



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 frankincense 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 occurred 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-to-treatment 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 erythematoses 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 (infectious, 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, stomach 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 | substantial 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>