Synopsis

TITLE OF TRIAL	Treatment of Optic Neuritis with Erythropoietin: a randomised, double-blind, placebo-controlled trial
SHORT TITLE	TONE
PROTOCOL NUMBER	Protocol Number: P000053
EUDRACT NO.	2013-002515-10
MAIN DIAGNOSIS	Optic neuritis (ON)
PHASE	Phase III Trial
OBJECTIVE(S)	Primary: Determination of the efficacy of erythropoietin compared to placebo given as add-on to methylprednisolone (standard of care) as assessed by measurements of global retinal nerve fibre layer thickness (RNFLT-G) and low contrast visual acuity (LCVA) in the affected eye 6 months after randomisation Secondary: Comparison of efficacy of erythropoietin compared to placebo given as add-on to methylprednisolone with respect to RNFLT and other functional changes 6 months after randomisation Assessment of safety in both treatment arms
INTERVENTION(S)	Experimental intervention: 33,000 IU human recombinant erythropoietin intravenously (i.v.) on days 1, 2, and 3 Control intervention: Placebo (0.9% saline) i.v. on days 1, 2, and 3 Follow-up per patient: At 1, 4, 16, 26 weeks and 24 months after commencement of treatment, respectively Duration of intervention per patient: 3 days
(KEY) INCLUSION CRITERIA	(Key) inclusion criteria: 1. Optic neuritis as clinically isolated syndrome, high contrast visual acuity (HCVA) ≤ 0.5, onset of symptoms ≤ 10 days prior to the first administration of investigational product 2. Age from ≥ 18 to ≤ 50 years

(KEY) EXCLUSION CRITERIA	(Key) exclusion criteria: 1. Any other previous optic nerve, retinal, neurologic or vascular disease, pre-existing diagnosis of multiple sclerosis	
ENDPOINTS	Primary efficacy endpoint: The primary study endpoint is RNFLT-G-12 of the contralateral healthy eye at baseline minus RNFLT-G-12 of the affected eye 6 months after randomisation determined by spectral domain optical coherence (OCT) [µm], LCVA [score] 6 months after randomisation Key secondary endpoint(s): RNFLT-G-12 absolute values [µm], RNFLT in the papillomacular bundle (RNFLT-PMB-12) [µm], RNFLT in the temporal quadrant (RNFLT-T-12) [µm], total macular volume [mm^3], HCVA [score], contrast sensitivity [log], mean visual field defect [dB], latency [ms] and amplitude [µV] of visual evoked potentials (VEP), Expanded Disability Status Scale (EDSS) [score], NEI VFQ-25 questionnaire [score], all endpoints obtained 6 months after randomisation. Assessment of safety: Assessment of AEs / SAEs	
TRIAL DESIGN	Randomised, double-blinded, placebo-controlled multi-centre trial with two parallel arms, phase III	
STATISTICAL ANALYSIS	Efficacy: Linear regression model for RNFLT-G-12 and LCVA at 6 months after randomisation (primary endpoints as defined above) with treatment assignment, baseline measurement (RNFLT-G-12: of the contralateral healthy eye) and study site as covariates, providing an estimated treatment effect with a two-sided 95% confidence interval The primary efficacy analysis will be conducted according to the intention-to-treat principle and will therefore be based on the full analysis set, including all randomised patients Safety: Rates of adverse events and serious adverse events with two-sided 95% confidence intervals Secondary endpoints: Analysis of secondary endpoints analogous to primary endpoint	
SAMPLE SIZE	To be assessed for eligibility:	n = 200
	To be randomised to trial:	n = 100
	To be analysed:	n = 100
TRIAL DURATION	Recruitment period (months):	Approx. 30

	First patient in to last patient out (months):	Approx. 54 (including 24 months of follow-up)
	Duration of the entire trial (months):	Approx. 60
	Treatment duration per patient (months):	3 days; + 24 months follow-up
TIMETABLE	Enrolment of first patient (first patient first visit)	2014
	Enrolment of last patient (end of randomisation)	2016
	End of trial for last patient (last patient last visit)	2018
	Final statistical analysis	2018
	Planned interim analysis	2016
PARTICIPATING CENTERS	To be involved (n): 12 (planned); number may vary based on recruitment	

Table 1 Flow chart - Visit schedule and assessments

Action	Screening / Baseline Day 0 (-3 days)	Therapy Day 1	Therapy Day 2	Therapy Day 3	Week 1 (± 4 days)	Week 4 (± 4 days)	Week 16 (± 4 days)	Week 26 (± 7 days)	Month 24 (± 7 days)
Informed consent	X								
Demographics	X								
Inclusion / exclusion criteria	X								
Medical history	X								
Present complaints	X	X	X	X	X	X	X	X	X
MS relapse / ON recurrence						X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X
Physical examination	X[1]				X[1]	X[1]			
Vital signs[5]	X	3 X	3 X	3 X	X	X			
Body weight	X[1]				X[1]	X[1]			
Electrocardiogram	X[1]				X[1]				
Routine laboratory[3]	X				X	X		X	
Urinalysis (if clinically indicated)	X[1]				(X[1])	(X[1])	(X[1])	(X[1])	
Pregnancy test	X[1]								
EPO antibodies (analysis in central lab)	X							X	
Aquaporin 4 antibodies	X								
Methylprednisolone therapy		X (standard of care)	X (standard of care)	X (standard of care)					
EPO / placebo administration		X	X	X					
AE-reporting	X	X	X	X	X	X	X	X	X[6]
Neurological examination, EDSS[4]	X				X	X	X	X	X
Randomisation	X								
Refraction	X				X	X	X	X	X
OCT (optical coherence tomography)	X					X	X	X	X
LCVA (low contrast visual acuity)	X				X	X	X	X	X
HCVA (high contrast visual acuity)	X				X	X	X	X	X
CS (contrast sensitivity)	X				X	X	X	X	X
Perimetry	X				X	X	X	X	X
NEI VFQ-25	X							X	X
VEP (visual evoked potentials)	X					X	X	X	X
MRI (magnetic resonance imaging)	X							X[2]	(X)

[1]test to be performed, but not recorded on CRF, [2]recommended, [3]CRF: only Haemoglobin (Hb), [4]CRF: only EDSS; [5]CRF: only blood pressure; [6](S)AE: to be reported only if related to investigational product