



## Clinical trial results:

**Double blind, randomised, prospective placebo controlled parallel group phase III study to investigate the Effect of EGCG supplementation on disease progression of patients with Multiple System Atrophy (MSA)**

### Summary

EudraCT number	2012-000928-18
Trial protocol	DE
Global end of trial date	16 September 2016

### Results information

Result version number	v1 (current)
This version publication date	27 August 2021
First version publication date	27 August 2021

### Trial information

#### Trial identification

Sponsor protocol code	PROMESA
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02008721
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Hospital of the Ludwig-Maximilians-University of Munich
Sponsor organisation address	Marchioninistrasse 15, Munich, Germany, 81377
Public contact	Sponsor delegated person: Dr. Levin, Hospital of the Ludwig-Maximilians-University of Munich , +49 89440074812, jlevin@med.uni-muenchen.de
Scientific contact	Sponsor delegated person: Dr. Levin, Hospital of the Ludwig-Maximilians-University of Munich , +49 89440074812, jlevin@med.uni-muenchen.de

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	16 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 September 2016
Global end of trial reached?	Yes
Global end of trial date	16 September 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of EGCG vs. Placebo to reduce the progression in the motor examination (ME) of the Unified MSA Rating Scale (UMSARS-ME) from V1 to V7, (80% power, 5% P-level, 50% effect size, i.e. an expected mean yearly UMSARS-ME increase of 3.9 under verum treatment compared to  $7.8 \pm 6.8$  (mean  $\pm$  standard deviation) under Placebo-treatment.

Protection of trial subjects:

The reported data suggested a safe pharmacological profile of the compound apart from individual cases of hepatotoxicity which could be controlled for by routine serum liver parameters. The preclinical data suggest a molecular mode of action for EGCG which appears to target core pathological mechanisms active in MSA. In absence of any effective symptomatic, protective or curative intervention in this devastating disorder, the risk benefit evaluation justifies the conduct of the proposed clinical trial. Exclusion criteria included liver disease with aminotransferases and bilirubin concentrations twice the upper limit of normal or higher; regular intake of hepatotoxic drugs; known hypersensitivity to epigallocatechin gallate or to drugs with similar chemical structures.

Background therapy:

Eligible patients had to be on stable anti-Parkinson's, anti-dysautonomia, anti-dementia, and anti-depressant regimens (if necessary) for at least 1 month without a foreseeable need to change the regimens during the next year.

Evidence for comparator: -

Actual start date of recruitment	23 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 92
Worldwide total number of subjects	92
EEA total number of subjects	92

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)	52
From 65 to 84 years	40
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Between April 23, 2014, and Sept 3, 2015, 127 participants were screened and 92 were randomly assigned—47 to epigallocatechin gallate and 45 to placebo at 12 specialist centres for diagnosis and treatment of parkinsonism in Germany.

### Pre-assignment

Screening details:

Eligible patients were older than 30 years; met the diagnostic criteria for possible or probable parkinsonism-predominant or cerebellar-ataxia-predominant multiple system atrophy; could ambulate independently (ie, Hoehn and Yahr stages 1–3); and had to be on stable anti-Parkinson's, anti-dysautonomia, anti-dementia, and anti-depressant regimens.

### Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Participants were randomly assigned (1:1) to epigallocatechin gallate or placebo (mannitol) via a web-generated permuted blockwise randomisation list (block size=2) that was stratified by disease subtype parkinsonism-predominant disease vs cerebellar-ataxia-predominant disease). All participants and study personnel were masked to treatment assignment.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	EGCG (epigallocatechin gallate)

Arm description:

Participants were older than 30 years; met consensus criteria for possible or probable multiple system atrophy and could ambulate independently (ie, were at Hoehn and Yahr stages 1–3); and were on stable anti-Parkinson's, anti-dysautonomia, anti-dementia, and anti-depressant regimens (if necessary) for at least 1 month.

They were given one hard gelatin capsule (containing 400 mg epigallocatechin gallate) orally once daily for 4 weeks, then one capsule twice daily for 4 weeks, and then one capsule three times daily for 40 weeks. After 48 weeks, all patients underwent a 4-week wash-out period.

Arm type	Active comparator
Investigational medicinal product name	epigallocatechin gallate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Gastroenteral use

Dosage and administration details:

Participants were given one hard gelatin capsule (containing 400 mg epigallocatechin gallate) orally once daily for 4 weeks, then one capsule twice daily for 4 weeks, and then one capsule three times daily for 40 weeks.

<b>Arm title</b>	Placebo (mannitol)
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Arm description:

Eligible participants were older than 30 years; met consensus criteria for possible or probable multiple system atrophy and could ambulate independently (ie, were at Hoehn and Yahr stages 1–3); and were on stable anti-Parkinson's, anti-dysautonomia, anti-dementia, and anti-depressant regimens (if necessary) for at least 1 month.

Participants in the Placebo arm were given one hard gelatin capsule (containing 400 mg mannitol) orally once daily for 4 weeks, then one capsule twice daily for 4 weeks, and then one capsule three times daily for 40 weeks.

Arm type	Placebo
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Investigational medicinal product name	Placebo (mannitol)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Gastroenteral use

Dosage and administration details:

Participants were given one hard gelatin capsule (containing 400 mg mannitol) orally once daily for 4 weeks, then one capsule twice daily for 4 weeks, and then one capsule three times daily for 40 weeks.

Investigational medicinal product name	epigallocatechin gallate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Gastroenteral use

Dosage and administration details:

Participants were given one hard gelatin capsule (containing 400 mg epigallocatechin gallate) orally once daily for 4 weeks, then one capsule twice daily for 4 weeks, and then one capsule three times daily for 40 weeks.

<b>Number of subjects in period 1</b>	EGCG (epigallocatechin gallate)	Placebo (mannitol)
Started	47	45
completion of study treatment	32	35
completion of study assessment	31	33
completed without protocol violations	30	33
participation in MRI substudy	17 <sup>[1]</sup>	15 <sup>[2]</sup>
completion of MRI substudy	11 <sup>[3]</sup>	8 <sup>[4]</sup>
Completed	30	33
Not completed	17	12
Adverse event, serious fatal	4	2
Consent withdrawn by subject	4	1
Adverse event, non-fatal	4	7
did not give reason	1	-
Protocol deviation	4	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Please consider the MRI substudy (17 of 47 participants) as an additional group arm.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Please consider the MRI substudy (15 of 45 participants) as an additional group arm.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only part of the 47 participants in this arm were able to take part in the MRI substudy. In

this arm, 17 participants took part and of these, 11 participants completed the substudy, hence the diverging numbers.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Of the 45 participants in this arm, only 15 could participate in the MRI substudy. Of those, only 8 completed the substudy, hence the diverging numbers.

## Baseline characteristics

### Reporting groups

Reporting group title	overall trial
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Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	92	92	
Age categorical			
Units: Subjects			
Adults (18-64 years)	52	52	
From 65-84 years	40	40	
Age continuous			
Units: years			
median	62		
inter-quartile range (Q1-Q3)	57 to 70	-	
Gender categorical			
Units: Subjects			
Female	37	37	
Male	55	55	

### Subject analysis sets

Subject analysis set title	Full analysis set
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Subject analysis set type	Full analysis
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Subject analysis set description:

All participants who received at least one dose of study medication (ie, the full analysis set)

Reporting group values	Full analysis set		
Number of subjects	92		
Age categorical			
Units: Subjects			
Adults (18-64 years)	52		
From 65-84 years	40		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical			
Units: Subjects			
Female			
Male			

## End points

### End points reporting groups

Reporting group title	EGCG (epigallocatechin gallate)
Reporting group description: Participants were older than 30 years; met consensus criteria for possible or probable multiple system atrophy and could ambulate independently (ie, were at Hoehn and Yahr stages 1–3); and were on stable anti-Parkinson's, anti-dysautonomia, anti-dementia, and anti-depressant regimens (if necessary) for at least 1 month. They were given one hard gelatin capsule (containing 400 mg epigallocatechin gallate) orally once daily for 4 weeks, then one capsule twice daily for 4 weeks, and then one capsule three times daily for 40 weeks. After 48 weeks, all patients underwent a 4-week wash-out period.	
Reporting group title	Placebo (mannitol)
Reporting group description: Eligible participants were older than 30 years; met consensus criteria for possible or probable multiple system atrophy and could ambulate independently (ie, were at Hoehn and Yahr stages 1–3); and were on stable anti-Parkinson's, anti-dysautonomia, anti-dementia, and anti-depressant regimens (if necessary) for at least 1 month. Participants in the Placebo arm were given one hard gelatin capsule (containing 400 mg mannitol) orally once daily for 4 weeks, then one capsule twice daily for 4 weeks, and then one capsule three times daily for 40 weeks.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: All participants who received at least one dose of study medication (ie, the full analysis set)	

### Primary: Scores on the motor examination of the UMSARS from baseline to week 52

End point title	Scores on the motor examination of the UMSARS from baseline to week 52
End point description: The primary endpoint was the change from baseline to week 52 in motor examination scores on the Unified MSA Rating Scale (UMSARS), which assesses 14 operationalised signs of multiple system atrophy. <sup>25</sup> Scores for all 14 items range from 0 to 4, thus total scores range from 0 to 56. A higher score means a worse outcome.	
End point type	Primary
End point timeframe: 52 weeks	

End point values	EGCG (epigallocatechin gallate)	Placebo (mannitol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	45		
Units: 14				
median (standard error)	5.66 (± 1.01)	6.60 (± 0.99)		

### Statistical analyses

Statistical analysis title	modified intention-to-treat analysis
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#### Statistical analysis description:

For the primary and secondary outcomes, we did a modified intention-to-treat analysis, which included all participants who received at least one dose of study medication (ie, the full analysis set).

We used a linear mixed-effects model to test the primary hypothesis—ie, to compare differences in the change in motor examination scores on UMSARS between baseline and week 52 between the study groups.

Comparison groups	EGCG (epigallocatechin gallate) v Placebo (mannitol)
Number of subjects included in analysis	92
Analysis specification	Post-hoc
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.51
Method	Mixed models analysis

#### Notes:

[1] - We did a post-hoc power calculation based on the mean change in motor examination scores on UMSARS and SDs in the placebo group of the per-protocol study completer set to test the assumptions of our initial power calculation.

### Secondary: Change in the UMSARS total score from baseline to week 52

End point title	Change in the UMSARS total score from baseline to week 52
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#### End point description:

Secondary efficacy end point was the change from baseline to week 52 in the UMSARS total score. The UMSARS total score comprises a historical review (12 items) and the motor examination part (14 items). Scores for each item reach from 0 - 4, thus the total score ranges from 0 to 104. A higher score means a worse outcome.

End point type	Secondary
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#### End point timeframe:

52 weeks

End point values	EGCG (epigallocatechin gallate)	Placebo (mannitol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	45		
Units: 26				
median (standard error)	10.33 (± 1.73)	10.35 (± 1.71)		

### Statistical analyses

<b>Statistical analysis title</b>	modified intention-to-treat analysis
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#### Statistical analysis description:

We used a linear mixed-effects model to compare differences in the change of scores on the UMSARS total score between baseline and week 52 between the study groups.

Comparison groups	EGCG (epigallocatechin gallate) v Placebo (mannitol)
Number of subjects included in analysis	92
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.99
Method	Mixed models analysis

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**Secondary: Scores on the motor examination of the UMSARS in the wash-out phase**

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End point title	Scores on the motor examination of the UMSARS in the wash-out phase
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End point description:

Change in the score of the UMSARS-ME during wash-out phase V6-V7 (symptomatic effect)  
The secondary endpoint was the change from week 48 to week 52 (washout phase) in motor examination scores on UMSARS, which assesses 14 operationalised signs of multiple system atrophy. Scores for all 14 items range from 0 to 4, thus total scores range from 0 to 56. A higher score means a worse outcome.

End point type	Secondary
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End point timeframe:

During the wash-out phase V6-V7 (week 48- week 52), i.e. 4 weeks

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End point values	EGCG (epigallocatechin gallate)	Placebo (mannitol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	45		
Units: 14				
median (standard error)	0.68 (± 0.60)	0.49 (± 0.58)		

**Statistical analyses**

<b>Statistical analysis title</b>	modified intention-to-treat analysis
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Statistical analysis description:

For the primary and secondary outcomes, we did a modified intention-to-treat analysis, which included all participants who received at least one dose of study medication (ie, the full analysis set). We used a linear mixed-effects model to test the primary hypothesis—ie, to compare differences in the change in motor examination scores on UMSARS between baseline and week 52 between the study groups.

Comparison groups	EGCG (epigallocatechin gallate) v Placebo (mannitol)
Number of subjects included in analysis	92
Analysis specification	Post-hoc
Analysis type	superiority <sup>[2]</sup>
P-value	= 0.82
Method	Mixed models analysis

Notes:

[2] - We did a post-hoc power calculation based on the mean change in motor examination scores on UMSARS and SDs in the placebo group of the per-protocol study completer set to test the assumptions of our initial power calculation.

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**Secondary: Change in the UMSARS total score in the washout phase**

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End point title	Change in the UMSARS total score in the washout phase
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End point description:

Secondary efficacy end point was the change from week 48 to week 52 (washout phase) in the UMSARS total score. The UMSARS total score comprises a historical review (12 items) and the motor examination part (14 items). Scores for each item reach from 0 - 4, thus the total score ranges from 0 to 104. A higher score means a worse outcome.

End point type	Secondary
End point timeframe:	
4 weeks (washout phase from week 48 to week 52)	

End point values	EGCG (epigallocatechin gallate)	Placebo (mannitol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	45		
Units: 26				
median (standard error)	0.70 (± 0.21)	-0.29 (± 0.88)		

## Statistical analyses

<b>Statistical analysis title</b>	modified intention-to-treat analysis
Statistical analysis description:	
We used a linear mixed-effects model to compare differences in the change of scores on the UMSARS total score between week 48 and week 52 between the study groups.	
Comparison groups	EGCG (epigallocatechin gallate) v Placebo (mannitol)
Number of subjects included in analysis	92
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.43
Method	Mixed models analysis

## Secondary: Effect of treatment (EGCG vs. Placebo) on striatal volume loss in MRI

End point title	Effect of treatment (EGCG vs. Placebo) on striatal volume loss in MRI
End point description:	
To assess the efficacy of EGCG vs. Placebo to reduce the progression from V1 to V7 in striatal volume loss (3D MPRAGE MRI volumetry, 3D FLAIR)	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	EGCG (epigallocatechin gallate)	Placebo (mannitol)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11 <sup>[3]</sup>	8 <sup>[4]</sup>		
Units: % of annual striatal volume loss				
number (not applicable)	3.4	7.3		

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Notes:

[3] - 11 patients completed the MRI sub-study

[4] - 8 patients completed the MRI substudy

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### **Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

April 23, 2014 until September 11, 2016

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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### Reporting groups

Reporting group title	EGCG (= verum) group
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Reporting group description: -

Reporting group title	Placebo group
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Reporting group description: -

Serious adverse events	EGCG (= verum) group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 47 (38.30%)	8 / 45 (17.78%)	
number of deaths (all causes)	4	2	
number of deaths resulting from adverse events	4	2	
Injury, poisoning and procedural complications			
fracture of femoral bone			
subjects affected / exposed	1 / 47 (2.13%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
synkope			
subjects affected / exposed	1 / 47 (2.13%)	1 / 45 (2.22%)	
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			
subjects affected / exposed	1 / 47 (2.13%)	3 / 45 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			

subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	4 / 47 (8.51%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
General worsening of overall health			
subjects affected / exposed	0 / 47 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
heat stroke and exsikkosis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
gastrointestinal adverse event			
subjects affected / exposed	5 / 47 (10.64%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
hepatotoxicity			
subjects affected / exposed	2 / 47 (4.26%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
pneumonia due to aspiration			
subjects affected / exposed	3 / 47 (6.38%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Skin and subcutaneous tissue disorders			
Phlegmone hand			

subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
UTI			
subjects affected / exposed	0 / 47 (0.00%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	EGCG (= verum) group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 47 (53.19%)	33 / 45 (73.33%)	
Vascular disorders			
edema			
subjects affected / exposed	3 / 47 (6.38%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
Nervous system disorders			
Dysphagia			
subjects affected / exposed	4 / 47 (8.51%)	0 / 45 (0.00%)	
occurrences (all)	5	0	
Dysarthria			
subjects affected / exposed	0 / 47 (0.00%)	4 / 45 (8.89%)	
occurrences (all)	0	4	
falls			
subjects affected / exposed	17 / 47 (36.17%)	17 / 45 (37.78%)	
occurrences (all)	26	31	
orthostatic hypotension			

subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 6	5 / 45 (11.11%) 5	
swallowing problems subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 5	0 / 45 (0.00%) 0	
worsening of parkinsonism, ataxia, autonomic dysfunction subjects affected / exposed occurrences (all)	10 / 47 (21.28%) 24	9 / 45 (20.00%) 17	
Gastrointestinal disorders gastrointestinal adverse event subjects affected / exposed occurrences (all)	17 / 47 (36.17%) 28	13 / 45 (28.89%) 21	
Hepatobiliary disorders hepatotoxicity subjects affected / exposed occurrences (all)	6 / 47 (12.77%) 6	0 / 45 (0.00%) 0	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	5 / 47 (10.64%) 5	2 / 45 (4.44%) 2	
Renal and urinary disorders UTI subjects affected / exposed occurrences (all)	9 / 47 (19.15%) 14	12 / 45 (26.67%) 18	
urinary dysfunction subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	6 / 45 (13.33%) 6	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial was powered to detect a 50% reduction in disease progression, not to detect smaller changes. The assumed dropout rate was 20% while the observed drop out rate was approximately 27%. Only 4 of the 12 centres recruited 10 or more patients.
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31278067>