Universitätsklinikum Hamburg-Eppendorf

IIT Clinical Study Report (ICH GCP E3 „Structure and Content of Clinical Study Reports“)	7.3.10 Anlage 02 Stand: 22.01.2015

Name of Sponsor/Company: UKE Name of Finished Product: f.e. Urbasaon© Name of Active Ingredient: Methylpednisolone Plasmapheresis	Individual Study Table Referring to Page 9 of the study protocol Internal protocol inims-004 EudraCT Num,ber 2012-004807-10	*(For Competent Authority only)*
Title of Study: Relapse Escalation treatment trial in Optic Neuritis (RESCON) - Multi-centre RCT to study the effectiveness of plasma exchange (PE) as an escalation treatment strategy in steroid-unresponsive Optic Neuritis		
Principal Investigator (for single-center studies) or Coordinating Investigator (for multi-center studies): Prof. C. Heesen		
Study centre(s): UKE Hamburg, Universitätsklinikum Hannover, Charité Berlin und Universitätsklinikum Düsseldorf)		
Publication (reference): none		
Studied period (years): 1.9.2013-31.12.2015 date of first enrolment: 1.11.2013 date of last completed: 31.12.2015	Phase of development: PHASE III	

Objectives: Plasma exchange (PE) has been used as an escalation treatment as well or even after failure of ultradoses of steroids in the treatment of optic neuritis. However until now only one RCT has evaluated PE for the treatment of MS relapses. The current experience in treating steroid-unresponsive optic neuritis with PE is only based on case series. This trial will provide the first rigorous RCT in severe optic neuritis refractory to steroids. It will add substantial evidence to question of effectiveness of PE in ON.

Primary objectives:

- to gain further evidence for the efficacy of plasma exchange in steroid-unresponsive optic neuritis
- to study new outcome tools for neuronal regeneration in the ON model via OCT

Secondary objectives:

- to study MRI parameters in patients with steroid-unresponsive optic neuritis treated with plasma exchange (contrast-enhancement, T2-signal, edema and atrophy will be assessed as well as DTI at baseline, week 16 and 52)

- to further study biomarkers for ON heterogeneity and neurodegeneration

Methodology: RCT in patients who suffer from severe Optic Neuritis without satisfying improvement after treatment with steroids (3-5 days with 1 g daily at least 7 days prior to randomization) and with persisting visual acuity < 0.7, duration of symptoms should be ≤ 4 weeks

Number of patients (planned and analysed): 40 geplant, 9 analysiert

Indication and main in- and exclusion criteria: **Inclusion/enrolment criteria:**

- Optic neuritis with visual acuity < 0.7 after steroid treatment (3-5x1g)
- Duration of symptoms from onset < 4 weeks
- Age: 18-60 years
- EDSS: 1.0 – 6.5
- CIS, RR-MS or SP-MS

Exclusion criteria:

- absence of evidence of inflammatory activity which is defined as a lack of inflammatory CSF signs (pleocytosis and/or OCBs) or a present MRI without at least 2 MS-typical lesions
- bilateral optic neuritis
- current treatment with natalizumab
- patients with neuromyelitis optica (including NMO spectrum disorders, AQU-4-Antobodies must be negative within 1 year before inclusion, otherwise patients will be tested at screening. Patients may be included and randomized without a result from screening, but must be excluded if positive.)
- Pregnancy
- Unwillingness or inability to comply with the requirements of this protocol including the presence of any condition (physical, mental, or social) that is likely to affect the patient returning for follow-up visits on schedule.
- Patients with cognitive impairments who are unable to provide written, informed consent prior to any testing under this protocol

Participation in other pharmaceutical trials during this study or 3 months before

Test product, dose and mode of administration, batch number:
5 cycles of plasma exchange (PE)

Duration of treatment: 5-10 days

Reference therapy, dose and mode of administration, batch number:
2g methlyprednisolon on 5 consecutive days

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Criteria for evaluation:

Efficacy: Primary endpoint: Mean retina nerve fiber layer thickness at week 16 after treatment in comparison between groups

Secondary endpoints: Treatment failure at week 2, Visual acuity, visual evoked potential latency, MRI parameters at week 1, 16, 52

Safety: Both treatment options in this study – high-dose steroid-treatment and plasma exchange – are established therapies so we do not expect to observe unpredictable risks or side effects. If patients in the steroid-treatment arm show a lower response to therapy we offer the rescue treatment with plasma exchange 8 weeks after the steroid treatment.

Statistical methods: Sample size estimation is based on a recent trial (Sühs 2012) on treating optic neuritis which showed preserved RNFL in the intervention group. The sample size estimation is based on data on RNFL thickness, which ranges around 100 µm in healthy subjects. Within the aforementioned trial with a putatively neuroprotective drug RNFL thickness change at week 16 in the ITT cohort (n=37) was 10.55 um (SD 17.54), median 7.5 (IQR 1.5 to 14.5) compared to 22.65 um (SD 29.18), median 16.0 {IQR 8.0 to 20.0} which means 50% less degeneration. Applying a two-stage design concept sample sizes of 63 (IG) and 63 (CG) are needed to achieve 81% power to detect a RFNL difference of 12.00 between the groups. The predefined interim analysis after n=40 patients will detect a delta RFNL of 12 with a power of 17%. This estimate is based on means with the above-mentioned standard deviations of 17.00 and 29.00 at a significance level (alpha) of 0.049273 using a two-sided z-test. These results assume that 2 sequential tests are made using the O'Brien-Fleming (1979) spending function to determine the test boundaries. (O'Brien, P.C. and Fleming, T.R. 1979. 'A multiple testing procedure for clinical trials.' Biomet-rics, 35, pages 549-556).

SUMMARY-CONCLUSIONS

EFFICACY RESULTS:

8 patients were recruited in Hamburg. 2x2 were randomised to PE or steroids. 3 patients received rescue plasmapheresis and 1 patient dropped out because of unability to follow the study protocol. Recruitment in other study centers was not possible, so that the study was closed end of 2015. In all cases symptoms did improve until the end of the observation period.

SAFETY RESULTS:

AEs were minor and mostly already known based on high dose steroid side effects. These were: insomnia, hypergylcemia, facial flush and mild nausea, stomach ache, gastric ache, joint and muscular pain, palpitations, concentration difficulties, increase of weight. Plasmapheresis was well tolerated. The only more relevant adverse events was one case of relevant ankle edema on both legs in one steroid treated case which resolved within 14 days and a case of prolonged hypofibrigenemia under plasma exchange which lead to PE discontinuation.

CONCLUSION:

Although study acceptance and recruitment was high in Hamburg, it was not possible to really engage other centers. Side effects occurred as anticipated. Close interaction of Dep. of Neurology and Dep. of Ophthalmology is needed. Possibly the general availability of steroids and PE outside a trial inhibited contribution as well. Thus comparison of established treatments in pragmatic clinical trials remains a challenge.

Date of Report:

14.1.2020 based on final report to BMBF on 10.6.2016

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S) OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: Relapse Escalation treatment trial in Optic Neuritis (RESCON)

- Multi-centre RCT to study the effectiveness of plasma exchange (PE) as an escalation treatment strategy in steroid-unresponsive Optic Neuritis

STUDY AUTHOR(S):

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

INVESTIGATOR OR SPONSORS RESPONSIBLE MEDICAL OFFICER

SIGNATURE(S)

AFFILIATION: INIMS UKE

Prof. C. Heesen

DATE: 15/1/20

