Clinical trial results:
SAFETY, TOLERABILITY AND MECHANISM OF ACTION OF BOSWELLIC ACIDS (BA) IN MULTIPLE SCLEROSIS (MS) AND CLINICALLY ISOLATED SYNDROME (CIS):
A MRI-CONTROLLED, MULTICENTER, BASELINE-TO-TREATMENT, 32-WEEKS, OPEN-LABEL, PHASE IIA TRIAL IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS OR CLINICALLY ISOLATED SYNDROME

Summary

EudraCT number	2009-014724-32
Trial protocol	DE
Global end of trial date	07 March 2017

Results information

Result version number	v1 (current)
This version publication date	25 October 2022
First version publication date	25 October 2022
Summary attachment (see zip file)	SABA_Synopsis results 2018_01_20 (SABA_Synopsis results 2018_01_20.pdf)

Trial information

Trial identification

Sponsor protocol code	SABA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01450124
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Medical Center Hamburg-Eppendorf (UKE)
Sponsor organisation address	Martinistrasse 52, Hamburg, Germany,
Public contact	MS Outpatient Unit, Institute for Neuroimmunology and Clinical Multiple Sclerosis (MS) Research, UKE, +49 40741054076, multiplesklerose@uke.uni-hamburg.de
Scientific contact	MS Outpatient Unit, Institute for Neuroimmunology and Clinical Multiple Sclerosis (MS) Research, UKE, +49 40741054076, multiplesklerose@uke.uni-hamburg.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	24 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2017
Global end of trial reached?	Yes
Global end of trial date	07 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and tolerability of a standardized frankincense extract ("Boswelan") in subjects with multiple sclerosis or clinically isolated syndrome

Protection of trial subjects:

Patients were regularly and frequently monitored by clinical visits, laboratory parameters and magnetic resonance imaging. An independent data-safety monitoring board of three international Multiple Sclerosis experts followed all adverse events up during the trial.

The study protocol and the trial was conducted by treating and examining all patients in accordance with the national (German) applicable laws, the international guidelines on good clinical practice (ICH-GCP), and the declaration of Helsinki.

Further details are given in the study protocol (available via klarissa.stuerner@uksh.de).

Background therapy:

best medical care

Evidence for comparator:

in-vitro data inhibiting TH17 polarization in Multiple Sclerosis patients in cell culture

Actual start date of recruitment	01 September 2011
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: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	38
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Multiple Sclerosis patients between 18 and 55 years were recruited at the UK Hamburg Eppendorf, Department of neurology or at the NeuroCure Research Center at the Charité Berlin. Of 80 screened patients 38 patients were enrolled to the trial.
Further details can be found at: https://jnnp.bmj.com/content/89/4/330

Pre-assignment

Screening details:

Subjects with clinically isolated syndrome (CIS) or clinically definite relapsing remitting multiple sclerosis (RRMS) fulfilling MRI inclusion criteria who either failed standard treatment by
clinical measures or were not eligible for any of the standard treatments were given the opportunity to participate in the trial.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Single Arm

Arm description:

We performed an investigator-initiated, bicentric phase IIa, open-label, baseline-totreatment pilot study with an oral SFE in patients with RRMS. After a 4-month baseline observation phase, patients were treated for 8 months with an option to extend treatment for up to 36 months. The primary outcome measures were the number and volume of contrast-enhancing lesions (CEL) measured in MRI during the 4-month treatment period compared with the 4-month baseline period. Eighty patients were screened at two centres, 38 patients were included in the trial, 28 completed the 8-month treatment period and 18 of these participated in the extension period.

Arm type	Experimental
Investigational medicinal product name	standardised frankincence extract (SFE)
Investigational medicinal product code	
Other name	SFE
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

The SFE was provided as capsules containing 400 mg. After a 3-month baseline observation phase (stage 1) the patient participated in an individualised dose-finding phase (stage 2) during the first 8 weeks. Stage 2 was divided into two parts. In part 1, up to 400 mg capsules of an SFE were used to titrate up to a maximum well-tolerated dose or to a maximum of 4800 mg/day (whichever occurrd first), that is, 1600 mg three times a day in the first 28 days by adding one capsule every second or third day. After the individual maximum well-tolerated dose had been determined, the patients continued with that dose for another 28 days (part 2) for stabilisation and to assess tolerability. This was followed by 6 months of continuous treatment at this dose (stage 3). A minimum tolerated dose of 2400 mg/day was mandatory to continue with the trial. If a relapse occurred during the study, the patients were offered the option to discontinue the trial and revert to standard treatment.

Number of subjects in period 1	Single Arm
Started	38
completed month 8	28
Completed	28
Not completed	10
Consent withdrawn by subject	3
Physician decision	4
non-compliance to protocol	3

Baseline characteristics

Reporting groups

Reporting group title	Single Arm

Reporting group description:

We performed an investigator-initiated, bicentric phase IIa, open-label, baseline-totreatment pilot study with an oral SFE in patients with RRMS. After a 4-month baseline observation phase, patients were treated for 8 months with an option to extend treatment for up to 36 months. The primary outcome measures were the number and volume of contrast-enhancing lesions (CEL) measured in MRI during the 4-month treatment period compared with the 4-month baseline period. Eighty patients were screened at two centres, 38 patients were included in the trial, 28 completed the 8-month treatment period and 18 of these participated in the extension period.

Reporting group values	Single Arm	Total	
Number of subjects	38	38	
Age categorical			
Eligible patients were male or female between the ages of 18 and 55.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	38	38	
From 65-84 years	0	0	
85 years and over	0	0	
Not recorded	0	0	
Age continuous			
Units: years			
median	37.2		
standard deviation	± 10.0	-	
Gender categorical			
Units: Subjects			
Female	29	29	
Male	9	9	
Not recorded	0	0	
EDSS AT BASELINE			
Expanded Disability Status Scale			
Units: Subjects			
EDSS score	38	38	

Subject analysis sets

Subject analysis set title	Baseline (months -3 to 0)
Subject analysis set type	Per protocol

Subject analysis set description:

Baseline (months -3 to 0)

Subject analysis set title	Treatment (months 5-8)

Subject analysis set type	Per protocol

Subject analysis set description:

Treatment (months 5-8)

Reporting group values	Baseline (months -3 to 0)	Treatment (months 5-8)	
Number of subjects	28	28	
Age categorical			
Eligible patients were male or female between the ages of 18 and 55.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	28	28	
From 65-84 years	0	0	
85 years and over	0	0	
Not recorded	0	0	
Age continuous			
Units: years			
median	38.0	38.0	
standard deviation	± 10.5	± 10.5	
Gender categorical			
Units: Subjects			
Female			
Male			
Not recorded			
EDSS AT BASELINE			
Expanded Disability Status Scale			
Units: Subjects			
EDSS score			

End points

End points reporting groups

Reporting group title	Single Arm
Reporting group description:	
We performed an investigator-initiated, bicentric phase IIa, open-label, baseline-totreatment pilot study with an oral SFE in patients with RRMS. After a 4-month baseline observation phase, patients were treated for 8 months with an option to extend treatment for up to 36 months. The primary outcome measures were the number and volume of contrast-enhancing lesions (CEL) measured in MRI during the 4-month treatment period compared with the 4-month baseline period. Eighty patients were screened at two centres, 38 patients were included in the trial, 28 completed the 8-month treatment period and 18 of these participated in the extension period.	
Subject analysis set title	Baseline (months -3 to 0)
Subject analysis set type	Per protocol
Subject analysis set description:	
Baseline (months -3 to 0)	
Subject analysis set title	Treatment (months 5-8)
Subject analysis set type	Per protocol
Subject analysis set description:	
Treatment (months 5-8)	

Primary: Number of total Gadolinium-enhancing lesions

End point title	Number of total Gadolinium-enhancing lesions
End point description:	
End point type	Primary
End point timeframe:	
Baseline (Months -3 to 0) versus Treatment (months 5 to 8)	

End point values	Single Arm	Baseline (months -3 to 0)	Treatment (months 5-8)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	28[1]	28	28	
Units: number				
median (inter-quartile range (Q1-Q3))	-0.625 (-1.25 to -0.50)	1.00 (0.75 to 3.38)	0.50 (0.00 to 1.13)	

Notes:

[1] - per-protocol cohort (n=28)

Statistical analyses

Statistical analysis title	MRI outcomes PP
Comparison groups	Single Arm v Baseline (months -3 to 0) v Treatment (months 5-8)

Number of subjects included in analysis	84
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided

Primary: Volume of total enhancing lesions (new and persisting)

End point title	Volume of total enhancing lesions (new and persisting)

End point description:

End point type	Primary

End point timeframe:

baseline (months -3 to 0) versus treatment (months 5-8)

End point values	Single Arm	Baseline (months -3 to 0)	Treatment (months 5-8)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	28[2]	28	28	
Units: mm^3				
median (inter-quartile range (Q1-Q3))	-829.0 (-2188 to -184)	1753.5 (553.0 to 4974.5)	185.00 (0.00 to 1450.00)	

Notes:

[2] - per-protocol cohort

Statistical analyses

Statistical analysis title	MRI outcomes PP
Comparison groups	Single Arm v Baseline (months -3 to 0) v Treatment (months 5-8)
Number of subjects included in analysis	84
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.0481
Method	t-test, 2-sided

Primary: Volume of new enhancing lesions

End point title	Volume of new enhancing lesions

End point description:

End point type	Primary

End point timeframe:

baseline (months -3 to 0) versus treatment (months 5 to 8)

End point values	Single Arm	Baseline (months -3 to 0)	Treatment (months 5-8)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	28[3]	28	28	
Units: mm^3				
median (inter-quartile range (Q1-Q3))	-611.0 (-1094 to -92)	1087.00 (407.50 to 3343.00)	92.50 (0.00 to 725.00)	

Notes:

[3] - per-protocol cohort

Statistical analyses

Statistical analysis title	MRI outcomes PP
Comparison groups	Single Arm v Treatment (months 5-8) v Baseline (months -3 to 0)
Number of subjects included in analysis	84
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.0243
Method	t-test, 2-sided

Secondary: Number of new Gadolinium-enhancing lesions

End point title	Number of new Gadolinium-enhancing lesions

End point description:

Number of new or enlarging gadolinium-enhancing lesions in cerebral MRI

End point type	Secondary

End point timeframe:

Baseline (Months -3 to 0) versus Treatment (months 5 to 8)

End point values	Single Arm	Baseline (months -3 to 0)	Treatment (months 5-8)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	28[4]	28	28	
Units: number				
median (inter-quartile range (Q1-Q3))	-0.625 (-1.25 to -0.50)	0.88 (0.63 to 2.63)	0.25 (0.00 to 0.75)	

Notes:

[4] - per-protocol cohort

Statistical analyses

Statistical analysis title	MRI outcomes PP
Comparison groups	Single Arm v Baseline (months -3 to 0) v Treatment (months 5-8)
Number of subjects included in analysis	84
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided

Secondary: Number of new T2 lesions

End point title	Number of new T2 lesions

End point description:

End point type	Secondary

End point timeframe:

Baseline (Months -3 to 0) versus Treatment (months 5 to 8)

End point values	Single Arm	Baseline (months -3 to 0)	Treatment (months 5-8)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	28[5]	28	28	
Units: number				
median (inter-quartile range (Q1-Q3))	-6.50 (-10.25 to -4.00)	7.50 (4.88 to 12.88)	0.25 (0.00 to 0.75)	

Notes:

[5] - per-protocol cohort

Statistical analyses

Statistical analysis title	MRI outcomes PP
Comparison groups	Single Arm v Baseline (months -3 to 0) v Treatment (months 5-8)
Number of subjects included in analysis	84
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided

Secondary: Change in volume of T2 lesions

End point title	Change in volume of T2 lesions

End point description:

End point type	Secondary

End point timeframe:
baseline (months -3 to 0) versus treatment (months 5 to 8)

End point values	Single Arm	Baseline (months -3 to 0)	Treatment (months 5-8)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	28[6]	28	28	
Units: mm^3				
median (inter-quartile range (Q1-Q3))	-34.5 (-582 to 435)	264.50 (-1048.50 to 1304.00)	301.50 (-123.50 to 1045.00)	

Notes:
[6] - per-protocol cohort

Statistical analyses

Statistical analysis title	MRI outcomes PP
Comparison groups	Single Arm v Baseline (months -3 to 0) v Treatment (months 5-8)
Number of subjects included in analysis	84
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.9118
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline till end of trial for each patient

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	SFE treated patients

Reporting group description:

all patients included in the trial who participated in the treatment phase (even if only for hours or days); so anyone who has been exposed is reported here.

Serious adverse events	SFE treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 38 (10.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Broken ankle	Additional description: Broken ankle after accidental fall after 27 months of SFE intake		
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture	Additional description: Tibia fracture during sports		
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Lupus vasculitis	Additional description: Newly diagnosed Lupus erythematodes after 25 months of SFE intake		
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal fissure	Additional description: need for emergency proctological procedure after diarrhea (infectios, had been acquired abroad in Asia)		

subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SFE treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 38 (89.47%)		
Gastrointestinal disorders			
diarrhea, gastric pain, stomache ache			
subjects affected / exposed	32 / 38 (84.21%)		
occurrences (all)	32		
Infections and infestations			
common cold			
subjects affected / exposed	26 / 38 (68.42%)		
occurrences (all)	26		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2015	substancial amendment and new patient information (due to information about 2 cases of rheumatic disease in the trial and further information on estragole)

Notes:

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.

no placebo cohort; this was only a pilot trial using a baseline-to-treatment design

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29248894