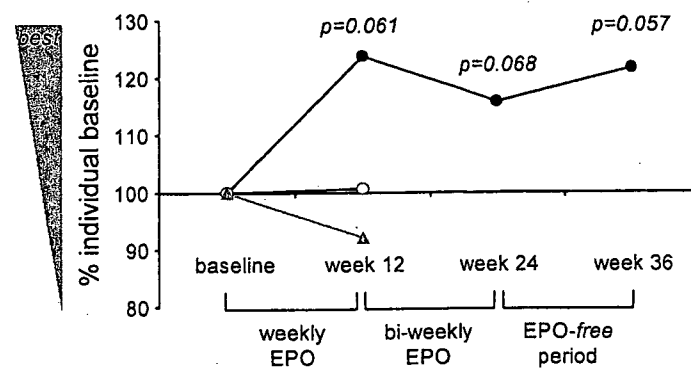
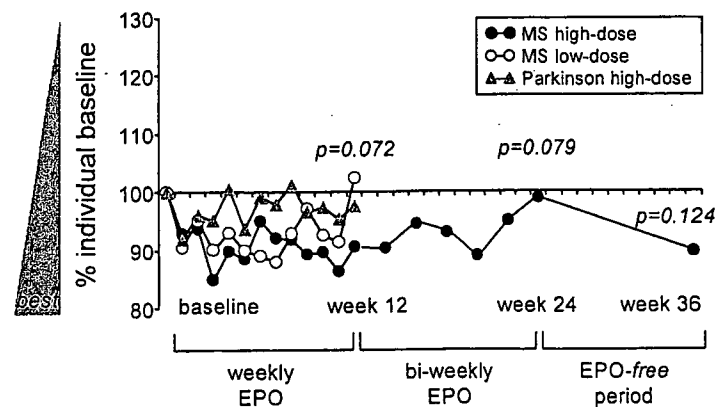
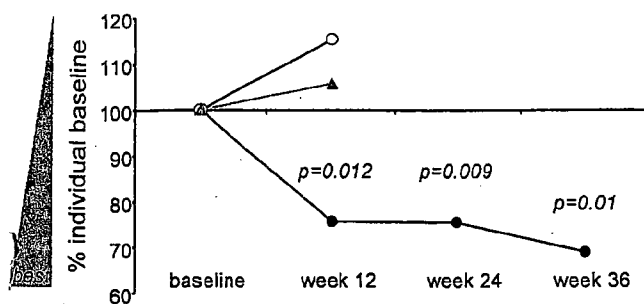
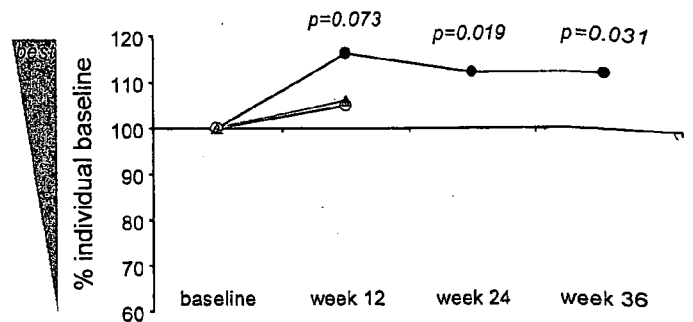
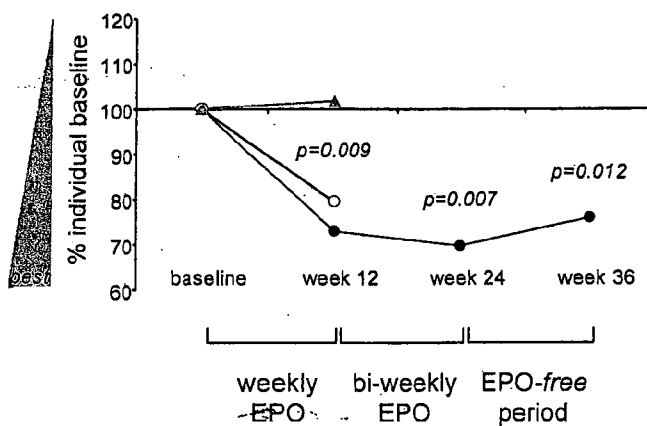
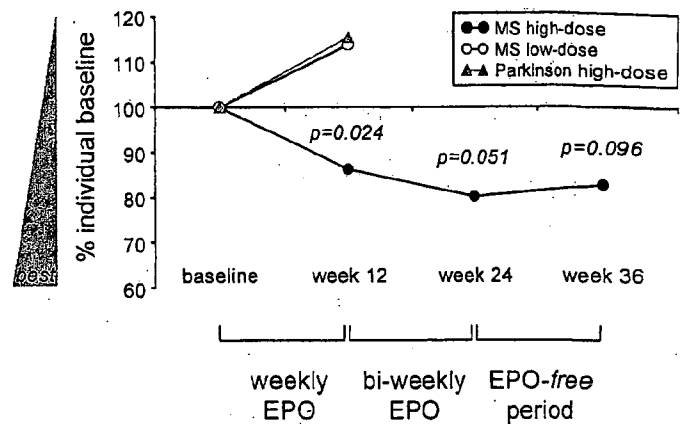
a MacQuarrie Tapping**b MacQuarrie Dotting****c 9-Hole Peg Test (non-dominant hand)**

Figure 5

a Trail Making – Part B**b** WMS-R Letter Number Sequencing**c** Visual Scanning – critical trials**d** Working Memory

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/000728

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/18 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/61164 A (KENNETH S WARREN LAB [US]) 19 October 2000 (2000-10-19) cited in the application	1-3, 9-17, 23-27
Y	see claims 1-26 and example 12	1-3, 9-17, 23-27
X,P	WO 2007/085453 A (EHRENREICH HANNELORE [DE]; NAVE KLAUS-ARMIN [DE]) 2 August 2007 (2007-08-02) see the whole document	1-27
X	EP 1 295 604 A (TOKYO METROPOLITAN INST OF GER [JP]; CHUGAI PHARMACEUTICAL CO LTD [JP]) 26 March 2003 (2003-03-26)	1-3, 9-17, 23-27
Y	see claims 1-4	1-3, 9-17, 23-27
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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- * & * document member of the same patent family

Date of the actual completion of the international search

8 July 2008

Date of mailing of the international search report

17/07/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Merckling-Ruiz, V

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/000728

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SAVINO ET AL: "Delayed administration of erythropoietin and its non-erythropoietic derivatives ameliorates chronic murine autoimmune encephalomyelitis" JOURNAL OF NEUROIMMUNOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, XX, vol. 172, no. 1-2, 1 March 2006 (2006-03-01), pages 27-37, XP005303938 ISSN: 0165-5728 see abstract -----	1-3, 9-17, 23-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/000728

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EP 1295604	A	26-03-2003	AU 6788201 A	14-01-2002
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