**SYNOPSIS**

according Annex 1 der *Note for guidance on structure and content of clinical study reports* (CPMP/ICH/137/95) - ICH Topic E 3

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| *Name of Sponsor/ Representative of Sponsor:*<br>Charité - Universitätsmedizin Berlin/<br>Prof. Dr. med. Friedemann Paul | *Individual Study Table Referring to Part of the Dossier*<br>not applicable | *(For National Authority Use only)* |
| *Name of Finished Product:*<br>Sunphenon® | | |
| *Name of Active Ingredient:*<br>Epigallocatechin gallate (EGCG) | | |

*Title of Study:*

**Sunphenon in progressive forms of multiple sclerosis (SUPREMES)**
**Monocentric, prospective, double-blind, randomized/stratified, placebo-controlled, two-arm study to evaluate the effect of Sunphenon EGCg (green tea extract, main component epigallocatechin gallate) on the increase in brain atrophy in cerebral magnetic resonance imaging over a 36-month treatment period in patients with primary or secondary chronic progressive multiple sclerosis**

*Final study protocol:*

Version 1.3 dated 04.10.2011 (reason: Change from internal pilot study of 30 months with sample size recalculation to pilot study of 36 months (extension of the study by 6 months) and optional one-arm extension phase of 12 months; Elevation of the study medication EGCG from 800 mg to 1200 mg daily in the time month 30 to month 36 and in the optional open extension phase.)

*Previous protocol versions:*

Version 1.0 dated 14.08.2008 (initial version)
Version 1.1 dated 29.09.2008 (reason: adjustment of inclusion criteria)
Version 1.2 dated 03.04.2009 (reason: change of PI)

*EudraCT-Number:* EudraCT-No. 2008-005213-22

*Principal Investigator:* Prof. Dr. Friedemann Paul

*Study centre:*

Neurocure Clinical Research Center NCRC, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin

*Publication (reference):* Study results not published so far

| *Studied period (years):* | *Phase of development:* Phase II |
|---|---|
| (date of first enrolment) 08.05.2009<br>(date of last participant completed) 02.03.2016 | |

*Objectives:*

The aim of the study was to demonstrate in progressive multiple sclerosis (PMS) the safety, tolerability and effects on radiographic and clinical disease activity of oral Sunphenon EGCG versus placebo as measured by brain atrophy. Instrument is the decrease in brain parenchymal fraction and the percentage brain volume change (PBVC), number and volume

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of T2 lesions in MRI and a number of other MRI parameters, as well as clinical parameters (EDSS, MSFC, annual relapse rate, progression measured by EDSS and cognitive parameters and fatigue (see primary and secondary endpoints).

Safety and tolerability were checked by regular and thorough clinical (medical, neurological) and paraclinical examinations (vital signs, ECG, laboratory parameters, MRI examinations).

Primary endpoint:

- Decrease in brain volume ("brain parenchymal fraction") after 36 months

Secondary endpoints:

- Number of T2 lesions at screening/randomisation and after 12, 24 and 36 months
- Volume of T2 lesions at screening/randomisation and after 12, 24 and 36 months
- Number of contrast enhancing lesions after 36 months
- Volume of contrast enhancing lesions after 36 months
- NAA/Cr quotient in MR spectroscopy at screening/randomization and after 36months
- Relapse rate in 36 months
- Progression of disability in 36 months as measured by EDSS/MSFC and cognitive tests (neuropsychological examination, fatigue scale)
- Number/proportion of relapse-free patients in 36 months
- Number/proportion of progression free patients in 36 months

*Methodology:*

Study design

The study is designed as monocentric, prospective, phase II, double-blind, randomized, placebo-controlled, parallel-group study over 36 months for the main study and optionally for 12 more months as an open extension phase, where all participants received EGCG. Sample size calculation before the study was not possible due to lacking data. As a pilot study, an inclusion of 30 patients per group (i.e. a total of 60 patients) was planned.

Patients, who meet the inclusion criteria and were enrolled in the study after the screening visit, were stratified according to the following criteria to avoid inhomogeneity in verum and placebo group: Sex (male, female) and diagnosis (primary progressive multiple sclerosis/PPMS or secondary progressive multiple sclerosis/SPMS). Patients were randomly assigned to the two study groups (Sunphenon EGCG, placebo). Randomisation was carried out via the pharmacy using the prepared randomization list considering stratification. Each participant received a randomization number, which was also noted in the CRF.

During treatment, each patient visited the study centre every 3 months (14 appointments in total), in addition 2 more appointments for the optional open extension phase. Patients who dropped out of the study prematurely were monitored until the end of the study on the

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scheduled dates, unless consent was withdrawn and/or the patient could not be tracked longer.

Unblinding
One patient was prematurely unblinded by having the study medication analyzed in an external laboratory on his own discretion in absence of an emergency. This lead to an exclusion from the study.
The regular unblinding was performed on visit 14 (after 36 months) of each patient and was documented when the database was closed on 10.05.2019.

Documentation and quality management
The data collected was documented in paper-based case report forms (CRF). All collected data, original printouts, original findings, etc. were stored as source data in the patient record. A copy of the consent form is stored in the investigator trial file. In the investigator trial file all essential documents were stored in accordance with ICH-GCP at the local trial site. The study medication was obtained from the Charité pharmacy. The receipt of the study medication at the trial centre was documented by the investigator or the study assistant (date, number of packaging units). The medication was distributed to the study participants in sealed medication containers for three months at a time. The dispensing was documented by the investigator or study assistant in the CRF (date, number of packaging units). Every three months, the study participant returned the containers with unused study medication to the trial centre, where the returned medication was counted and the return documented in the CRF. Empty containers also had to be returned. The returned medication was safely stored in the study centre and returned to the pharmacy at regular intervals for destruction. which was documented again.
The study was conducted strictly according to protocol. This included in particular the exact adherence to the inclusion and exclusion criteria and the randomization procedure, the maintenance of blinding and the adherence to the time limits for the respective study dates. The study physicians received a briefing on the study and investigational product-specific aspects prior to the start of the study.
The NeuroCure Clinical Research Center (NCRC) office provided monitoring by a qualified and independent person otherwise not involved with the study. The monitor regularly reviewed the study documents during the course of the study and after completion of treatment of the last study patient. The monitor was responsible for verifying the conduct of the study according to the study protocol together with the investigator. The confidentiality of the study documents, including patient data, had to be maintained.

Data entry and data management
All patient-related data were recorded in pseudonymised form. Each patient was unmistakably identified by a patient number or pseudonym assigned during the screening phase and a randomization number. The investigator kept a confidential patient list in which

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the identification data were linked to the full patient name. The confidential patient list is stored in a password-protected file at a server compartment of the Charité in accordance with the approved data protection concept. Only the investigator, the study assistant and the clinical trial manager have access to the patient list.
The data collection was based on paper-based CRFs. Entries in the CRF could be made by the investigator, the study assistant or the head of the clinical trial. Changes in the CRF were documented in the so-called "audit trail". For data digitization after the study was finished, all relevant data were recorded in a redcap database file by one person and validated by a second independent person. The accuracy of the data was checked by range, validity and consistency checks. Implausible or missing data could be corrected or supplemented after consultation with the investigator. The correction documents were kept together with the test sheets.

*Number of patients (planned and analyzed):*

Planned number of cases = 60
see also CONSORT flow diagram Appendix 1

Subjects assessed for eligibility (screening) = 79
Screening failure = 8
Subjects declined to participate = 10
Randomized subjects = 61
Drop-outs (after randomization) = 23
Subjects evaluated (data sets) = 38

*Diagnosis and main criteria for inclusion:*

Diagnosis: Secondary progressive multiple sclerosis (SPMS)
Primary progressive multiple sclerosis (PPMS)

Inclusion criteria:

- Diagnosis of primary or secondary progressive multiple sclerosis, comprised fulfilment of the 2005 revised McDonald criteria for primary and secondary progressive multiple sclerosis,
- Age between 18 and 65 years at the time of recruitment,
- Expanded Disability Status Scale (EDSS) of 3 to 8 at screening,
- Relapse free period of at least 30 days prior to randomization.

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- Women of childbearing age must agree to use highly effective methods of contraception (failure rate <1%, e.g. sterilisation man/woman, oral hormonal contraception (pill), depot injection, hormone implant, hormone coil, transdermal patch) correctly and consistently throughout the duration of the study; a negative pregnancy test is a prerequisite for inclusion
- Signed informed consent
- Patients are allowed to drink a maximum of two cups of black tea per day during participation in the study, green tea consumption is not permitted. The consumption of higher amounts of grapefruit juice (>500 ml/d) is also not permitted due to possible hepatic interactions.
- Patients, who could have Mitoxantron therapy (SPMS patients), had to decide against this therapy independently from the study.

Exclusion criteria

- Relapsing remitting form of MS
- Any disease other than MS that could better explain the patient's symptoms
- Any condition that might interfere with or prevent the performance of an MRI examination or other examinations
- Clinically relevant gastrointestinal diseases (all neoplasms, gastric and duodenal ulcers, Crohn's disease, ulcerative colitis, malabsorption/malassimilation syndromes of any aetiology)
- Clinically relevant lung, infectious, cardiac or other CNS diseases (all neoplasms of the mentioned organ systems, COPD, pulmonary fibrosis, serological evidence of systemic infections (HIV, lues, borreliosis), clinical or paraclinical suspicion of tuberculosis*, suspicion of degenerative CNS diseases (Parkinson's disease, Huntington's disease, Alzheimer's disease), history of vascular CNS diseases)
- Clinically relevant liver diseases (neoplasms, serological diagnosis of chronic active hepatitis B and C (exception: hepatitis A in remission without complications), liver insufficiency (pseudocholinesterase and/or Quick <80% of the lowest norm value),
- Clinically relevant liver, kidney or bone marrow dysfunction, as defined by the following laboratory values:
  - Bone marrow dysfunction: HB < 8.5 g/dl<br>WBC < 2.5/nl<br>Thrombocytes < 125/nl
  - Kidney dysfunction: Creatinine clearance according to the Cockroft Gault formula: Cl < 110ml/min (men) or Cl < 95ml/min (women), from the age of 30 the limit decreases by 10ml/min per decade
  - Liver dysfunction: ASAT/ALAT > 3.5 x higher than highest reference value, Bilirubin > 2.0 mg/dl

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- Known allergy to Gd-DTPA
- Known allergy to components of Sunphenon EGCG or the additives of the test medication or placebo capsules
- Treatment with liver-toxic drugs
- Treatment with cytochrome P450 3A4 inhibitors or inductors, such as azole-type antifungals (e.g. ketoconazole) or macrolide antibiotics (e.g. erythromycin)
- Presence of anamnestic or paraclinical indications of alcohol abuse, drug abuse (urine drug screening)
- Pregnancy or lactation
- Participation in any clinical trial according to German Drugs Act (AMG) and/or German Medical Products Act (MPG) within the last 3 months or for the entire duration of the trial.
- Pre-treatment with the following substances prior to recruitment into the study within the following periods:
  - Complete lymph irradiation, anti lymphocyte antibody treatment (e.g. anti-CD4, Campath 1H) at any time
  - 3 months before start of study: mitoxantrone, cyclophosphamide, cyclo-sporine, human antibodies, all other immunomodulating or immunosup-pressive substances with the exception of methylprednisolone for relapse therapy.
- Medical, psychiatric, or other conditions that limit the patient's ability to understand patient information, give informed consent, abide by protocol rules, or complete the study.

* If clinical or paraclinical indications for the presence of TBC exist, an intradermal test (Mendel-Mantoux) and the patient would be referred to pulmonology.

*Test product, dose and mode of administration, batch number:*

Sunphenon Epigallocatechin-3-Gallate (EGCG)
Following randomization, patients started treatment with Sunphenon EGCG capsules 200 mg daily (1x 200 mg capsule in the morning). They were escalated after 3 months to 400 mg daily (2 times daily 1 capsule with 200mg) , after 6 months to 600 mg daily (2 capsules with 200 mg in the morning, 1 capsule with 200 mg in the evening), after 18 months to 800 mg (2 times daily 2 capsules with 200 mg each), after 30 months to 1200 mg daily (3 times daily 2 capsules with 200 mg each) until the end of the study at month 36.

For the patients treated with EGCG the dosage was maintained also in the open label extension until month 48 if they participated.

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*Reference therapy, dose and mode of administration, batch number:*

Placebo

Following randomization, patients started treatment with placebo capsules 200 mg daily (1x 200 mg capsule in the morning). They were escalated after 3 months to 400 mg daily (2 times daily 1 capsule with 200mg) , after 6 months to 600 mg daily (2 capsules with 200 mg in the morning, 1 capsule with 200 mg in the evening), after 18 months to 800 mg (2 times daily 2 capsules with 200 mg each), after 30 months to 1200 mg daily (3 times daily 2 capsules with 200 mg each) until the end of the study at month 36.

Patients initially treated with placebo who decided to participate in the 12-month open-label extension started treatment with Sunphenon EGCG capsules 200 mg daily (1x 200 mg in the morning) and escalated every 2 weeks for 200 mg, reaching 1200 mg after 10 weeks (3 times daily 2 capsules with 200 mg each).

*Duration of treatment:*

Each individual study period was 36 months (duration of treatment per patient) according to the scheme above, followed by optional 12 months for the open label extension phase.

*Criteria for evaluation:*

**Efficacy:**

MRI:

- BPF at visit 36 in comparison with visit 0
- PBVC every year
- Total number of T2 hyperintense lesions every year
- Total volume of T2 hyperintense lesions every year
- Total number of contrast-enhancing lesions at visit 0 and visit 36
- Total volume of contrast-enhancing lesions at visit 0 and visit 36

Clinical:

- Recording of MS relapses in 18 and 36 months (annualized relapse rate)
- Clinical examination (Expanded Disability Status Scale (EDSS))
- Multiple Sclerosis Functional Composite (MSFC) incl. subscores
- Fatigue Scales: Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale (FSS)
- Disability progression in 36 months, measured by the EDSS, and number of progression free patients in 36 months
- Cognitive test (PASAT)

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***Safety:***

- Vital signs
- Physical examination
- ECG
- Laboratory tests
- Occurrence of (severe) adverse events in both arms
- Number of dropouts in both arms.

Schedule of activities (see Appendix 2)

*Statistical methods:*

The study was initially planned as a double-blind pilot study with recalculation of sample size with a total of 60 patients. However, according to an amendment on 09/28/2011 at the end of the blinded phase (after 36 month of study), the unblinded recalculation of sample size , was not carried out as a continuation of the study did not seem realistic due to recruitment problems. Consequently, the study was terminated, including 61 patients altogether (30 verum, 31 placebo). Furthermore, an open-label extension of 12 months was offered to all patients of the study (see CONSORT diagram, Figure 1).

Results are expressed as arithmetic mean ± standard deviation (SD), median (range), or frequencies (%). The primary endpoint was the change of BPF from baseline to month 36; this was assessed using the exact Mann-Whitney test.

Continuous secondary endpoints were tested for differences between groups by using the non-parametric (exact) Mann-Whitney test for independent groups. Differences in categorical variables were tested by Fisher's exact test.

Differences between the verum and placebo groups with respect to the whole time course were analysed using nonparametric analysis of longitudinal data in a two-factorial design was applied (1$^{st}$ factor (independent): treatment groups, 2$^{nd}$ factor (dependent): study visits). When appropriate, multivariate nonparametric analysis of covariance (MANCOVA) using baseline values as covariates was complemented.

An ITT approach was planned as primary analysis. Additionally, a per-protocol analysis (PP, 37 patients) was performed, i.e. omitting patients who stopped treatment due to adverse reaction or who severely violated study protocol.

A p-value $< 0.05$ was considered statistically significant. All tests of secondary endpoints were conducted in the area of exploratory data analysis. Therefore, no adjustments for multiple testing were made.

Numerical calculations were performed using SAS Version 9.4 [TS1M3] Copyright 2002-2012 by SAS Institute Inc., Cary, NC, USA, IBM SPSS Statistics, Version 25, Copyright 1989, 2010 SPSS Inc., an IBM Company, Chicago, IL, USA and The R Project for Statistical Computing, Version 3.0.2 (2017-04-21).

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*Summary - Conclusions*

**Efficacy Results:**

The results for the MRI outcome parameters are summarized in Table 1. Regarding the primary endpoint (Difference (BPF baseline – BPF month 36)), we observed no difference, furthermore there was no difference between groups in the PBVC, the number of T1 lesion count and volume and T2 lesion count and volume (Table 1) over 36 months.

Table 1: MRI outcome parameters

| | EGCG (n=19) | Placebo (n=19) | p value |
|---|---|---|---|
| BPF Month 36 | 0.6943 (0.0502) | 0.6867 (0.0439) | 0.608[1] |
| BPF change from baseline to month 36 | 0.0092 (0.0152) | 0.0078 (0.0159) | 0.670[1] |
| Percent brain volume change | -0.5659 (0.9818) | -0.8013 (1.1996) | 0.603[1] |
| Number of T2w-lesions | 35.21 (16.84) | 39.32 (19.28) | 0.501[1] |
| T2w-lesions change from baseline | 1.5263 (4.2343) | 3.7894 (4.8828) | 0.146 |
| Volume of T2w-lesions (ml) | 17.5741(16.4686) | 16.9076 (17.2963) | 0.773[1] |
| T2w-lesions change from baseline(ml) | 1.0439 (1.4783) | 0.5243 (2.3606) | 0.043 |
| Number of CEL | 0.00 (0.0) | 0.13 (0.342) | 0.964[1] |
| Volume of CEL (ml) | 0.00 (0.0) | 0.0029 (0.0096) | 0.984[1] |

Data are mean (SD), Number and Volume of CEL for 18 patients EGCG and 16 patients of placebo group, [1] exact Mann-Whitney test.

EGCG epigallocatechin-3-gallate; BPF Brain parenchymal fraction ; CEL Contrast enhancing lesions;

Regarding clinical endpoints (Table 2), the EGCG group and the placebo group did not differ in EDSS, confirmed EDSS (confirmation after 6 months), the mean change in EDSS between baseline and at 36 months or in decline of the MSFC including subscores PASAT, 9-HPT and TWT, as well as Beck Depression Inventory (BDI) score and Fatigue-Scores (FSS, FSS-S and MFIS including subscores (physical, psychosocial, cognitive)). Furthermore, there was no difference between EGCG and placebo group in annual relapse rate at 18 and 36 months, and in progression by EDSS.

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Table 2: Clinical outcome parameters

| | EGCG | Placebo | p value |
|---|---|---|---|
| EDSS | (n = 19) | ( n = 20) | |
| Month 36 | 6.08 (3.0-8.0) | 5.73 (3.5-8.0) | 0.098[1] |
| Change from baseline | 0.2631 (0.4524) | 0.5750 (0.9904) | 0.421 |
| Annualized relapse rate | (n = 19) | (n = 20) | |
| Month 0 till Month 36 | 0.24 (0.46) | 0.19 (0.44) | 0.513[1] |
| Progression by EDSS | (n = 18) | (n = 19) | |
| Month 36 | 6 (33.3 %) | 8 (42.1 %) | 0.737[2] |
| Multiple Sclerosis Functional Composite (z-score) | (n = 12) | (n = 15) | |
| Month 36 | 0.5577 (0.4473) | 0.0680 (0.7503) | 0.931[1] |
| Change from baseline | 0.1605 (0.3653) | -0.1289 (0.3750) | 0.126 |
| Paced Auditory Serial Addition Test | (n = 17) | (n = 20) | |
| Month 36 | 51.35 (10.95) | 42.05 (14.90) | 0.051[1] |
| Change from baseline | 3.8235 (9.6516) | 1.0000 (5.7947) | 0.292 |
| 9-Hole Peg Test (mean) | (n = 16) | (n = 19) | |
| Month 36 | 27.64 (11.36) | 31.27 (8.32) | 0.117 |
| Change from baseline | 1.4813 (7.9363) | 2.9996 (6.8182) | 0.172 |
| Timed 25-Foot Walk Test (mean) | (n = 14) | (n = 16) | |
| Month 36 | 14.19 (10.61) | 10.98 (8.07) | 0.275 |
| Change from baseline | 1.9942 (8.9991) | 2.2319 (5.8549) | 0.880 |
| FSS (mean) | (n = 10) | (n = 11) | |
| Month 36 | 4.4125 (2.0684) | 4.5417 (1.7628) | 0.931 |
| Change from baseline | -.8997 (1.8609) | -.379630 (1.9553637) | 0.813 |
| MFIS | (n = 18) | (n = 19) | |
| Month 36 | 38.89 (21.65) | 34.11 (13.59) | 0.412 |
| Change from baseline | -3.764706 (12.6270019) | 2.0588 (12.1061) | 0.178 |
| BDI | (n = 18) | (n = 18) | |
| Month 36 | 9.78 (7.37) | 9.00 (6.37) | 0.820[1] |
| Change from baseline | 0.1250 (4.9782) | 0.4117 (5.1727) | 0.610 |

Data are mean (SD), number (%) or mean (range), [1] exact Mann-Whitney test, [2] exact Chi-Square Test.
EGCG epigallocatechin-3-gallate; EDSS Expanded Disability Status Scale; FSS Fatigue Severity Scale; MFIS Modified Fatigue Impact Scale; BDI Beck Depression Inventory.

The results of the per protocol analyses (completers without a major protocol violation, EGCG group n=18, placebo group n=19) concerning primary as well as all secondary outcome parameters did not differ in their statistical significance from those of the ITT analyses.

Longitudinal analyses of the entire time course including all available time points (0, 12, 24, 36 months) also did neither show difference in MRI parameters for the primary and secondary endpoints nor in clinical parameters between both groups.

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## Safety Results:

Table 3: AE and SAE

| | EGCG n=30 | Placebo n=31 | p-value |
|---|---|---|---|
| Number of patients with any adverse event | 29 (96.7%) | 28 (90.3%) | |
| Number of adverse events | 155 | 155 | |
| Cause of most common adverse events (> 3% per group) | | | |
| Flu-like infection | 24 (15.6%) | 13 (8.4%) | 0.099 |
| Fracture after fall | 5 (3.3%) | 5 (3.3%) | 1.000 |
| Contusion after fall | 11 (7.1%) | 3 (1.9%) | 0.057 |
| Pain | 2 (1.3%) | 8 (5.2%) | 0.109 |
| Urinary tract infection | 5 (3.3%) | 6 (3.9%) | 1.000 |
| Respiratory infection | 2 (1.3%) | 5 (3.3%) | 0.453 |
| GPT elevation | 6 (3.9%) | 4 (2.6%) | 0.754 |
| GOT elevation | 5 (3.3%) | 2 (1.3%) | 0.453 |
| Number of patients with serious adverse event | 11 (36.7%) | 10 (32.3%) | |
| Number of serious adverse events during the main study | 17 | 11 | |
| *Cause of serious adverse events* | | | |
| Fracture Weber B | 1 | | |
| Serial rib fracture | | 1 | |
| Fall with headache | 1 | | |
| Micturition dysfunction | 2 | | |
| Fracture ankle joint | 1 | | |
| Benign paroxysmal positional vertigo | | 1 | |
| In-patient MS rehabilitation | | 1 | |
| Injection abscess | | 1 | |
| Seizure | 1 | | |
| Pelvic fracture | 1 | | |
| Parkinson disease | 3 | | |
| Somatization disorder in depression | 3 | | |
| Filiform ACI stenosis | 1 | | |
| Multilocular pain syndrome | 2 | | |
| AV block 3rd degree | | 1 | |
| Pain right flank | | 1 | |
| Fracture lower leg | | 1 | |
| Femur fracture | | 1 | |
| Removal of material after femur fracture | | 1 | |
| Incrusted permanent suprapubic catheter | | 1 | |
| Stroke | | 1 | |
| Bronchopneumonia | 1 | | |

Data are numbers (%)

In the Sunphenon EGCG group, 2 patients reported intolerability of the study medication and 1 had to stop study medication because of elevated liver enzymes higher than 3.5 times the upper limit of normal; elevated values soon returned to normal after stopping medication.

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| *Name of Active Ingredient:*<br>Epigallocatechin gallate (EGCG) | | |

29 of the 30 participants in the EGCG group (96,7%) and 28 of the 31 participants in the placebo group (90,3%) experienced one or more adverse event (AE), with 11 (36,7%) in the EGCG and 10 (32,3%) in the placebo group having a serious adverse event (SAE). None of the SAEs were considered related to the study drug. All occurred due to hospitalization of study participants for various reasons (Table 3).
The incidence of SAEs and the most common AEs (>3%) was similar in both study groups. The most common AEs were flu-like infections, urinary tract infections, fractures and contusions after fall and elevated liver enzymes, for which there was no statistical difference between the groups.

Conclusion:
After a recruitment period of more than 3 years, 61 participants were included, and the study was regularly completed in strict compliance with the protocol. EGCG at a dosage of up to 1200 mg daily was safe and well tolerated in patients with PMS over a period of 36 or even 48 months.
Our randomized, placebo-controlled study failed to show an effect of oral EGCG on radiographic or clinical disease markers in patients with PMS without additional immunomodulatory treatment.
Reasons could be due to the design of the study as a pilot study without sample size calculation for study planning. The change in in the primary outcome (brain atrophy, PBVC/BPF) over time was small; therefore, a much higher sample size would have been necessary to detect a difference by statistical means. Additionally, the study had a relatively high dropout rate, which lowed the number of analysable datasets even more. Also in clinical context the study cohort remained remarkably stable as only a few of the patients of each group showed progression of the disease (progression by EDSS).
A further explanation may be an insufficient therapeutic EGCG dosage, as 30 months of the 36 months of the main study the daily intake of the investigational product was 800 mg and less.
EGCG at a dose of up to 1200 mg daily was safe and well tolerated in patients with PMS over a period of 36 or even 48 months. Future studies have to investigate the efficacy of EGCG in progressive MS with an adapted study design based on the study data presented here and, if necessary, a further developed substance.

Date of the report: 08.03.2020

| | | |
|---|---|---|
| *Name of Sponsor/ Representative of Sponsor:*<br>Charité - Universitätsmedizin Berlin/<br>Prof. Dr. med. Friedemann Paul | *Individual Study Table Referring to Part of the Dossier*<br>not applicable | *(For National Authority Use only)* |
| *Name of Finished Product:*<br>Sunphenon® | | |
| *Name of Active Ingredient:*<br>Epigallocatechin gallate (EGCG) | | |

# Signatures

The undersigned authors agree with the contents of the present report by their signature. The clinical trial reported here was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and the applicable laws.

Sponsor representative and Leiter der Klinischen Prüfung

Prof. Dr. med. Friedemann Paul — Date 09/03/2020

Further Authors of the report

Dr. med. Judith Bellmann-Strobl — Date 05/03/2020

Rebekka Rust — Date 09.03.2020

**SYNOPSIS**
according Annex 1 der *Note for guidance on structure and content of clinical study reports* (CPMP/ICH/137/95) - ICH Topic E 3

| | | |
|---|---|---|
| *Name of Sponsor/ Representative of Sponsor:*<br>Charité - Universitätsmedizin Berlin/<br>Prof. Dr. med. Friedemann Paul | *Individual Study Table Referring to Part of the Dossier*<br>not applicable | *(For National Authority Use only)* |
| *Name of Finished Product:*<br>Sunphenon® | | |
| *Name of Active Ingredient:*<br>Epigallocatechin gallate (EGCG) | | |

Appendix 1

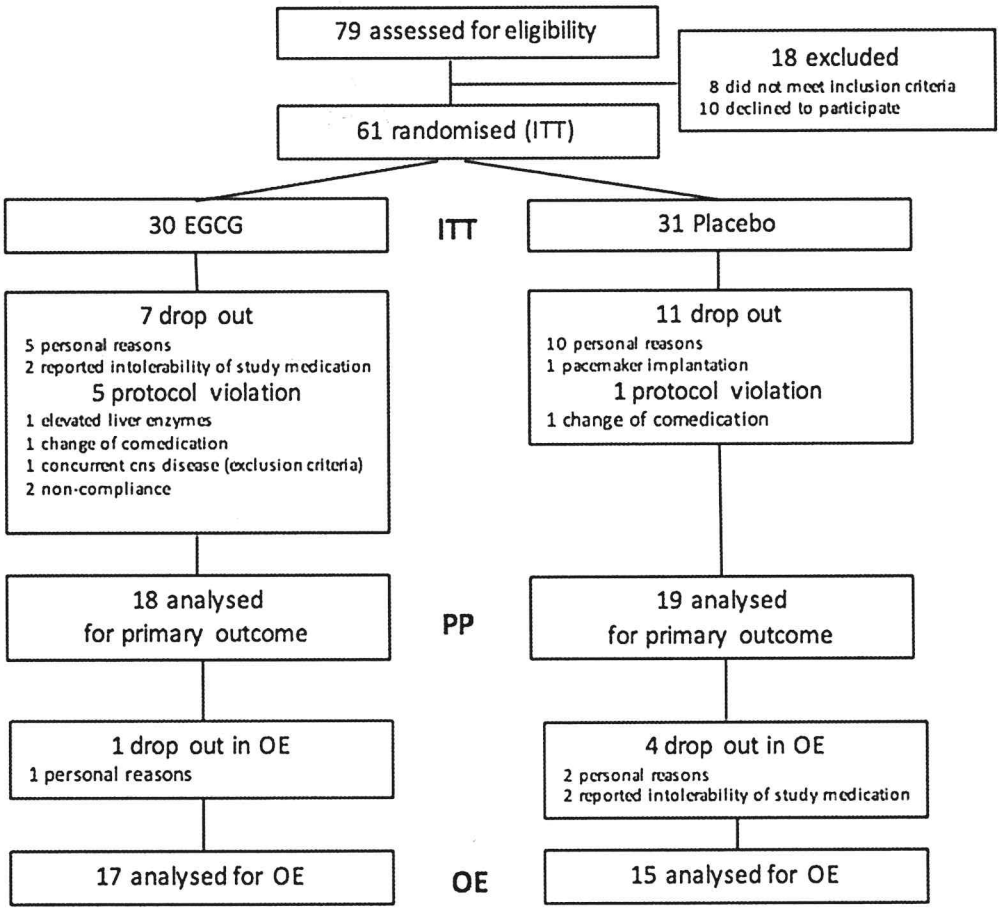


Figure 1: Consort diagram; Abbreviations: ITT intention to treat, PP per protocol, OE Open extend phase.

Appendix 2 Schedule of activities

| Event | Screening (W -2) | Random (Mo 0) ± 10 d | Tel-V 1 (W +1) ± 3 d | V1(Month +3) ± 3 W | Tel-V 2 (W +1) ± 3 d | V2 (Month +6) ± 3 W | Tel-V 3 (W +1) ± 3 d | V3 (Month +8) ± 3 W | V4 (Month +10) ± 3 W | V5 (Month +12) ± 3 W | V6 (Month +15) ± 3 W | V7 (Month +18) ± 3 W | Tel-V 4 (W +1) ± 3 d | V8 (Month +20) ± 3 W | V9 (Month +22) ± 3 W | V10 (Month +24) ± 3 W | V11 (Month +27) ± 3 W | V12 (Month +30) ± 3 W | Tel-V 5 (W +1) ± 3 d | V13 (Month +33) ± 3 W | V14 (Month +36) ± 3 W | V15 (Month +42) Optional, ± 3 W | V16 (Month +48) Optional, ± 3 W |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Signed Consent | X | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion criteria. | X | X | | | | | | | | | | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | | | | | | | | | | |
| Demographic Data | X | | | | | | | | | | | | | | | | | | | | | | |
| Gynaecological history | X | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy Test | X | | | | | | | | | | | | | | | | | | | | | | |
| MS Diagnosis | X | | | | | | | | | | | | | | | | | | | | | | |
| Relapse history | X | X | | X | | X | | X | X | X | X | X | | X | X | X | X | X | | X | X | X | X |
| MS history | X | | | | | | | | | | | | | | | | | | | | | | |
| Medication history | X | X | | X | | X | | X | X | X | X | X | | X | X | X | X | X | | X | X | X | X |
| Physical examination | X | | | | | X | | | | X | | X | | | | X | | X | | | X | | X |
| Vital signs | X | X | | X | | X | | X | X | X | X | X | | X | X | X | X | X | | X | X | X | X |
| Weight | X | | | | | | | | | | | | | | | | | ~~X~~ | | | X | | X |
| MSFC | X | | | | | X | | | | X | | X | | | | X | | X | | | X | | X |
| EDSS | X | | | | | X | | | | X | | X | | | | X | | X | | | X | | X |
| ECG | X | | | | | | | | | | | | | | | | | ~~X~~ | | | X | | X |
| Extended laboratory workup* | X | | | | | | | | | | | | | | | | | | | | | | |
| Basic laboratory workup* | | | | X | | X | | X | X | X | X | X | | X | X | X | X | X | | | X | | X |
| Blood sampling immunology lab* | X[1] | X[2] | | | | | | | | X | | | | | | X | | ~~X~~ | | | X | | X |
| MR-Spectroscopy | X | | | | | | | | | | | | | | | | | ~~X~~ | | | X | | X |
| MRI | X | | | | | | | | | X | | | | | | X | | ~~X~~ | | | X | | X |
| Fatigue scale | X | | | | | | | | | | | | | | | | | ~~X~~ | | | X | | X |
| Neuropsychology | X | | | | | | | | | | | | | | | | | ~~X~~ | | | X | | X |
| OCT | X | | | | | | | | | | | | | | | | | ~~X~~ | | | X | | X |
| Adverse Events | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Query hospitalization | X | X | | X | | X | | X | X | X | X | X | | X | X | X | X | X | | X | X | X | X |
| Dispensing of the study medication | | X | | X | | X | | | | X | | X | | | | X | | | | | X | | X |
| Drug account | | | | | | X | | | | X | | X | | | | X | | X | | | X | | X |
| Dose increase | | | | X | | X | | | | | | X | | | | | | X | | | | | |