Zusammenfassende Ergebnisberichte/Schlussberichte für IIT	7.3.10 Anlage 02 Stand: 20.01.2018

Name of Sponsor/Company: Sponsor: UKE	Individual Study Table Referring to page 61 of the Study Protocol Version 2.6 Internal Protocol Number: inims-003 EudraCT Number: 2009-014724-32	*(For Competent Authority only)*
Name of Finished Product: BOSWELAN		
Name of Active Ingredient: Boswellic acid		

Title of Study	**S**AFETY, TOLERABILITY AND MECHANISM OF **A**CTION OF **B**OSWELLIC **A**CIDS (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
Principal Investigator	Prof. Dr. Christoph Heesen
Study centre(s)	Hamburg (INIMS) und Berlin (NeuroCure Research Centre, Charité)
Publication (reference)	Stürner KH, Stellmann JP, Dörr J, Paul F, Friede T, Schammler S, Reinhardt S, Gelissen S, Weissflog G, Faizy T, Werz O, Fleischer S, Vaas LAI, Herrmann F, Pless O, Martin R and Heesen C: A Standardized Frankincense Extract Reduces Disease Activity in Relapsing-Remitting Multiple Sclerosis (The SABA phase IIa trial) J Neurol Neurosurg Psychiatry 2018 Apr;89(4):330-338. doi: 10.1136/jnnp-2017-317101. Epub 2017 Dec 16.
Studied period (years):	Date of first enrolment: 02nd Sep 2011
	Date of last completed: 07th March 2017
Phase of development	Phase IIa (pilot trial)
Objectives	To investigate whether oral administration of a standardized frankincense extract (SFE) is safe and reduces disease activity in patients with relapsing-remitting multiple sclerosis (RRMS).
Methodology	Pilot trial using a frequent MRI baseline-to-treatment-design

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Number of patients (planned and analysed)	planned patients n = 30; included n = 38 patients; analysed n = 28 patients	
Indication and main in- and exclusion criteria	- <u>Inclusion criteria:</u> - Aged 18 to 65 years - Females and males (as no specific gender-related differences are expected, no specific gender distribution is planned. See GCP-V § 7 (2) Nr. 12) - Subjects with a clinically isolated syndrome (high risk of conversion to MS) as well as subjects with clinically definite relapsing-remitting MS according to published criteria (Polman *et al.*, 2011) - Subject is able to give informed consent - Signed informed consent - EDSS score between 0.0 and 5.5. - Disease is clinically stable, i.e. without relapse and patient not having received steroids within 30 days prior to inclusion - Patients have either failed to respond to standard treatment (interferon beta, glatiramer acetate) by clinical measures, or were not eligible for any of the available standard treatments, or chose not to start or continue with any of these treatments NOTE: The decision not to start or not to continue with any of the standard treatments has to be made by the patient after discussion with an independent neurologist not involved in this study, and has to be signed in the informed consent. - <u>Eligibility Criteria for Initiating Therapy</u> - To be eligible to proceed to the treatment phase of the study (Stage 1-4), subjects must have an average of at least 0.5 Gd-enhancing lesions per month over the four-month pre-treatment baseline period. - Subjects must not have had a relapse during the 30 days before initiation of treatment. If a relapse occurs during the last 30 days of the pre-treatment baseline period and eligibility MRI criteria are fulfilled, treatment begin (day 1) is delayed at least until treatment starts not earlier than 30 days after the relapse and not earlier than 60 days in case i.v. corticosteroids had been given.	

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Indication and main in- and exclusion criteria (continued)	- <u>Exclusion Criteria</u> - The results of blood tests exceeding any of the limits defined below will necessitate exclusion from the study: - ALT (SGPT) or AST (SGOT) > three times the upper limit of normal - Total white blood cell count < 3,000mm^{-3} - Platelet count < 85,000mm^{-3} - Creatinine > 132.63µmol L^{-1} - Serological evidence of active hepatitis B or C infection, or other chronic liver disease - Positive pregnancy test, or on-going breast-feeding - Nausea and/or vomiting as a frequent complaint - History or signs of immunodeficiency - Similar clinical neurological symptoms caused by other diseases (e.g. syphilis, borreliosis, collagenosis or vasculitis) - Concurrent, clinically significant (as determined by the investigator) cardiac, immunological, pulmonary, neurological, renal, and/or other major disorders - History of alcohol or drug abuse within the five years prior to enrolment - Female subjects who are not post-menopausal or surgically sterile, or who are not using a highly effective method of birth control. Highly effective is defined as having a failure rate of <1%. Written documentation that the subject is post-menopausal or surgically sterile must be presented prior to study begin - Unwillingness or inability to comply with the requirements of this protocol, including the presence of any condition (physical, mental, or social) that is likely to interfere with the subject's returning for follow-up visits on schedule - Previous participation in this study - Participation in other pharmaceutical trials during this study or during the three months before - Patients hospitalised due to juridical or legal regulation - Known hypersensitivity to BA - Known contraindications for MRI examinations including hypersensitivity to gadolinium, severe renal insufficiency, a mechanical heart valve or any kind of metallic implants - Patients with difficulties in swallowing up to 12 capsules per day should not be recruited for screening.	

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	- - Treatment history If prior treatment had been received, the subject must have been off treatment for the required period prior to first investigational drug dose (see Supplementary Table 2).	

Agent	Required time off the agent prior to trial drug administration
Glatiramer acetate (Copaxone™), Interferon beta (Betaferon™, Avonex™, Rebif™)	12 weeks
IV Ig, azathioprine (Imurek™), methotrexate, cyclophosphamide (Cytoxan™), mitoxantrone, plasma exchange, cyclosporine, oral myelin, cladribine, natalizumab, and other immunosuppressive treatments	24 weeks
Corticosteroids, ACTH	8 weeks

Test product, dose and mode of administration, batch number	Boswelan BSR001, 400mg soft gel capsules; BATCH BSR001 "neu"
Duration of treatment	Core study: 8 months Extension of the study: up to maximal 36 month
Reference therapy, dose and mode of administration, batch number	none
Criteria for evaluation	Safety: Number of total adverse events; number of adverse events during screening phase (320 patient months) versus number of adverse events during treatment phase (706 patient months) Safety laboratory parameters (no significant changes)

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	Efficacy: **Primary outcome measure** • Number and volume of total Gd-enhancing lesions **Secondary outcome measures** • Number of persisting Gd-enhancing lesions • Number of new active lesions (new Gd-enhancing lesions +new or enlarging non-enhancing T2 lesions) • Number of new Gd-enhancing lesions evolving into persistent hypointense lesions • T2 lesion volume • T1 hypointense lesion volume • Number of persisting T1 lesions • Brain atrophy (brain parenchymal fraction) • Magnetization Transfer Ratio (MTR) • Relapse rate **Tertiary outcome measures** • MRS (multi-voxel magnetic resonance spectroscopy) • Neurological measures: Expanded disability status scale (EDSS), SCRIPPS neurological rating scale (SNRS), MS functional composite (MSFC) consisting of 9-HP-test (Nine-Hole-Peg Test), timed 25 foot walk, paced auditory serial addition test (PASAT), Depression scale (Hospital Anxiety and Depression Scale) and a fatigue scale (Fatigue severity scale according to Flachenecker et al.), Hamburg Relapse Assessement Scale (HARAS) • Immunological parameters • Biomarker assessment (Cathepsin G activity and PGE_2 levels) •
Statistical methods	Based on analyses of a natural history cohort studied with monthly MRIs for a minimum of one year, a baseline-to-treatment designed trial incorporating 4 baseline MRIs and 4 treatment MRIs will require 30 patients to detect a 40% reduction in Gd-enhancing lesions with an alpha of 0.05 (one-sided). The primary and secondary endpoints were summarised as medians

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	with interquartile ranges (IQR). Changes from baseline to follow-up are described by their medians with 95% confidence intervals and tested for deviation from 0 using the Wilcoxon signed-rank test as specified in the study protocol. To determine the sensitivity of the results to missing data, changes in outcome from baseline to follow-up were imputed as 0 ("intention-to-treat analysis"). This corresponds to a baseline-carried-forward analysis, which was considered a conservative assessment. Secondary and tertiary endpoints were analyzed in a similar manner. Relapses were analyzed using a Poisson regression model with adjustment for overdispersion.	
SUMMARY-CONCLUSIONS		
Efficacy results	The primary outcome reached statistical significance for the total number of contrast-enhancing lesions (CELs) as well as the volume of CELs (Table 2 and Figure 2A). The total number of CELs decreased significantly from a baseline median of 1.0 (IQR 0.75-3.38) to 0.5 (IQR 0.00-1.13) during the treatment period (months 5 to 8; $p < 0.0001$). The volume of the lesions decreased significantly from a median of 1753.5 mm^3 (IQR 553-4974.5 mm^3) during the baseline phase (Months -3-0) to 185 mm^3 (IQR (0.00-1450.00 mm^3; n = 28; p=0.0481). The intention-to-treat (ITT) analysis of the data also gave significant results. Both analyses showed more than 60% reduction of the total number of CELs between the baseline and treatment phase. Correspondingly, the number of new T2-lesions decreased significantly between baseline and treatment phase from 7.5 to 0.25 new T2-lesions per month. The effect on T2-lesion reduction was maintained throughout the extension period in those patients who chose to continue the study beyond month 8 of the trial. The change in T2-lesion volumes was not significantly different between baseline and treatment phase. In addition, we observed a modest loss of brain volume during the four baseline scans (PBVC -0.12, IQR -0.36-0.13%) while we observed a small increase for brain volume during treatment (PBVC 0.11, IQR -0.06-0.6%). This difference, albeit small, was highly significant (p=0.0081). The annualised relapse rate (ARR) decreased from 0.93 during the year before the start of treatment to 0.48 during the first year of treatment ($p = 0.0422$, Table 4). Clinical signs of disease activity remained absent beyond month 12 in patients continuing the study (Figure 3). Clinical endpoints are given in Table 4. EDSS and SNRS remained	

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	unchanged at month 8 compared to baseline. MSFC improved significantly between baseline (month 0) and months 8 and 12, respectively. SDMT improved significantly during the baseline phase, possibly due to a training effect. However, there was an additional significant improvement until month 8. PASAT improved significantly only at month 12 compared to baseline z-scores. Health-related quality improved at months 8 and 12, respectively.	
Safety results	Two hundred and twenty adverse events (AE) were reported during the treatment phase. These were generally mild or moderate (57.7% resp. 38.6% of all AEs, Table 3). The two most frequent AE entities were minor infections (n=72, 32.7%), of which the common cold accounted for about 60%, and gastrointestinal symptoms (n=38, 17.3%). The frequency of gastrointestinal AEs peaked during the first four weeks and decreased afterwards. Fifteen percent (n=6) of the patients reported recurrent mild gastrointestinal AEs throughout the exposure time. No patient discontinued the SFE due to gastrointestinal AEs. The four serious adverse events (SAEs) reported in our study were a fracture of the tibia after an accidental fall at month 7, an emergency minor proctologic in-patient treatment at month 20, hospital admission due to a newly diagnosed lupus erythematodes at month 25 and the fracture of both ankles after an accidental fall at month 27. Two AEs received special attention and were intensively discussed with the data safety monitoring board and authorities. One patient developed rheumatoid arthritis at month 12, and another lupus erythematodes at month 25 (see above). After the second rheumatologic AE was reported, we reanalysed the serum samples of all patients for antinuclear antibody titers, anti-CCP and rheumatoid factor, which had been either not detectable or unchanged during treatment (Supplementary Figure 3). Prospectively collected serum samples showed no changes in TNF-α levels. It is important to note that one patient was known to have rheumatoid arthritis before entering the trial and reported no changes of her rheumatologic symptoms throughout the entire 24-month treatment phase. General laboratory monitoring throughout the study showed no significant changes in any patient.	
Conclusion	The oral SFE BOSWELAN was safe, tolerated well and exhibited beneficial effects on RRMS disease activity warranting further investigation in a controlled phase IIb or III trial.	

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Date of Report:	20.01.2018	

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S) OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE:

STUDY AUTHOR(S):

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

INVESTIGATOR OR SPONSORS RESPONSIBLE MEDICAL OFFICER

SIGNATURE(S)

AFFILIATION: INIMS UKE Prof. C. Heesen

DATE: 15/11/20

A: Study design of the SABA trial; B: Study recruitment, drop-outs and patients analysed

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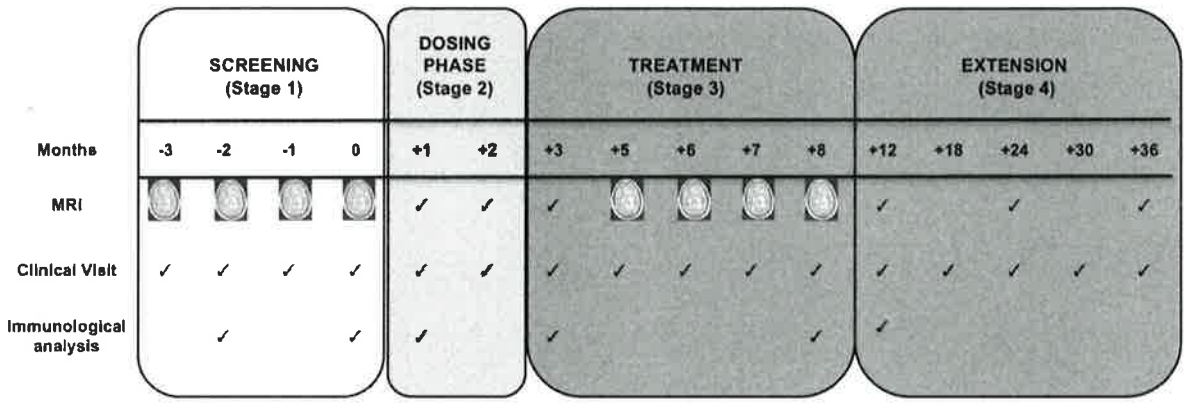

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