Clinical trial results:
SUPREMES - Sunphenon in progressive forms of multiple sclerosis

Summary

EudraCT number	2008-005213-22
Trial protocol	DE
Global end of trial date	02 March 2016

Results information

Result version number	v1 (current)
This version publication date	23 December 2021
First version publication date	23 December 2021
Summary attachment (see zip file)	supremes_result_report (2020-03-08_SUPREMES_Ergebnisbericht.pdf)

Trial information

Trial identification

Sponsor protocol code	SUPREMES-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00799890
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité- Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 March 2016
Global end of trial reached?	Yes
Global end of trial date	02 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy and safety of Sunphenon EGCg in progressive forms of multiple sclerosis after a 36 months treatment compared to the placebo-group, primary outcome criteria being reduction of Brain Parenchymal Fraction (atrophy)

Protection of trial subjects:

Safety: Vital signs, Physical examination, ECG, laboratory tests, occurence of (severe) adverse events in both arm and for more parameter see manuscript

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 May 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	61
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Start: 08.05.2009;
End: 08.05.2012;
Subjects assessed of eligibility (screening) = 79;
Screening failure =8;
Subjects declined to participants = 10;

Pre-assignment

Screening details:

Eligibility criteria comprised fulfillment of the revised McDonald criteria for MS and the diagnosis of PPMS or SPMS, Expanded Diability Status Scale score of 3 to 8
and relapse-free period of at least 30 days before randomization. Exclusion criteria were relapsing-remitting from MS, a major systemic or CNS disease, laboratory abnormalities.

Period 1

Period 1 title	Baseline to 36 months
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Control placebo group

Arm description:

Subjects treated with Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo (identical with study drug apart from active ingredient)

Arm title	EGCG

Arm description:

Subjects treated with Sunphenon

Arm type	Experimental
Investigational medicinal product name	Sunphenon
Investigational medicinal product code	
Other name	Sunphenon EGCg
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received
0-3 month: 200mg daily (1x in the morning),
after 3 to 6 months: 400mg (2x 200mg times daily),
after 6 to 18 months: 600 mg daily (400 mg in the morning, 200mg in the evening),
after 18 to 30 months: 800 mg (2x 400mg times daily) and
after 30 to 36 month: 1200 mg (3x 400 mg times daily)

Number of subjects in period 1	Control placebo group	EGCG
Started	31	30
Completed	19	18
Not completed	12	12
Adverse event, non-fatal	-	3
personal reasons	10	5
non-compliance	-	2
Protocol deviation	2	2

Period 2	
Period 2 title	open-label extension
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Control placebo group with EGCG

Arm description:

Patients initially treated with placebo, started with EGCG in the 12 month open label extension

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

treatment starts with daily 1x 200mg capsule(1-0-0). After 3 months to 400mg daily (2x200mg, 2-0-0). After 6 months to 600mg (3x1 200mg capsules, 2-0-1). After 18 months to 800mg (2x2 200mg capsules, 2-0-2). After 30 months to 1200mg daily (3x2 200mg, 2-2-2)

Investigational medicinal product name	Sunphenon Epigallocatechin-3-Gallte (EGCG
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Ocular use

Dosage and administration details:

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

Arm title	EGCG+OE

Arm description:

Continue 1200mg daily treatment for 12 months

Arm type	Experimental
Investigational medicinal product name	Sunphenon
Investigational medicinal product code	
Other name	Sunphenon EGCg
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Sunphenon Eigallocatechin-3-Gallate (EGCG). Sunphenon EGCG capsules 200mg daily (1x 200mg, 1-0-0). They were escalated after 3 months to 400mg daily (2x 200mg, 2-0-0). After 6 months to 600mg daily (3x1 200mg, 2-0-1),after 18 months to 800mg daily (4x400mg, 2-0-2), after 30months to 1200mg daily (6x200mg, 2-2-2) until the end of the study at 36 month.

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

Number of subjects in period 2	Control placebo group with EGCG	EGCG+OE
Started	19	18
Completed	15	17
Not completed	4	1
Physician decision	2	-
personal reasons	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Control placebo group
Reporting group description:	
Subjects treated with Placebo	
Reporting group title	EGCG
Reporting group description:	
Subjects treated with Sunphenon	

Reporting group values	Control placebo group	EGCG	Total
Number of subjects	31	30	61
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	31	30	61
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	48.84	49.50	
standard deviation	± 7.56	± 7.70	-
Gender categorical			
Units: Subjects			
Women	13	14	27
Men	18	16	34
disease type			
Diagnosis: Secondary progressive multiple sclerosis (SPMS) primary progressive multiple sclerosis (PPMS)			
Units: Subjects			
PPMS	12	11	23
SPMS	19	19	38
Expanded Disability Status Scale			
Units: Score			
median	6	6	
inter-quartile range (Q1-Q3)	3.0 to 7.0	3.0 to 6.0	-
Expanded Disability Status Scale			
Units: Score			
arithmetic mean	5.29	5.5	
standard deviation	± 1.2	± 1.3	-
Disease duration			
Units: year			

arithmetic mean	9.42	11.08	
standard deviation	± 6.18	± 8.98	-
Duration of Progression			
Units: years			
arithmetic mean	5.05	6.48	
standard deviation	± 3.66	± 5.13	-
MSFC Z-score			
Multiple Sclerosis Functional Composite			
Units: score			
arithmetic mean	0.01	0.15	
standard deviation	± 0.64	± 0.58	-
PASAT			
Paced Auditory Serial Addition Test			
Units: Score			
arithmetic mean	42.23	43.30	
standard deviation	± 12.53	± 11.90	-
TWT average speed			
Timed 25-Foot Walk Test			
Units: seconds			
arithmetic mean	11.72	12.65	
standard deviation	± 11.73	± 8.74	-
9-HPT average			
9-Hole-Peg Test			
Units: seconds			
arithmetic mean	30.90	30.53	
standard deviation	± 9.95	± 14.25	-
Brain parenchymal fraction			
BPF			
Units: Score			
arithmetic mean	0.7008	0.7067	
standard deviation	± 0.0415	± 0.0571	-
CEL count			
Contrast enhancing lesions			
Units: Count			
arithmetic mean	0.48	0.25	
standard deviation	± 2.00	± 0.52	-
CEL volume			
Contrast enhancing lesions			
Units: ml			
arithmetic mean	0.05	0.05	
standard deviation	± 0.07	± 0.05	-
T2w lesion count			
Units: count			
arithmetic mean	44.19	41.30	
standard deviation	± 26.97	± 22.29	-
T2w lesion volume			
Units: ml			
arithmetic mean	15.64	18.42	
standard deviation	± 14.46	± 17.07	-

End points

End points reporting groups	
Reporting group title	Control placebo group
Reporting group description: Subjects treated with Placebo	
Reporting group title	EGCG
Reporting group description: Subjects treated with Sunphenon	
Reporting group title	Control placebo group with EGCG
Reporting group description: Patients initially treated with placebo, started with EGCG in the 12 month open label extension	
Reporting group title	EGCG+OE
Reporting group description: Continue 1200mg daily treatment for 12 months	

Primary: Brain parenchymal fraction change from baseline to month 36	
End point title	Brain parenchymal fraction change from baseline to month 36
End point description: Decrease in brain volume, brain parenchymal fraction (BPF) after 36 months	
End point type	Primary
End point timeframe: From baseline to month 36	

End point values	Control placebo group	EGCG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: percentage, volume				
arithmetic mean (standard deviation)				
BPF	0.6867 (± 0.0439)	0.6943 (± 0.0502)		
change from baseline	0.0078 (± 0.0159)	0.0092 (± 0.0152)		
Percent brain volume	-0.8013 (± 1.1996)	-0.5659 (± 0.9818)		

Statistical analyses

Statistical analysis title	Mann-Whitney test
Statistical analysis description: The primary end point was the change of BPF from baseline to month 36	
Comparison groups	EGCG v Control placebo group

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Expanded Disability Status Scale

End point title	Expanded Disability Status Scale

End point description:

Secondary clinical outcome measurments were disability progression as measured by EDSS and confirmed progression (CDP) defined as a 1-point increase in the EDSS if the baselinbe score was 3.0-5.5, or 0.5-point increase if the baseline score was 6.0 and above, confirmed at a scheduled visit 6 months later.

End point type	Secondary

End point timeframe:

from baseline to month 36

End point values	Control placebo group	EGCG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Score	20	19		

Statistical analyses

No statistical analyses for this end point

Secondary: EDSS Month 36

End point title	EDSS Month 36

End point description:

End point type	Secondary

End point timeframe:

36 months

End point values	Control placebo group	EGCG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: score				
arithmetic mean (full range (min-max))				
Median	5.73 (3.5 to 8.0)	6.08 (3.0 to 8.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: EDSS Change from baseline

End point title	EDSS Change from baseline

End point description:

End point type	Secondary

End point timeframe:

36 months

End point values	Control placebo group	EGCG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: score				
arithmetic mean (standard deviation)				
change	0.5750 (± 0.9904)	0.2631 (± 0.4524)		

Statistical analyses

No statistical analyses for this end point

Secondary: T2w and CE lesions

End point title	T2w and CE lesions

End point description:

End point type	Secondary

End point timeframe:

36 months

End point values	Control placebo group	EGCG		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: volume				
arithmetic mean (standard deviation)				
Number of T2w-lesions	39.32 (± 19.28)	35.21 (± 16.84)		
T2w-lesions chane from baselin	3.7894 (± 4.8828)	1.5263 (± 4.2343)		
Volume of T2w-lesions (ml)	16.9076 (± 17.2964)	17.5741 (± 16.4686)		
T2w-lesions change from baseline (ml)	0.5243 (± 2.3606)	1.0439 (± 1.4783)		
Number of CEL	0.13 (± 0.342)	0.00 (± 0.00)		
Volume of CEL (CEL)	0.0029 (± 0.0096)	0.00 (± 0.00)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

day of assesment to month 36

Adverse event reporting additional description:

None of the SAEs were considered related to the study drug. All occurred due to hospitalization of the study participants for various reasons (Table 3 of the report). The most common AEs were flu-like infections, urinary tract infections, fractures and contusions after all and elevated enzymes.

Assessment type	Systematic

Dictionary used

Dictionary name	own
Dictionary version	1

Reporting groups

Reporting group title	EGCG

Reporting group description:

see manuscript page 11

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	EGCG	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 30 (36.67%)	11 / 31 (35.48%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	3 / 30 (10.00%)	3 / 31 (9.68%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall with headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular fragility			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgery			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	6 / 30 (20.00%)	4 / 31 (12.90%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Multiocular pain syndrom			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Micturition dysfunction			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchopneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Injection Abscess			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	EGCG	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 30 (96.67%)	28 / 31 (90.32%)	
Investigations			
Overall	Additional description: The common AEs (>3%) was smiliar in both groups. The most common AEs were flu like infections, urinary tract infections, fracture and contusions after fall and elevated liver enzymes, for which there was no statistical difference between the groups.		
subjects affected / exposed	29 / 30 (96.67%)	28 / 31 (90.32%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2011	The study was initially planned as double-blind pilot study with recalculation of sample size with a total of 60 patients. At the end of the blinded phase (afther 36 month of study), the unblinded recalculation of sample size, was not carried out a continuation of the study did not seem realistic die to recruitment problems.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported