Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Crossover Study to Investigate the Mechanism of Action of an Oral Enzyme Treatment with Bromelain, Trypsin and Rutoside versus Placebo in Subjects with OsTeoarthritis (WOBE-SMART)

Summary

EudraCT number	2020-003154-80
Trial protocol	BE
Global end of trial date	30 January 2023

Results information

Result version number	v1 (current)
This version publication date	29 June 2025
First version publication date	29 June 2025

Trial information

Trial identification

Sponsor protocol code	2020CLI

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05038410
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mucos Pharma GmbH & Co KG
Sponsor organisation address	Miraustr. 17, Berlin, Germany, 13509
Public contact	Artialis, Artialis SA, investigators_clinicaltrials@artialis.com
Scientific contact	Artialis, Artialis SA, investigators_clinicaltrials@artialis.com

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	07 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 October 2022
Global end of trial reached?	Yes
Global end of trial date	30 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the pharmacodynamic profile of an oral enzyme treatment with bromelain, trypsin and rutoside in participants with osteoarthritis

Protection of trial subjects:

Only subjects who were considered eligible by investigators based on the protocol-specific inclusion and exclusion criteria were to be entered in the study.
All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy:

All participants had concomitant medication at baseline. The most frequent concomitant medications comprised: paracetamol, ibuprofen, cholecalciferol, acetylsalicylic acid, COVID-19 vaccine, pantoprazole, levothyroxine sodium, bisoprolol, amoxicillin, diclofenac and dextromethorphan

Evidence for comparator: -

Actual start date of recruitment	01 December 2020
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	Belgium: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	24
From 65 to 84 years	20
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were recruited by five study sites across Belgium. Due to challenges in participant recruitment during the global SARS-CoV2 pandemic study timelines were impacted

Pre-assignment

Screening details:

All subjects were screened for eligibility to the trial. Investigator ensure that subjects met all strict inclusion/exclusion criteria. Thus, out of 56 screened patients, 11 patients failed screening. Additionally, one participant (WO-03-002) was randomized, while a screening failure was indicated in "Other reason for drop-out"

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

Arms

Arm title	WOBENZYM® versus Placebo

Arm description:

Participants were to be randomized to the WOBENZYM® or placebo group to be treated from Visit 0 to 2 (8 weeks of randomized study drug) and then discontinue study drug at Visit 2 and undergo a 4 week washout period. At Visit 3 each participant underwent treatment crossover to continue blinded treatment to Visit 5 or 6 (8- or 24-weeks of randomized study drug). All participants received both WOBENZYM® and placebo in one of the two study arms: WOBENZYM®/placebo or placebo/WOBENZYM®

Arm type	Cross over
Investigational medicinal product name	WOBENZYM®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 tablets (INN: bromelain, 67.5 mg to 76.5 mg, adjusted to 450 International Pharmaceutical Federation units; trypsin, 32 mg to 48 mg, adjusted to 24 µkat; and rutoside trihydrate, 100 mg) administered morning and evening at least 30 minutes before a meal or 90 minutes after a meal. Total daily dose was 6 tablets

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 tablets administered morning and evening at least 30 minutes before a meal or 90 minutes after a meal. Total daily dose was 6 tablets

Number of subjects in period 1	WOBENZYM® versus Placebo
Started	45
Completed	38
Not completed	7
Other reason for drop-out	1
Consent withdrawn by subject	1
Adverse event, non-fatal	4
Start of Xarelto	1

Baseline characteristics

Reporting groups

Reporting group title	WOBENZYM® versus Placebo

Reporting group description:

Participants were to be randomized to the WOBENZYM® or placebo group to be treated from Visit 0 to 2 (8 weeks of randomized study drug) and then discontinue study drug at Visit 2 and undergo a 4 week washout period. At Visit 3 each participant underwent treatment crossover to continue blinded treatment to Visit 5 or 6 (8- or 24-weeks of randomized study drug). All participants received both WOBENZYM® and placebo in one of the two study arms: WOBENZYM®/placebo or placebo/WOBENZYM®

Reporting group values	WOBENZYM® versus Placebo	Total	
Number of subjects	45	45	
Age categorical			
In the Clinical Study Report (CSR), baseline demographic data are provided for modified intention-to-treat (mITT) population (n=43), but data for the randomized subjects (n=45) are available in the database and were included for EudraCT reporting			
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)	24	24	
From 65-84 years	20	20	
85 years and over	1	1	
Age continuous			
In the Clinical Study Report (CSR), baseline demographic data are provided for modified intention-to-treat (mITT) population (n=43), but data for the randomized subjects (n=45) are available in the database and were included for EudraCT reporting			
Units: years			
arithmetic mean	63.6		
standard deviation	± 10.2	-	
Gender categorical			
In the Clinical Study Report (CSR), baseline demographic data are provided for modified intention-to-treat (mITT) population (n=43), but data for the randomized subjects (n=45) are available in the database and were included for EudraCT reporting			
Units: Subjects			
Female	25	25	
Male	20	20	

End points

End points reporting groups

Reporting group title	WOBENZYM® versus Placebo

Reporting group description:

Participants were to be randomized to the WOBENZYM® or placebo group to be treated from Visit 0 to 2 (8 weeks of randomized study drug) and then discontinue study drug at Visit 2 and undergo a 4 week washout period. At Visit 3 each participant underwent treatment crossover to continue blinded treatment to Visit 5 or 6 (8- or 24-weeks of randomized study drug). All participants received both WOBENZYM® and placebo in one of the two study arms: WOBENZYM®/placebo or placebo/WOBENZYM®

Primary: Cartilage biomarker sColl2-1

End point title	Cartilage biomarker sColl2-1[1]

End point description:

Comparison of change from baseline in cartilage biomarker levels following 8-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: nM				
least squares mean (standard error)	-10.519 (± 13.924)			

Statistical analyses

No statistical analyses for this end point

Primary: Cartilage biomarker sColl2-1NO2

End point title	Cartilage biomarker sColl2-1NO2[2]

End point description:

Comparison of change from baseline in cartilage biomarker levels following 8-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: pg/ml				
least squares mean (standard error)	0.008 (± 0.036)			

Statistical analyses

No statistical analyses for this end point

Primary: Cartilage biomarker sCOMP

End point title	Cartilage biomarker sCOMP[3]

End point description:

Comparison of change from baseline in cartilage biomarker levels following 8-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: ng/ml				
least squares mean (standard error)	-0.043 (± 0.030)			

Statistical analyses

No statistical analyses for this end point

Primary: Cartilage biomarker sPIIANP

End point title	Cartilage biomarker sPIIANP[4]

End point description:

Comparison of change from baseline in cartilage biomarker levels following 8-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: ng/ml				
least squares mean (standard error)	-0.078 (± 0.053)			

Statistical analyses

No statistical analyses for this end point

Primary: Cartilage biomarker uCTXII

End point title	Cartilage biomarker uCTXII[5]

End point description:

Comparison of change from baseline in cartilage biomarker levels following 8-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: ng/ml				
least squares mean (standard error)	-0.119 (± 0.055)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker classical monocytes

End point title	Innate immune response marker classical monocytes[6]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	0.051 (± 0.041)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker intermediary monocytes

End point title	Innate immune response marker intermediary monocytes[7]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	0.202 (± 0.096)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker non-classical monocytes

End point title	Innate immune response marker non-classical monocytes[8]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	0.051 (± 0.071)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker total monocytes - CD80-PC7

End point title	Innate immune response marker total monocytes - CD80-

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as

random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-0.032 (± 0.028)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker total monocytes - CD86-PE

End point title	Innate immune response marker total monocytes - CD86-PE[10]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	1.448 (± 1.012)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker total monocytes - CD206-BB515

End point title	Innate immune response marker total monocytes - CD206-BB515[11]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-0.019 (± 0.099)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker total monocytes - CD163-AF647

End point title	Innate immune response marker total monocytes - CD163-AF647[12]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-0.063 (± 0.081)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker classical monocytes - CD80-PC7

End point title	Innate immune response marker classical monocytes - CD80-PC7[13]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-0.03 (± 0.024)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker classical monocytes - CD86-PE

End point title	Innate immune response marker classical monocytes - CD86-PE[14]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	0.361 (± 0.557)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker classical monocytes - CD206-BB515

End point title	Innate immune response marker classical monocytes - CD206-BB515[15]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-0.028 (± 0.099)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker classical monocytes - CD163-AF647

End point title	Innate immune response marker classical monocytes - CD163-AF647[16]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model

(GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-0.054 (± 0.088)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker intermediary monocytes - CD80-PC7

End point title	Innate immune response marker intermediary monocytes - CD80-PC7[17]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-0.03 (± 0.037)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker intermediary monocytes - CD86-PE

End point title	Innate immune response marker intermediary monocytes - CD86-PE[18]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	3.087 (± 2.249)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker intermediary monocytes - CD206-BB515

End point title	Innate immune response marker intermediary monocytes - CD206-BB515[19]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-0.007 (± 0.101)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker intermediary monocytes - CD163-AF647

End point title	Innate immune response marker intermediary monocytes - CD163-AF647[20]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-0.112 (± 0.088)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker non-classical monocytes - CD80-PC7

End point title	Innate immune response marker non-classical monocytes - CD80-PC7[21]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	0.07 (± 0.093)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker non-classical monocytes - CD86-PE

End point title	Innate immune response marker non-classical monocytes - CD86-PE[22]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-3.464 (± 2.685)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker non-classical monocytes - CD206-BB515

End point title	Innate immune response marker non-classical monocytes - CD206-BB515[23]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model

(GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-0.029 (± 0.104)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker non-classical monocytes - CD163-AF647

End point title	Innate immune response marker non-classical monocytes - CD163-AF647[24]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: cells/µl				
least squares mean (standard error)	-0.012 (± 0.018)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker NLRP3 inflammasome

End point title	Innate immune response marker NLRP3 inflammasome[25]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: ng/ml				
least squares mean (standard error)	0.006 (± 0.039)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker α2-macroglobulin

End point title	Innate immune response marker α2-macroglobulin[26]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: g/l				
least squares mean (standard error)	0.027 (± 0.013)			

Statistical analyses

No statistical analyses for this end point

Primary: Systemic inflammatory marker IL-1β

End point title	Systemic inflammatory marker IL-1β[27]

End point description:

Comparison of change from baseline in markers of systemic inflammation following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: pg/ml				
least squares mean (standard error)	0.158 (± 0.236)			

Statistical analyses

No statistical analyses for this end point

Primary: Systemic inflammatory marker TNFα

End point title	Systemic inflammatory marker TNFα[28]

End point description:

Comparison of change from baseline in markers of systemic inflammation following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: pg/ml				
least squares mean (standard error)	0.112 (± 0.179)			

Statistical analyses

No statistical analyses for this end point

Primary: Systemic inflammatory marker IL-6

End point title	Systemic inflammatory marker IL-6[29]

End point description:

Comparison of change from baseline in markers of systemic inflammation following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: pg/ml				
least squares mean (standard error)	0.014 (± 0.075)			

Statistical analyses

No statistical analyses for this end point

Primary: Systemic inflammatory marker IL-10

End point title	Systemic inflammatory marker IL-10[30]

End point description:

Comparison of change from baseline in markers of systemic inflammation following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[30] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: fg/ml				
least squares mean (standard error)	0.341 (± 0.073)			

Statistical analyses

No statistical analyses for this end point

Primary: Systemic inflammatory marker IL-4

End point title	Systemic inflammatory marker IL-4[31]

End point description:

Comparison of change from baseline in markers of systemic inflammation following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: pg/ml				
least squares mean (standard error)	-0.234 (± 0.152)			

Statistical analyses

No statistical analyses for this end point

Primary: TGF-β1

End point title	TGF-β1[32]

End point description:

Comparison of change from baseline in serum growth factor concentrations following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[32] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: ng/ml				
least squares mean (standard error)	0.057 (± 0.04)			

Statistical analyses

No statistical analyses for this end point

Primary: TGF-β2

End point title	TGF-β2[33]

End point description:

Comparison of change from baseline in serum growth factor concentrations following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: ng/ml				
least squares mean (standard error)	0.066 (± 0.029)			

Statistical analyses

No statistical analyses for this end point

Primary: TGF-β3

End point title	TGF-β3[34]

End point description:

Comparison of change from baseline in serum growth factor concentrations following 8 weeks of

treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[34] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: ng/ml				
least squares mean (standard error)	0.693 (± 0.121)			

Statistical analyses

No statistical analyses for this end point

Primary: C-reactive Protein Metabolites (CRPM)

End point title	C-reactive Protein Metabolites (CRPM)[35]

End point description:

Comparison of change from baseline following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[35] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: ng/ml				
least squares mean (standard error)	-0.024 (± 0.021)			

Statistical analyses

No statistical analyses for this end point

Primary: Advanced Glycation End Product (AGE)

End point title	Advanced Glycation End Product (AGE)[36]

End point description:

Comparison of change from baseline following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[36] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: µg/ml				
least squares mean (standard error)	-0.048 (± 0.031)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker classical monocytes %

End point title	Innate immune response marker classical monocytes %[37]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
least squares mean (standard error)	-2.971 (± 1.769)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker intermediary monocytes %

End point title	Innate immune response marker intermediary monocytes %[38]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[38] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
least squares mean (standard error)	3.143 (± 1.739)			

Statistical analyses

No statistical analyses for this end point

Primary: Innate immune response marker non-classical monocytes %

End point title	Innate immune response marker non-classical monocytes %[39]

End point description:

Comparison of change from baseline in markers of innate immune response following 8 weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Primary

End point timeframe:

8-weeks of treatment

Notes:

[39] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All patients received both WOBENZYM® and Placebo, so a single reporting group is considered. Change from baseline in each patient was analyzed using a general linear mixed model (GLMM) with treatment, period and sequence (i.e. period x treatment) as fixed factors and participant as random factors. Endpoint values provided as least squares mean represent the GLLM estimator

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
least squares mean (standard error)	-0.354 (± 0.633)			

Statistical analyses

No statistical analyses for this end point

Secondary: Knee Pain at rest

End point title	Knee Pain at rest

End point description:

Comparison of change from baseline following 8- or 24-weeks in knee pain at rest measured by a visual analogue scale (VAS) of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mm				
least squares mean (standard error)	-1.688 (± 2.722)			

Statistical analyses

No statistical analyses for this end point

Secondary: Knee Pain at walking

End point title	Knee Pain at walking

End point description:

Comparison of change from baseline following 8- or 24-weeks in knee pain at walking measured by a visual analogue scale (VAS) of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mm				
least squares mean (standard error)	1.668 (± 2.722)			

Statistical analyses

No statistical analyses for this end point

Secondary: Knee function KOOS - Symptoms score

End point title	Knee function KOOS - Symptoms score

End point description:

Comparison of change from baseline in Knee Injury and Osteoarthritis Outcome Score (KOOS) following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
least squares mean (standard error)	3.651 (± 1.536)			

Statistical analyses

No statistical analyses for this end point

Secondary: Knee function KOOS - Pain score

End point title	Knee function KOOS - Pain score

End point description:

Comparison of change from baseline in Knee Injury and Osteoarthritis Outcome Score (KOOS) following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
least squares mean (standard error)	3.62 (± 1.766)			

Statistical analyses

No statistical analyses for this end point

Secondary: Knee function KOOS- ADL score

End point title	Knee function KOOS- ADL score

End point description:

Comparison of change from baseline in Knee Injury and Osteoarthritis Outcome Score (KOOS) following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
least squares mean (standard error)	3.707 (± 1.737)			

Statistical analyses

No statistical analyses for this end point

Secondary: Knee function KOOS -Sports score

End point title	Knee function KOOS -Sports score

End point description:

Comparison of change from baseline in Knee Injury and Osteoarthritis Outcome Score (KOOS) following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
least squares mean (standard error)	1.071 (± 2.062)			

Statistical analyses

No statistical analyses for this end point

Secondary: Knee function KOOS -Quality of life score

End point title	Knee function KOOS -Quality of life score

End point description:

Comparison of change from baseline in Knee Injury and Osteoarthritis Outcome Score (KOOS) following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
least squares mean (standard error)	0.54 (± 1.758)			

Statistical analyses

No statistical analyses for this end point

Secondary: Knee function KOOS - Global score

End point title	Knee function KOOS - Global score

End point description:

Comparison of change from baseline in Knee Injury and Osteoarthritis Outcome Score (KOOS) following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
least squares mean (standard error)	2.821 (± 1.515)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Assessment of Disease Activity (PGADA)

End point title	Patient Global Assessment of Disease Activity (PGADA)

End point description:

Comparison of change from baseline in Patient Global Assessment of Disease Activity (PGADA) measured by a visual analogue scale (VAS) following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	-0.368 (± 2.542)			

Statistical analyses

No statistical analyses for this end point

Secondary: Global Physical Activity Parameter (GPA) heart rate

End point title	Global Physical Activity Parameter (GPA) heart rate

End point description:

Comparison of change from baseline in in global physical activity parameters following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: bpm				
least squares mean (standard error)	-0.31 (± 0.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Global Physical Activity (GPA) daily number of steps

End point title	Global Physical Activity (GPA) daily number of steps

End point description:

Comparison of change from baseline in in global physical activity parameters following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	0.034 (± 0.021)			

Statistical analyses

No statistical analyses for this end point

Secondary: Global Physical Activity (GPA) Climbed stairs

End point title	Global Physical Activity (GPA) Climbed stairs

End point description:

Comparison of change from baseline in in global physical activity parameters following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	-0.38 (± 0.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Global Physical Activity (GPA) Intensive minutes

End point title	Global Physical Activity (GPA) Intensive minutes

End point description:

Comparison of change from baseline in in global physical activity parameters following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	-0.51 (± 1.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Global Physical Activity (GPA) Calories burned

End point title	Global Physical Activity (GPA) Calories burned

End point description:

Comparison of change from baseline in in global physical activity parameters following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	-0.03 (± 0.028)			

Statistical analyses

No statistical analyses for this end point

Secondary: WORMS Cartilage - patellofemoral joint

End point title	WORMS Cartilage - patellofemoral joint

End point description:

Comparison of change from baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) in specific joint parameters following 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	-0.27 (± 1.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: WORMS Cartilage global score

End point title	WORMS Cartilage global score

End point description:

Comparison of change from baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) in specific joint parameters following 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	1.66 (± 3.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: WORMS Bone marrow - patellofemoral joint

End point title	WORMS Bone marrow - patellofemoral joint

End point description:

Comparison of change from baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) in specific joint parameters following 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	-0.31 (± 0.50)			

Statistical analyses

No statistical analyses for this end point

Secondary: WORMS Bone marrow - medial tibiofemoral joint

End point title	WORMS Bone marrow - medial tibiofemoral joint

End point description:

Comparison of change from baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) in specific joint parameters following 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	-0.27 (± 0.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: WORMS Bone marrow - lateral tibiofemoral joint

End point title	WORMS Bone marrow - lateral tibiofemoral joint

End point description:

Comparison of change from baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) in specific joint parameters following 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	1.15 (± 0.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: WORMS Bone marrow global score

End point title	WORMS Bone marrow global score

End point description:

Comparison of change from baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) in specific joint parameters following 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	0.81 (± 0.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: WORMS Cyst - patellofemoral joint

End point title	WORMS Cyst - patellofemoral joint

End point description:

Comparison of change from baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) in specific joint parameters following 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	0.38 (± 0.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: WORMS Cyst global score

End point title	WORMS Cyst global score

End point description:

Comparison of change from baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) in specific joint parameters following 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	1.41 (± 0.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: WORMS Effusion maximal distension of the synovial cavity

End point title	WORMS Effusion maximal distension of the synovial cavity

End point description:

Comparison of change from baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) in specific joint parameters following 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	0.31 (± 0.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: WORMS Size of synovial cysts

End point title	WORMS Size of synovial cysts

End point description:

Comparison of change from baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) in specific joint parameters following 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)	0.00 (± 0.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Joint Effusion

End point title	Joint Effusion

End point description:

Comparison of change from baseline following 24-weeks of treatment with WOBENZYM® versus placebo in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mm				
least squares mean (standard error)	0.25 (± 0.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Responder Rate

End point title	Treatment Responder Rate

End point description:

Comparison of change from baseline of treatment responder rate, defined as changes in knee pain and/or knee function and/or disease activity, following 8- or 24-weeks of treatment with WOBENZYM® versus placebo in in modified intention-to-treat (mITT) population

End point type	Secondary

End point timeframe:

8- or 24-weeks of treatment

End point values	WOBENZYM® versus Placebo			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: N/A				
least squares mean (standard error)				
GEE analysis	0.37 (± 0.32)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment-emergent AEs were assessed from the start of dosing with study drug (Visit 1) through the entire study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	WOBENZYM
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	WOBENZYM	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiac fibrillation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	WOBENZYM	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 45 (75.56%)	39 / 45 (86.67%)	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	2 / 45 (4.44%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
General disorders and administration site conditions			

Condition aggravated			
subjects affected / exposed	2 / 45 (4.44%)	3 / 45 (6.67%)	
occurrences (all)	2	5	
Oedema peripheral			
subjects affected / exposed	1 / 45 (2.22%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Reproductive system and breast disorders			
Reproductive system disorders			
subjects affected / exposed	3 / 45 (6.67%)	0 / 45 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 45 (6.67%)	0 / 45 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	4 / 45 (8.89%)	2 / 45 (4.44%)	
occurrences (all)	4	3	
Investigations			
Investigations			
subjects affected / exposed	3 / 45 (6.67%)	3 / 45 (6.67%)	
occurrences (all)	3	4	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	3 / 45 (6.67%)	6 / 45 (13.33%)	
occurrences (all)	4	7	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 45 (8.89%)	7 / 45 (15.56%)	
occurrences (all)	8	11	
Migraine			
subjects affected / exposed	3 / 45 (6.67%)	6 / 45 (13.33%)	
occurrences (all)	6	15	
Gastrointestinal disorders			
Gastrointestinal pain			

subjects affected / exposed	4 / 45 (8.89%)	0 / 45 (0.00%)	
occurrences (all)	4	0	
Diarrhea			
subjects affected / exposed	3 / 45 (6.67%)	5 / 45 (11.11%)	
occurrences (all)	3	6	
Abdominal pain upper			
subjects affected / exposed	3 / 45 (6.67%)	5 / 45 (11.11%)	
occurrences (all)	6	5	
Toothache			
subjects affected / exposed	3 / 45 (6.67%)	2 / 45 (4.44%)	
occurrences (all)	4	5	
Nausea			
subjects affected / exposed	2 / 45 (4.44%)	3 / 45 (6.67%)	
occurrences (all)	2	3	
Abdominal pain			
subjects affected / exposed	1 / 45 (2.22%)	3 / 45 (6.67%)	
occurrences (all)	4	8	
Abdominal discomfort			
subjects affected / exposed	0 / 45 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	
Dyspepsia			
subjects affected / exposed	0 / 45 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous disorders			
subjects affected / exposed	5 / 45 (11.11%)	3 / 45 (6.67%)	
occurrences (all)	6	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 45 (33.33%)	14 / 45 (31.11%)	
occurrences (all)	70	32	
Back pain			
subjects affected / exposed	6 / 45 (13.33%)	3 / 45 (6.67%)	
occurrences (all)	7	4	
Pain in extremity			

subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 10	5 / 45 (11.11%) 6	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) COVID-19 subjects affected / exposed occurrences (all)	 4 / 45 (8.89%) 5 2 / 45 (4.44%) 2	 1 / 45 (2.22%) 1 3 / 45 (6.67%) 3	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	 3 / 45 (6.67%) 3	 2 / 45 (4.44%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2021	• Permitted the inclusion of participants taking low-dose (100 mg) aspirin that had no identifiable effect on their bleeding risk based on review of their medical history by the principal investigator. • Reduced the number of parameters assessed from watch data and specified analysis of mobility data comprising: heart rate, daily number of steps, stairs climbed, intensive activity minutes, and calories burned. It also described the requirement that the participant regularly download data from the activity watch. This reflected clarification of those data considered most pertinent to studying fitness and health in participants with osteoarthritis. • Removed the requirement to test eccentric 30°S hamstrings during isokinetic analyses. This reflected clarification of those data considered most pertinent to assessing muscle strength in participants with osteoarthritis. • Allowed for the optional collection of fecal samples for gut microbiome and metabolome analysis.
23 May 2022	• Replaced inflammatory aging clock with assessment of AGE biomarkers and CRPM to estimate chronic inflammation and inflammatory age respectively. • Specified that participants were to attend four or five study visits (up to Visit 5 or 6 respectively). This was due to challenges in participant recruitment during the global SARSCoV2 pandemic that had an associated impact on study timelines. As a result the study drug batch reached its expiry date (on 30 Sep 2022) before Visit 6 for the 6 participants recruited after February 2022. The potential for mitigating the issue by study drug re-supply was compromised by a global shortage at that time of pharmaceutical-grade bromelain. As a result, it was not possible for all participants to complete the study to Visit 6. Consequently, participants recruited after February 2022 were to exit the study at Visit 5 rather than Visit 6 as planned. • Specified the study duration as 22 to 24 weeks to support the primary objective and 40 weeks to support exploratory objectives. It was specified that participants would undergo an initial 8-week treatment period followed by a second 8-week treatment period for those recruited after February 2022 or 24-week treatment period for those recruited earlier.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported