



Clinical trial results:

Reduction of post-traumatic systemic inflammatory response by Phlogenzym® using total hip replacement as a model.

Summary

EudraCT number	2016-003078-41
Trial protocol	CZ
Global end of trial date	15 October 2020

Results information

Result version number	v1 (current)
This version publication date	28 August 2022
First version publication date	28 August 2022

Trial information

Trial identification

Sponsor protocol code	MUC-2/16
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	MUCOS Pharma CZ
Sponsor organisation address	Uhřetěveská 448, Průhonice, Czechia, 25243
Public contact	Clinical department, MUCOS Pharma CZ, +420 267 750 003, akocar@mucos.cz
Scientific contact	Clinical department, MUCOS Pharma CZ, +420 267 750 003, akocar@mucos.cz

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	23 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2020
Global end of trial reached?	Yes
Global end of trial date	15 October 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to explore the validity and clinical feasibility of methods for assessment of perioperative efficacy of Phlogenzym in terms of symptoms of systemic (CRP, hemocoagulation) and local inflammation and short- and mid-term course of rehabilitation.

Protection of trial subjects:

The subjects were closely monitored during hospitalization and rehabilitation period via physical and laboratory examinations.

Occurrence of adverse events was monitored and evaluated at each study visit.

The subjects were provided with contact details for emergent situations.

Background therapy:

Planned concomitant medication per protocol involves:

- rivaroxaban (Xarelto®) as prevention of thromboembolism
- standard analgesics medication
- antibiotics i.v. or s.c. to cover the postoperative inflammatory complications per local standard.
- Rescue analgesic medication (its consumption evaluated as an efficacy variable)

Evidence for comparator:

An identically appearing placebo was used as comparator

Actual start date of recruitment	19 March 2019
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	Czechia: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	12
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study subjects were recruited on orthopedics department in Czech republic from patients considered for planned total hip replacement. The recruitment started on 19MAR2019 and was finished prematurely due to the COVID-19 epidemic on 15OCT2020.

Pre-assignment

Screening details:

40 patients with primary diagnosis of Non-Inflammatory Degenerative Joint Disease, candidates for total hip replacement, 20 in each treatment group and stratified by gender in 1:1 ratio, were planned to be enrolled to the study

Period 1

Period 1 title	Pre-operation phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

The random numbers were generated using SAS in constant block size of 4 subjects; Verum/placebo 1:1.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phlogenzym

Arm description:

Subjects using active IMP Phlogenzym in a double-blind manner

Arm type	registered drug
Investigational medicinal product name	Phlogenzym
Investigational medicinal product code	marketing authorization No. 87/084/95-C
Other name	Composition: Trypsinum 48 mg (corresponds to 24 µkat), Bromelaina 90 mg (corresponds to 450 F.I.P.-u.), and Rutosidum trihydricum 100 mg and additional compound
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing of Phlogenzym® or Placebo was fixed-changing according to the following schedule:

- preoperative day -4 to -2: 3 tbl b.i.d. (Σ = 18 tbl);
- preoperative Day - 1: 3 tbl in the morning (Σ = 3 tbl);
- operation day: no dosing;
- postoperative Day 1 - 7: 6 tbl b.i.d. (Σ = 84 tbl);
- postoperative Day 8 - 42: 5 tbl b.i.d. (Σ = 350 tbl).

A total dose of Phlogenzym® / placebo per study is 455 tablets provided all visits take place exactly as scheduled.

Arm title	Placebo
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Arm description:

Subjects treated with placebo

Arm type	Placebo
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Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing of Phlogenzym® or Placebo was fixed-changing according to the following schedule:

- preoperative day -4 to -2: 3 tbl b.i.d. (Σ = 18 tbl);
- preoperative Day - 1: 3 tbl in the morning (Σ = 3 tbl);
- operation day: no dosing;
- postoperative Day 1 - 7: 6 tbl b.i.d. (Σ = 84 tbl);
- postoperative Day 8 - 42: 5 tbl b.i.d. (Σ = 350 tbl).

A total dose of Phlogenzym® / placebo per study is 455 tablets provided all visits take place exactly as scheduled.

Number of subjects in period 1	Phlogenzym	Placebo
Started	16	18
Completed	15	18
Not completed	1	0
Adverse event, non-fatal	1	-

Period 2

Period 2 title	Post-operation phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

The random numbers were generated using SAS in constant block size of 4 subjects; Verum/placebo 1:1

Arms

Are arms mutually exclusive?	Yes
Arm title	Phlogenzym

Arm description:

Subjects using active IMP Phlogenzym in a double-blind manner

Arm type	registered drug
Investigational medicinal product name	Phlogenzym
Investigational medicinal product code	marketing authorization No. 87/084/95-C
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing of Phlogenzym® or Placebo was fixed-changing according to the following schedule:

- preoperative day -4 to -2: 3 tbl b.i.d. (Σ = 18 tbl);
- preoperative Day - 1: 3 tbl in the morning (Σ = 3 tbl);
- operation day: no dosing;

- postoperative Day 1 - 7: 6 tbl b.i.d. (Σ = 84 tbl);
- postoperative Day 8 - 42: 5 tbl b.i.d. (Σ = 350 tbl).

A total dose of Phlogenzym® / placebo per study is 455 tablets provided all visits take place exactly as scheduled.

Arm title	Placebo
Arm description:	
Subjects using placebo in a double-blind manner	
Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing of Phlogenzym® or Placebo was fixed-changing according to the following schedule:

- preoperative day -4 to -2: 3 tbl b.i.d. (Σ = 18 tbl);
- preoperative Day - 1: 3 tbl in the morning (Σ = 3 tbl);
- operation day: no dosing;
- postoperative Day 1 - 7: 6 tbl b.i.d. (Σ = 84 tbl);
- postoperative Day 8 - 42: 5 tbl b.i.d. (Σ = 350 tbl).

A total dose of Phlogenzym® / placebo per study is 455 tablets provided all visits take place exactly as scheduled.

Number of subjects in period 2	Phlogenzym	Placebo
Started	15	18
Completed	10	18
Not completed	5	0
Consent withdrawn by subject	2	-
Adverse event, non-fatal	3	-

Baseline characteristics

Reporting groups

Reporting group title	Phlogenzym
Reporting group description:	
Subjects using active IMP Phlogenzym in a double-blind manner	
Reporting group title	Placebo
Reporting group description:	
Subjects treated with placebo	

Reporting group values	Phlogenzym	Placebo	Total
Number of subjects	16	18	34
Age categorical			
Units: Subjects			
Adults (18-64 years)	4	8	12
From 65-84 years	12	10	22
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	9	10	19
Male	7	8	15

Subject analysis sets

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects without major protocol deviation	

Reporting group values	Per Protocol		
Number of subjects	33		
Age categorical			
Units: Subjects			
Adults (18-64 years)	12		
From 65-84 years	21		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	19		
Male	14		

End points

End points reporting groups

Reporting group title	Phlogenzym
Reporting group description:	
Subjects using active IMP Phlogenzym in a double-blind manner	
Reporting group title	Placebo
Reporting group description:	
Subjects treated with placebo	
Reporting group title	Phlogenzym
Reporting group description:	
Subjects using active IMP Phlogenzym in a double-blind manner	
Reporting group title	Placebo
Reporting group description:	
Subjects using placebo in a double-blind manner	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects without major protocol deviation	

Primary: 2- Local pain at rest (VAS)

End point title	2- Local pain at rest (VAS)
End point description:	
Self-assessment of pain on 100 mm scale; The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.	
End point type	Primary
End point timeframe:	
Day 1 to Day 7 following operation, average of the morning + evening assessment.	

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: cm				
arithmetic mean (standard deviation)				
V2_Day1	2.8 (± 1.5)	2.0 (± 1.6)		
V3_Day2	2.2 (± 1.9)	2.7 (± 1.7)		
V4_Day3	2.0 (± 1.2)	3.0 (± 1.7)		
V5_Day5	1.9 (± 1.5)	2.5 (± 1.9)		
V6_Day7	1.8 (± 1.7)	1.7 (± 1.4)		

Attachments (see zip file)	EP2/Endpoint 2_VAS.docx
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Statistical analyses

Statistical analysis title	Visual Analogue Scale (VAS)
Statistical analysis description: ANOVA with treatment as grouping variable and visit as repeating variable	
Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 ^[1]
Method	ANOVA

Notes:

[1] - Interaction of treatment vs. visit

No adjustment for multiplicity

Primary: 9- Local pain at rest (VAS), weekly morning+evening average assessments, Day 7 to Day 42

End point title	9- Local pain at rest (VAS), weekly morning+evening average assessments, Day 7 to Day 42
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End point description:

The average of the morning and evening assessment of pain on the 100 mm visual analogue scale, performed by patient

The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.

End point type	Primary
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End point timeframe:

Day 7 to Day 42 following operation

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: cm				
arithmetic mean (standard deviation)				
V6_Day 7	1.8 (± 1.7)	1.7 (± 1.4)		
V7_Day 14	1.0 (± 0.8)	0.8 (± 0.8)		
V8_Day 21	0.7 (± 0.7)	0.9 (± 1.1)		
V9_Day 28	0.3 (± 0.3)	0.5 (± 0.4)		
V10_Day 42	0.2 (± 0.2)	0.4 (± 0.6)		

Attachments (see zip file)	Endpoint 9_Local pain at rest/Endpoint 9_Local pain at rest
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Statistical analyses

Statistical analysis title	Local pain at rest (VAS)
Statistical analysis description: ANOVA with treatment as grouping variable and visit as repeating variable	
Comparison groups	Phlogenzym v Placebo

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.958
Method	ANOVA

Notes:

[2] - No interaction of treatment vs. visit

No adjustment for multiplicity

Other pre-specified: 1- CRP postoperative

End point title	1- CRP postoperative
End point description:	
CRP in serum	
End point type	Other pre-specified
End point timeframe:	
Day 1 to Day 7 following operation	

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: AUC				
arithmetic mean (standard deviation)	222 (± 84.6)	327.3 (± 165.9)		

Attachments (see zip file)	CRP in serum, Day 1 to Day 7 following operation/Endpoint 1.
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Statistical analyses

Statistical analysis title	CRP 7 days after operation
Statistical analysis description:	
Analysis of non-monotonous change	
Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034 ^[3]
Method	ANOVA

Notes:

[3] - No adjustment for multiplicity

Other pre-specified: 3- Redon Drain Discharge

End point title	3- Redon Drain Discharge
End point description:	
Discharge of drain in the operation wound	
The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable).	

End point type	Other pre-specified
End point timeframe:	
Day 1 to Day 7 following operation	

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: L.				
arithmetic mean (standard deviation)				
V2_D1	0.398 (± 0.231)	0.428 (± 0.214)		
V3_D2	0.178 (± 0.144)	0.181 (± 0.151)		
Cumulative Redon drain discharge	0.576 (± 0.290)	0.576 (± 0.609)		

Statistical analyses

Statistical analysis title	Redon Drain Discharge
Statistical analysis description:	
ANOVA with treatment as grouping variable and visit as repeating variable	
Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.723 ^[4]
Method	ANOVA

Notes:

[4] - No interaction of treatment vs. visit
No adjustment for multiplicity

Other pre-specified: 4- Thigh circumference on Day 1 to Day 7 following operation

End point title	4- Thigh circumference on Day 1 to Day 7 following operation
End point description:	
Thigh circumference measured by a flexible ruler The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.	
End point type	Other pre-specified
End point timeframe:	
Day 1 to Day 7 following operation	

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: cm				
arithmetic mean (standard deviation)				
V2_Day 1	44.3 (± 7)	48.9 (± 7)		
V3_Day 2	47 (± 5)	49.6 (± 5.8)		
V4_Day 3	47.4 (± 4.9)	50.1 (± 5.6)		
V5_Day 5	48 (± 4.4)	50.7 (± 6)		
V6_Day 7	48.2 (± 5.5)	50.9 (± 6.1)		

Attachments (see zip file)	EP4/Endpoint 4_Thigh circumference.docx
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Statistical analyses

Statistical analysis title	Thigh circumference on Day 1 to Day 7
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Statistical analysis description:

ANOVA with treatment as grouping variable and visit as repeating variable

Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.448 ^[5]
Method	ANOVA

Notes:

[5] - No interaction of treatment vs. visit
No adjustment for multiplicity

Other pre-specified: 5- Calf circumference on Day 1 to Day 7 following operation

End point title	5- Calf circumference on Day 1 to Day 7 following operation
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End point description:

Calf circumference measured by a flexible ruler.

The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.

End point type	Other pre-specified
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End point timeframe:

Day 1 to Day 7 following operation

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: cm				
arithmetic mean (standard deviation)				
V2_Day 1	35.8 (± 3.1)	37.6 (± 4.0)		
V3_Day 2	36.0 (± 3.7)	37.6 (± 3.9)		
V4_Day 3	36.1 (± 3.6)	37.7 (± 3.8)		

V5_Day 5	36.7 (± 4.2)	38.8 (± 4.0)		
V6_Day 7	36.9 (± 4.7)	38.7 (± 4.1)		

Attachments (see zip file)	EP5/Endpoint 5_Calf circumference.docx
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Statistical analyses

Statistical analysis title	Calf circumference on Day 1 to Day 7
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Statistical analysis description:

ANOVA with treatment as grouping variable and visit as repeating variable

Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.776 ^[6]
Method	ANOVA

Notes:

[6] - No interaction of treatment vs. visit
No adjustment for multiplicity

Other pre-specified: 6- Temperature in axilla

End point title	6- Temperature in axilla
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End point description:

Body temperature measured in axilla in the morning.

The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.

End point type	Other pre-specified
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End point timeframe:

Day 1 to Day 7 following operation

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: °C				
arithmetic mean (standard deviation)				
V2_Day 1	36.7 (± 0.3)	36.6 (± 0.2)		
V3_Day 2	36.6 (± 0.1)	36.7 (± 0.2)		
V4_Day 3	36.5 (± 0.2)	36.7 (± 0.3)		
V5_Day 5	36.5 (± 0.1)	36.6 (± 0.2)		
V6_Day 7	36.4 (± 0.1)	36.5 (± 0.2)		

Attachments (see zip file)	EP6/Endpoint 6_Temperature in axilla.docx
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Statistical analyses

Statistical analysis title	Temperature in axilla on Day 1 to Day 7
Statistical analysis description: ANOVA with treatment as grouping variable and visit as repeating variable	
Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.167 ^[7]
Method	ANOVA

Notes:

[7] - No interaction of treatment vs. visit; No adjustment for multiplicity

Other pre-specified: 7- Knee extension strength, Day 5 and Day 7 after operation

End point title	7- Knee extension strength, Day 5 and Day 7 after operation
End point description: Maximal isometric knee-extension force measured by means of a hand-held dynamometer The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.	
End point type	Other pre-specified
End point timeframe: Day 5 to and Day 7 following operation	

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	18		
Units: N*m*kg-1				
arithmetic mean (standard deviation)				
V5_D5	3.0 (± 1.1)	2.9 (± 1.0)		
V6_D7	3.5 (± 1.2)	3.1 (± 1.1)		

Attachments (see zip file)	Endpoint 7 Knee extension strenght/Endpoint 7_Knee
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Statistical analyses

Statistical analysis title	Knee extension strength, D5 and D7 after operation
Statistical analysis description: ANOVA with treatment as grouping variable and visit as repeating variable	
Comparison groups	Phlogenzym v Placebo

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.074
Method	ANOVA

Notes:

[8] - No interaction of treatment vs. visit

No adjustment for multiplicity

Other pre-specified: 8- Harris Hip Score, performance from Day 7 to Day 42

End point title	8- Harris Hip Score, performance from Day 7 to Day 42
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End point description:

Hip function questionnaire which includes items reflecting a patient's ability to perform normal daily activities and the goniometric assessments

The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.

End point type	Other pre-specified
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End point timeframe:

Day 7 to Day 42 following operation

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: score				
arithmetic mean (standard deviation)				
V1_screening	60.1 (± 12.7)	62.2 (± 15.5)		
V6_Day 7	56.0 (± 8.7)	54.3 (± 7.7)		
V7_Day 14	66.5 (± 14.4)	63.0 (± 10.5)		
V8_Day 21	78.1 (± 11.4)	73.7 (± 9.9)		
V9_Day 28	80.4 (± 9.5)	78.4 (± 7.3)		
V10_Day 42	84.6 (± 5.4)	84.1 (± 2.7)		

Attachments (see zip file)	Endpoint 8_Harris Hip Score/Endpoint 8_Harris Hip Score.docx
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Statistical analyses

Statistical analysis title	Harris Hip Score, performance from Day 7 to Day 42
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Statistical analysis description:

ANOVA with treatment as grouping variable and visit as repeating variable

Comparison groups	Phlogenzym v Placebo
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Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.297
Method	ANOVA

Notes:

[9] - No interaction of treatment vs. visit
No adjustment for multiplicity

Other pre-specified: 10- Knee Extension Strength of operated leg, weekly assessments, Day 7 to Day 42

End point title	10- Knee Extension Strength of operated leg, weekly assessments, Day 7 to Day 42
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End point description:

Maximal isometric knee-extension force measured by means of a hand-held dynamometer
The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.

End point type	Other pre-specified
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End point timeframe:

Day 7 to Day 42 following operation

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: Nm/kg				
arithmetic mean (standard deviation)				
V6_Day 7	199.7 (± 71.3)	186.6 (± 70.3)		
V7_Day 14	210.4 (± 69.8)	220.0 (± 76.7)		
V8_Day 21	248.6 (± 68.6)	251.5 (± 87.0)		
V0_Day 28	277.8 (± 93.0)	266.6 (± 98.0)		
V10_Day 42	298.5 (± 86.9)	284.1 (± 81.2)		

Attachments (see zip file)	Endpoint 10_Knee extension strength/Endpoint 10_Knee
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Statistical analyses

Statistical analysis title	Knee Extension Strength of operated leg, weekly as
Statistical analysis description:	
ANOVA with treatment as grouping variable and visit as repeating variable	
Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.074
Method	ANOVA

Notes:

[10] - No interaction of treatment vs. visit
No adjustment for multiplicity

Other pre-specified: 11- Performance in timed Up&Go Test (TUG)

End point title	11- Performance in timed Up&Go Test (TUG)
End point description: The time (in seconds) it takes the patients to rise from a chair as quickly and safely as possible, walk 3 m to a line drawn on the floor, and return to the chair. The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.	
End point type	Other pre-specified
End point timeframe: Day 7 to Day 42 following operation	

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: seconds				
arithmetic mean (standard deviation)				
V6_Day 7	22.9 (± 6.2)	23.0 (± 7.5)		
V7_Day 14	14.6 (± 6.7)	18.7 (± 6.7)		
V8_Day 21	12.4 (± 4.5)	15.7 (± 4.5)		
V9_Day 28	12.3 (± 5.6)	14.0 (± 5.6)		
V10_Day 42	9.7 (± 3.4)	11.9 (± 3.4)		

Attachments (see zip file)	Endpoint 11_Performance in timed/Endpoint 11_Performance in
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Statistical analyses

Statistical analysis title	Performance in timed Up&Go Test (TUG)
Statistical analysis description: ANOVA with treatment as grouping variable and visit as repeating variable	
Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.772 ^[12]
Method	ANOVA

Notes:

[11] - No interaction of treatment vs. visit
No adjustment for multiplicity

[12] - No interaction of treatment vs. visit
No adjustment for multiplicity

Other pre-specified: 12- Thigh circumference, weekly assessments, Day 7 to Day 42

End point title	12- Thigh circumference, weekly assessments, Day 7 to Day 42
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End point description:

Thigh circumference measured by a flexible ruler.

The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.

End point type	Other pre-specified
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End point timeframe:

Day 7 to Day 42 following operation

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: cm				
arithmetic mean (standard deviation)				
V6_Day 7	48.2 (± 5.5)	50.9 (± 6.1)		
V7_Day 14	45.7 (± 4.5)	49.2 (± 5.8)		
V8_Day 21	44.4 (± 4.7)	48.2 (± 6.1)		
V9_Day 28	44.8 (± 5.8)	47.5 (± 8.3)		
V10_Day 42	45.3 (± 5.9)	48.9 (± 6.2)		

Attachments (see zip file)

Endpoint 12_Thigh circumference-weekly assessment.docx

Statistical analyses

Statistical analysis title	Thigh circumference, weekly assessments
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Statistical analysis description:

ANOVA with treatment as grouping variable and visit as repeating variable

Comparison groups	Phlogenzym v Placebo
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Number of subjects included in analysis	30
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Analysis specification	Pre-specified
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Analysis type	superiority ^[13]
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P-value	= 0.074
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Method	ANOVA
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Notes:

[13] - No interaction of treatment vs. visit

No adjustment for multiplicity

Other pre-specified: 13- Calf circumference, weekly assessments, Day 7 to Day 42.

End point title	13- Calf circumference, weekly assessments, Day 7 to Day 42.
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End point description:

Calf circumference measured by a flexible ruler.

The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.

End point type	Other pre-specified
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End point timeframe:

Day 7 to Day 42 following operation

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: cm				
arithmetic mean (standard deviation)				
V6_Day 7	36.9 (± 4.7)	38.7 (± 4.1)		
V7_Day 14	35.7 (± 3.8)	38.9 (± 4.7)		
V8_Day 21	35.3 (± 3.3)	37.8 (± 3.8)		
V9_Day 28	35.7 (± 4.1)	38.0 (± 3.2)		
V10_Day 42	35.4 (± 3.2)	38.2 (± 4.4)		

Attachments (see zip file)	Endpoint 13_Calf circumference-weekly assessment.docx
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Statistical analyses

Statistical analysis title	Calf circumference, weekly assessments
Statistical analysis description:	
ANOVA with treatment as grouping variable and visit as repeating variable	
Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
P-value	= 0.074 ^[15]
Method	ANOVA

Notes:

[14] - No interaction of treatment vs. visit
No adjustment for multiplicity

[15] - No interaction of treatment vs. visit
No adjustment for multiplicity

Other pre-specified: 14- CGI Change Score by subject, weekly assessments, Day 7 to Day 42

End point title	14- CGI Change Score by subject, weekly assessments, Day 7 to Day 42
End point description:	
Self-assessment of global change of the subject's general condition during the observation period. The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.	
End point type	Other pre-specified
End point timeframe:	
Day 7 to Day 42 following operation	

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: score				
arithmetic mean (standard deviation)				
V6_Day 7	1.8 (± 0.6)	1.7 (± 0.8)		
V7_Day 14	1.6 (± 0.9)	1.6 (± 0.7)		
V8_Day 21	1.4 (± 0.7)	1.6 (± 1.0)		
V9_day 28	1.3 (± 0.5)	1.3 (± 0.5)		
V10_Day 42	1.2 (± 0.4)	1.3 (± 0.6)		

Statistical analyses

Statistical analysis title	CGI Change Score by subject, weekly assesment
Statistical analysis description:	
ANOVA with treatment as grouping variable and visit as repeating variable	
Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority ^[16]
P-value	= 0.943
Method	ANOVA

Notes:

[16] - No interaction of treatment vs. visit
No adjustment for multiplicity

Other pre-specified: 15- CGI Change Score by investigator, weekly assessments

End point title	15- CGI Change Score by investigator, weekly assessments
End point description:	
Assessment by the investigator of the global change of the subject's general condition during the observation period.	
The endpoint was evaluated by ANOVA for statistical significance of the interaction of the effect of treatment (grouping variable) and visit (repeating variable), see the attachment.	
End point type	Other pre-specified
End point timeframe:	
Day 7 to Day 42 following operation	

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: score				
arithmetic mean (standard deviation)				
V6_Day 7	1.4 (± 0.5)	1.6 (± 0.7)		
V7_Day 14	1.7 (± 1.0)	1.3 (± 0.5)		
V8_Day 21	1.3 (± 0.5)	1.3 (± 0.6)		
V9_Day 28	1.3 (± 0.5)	1.2 (± 0.4)		

V10_Day 42	1.2 (\pm 0.4)	1.1 (\pm 0.3)		
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Attachments (see zip file)	Endpoint 15_CGI Change Score by Investigator.docx
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Statistical analyses

Statistical analysis title	CGI Change Score by investigator
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Statistical analysis description:

ANOVA with treatment as grouping variable and visit as repeating variable

Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	= 0.943
Method	ANOVA

Notes:

[17] - No interaction of treatment vs. visit

No adjustment for multiplicity

Other pre-specified: 16- Cumulative number of the DDDs of rescue analgesics medication, Day 7 to Day 42

End point title	16- Cumulative number of the DDDs of rescue analgesics medication, Day 7 to Day 42
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End point description:

Count of DDDs of rescue analgesic medication doses between the study visits.

End point type	Other pre-specified
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End point timeframe:

Day 7 to Day 42 following operation

End point values	Phlogenzym	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	18		
Units: DDD				
arithmetic mean (standard deviation)				
V7	0.7 (\pm 0.8)	1.5 (\pm 2.1)		
V7+V8	1.0 (\pm 1.4)	2.1 (\pm 2.3)		
V7+V8+V9	1.2 (\pm 1.5)	2.2 (\pm 2.3)		
V7+V8+V9+V10	1.4 (\pm 2.1)	2.2 (\pm 2.3)		

Statistical analyses

Statistical analysis title	Cumulative number of the DDDs of rescue analgesics
Statistical analysis description:	
Mann-Whitney U-test for cumulative number of the DDDs of rescue analgesics, Day 7 to Day 42	
Comparison groups	Phlogenzym v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[18]
Method	Mann-Whitney U-test

Notes:

[18] - No adjustment for multiplicity

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening till final visit

Adverse event reporting additional description:

AEs were reported at study visits for all subjects.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Phlogenzym
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Reporting group description:

Subjects using active IMP Phlogenzym in a double-blind manner

Reporting group title	Placebo
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Reporting group description:

Subjects treated with placebo

Serious adverse events	Phlogenzym	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
Urinary infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (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 %

Non-serious adverse events	Phlogenzym	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)	8 / 18 (44.44%)	
Surgical and medical procedures			
wound discharge increase			
subjects affected / exposed	3 / 16 (18.75%)	1 / 18 (5.56%)	
occurrences (all)	3	1	
Intraoperative blood loss			

subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 18 (0.00%) 0	
Cardiac disorders			
palpitation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
bradycardia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
nausea			
subjects affected / exposed	3 / 16 (18.75%)	3 / 18 (16.67%)	
occurrences (all)	3	3	
diarrhea			
subjects affected / exposed	2 / 16 (12.50%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
vomiting			
subjects affected / exposed	1 / 16 (6.25%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
pneumonia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
urticaria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Infection urinary tract			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
back pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Infections and infestations			

Gingivitis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 18 (5.56%) 1	
Metabolism and nutrition disorders appetite lost subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 18 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 October 2020	Termination of recruitment	-

Notes:

Limitations and caveats

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

The planned number of subjects was not enrolled because of preliminary recruitment termination due to the COVID situation.
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Notes: