

**Clinical trial results:****Effects of Wobenzym® plus in healthy, sportive people after eccentric exercise - a randomized, two-stage, double-blind, placebo-controlled cross-over trial****Summary**

EudraCT number	2012-005003-40
Trial protocol	DE
Global end of trial date	13 August 2014

Results information

Result version number	v1 (current)
This version publication date	10 July 2016
First version publication date	10 July 2016
Summary attachment (see zip file)	Synopsis (Results.pdf)

Trial information**Trial identification**

Sponsor protocol code	BTS651/12
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01845558
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioTesys GmbH
Sponsor organisation address	Schelztorstraße 54-56, Esslingen, Germany, 73728
Public contact	Clinical Trial Information , BioTeSys GmbH, 0049 71131057147, c.reule@biotesys.de
Scientific contact	Clinical Trial Information , BioTeSys GmbH, 0049 71131057147, c.reule@biotesys.de
Sponsor organisation name	Mucos Pharma GmbH & Co. KG
Sponsor organisation address	Bajuwarenring 5, Oberhaching, Germany, 82041
Public contact	MUCOS Pharma GmbH & Co. KG , MUCOS Pharma GmbH & Co. KG, +49 89 638372400, info@mucos.de
Scientific contact	MUCOS Pharma GmbH & Co. KG , MUCOS Pharma GmbH & Co. KG, Dr. Stefanie Rau, +49 89 638372404, s.rau@mucos.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	No

1901/2006 apply to this trial?

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 August 2014
Global end of trial reached?	Yes
Global end of trial date	13 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the current study is to investigate the therapeutic effect of Wobenzym® plus, an anti-inflammatory drug containing proteolytic enzymes, on exercise induced muscle damage (eiMD) and recovery time in male amateur sportsmen with medium proficiency level compared to placebo. As primary objective, the reduction of maximal isokinetic strength after exercise in the stronger leg and subjective pain after exercise are assumed to be the most promising parameters. Therefore these parameters are combined in a multidimensional approach summarizing different parameters and points of time to strengthen the power. The period after the stress test will be separately calculated for the acute phase (3h, 6h) and the recovery phase (24h-48h).

Protection of trial subjects:

Informed consent after explanation of aims, methods, benefits and potential hazards. Screening visit to exclude patient with diseases, allergic reactions ect (see exclusion criteria). Every volunteer is free to refuse to participate in the study or withdraw their consent at any time and for any reason without incurring any penalty. Study site with Emergency Management Plan and Equipment.

Background therapy:

Not applicable.

Evidence for comparator:

No Comparator used (Placebo-controlled trial).

Actual start date of recruitment	01 February 2013
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: 74
Worldwide total number of subjects	74
EEA total number of subjects	74

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)	74
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Monocenter, double-blind, randomized, placebo-controlled, crossover study (stage I) designed to assess acute phase and recovery after eccentric stress test.

Stage II: parallel group design.

Pre-assignment

Screening details:

Stage I cross-over design:

Group 1 (N=15) Wobenzym plus from day 1 to day 7 and placebo from day 29 to day 35

Group 2 (N=15) Placebo from day 1 to day 7 and Wobenzym plus from day 29 to day 35

Wash-out phase of 21 days.

Stage II: parallel design, 2x22 randomized to Wobenzym plus or Placebo

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, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo Arm: Stage 1 Crossover Design (15) + stage II parallel design (22)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Four tablets three times per day. Medication will be taken 30 minutes before each meal on an empty stomach with one glass of water.

Arm title	Verum
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Arm description:

Active comparator Wobenzym plus

Arm type	Active comparator
Investigational medicinal product name	Wobenzym plus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Four tablets three times per day. Medication will be taken 30 minutes before each meal on an empty stomach with one glass of water.

Number of subjects in period 1	Placebo	Verum
Started	37	37
Completed	33	34
Not completed	4	3
Consent withdrawn by subject	1	-
Protocol deviation	1	3
Not treated	2	-

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	74	74	
Age categorical			
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)	74	74	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	31.6		
standard deviation	± 9.3	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	74	74	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo Arm: Stage 1 Crossover Design (15) + stage II parallel design (22)	
Reporting group title	Verum
Reporting group description:	
Active comparator Wobenzym plus	

Primary: Acute phase Primary endpoints

End point title	Acute phase Primary endpoints
End point description:	
Multidimensional: Reduction of maximal concentric strenght after stress test + pressure induced pain (Algometry) in the middle of the muscle belly of m. rectus femoris	
End point type	Primary
End point timeframe:	
Acute phase: 3 h and 6 h post stress test	

End point values	Placebo	Verum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: NM + NM/cm2				
number (not applicable)	33	34		

Statistical analyses

Statistical analysis title	Multivariate test Stage 1
Statistical analysis description:	
Multivariate test of first vonfirmatory hypothesis of stage 1 (multidimensional ensemble of peak torque and pressure induced pain at 3h and 6h)	
Comparison groups	Placebo v Verum
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0332
Method	Wei-Lachin
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	0.4922

Notes:

[1] - one-sided, directional test for superiority, Wei-Lachin procedure

Statistical analysis title	Mann-Whitney stage 1
Statistical analysis description: Associated effect size Mann-Whitney for hypothesis stage 1 acute phase	
Comparison groups	Placebo v Verum
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6153
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.6153
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.4922

Statistical analysis title	Multivariate test Stage 2
Statistical analysis description: multidimensional ensemble of peak torque and pressure induced pain at 3h and 6 hours (acute phase)	
Comparison groups	Placebo v Verum
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8596
Method	Wei-Lachin
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	0.325

Statistical analysis title	Mann-Whitney stage 2
Comparison groups	Placebo v Verum
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4379
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.4379

Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.325

Primary: Recovery phase: Primary endpoint

End point title	Recovery phase: Primary endpoint
End point description: Multidimensional: Reduction of maximal concentric strenght after stress test + pressure induced pain (Algometry) in the middle of the muscle belly of m. rectus femoris	
End point type	Primary
End point timeframe: 24 h and 48 h after stress test	

End point values	Placebo	Verum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: NM / NM/cm2				
number (not applicable)	33	34		

Statistical analyses

Statistical analysis title	Multivariate test Stage 1
Statistical analysis description: multidimensional ensemble of peak torque and pressure induced pain at 24h and 48h	
Comparison groups	Placebo v Verum
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0934
Method	Wei-Lachin
Parameter estimate	Wei-Lachin
Point estimate	0.0934
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	0.4556

Statistical analysis title	Mann-Whitney stage 1
Comparison groups	Placebo v Verum

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5917
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.5917
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.4556

Statistical analysis title	Multivariate test Stage 2
Statistical analysis description: multidimensional ensemble of peak torque and pressure induced pain at 24h and 48h	
Comparison groups	Placebo v Verum
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8783
Method	Wei-Lachin
Parameter estimate	Wei-Lachin
Point estimate	0.8783
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.3035

Statistical analysis title	Mann-Whitney Stage 2
Comparison groups	Placebo v Verum
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4267
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.4267
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.3035

Secondary: Secondary endpoints: Biomarkers	
End point title	Secondary endpoints: Biomarkers

End point description:

IL-6, Prostaglandin E metabolite derived from cyclooxygenase 2, Creatin kinase, LDH, Lactate, NK-cell-test, Redox-Status (TOS/TAS)

End point type Secondary

End point timeframe:

pre, 0h, 10 min, 30 min, 3h, 6h, 24h - depending on marker

End point values	Placebo	Verum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: not applicable				
number (not applicable)	33	34		

Statistical analyses

Statistical analysis title	Multivariate test pooled biomarkers
Comparison groups	Placebo v Verum
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [2]
Method	Wei-Lachin
Parameter estimate	Wei-Lachin
Point estimate	0.0001
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	0.5407

Notes:

[2] - Combined Stages 1 and 2

Statistical analysis title	Mann-Whitney pooled Biomarkers
Comparison groups	Placebo v Verum
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5847
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.5847
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.5407

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At each visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Stage 1
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Reporting group description: -

Reporting group title	Stage 2
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Reporting group description: -

Serious adverse events	Stage 1	Stage 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	0 / 44 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Stage 1	Stage 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 28 (46.43%)	1 / 44 (2.27%)	
Surgical and medical procedures			
Wisdom teeth extraction	Additional description: Assessed as Not Related		
subjects affected / exposed	0 / 28 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache	Additional description: All assessed as Not Related		
subjects affected / exposed	5 / 28 (17.86%)	0 / 44 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Diarrhea	Additional description: Assessed as Possible		
subjects affected / exposed	1 / 28 (3.57%)	0 / 44 (0.00%)	
occurrences (all)	1	0	

Respiratory, thoracic and mediastinal disorders			
Sore throat	Additional description: Assessed as Not Related		
subjects affected / exposed	2 / 28 (7.14%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Tonsillitis	Additional description: Assessed as Not Related		
subjects affected / exposed	1 / 28 (3.57%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Skin eruption	Additional description: Assessed as Unlikely		
subjects affected / exposed	2 / 28 (7.14%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Rash	Additional description: Acne-like rash, Assessed as Possible		
subjects affected / exposed	0 / 28 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscle strain	Additional description: Assessed as Not Related		
subjects affected / exposed	1 / 28 (3.57%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Disruption of Clavicle	Additional description: Assessed as Not Related		
subjects affected / exposed	1 / 28 (3.57%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Effusion	Additional description: Assessed as Not Related		
subjects affected / exposed	1 / 28 (3.57%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Coryza	Additional description: Assessed as Not Related		
subjects affected / exposed	1 / 28 (3.57%)	0 / 44 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2014	Within the framework of the pre-planned two-stage procedure according to Bauer-Köhne the following decision was made: - The study will be continued with Stage II. - Due to statistically significant carryover effects the stage II of the trial will be based on a simple parallel group scheme with one phase only (no crossover design). - The measurement of movement induced pain will be skipped due to zero dominated data in stage I. - The recalculated total sample size for stage II is 2 x 22 patients (sample size reassessment according to protocol and final SAP, one phase, no crossover design in stage II). - This decision is established within the framework of the adaptive design features of the two-stage procedure according to Bauer-Köhne and based on the definitions of the protocol and of the final SAP of stage I. - Stage I results and rationale for stage II decision are kept confidential as defined in the protocol (section 7.11) and in the final statistical analysis plan (SAP Stage I Version Final 1.0 from January 20th, 2014, Section 5.4.3).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported