Clinical trial results:
A Two Part Protocol Using Double Blind Placebo Control to Assess the Safety, Tolerability, and Pharmacokinetics of Single Escalating Intra-articular Doses Followed by Assessment of Efficacy, Safety, Tolerability and Pharmacokinetics of a Single Intra-articular Dose of the TrkA Inhibitor, GZ389988A, in Patients With Painful Osteoarthritis of the Knee

Summary

EudraCT number	2014-004805-34
Trial protocol	DE
Global end of trial date	13 September 2017

Results information

Result version number	v1 (current)
This version publication date	27 September 2018
First version publication date	27 September 2018

Trial information

Trial identification

Sponsor protocol code	TDU13828 – ACT13830

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02424942
WHO universal trial number (UTN)	U1111-1163-0806
Other trial identifiers	NCT Number for Part 2 Study (ACT13830): NCT02845271

Notes:

Sponsors

Sponsor organisation name	Genzyme, a Sanofi Company
Sponsor organisation address	500 Kendall Street, Cambridge, MA , United States, 02142
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement , contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.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	21 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess in subjects with painful osteoarthritis (OA) of the knee:
- Part 1: The tolerability and safety of GZ389988A after ascending single intra-articular (IA) doses.
- The pharmacokinetic (PK) parameters of GZ389988A after ascending single IA doses.
- To obtain preliminary pharmacodynamics (PD) evaluation of GZ389988A after ascending single IA doses.
- Part 2: The efficacy of a single IA dose of GZ389988A versus placebo.
- The tolerability and safety of a single IA dose of GZ389988A.
- The PK parameters of a single IA dose of GZ389988A.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 April 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 132
Worldwide total number of subjects	132
EEA total number of subjects	132

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)	81
From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at a single center in Germany. A total of 28 subjects were randomized and treated between 17 April 2015 and 13 July 2016 in Part 1 and a total of 104 subjects were randomized and treated between 22 July 2016 and 13 September 2017 in Part 2 .

Pre-assignment

Screening details:

Part 1 consisted of 5 ascending dose levels of GZ389988A to determine maximum tolerated dose (MTD). For confirmation of MTD, the dose level of dose 3 and 4 were duplicated in 4 additional subjects with the same staggered dosing. Part 2 of the study was conducted at the MTD analyzed in Part 1.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

For Part 2 of the study, GZ389988A and placebo were administered by a qualified orthopedic surgeon, supported by a nurse, both of whom were unblinded and not otherwise involved in the study (apart from identifying potential subjects for the study and taking synovial fluid samples).

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Placebo

Arm description:

Subjects received single dose of placebo (matched to GZ389988A) IA injection on Day 1. Data was pooled for all subjects who received placebo in Part1 and reported in this arm.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for parenteral use
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received single dose of placebo (matched to GZ389988A) IA injection in the knee joint on Day 1. To ensure safety conditions, dosing of each subject was staggered such that only one subject was dosed per day.

Arm title	Part 1: GZ389988A Dose 1

Arm description:

Subjects received single dose of GZ389988A dose 1 IA injection on Day 1.

Arm type	Experimental
Investigational medicinal product name	GZ389988A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received single dose of GZ389988A dose 1 IA injection in the knee joint on Day 1. To ensure safety conditions, dosing of each subject was staggered such that only one subject was dosed per day.

Arm title	Part 1: GZ389988A Dose 2

Arm description:

Subjects received single dose of GZ389988A dose 2 injection on Day 1.

Arm type	Experimental
Investigational medicinal product name	GZ389988A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received single dose of GZ389988A dose 2 IA injection in the knee joint on Day 1. To ensure safety conditions, dosing of each subject was staggered such that only one subject was dosed per day.

Arm title	Part 1: GZ389988A Dose 3

Arm description:

Subjects received single dose of GZ389988A dose 3 IA injection on Day 1.

Arm type	Experimental
Investigational medicinal product name	GZ389988A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received single dose of GZ389988A dose 3 IA injection in the knee joint on Day 1. To ensure safety conditions, dosing of each subject was staggered such that only one subject was dosed per day.

Arm title	Part 1: GZ389988A Dose 4

Arm description:

Subjects received single dose of GZ389988A dose 4 IA injection on Day 1.

Arm type	Experimental
Investigational medicinal product name	GZ389988A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received single dose of GZ389988A dose 4 IA injection in the knee joint on Day 1. To ensure safety conditions, dosing of each subject was staggered such that only one subject was dosed per day.

Arm title	Part 1: GZ389988A Dose 5

Arm description:

Subjects received single dose of GZ389988A dose 5 IA injection on Day 1.

Arm type	Experimental
Investigational medicinal product name	GZ389988A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received single dose of GZ389988A dose 5 IA injection in the knee joint on Day 1. To ensure safety conditions, dosing of each subject was staggered such that only one subject was dosed per day.

Arm title	Part 2: Placebo

Arm description:

Subjects received single IA dose of placebo (matched to GZ389988A) injection on Day 1.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for parenteral use
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received single dose of placebo (matched to GZ389988A) IA injection in the knee joint on Day 1.

Arm title	Part 2: GZ389988A Dose 4 from Part 1

Arm description:

Subjects received single IA dose of GZ389988A on Day 1 at dose 4 confirmed in Part 1.

Arm type	Experimental
Investigational medicinal product name	GZ389988A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Subjects received single dose of GZ389988A at dose 4 IA injection in the knee joint on Day 1.

Number of subjects in period 1	Part 1: Placebo	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2
Started	7	3	3
Completed	7	3	3

Number of subjects in period 1	Part 1: GZ389988A Dose 3	Part 1: GZ389988A Dose 4	Part 1: GZ389988A Dose 5
Started	6	6	3
Completed	6	6	3

Number of subjects in period 1	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1
Started	52	52
Completed	52	52

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Placebo
Reporting group description:	
Subjects received single dose of placebo (matched to GZ389988A) IA injection on Day 1. Data was pooled for all subjects who received placebo in Part1 and reported in this arm.	
Reporting group title	Part 1: GZ389988A Dose 1
Reporting group description:	
Subjects received single dose of GZ389988A dose 1 IA injection on Day 1.	
Reporting group title	Part 1: GZ389988A Dose 2
Reporting group description:	
Subjects received single dose of GZ389988A dose 2 injection on Day 1.	
Reporting group title	Part 1: GZ389988A Dose 3
Reporting group description:	
Subjects received single dose of GZ389988A dose 3 IA injection on Day 1.	
Reporting group title	Part 1: GZ389988A Dose 4
Reporting group description:	
Subjects received single dose of GZ389988A dose 4 IA injection on Day 1.	
Reporting group title	Part 1: GZ389988A Dose 5
Reporting group description:	
Subjects received single dose of GZ389988A dose 5 IA injection on Day 1.	
Reporting group title	Part 2: Placebo
Reporting group description:	
Subjects received single IA dose of placebo (matched to GZ389988A) injection on Day 1.	
Reporting group title	Part 2: GZ389988A Dose 4 from Part 1
Reporting group description:	
Subjects received single IA dose of GZ389988A on Day 1 at dose 4 confirmed in Part 1.	

Reporting group values	Part 1: Placebo	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2
Number of subjects	7	3	3
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	51.9	55.0	53.3
standard deviation	± 2.7	± 2.6	± 3.5
Gender categorical Units: Subjects			
Female	4	1	1
Male	3	2	2
Race Units: Subjects			
White	7	3	3
Asian	0	0	0
Other	0	0	0

Reporting group values	Part 1: GZ389988A	Part 1: GZ389988A	Part 1: GZ389988A

	Dose 3	Dose 4	Dose 5
Number of subjects	6	6	3
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.5	53.7	54.0
standard deviation	± 4.4	± 6.4	± 6.0
Gender categorical Units: Subjects			
Female	3	3	1
Male	3	3	2
Race Units: Subjects			
White	6	6	3
Asian	0	0	0
Other	0	0	0

Reporting group values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1	Total
Number of subjects	52	52	132
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.1	62.1	
standard deviation	± 8.1	± 9.4	-
Gender categorical Units: Subjects			
Female	25	26	64
Male	27	26	68
Race Units: Subjects			
White	50	52	130
Asian	1	0	1
Other	1	0	1

End points

End points reporting groups

Reporting group title	Part 1: Placebo
Reporting group description:	
Subjects received single dose of placebo (matched to GZ389988A) IA injection on Day 1. Data was pooled for all subjects who received placebo in Part1 and reported in this arm.	
Reporting group title	Part 1: GZ389988A Dose 1
Reporting group description:	
Subjects received single dose of GZ389988A dose 1 IA injection on Day 1.	
Reporting group title	Part 1: GZ389988A Dose 2
Reporting group description:	
Subjects received single dose of GZ389988A dose 2 injection on Day 1.	
Reporting group title	Part 1: GZ389988A Dose 3
Reporting group description:	
Subjects received single dose of GZ389988A dose 3 IA injection on Day 1.	
Reporting group title	Part 1: GZ389988A Dose 4
Reporting group description:	
Subjects received single dose of GZ389988A dose 4 IA injection on Day 1.	
Reporting group title	Part 1: GZ389988A Dose 5
Reporting group description:	
Subjects received single dose of GZ389988A dose 5 IA injection on Day 1.	
Reporting group title	Part 2: Placebo
Reporting group description:	
Subjects received single IA dose of placebo (matched to GZ389988A) injection on Day 1.	
Reporting group title	Part 2: GZ389988A Dose 4 from Part 1
Reporting group description:	
Subjects received single IA dose of GZ389988A on Day 1 at dose 4 confirmed in Part 1.	

Primary: Part 1: Number of Subjects With any Treatment-Emergent Adverse Events (TEAE)

End point title	Part 1: Number of Subjects With any Treatment-Emergent Adverse Events (TEAE)[1][2]
End point description:	
Any untoward medical occurrence in a subject who received investigational medicinal product (IMP) was considered an adverse event (AE) without regard to possibility of causal relationship with this treatment. TEAEs: AEs that occurred or worsened during the on-treatment period (time from the first dose of study medication administration up to the end of study [EOS] visit). Analysis was performed on safety population which included all subjects who were exposed to study drug administration.	
End point type	Primary
End point timeframe:	
From first dose of GZ389988A administration up to Day 84 (EOS)	

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: Since analysis is descriptive in nature, statistical data could not be provided.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 1 only.

End point values	Part 1: Placebo	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	3	6
Units: subjects	6	3	3	3

End point values	Part 1: GZ389988A Dose 4	Part 1: GZ389988A Dose 5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	3		
Units: subjects	5	3		

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Change From Baseline Average Over 4 Weeks (up to Day 28) in Weekly Mean score of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A1 Pain Subscore (Walking Pain) Collected Daily in the Target Knee

End point title	Part 2: Change From Baseline Average Over 4 Weeks (up to Day 28) in Weekly Mean score of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A1 Pain Subscore (Walking Pain) Collected Daily in the Target Knee[3]

End point description:

WOMAC index(VAS 3.1):health status measure questionnaire:24questions(Q)of 3subscales:pain(5Q),stiffness(2Q),physical function(17Q).Each Q measured on 0(no pain)-100(maximal pain)visual analog scale(VAS).WOMAC A1(measure of pain during walking on flat surface)was part of pain sub-scale from WOMAC index.Weekly mean score of WOMAC A1,defined as average of daily measurements over the week was calculated for each week.Statistical analysis was done on the change from baseline in weekly mean score calculated for each week.Negative change=improvement.Analysis performed on Modified intent-to-treat(mITT)population included all randomized subjects exposed to study treatment,without any major/critical deviations related to diagnosis of primary knee OA or rescue medication other than those allowed,and for whom any WOMAC A1 pain sub-score from electronic Diary(eDiary)as measured by the VAS were considered evaluable at baseline,with atleast 1 post baseline assessment after single IA injection.

End point type	Primary

End point timeframe:

Baseline, Day 1 to 28

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on a Scale				
least squares mean (standard error)	-15.7725 (±	-23.2590 (±		

3.0361)	3.0346)

Statistical analyses

Statistical analysis title	Over 4 weeks: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0441 [4]
Method	Linear Mixed Effect Model
Parameter estimate	Least Squares Mean Difference
Point estimate	-7.4865
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.7065
upper limit	-0.2665
Variability estimate	Standard error of the mean
Dispersion value	4.3476

Notes:

[4] - Specified one-sided P-value.

Secondary: Part 1: Maximum Plasma Concentration (Cmax) of GZ389988A

End point title	Part 1: Maximum Plasma Concentration (Cmax) of

End point description:

Cmax was defined as maximum plasma concentration of GZ389988A. Analysis was performed on PK population which included all subjects without any major deviations related to study drug administration, and for whom any PK parameters were available.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 144, 312, 480, 648, 984, 1320, 1656, and 1992 hours post-dose on Day 1

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Subjects treated with placebo were not included in the analysis of PK parameters.

End point values	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3	Part 1: GZ389988A Dose 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	6
Units: ng/mL				
arithmetic mean (standard deviation)	1.65 (± 1.22)	0.224 (± 0.114)	4.56 (± 4.31)	10.8 (± 6.16)

End point values	Part 1: GZ389988A Dose 5			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: ng/mL				
arithmetic mean (standard deviation)	17.7 (± 15.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Area Under the Plasma-Drug-Concentration Versus Time Curve From Time Zero to Last Quantifiable -Concentration (AUClast) of GZ389988A

End point title	Part 1: Area Under the Plasma-Drug-Concentration Versus Time Curve From Time Zero to Last Quantifiable -Concentration (AUClast) of GZ389988A[6]

End point description:

AUClast was defined as area under the plasma-drug-concentration versus time curve calculated using the trapezoidal method from time zero to the real time tlast where tlast was the time corresponding to the last concentration above the limit of quantification, Clast. Analysis was performed on PK population.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 144, 312, 480, 648, 984, 1320, 1656, and 1992 hours post-dose on Day 1

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Subjects treated with placebo were not included in the analysis of PK parameters.

End point values	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3	Part 1: GZ389988A Dose 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	6
Units: ng*h/mL				
arithmetic mean (standard deviation)	136 (± 22)	156 (± 105)	1230 (± 430)	2700 (± 827)

End point values	Part 1: GZ389988A Dose 5			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: ng*h/mL				
arithmetic mean (standard deviation)	4340 (± 2300)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Area Under the Plasma-Drug-Concentration Versus Time Curve From Time Zero to Infinity (AUCinf) of GZ389988A

End point title	Part 1: Area Under the Plasma-Drug-Concentration Versus Time Curve From Time Zero to Infinity (AUCinf) of GZ389988A[7]

End point description:

AUCinf was defined as area under the plasma-drug-concentration versus time curve from time zero extrapolated to infinity. Values with percentage of extrapolation >30% were not reported. Analysis was performed on PK population. Number of subjects analyzed=subjects with available data for this endpoint. Here, 999 represents that SD was not calculated as data was available only for two subjects.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 144, 312, 480, 648, 984, 1320, 1656, and 1992 hours post-dose on Day 1

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects treated with placebo were not included in the analysis of PK parameters.

End point values	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3	Part 1: GZ389988A Dose 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	0[8]	5	6
Units: ng*h/mL				
arithmetic mean (standard deviation)	148 (± 15.6)	()	1530 (± 300)	2860 (± 724)

Notes:

[8] - Since a log-linear terminal phase could not be determined and/or extrapolated area was >30%.

End point values	Part 1: GZ389988A Dose 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ng*h/mL				
arithmetic mean (standard deviation)	5640 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Terminal Half-Life (t1/2z) of GZ389988A

End point title	Part 1: Terminal Half-Life (t1/2z) of GZ389988A[9]

End point description:

t1/2z was defined as time measured for the plasma concentration of GZ389988A to decrease by one half. Analysis was performed on PK population. Here, 999 represents that data was not calculated as data was available only for two subjects.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 144, 312, 480, 648, 984, 1320, 1656, and 1992 hours post-dose on Day 1

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Subjects treated with placebo were not included in the analysis of PK parameters.

End point values	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3	Part 1: GZ389988A Dose 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	6
Units: hours				
arithmetic mean (standard deviation)	325 (± 283)	2000 (± 999)	692 (± 375)	439 (± 247)

End point values	Part 1: GZ389988A Dose 5			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: hours				
arithmetic mean (standard deviation)	647 (± 226)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Time to Reach Maximum Observed Plasma Concentration (Tmax) of GZ389988A

End point title	Part 1: Time to Reach Maximum Observed Plasma Concentration (Tmax) of GZ389988A[10]

End point description:

Tmax was defined as time to reach Cmax. Analysis was performed on PK population.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 144, 312, 480, 648, 984, 1320, 1656, and 1992 hours post-dose on Day 1

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Subjects treated with placebo were not included in the analysis of PK parameters.

End point values	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3	Part 1: GZ389988A Dose 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	6
Units: hours				
median (full range (min-max))	12 (8 to 23.9)	48 (24 to 1991)	48.1 (8 to 143)	36.2 (24 to 983)

End point values	Part 1: GZ389988A Dose 5			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: hours				
median (full range (min-max))	47.9 (36 to 48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Apparent Volume of Distribution (Vz/F) of GZ389988A

End point title	Part 1: Apparent Volume of Distribution (Vz/F) of

End point description:

Vz/F was defined as apparent terminal phase plasma volume of distribution, and was calculated as: Dose/AUC*λz. Analysis was performed on PK population. Number of subjects analyzed=subjects with available data for this endpoint. Here, 999 represents that data was not calculated as data was available only for two subjects.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 144, 312, 480, 648, 984, 1320, 1656, and 1992 hours post-dose on Day 1

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Subjects treated with placebo were not included in the analysis of PK parameters.

End point values	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3	Part 1: GZ389988A Dose 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	0[12]	5	6
Units: milliliter (mL)				
arithmetic mean (standard deviation)	9830000 (± 9300000)	()	17200000 (± 10100000)	14400000 (± 9510000)

Notes:

[12] - Since log-linear terminal phase could not be determined &/or extrapolated area was >30%.

End point values	Part 1: GZ389988A Dose 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: milliliter (mL)				
arithmetic mean (standard deviation)	15200000 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Apparent Total Body Clearance(CL/F) of GZ389988A

End point title	Part 1: Apparent Total Body Clearance(CL/F) of GZ389988A[13]

End point description:

CL/F was defined as apparent total body clearance of a drug from the plasma, and was calculated as: Dose/AUC. Analysis was performed on PK population. Number of subjects analyzed=subjects with available data for this endpoint. Here, 999 represents that data was not calculated as data was available only for two subjects.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 144, 312, 480, 648, 984, 1320, 1656, and 1992 hours post-dose on Day 1

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Subjects treated with placebo were not included in the analysis of PK parameters.

End point values	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3	Part 1: GZ389988A Dose 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	0[14]	5	6
Units: liters per hour (L/h)				
arithmetic mean (standard deviation)	20.5 (± 2.11)	()	20.3 (± 4.2)	22.2 (± 6.19)

Notes:

[14] - Since log-linear terminal phase could not be determined &/or extrapolated area was >30%.

End point values	Part 1: GZ389988A Dose 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: liters per hour (L/h)				
arithmetic mean (standard deviation)	18.2 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Synovial Fluid Concentrations of GZ389988A

End point title	Part 1: Synovial Fluid Concentrations of GZ389988A[15]

End point description:

Analysis was performed on PK population. Number of subjects analyzed=subjects with available data for this endpoint. Here 'n' signifies number of subjects with available data for specified category for each arm respectively. 9999 represents that data was not calculated as data was below lower limit of quantification (0.1 ng/mL). 999 represents standard deviation could not be calculated due to single evaluable subject.

End point type	Secondary

End point timeframe:

Pre-dose, at anytime on Day 28 and Day 84

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Synovial fluid concentrations were only collected for subjects who received placebo, GZ389988A Dose 4 and Dose 5.

End point values	Part 1: Placebo	Part 1: GZ389988A Dose 4	Part 1: GZ389988A Dose 5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	1	1	
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-dose (n= 2, 0, 1)	9999 (± 999)	9999 (± 999)	9999 (± 999)	
Day 28 (n= 1, 1, 0)	9999 (± 999)	312 (± 999)	9999 (± 999)	
Day 84 (n= 1, 0, 0)	9999 (± 999)	9999 (± 999)	9999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Change from Baseline in WOMAC Total Score at Day 7, 14, 21, 28, 42, 56, 70 and 84

End point title	Part 1: Change from Baseline in WOMAC Total Score at Day 7, 14, 21, 28, 42, 56, 70 and 84[16]

End point description:

WOMAC index is health status measure questionnaire of twenty-four questions comprising of 3 sub-scales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question was measured on a 100-millimeter (mm) visual analogue scale (VAS) ranging from 0=no pain to 100=maximal pain. Total score was sum of the 3 sub-scale scores, giving total score range of 0 to 2400 mm where higher scores indicated higher level of pain, stiffness and physical function. The change from baseline in WOMAC total score was calculated at each specified visit (Day 7, 14, 21, 28, 42, 56, 70, and 84). Analysis was performed on PD population which included all subjects without any major/critical deviations or AEs that would impact the PD response, and for whom any WOMAC sub-scores as measured by the 100-mm VAS were considered evaluable at baseline and at least 1 post-baseline measurements.

End point type	Secondary

End point timeframe:

Baseline, Day 7, 14, 21, 28, 42, 56, 70 and 84

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was evaluated for Part 1 only.

End point values	Part 1: Placebo	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	3	6
Units: millimeter				
arithmetic mean (standard deviation)				
Day 7	-1008.7 (± 706.6)	-789.3 (± 786.4)	-17.3 (± 56.4)	-1160.8 (± 633.5)
Day 14	-880.6 (± 817.1)	-637.3 (± 758.2)	79 (± 341.6)	-1250.3 (± 542.1)
Day 21	-938.7 (± 774.7)	-554.3 (± 725.9)	-120 (± 156.5)	-1223.3 (± 663.7)
Day 28	-899.9 (± 783.4)	-480.3 (± 771.4)	-139 (± 125.7)	-1069.5 (± 831.7)
Day 42	-1025.4 (± 681)	-499 (± 723.5)	-111.7 (± 125.4)	-1097.5 (± 867.8)
Day 56	-1006.4 (± 732.6)	-547.7 (± 791.1)	-222.3 (± 101.6)	-1083.2 (± 787.9)
Day 70	-1025.1 (± 680.3)	-476 (± 773.5)	-212 (± 137.4)	-1040.5 (± 780)
Day 84	-1011.7 (± 698.2)	-503 (± 755.3)	-286.3 (± 210.7)	-805.2 (± 733.3)

End point values	Part 1: GZ389988A Dose 4	Part 1: GZ389988A Dose 5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	2		
Units: millimeter				
arithmetic mean (standard deviation)				
Day 7	-655.7 (± 617)	-1008.5 (± 901.6)		
Day 14	-777.3 (± 657.4)	-1205.5 (± 881.8)		
Day 21	-769.3 (± 697.1)	-1215.5 (± 781.4)		
Day 28	-789.2 (± 742.7)	-966.5 (± 779.9)		
Day 42	-755.8 (± 722)	-963.5 (± 1089.7)		
Day 56	-823.5 (± 707.1)	-901 (± 1130)		
Day 70	-840 (± 729.1)	-683 (± 933.4)		
Day 84	-857 (± 711.2)	-502.5 (± 552.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Change From Baseline in WOMAC Pain Sub-score at Day 7, 14, 21, 28, 42, 56, 70 and 84

End point title	Part 1: Change From Baseline in WOMAC Pain Sub-score at Day 7, 14, 21, 28, 42, 56, 70 and 84[17]

End point description:

WOMAC index is health status measure questionnaire of twenty-four questions comprising of 3 subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question was measured on a 100-mm VAS ranging from 0=no pain to 100=maximal pain. WOMAC pain sub-score was sum of 5 questions with score ranging from 0 to 500 mm, where higher score indicated higher level of pain. The change from baseline in WOMAC pain sub-score was calculated at each specified visit (Day 7, 14, 21, 28, 42, 56, 70, and 84). Analysis was performed on PD population.

End point type	Secondary

End point timeframe:

Baseline, Day 7, 14, 21, 28, 42, 56, 70 and 84

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 1 only.

End point values	Part 1: Placebo	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	3	6
Units: millimeter				
arithmetic mean (standard deviation)				
Day 7	-208.9 (± 145.1)	-146.7 (± 158.7)	4.3 (± 38.1)	-265.8 (± 127.1)
Day 14	-180.1 (± 162.3)	-121 (± 167.2)	27 (± 61)	-278.2 (± 99.9)
Day 21	-193.3 (± 152.8)	-118.3 (± 161.3)	-23.7 (± 28.2)	-273.5 (± 120)
Day 28	-193.6 (± 144.9)	-91.3 (± 183.4)	-22.3 (± 8.5)	-241.8 (± 161.3)
Day 42	-215.7 (± 129)	-123.3 (± 151.1)	-11.3 (± 24.7)	-250.3 (± 175.5)
Day 56	-203.9 (± 145.2)	-127 (± 167.4)	-23.3 (± 35.8)	-247.3 (± 154.4)
Day 70	-210.3 (± 129.2)	-99.7 (± 162.5)	-37.7 (± 20.5)	-240.5 (± 153.1)
Day 84	-210.6 (± 141.2)	-102.3 (± 152.9)	-40.3 (± 52.6)	-194.3 (± 146.3)

End point values	Part 1: GZ389988A Dose 4	Part 1: GZ389988A Dose 5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	2		
Units: millimeter				
arithmetic mean (standard deviation)				
Day 7	-139 (± 119)	-205 (± 196.6)		
Day 14	-154.3 (± 128)	-232.5 (± 210)		
Day 21	-160.8 (± 155.7)	-236.5 (± 174.7)		
Day 28	-165.7 (± 155.8)	-195 (± 169.7)		
Day 42	-152.7 (± 154)	-197 (± 236.2)		
Day 56	-177.8 (± 149.6)	-178 (± 246.1)		
Day 70	-162.2 (± 153.8)	-144 (± 200.8)		
Day 84	-182 (± 149.3)	-98.5 (± 129.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Change From Baseline in WOMAC A1 Sub-score (Walking Pain) at Day 7, 14, 21, 28, 42, 56, 70 and 84

End point title	Part 1: Change From Baseline in WOMAC A1 Sub-score (Walking Pain) at Day 7, 14, 21, 28, 42, 56, 70 and 84[18]

End point description:

WOMAC A1 (measure of pain during walking on a flat surface) was part of the pain sub-scale (question 1) from the WOMAC index. WOMAC A1 was measured on a 100 mm VAS ranging from 0 to 100, where higher score indicated the higher level of pain. The change from baseline in WOMAC A1 sub-score was calculated at each specified visit (Day 7, 14, 21, 28, 42, 56, 70, and 84). Analysis was performed on PD population.

End point type	Secondary

End point timeframe:

Baseline, Day 7, 14, 21, 28, 42, 56, 70 and 84

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was evaluated for Part 1 only.

End point values	Part 1: Placebo	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	3	6
Units: millimeter				
arithmetic mean (standard deviation)				
Day 7	-39.9 (± 28.2)	-30.7 (± 36.5)	-5 (± 12.5)	-54.3 (± 20.3)
Day 14	-34.6 (± 32.6)	-25 (± 37.6)	-3.3 (± 3.8)	-57.7 (± 15.5)
Day 21	-36.9 (± 30.2)	-24.7 (± 36.5)	-9.7 (± 3.2)	-54 (± 20.7)

Day 28	-37.1 (± 29)	-20.7 (± 39.6)	-11.7 (± 3.1)	-50.3 (± 30.2)
Day 42	-41.1 (± 25.9)	-26.7 (± 33.2)	-11.7 (± 4.2)	-52 (± 32.6)
Day 56	-38.9 (± 28.8)	-28 (± 34.7)	-9 (± 8.7)	-52.2 (± 29.6)
Day 70	-38.3 (± 27.1)	-19.3 (± 34.8)	-16.3 (± 0.6)	-49.2 (± 29.3)
Day 84	-39.7 (± 29.1)	-24 (± 35.9)	-11.7 (± 12.1)	-44.5 (± 28.9)

End point values	Part 1: GZ389988A Dose 4	Part 1: GZ389988A Dose 5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	2		
Units: millimeter				
arithmetic mean (standard deviation)				
Day 7	-27 (± 21.6)	-39.5 (± 36.1)		
Day 14	-29.5 (± 25.3)	-46 (± 45.3)		
Day 21	-28.7 (± 35.3)	-44 (± 42.4)		
Day 28	-32.3 (± 29.9)	-39 (± 38.2)		
Day 42	-31.3 (± 30.7)	-39.5 (± 48.8)		
Day 56	-35.5 (± 31.2)	-34.5 (± 53)		
Day 70	-32.5 (± 32.5)	-31.5 (± 44.5)		
Day 84	-34.3 (± 31.9)	-15.5 (± 20.5)		

Statistical analyses

Statistical analysis title	Up to Day 28: GZ389988A Dose 1 vs Placebo
Statistical analysis description:	
Analysis was performed using linear mixed effect model with corresponding baseline as covariate and dose, week, week-by-dose interaction and gender as fixed effects.	
Comparison groups	Part 1: GZ389988A Dose 1 v Part 1: Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares mean difference
Point estimate	11.9984
Confidence interval	
level	90 %
sides	2-sided
lower limit	-22.6588
upper limit	46.6557

Statistical analysis title	Up to Day 28: GZ389988A Dose 2 vs Placebo
Statistical analysis description:	
Analysis was performed using linear mixed effect model with corresponding baseline as covariate and dose, week, week-by-dose interaction and gender as fixed effects.	
Comparison groups	Part 1: GZ389988A Dose 2 v Part 1: Placebo

Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares mean difference
Point estimate	24.1031
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.8636
upper limit	60.0698

Statistical analysis title	Up to Day 28: GZ389988A Dose 3 vs Placebo

Statistical analysis description:

Analysis was performed using linear mixed effect model with corresponding baseline as covariate and dose, week, week-by-dose interaction and gender as fixed effects.

Comparison groups	Part 1: GZ389988A Dose 3 v Part 1: Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares mean difference
Point estimate	-19.0405
Confidence interval	
level	90 %
sides	2-sided
lower limit	-46.943
upper limit	8.8621

Statistical analysis title	Up to Day 28: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

Analysis was performed using linear mixed effect model with corresponding baseline as covariate and dose, week, week-by-dose interaction and gender as fixed effects.

Comparison groups	Part 1: GZ389988A Dose 4 v Part 1: Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares mean difference
Point estimate	4.6515
Confidence interval	
level	90 %
sides	2-sided
lower limit	-23.6359
upper limit	32.939

Statistical analysis title	Up to Day 28: GZ389988A Dose 5 vs Placebo

Statistical analysis description:

Analysis was performed using linear mixed effect model with corresponding baseline as covariate and dose, week, week-by-dose interaction and gender as fixed effects.

Comparison groups	Part 1: GZ389988A Dose 5 v Part 1: Placebo
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares mean difference
Point estimate	-4.069
Confidence interval	
level	90 %
sides	2-sided
lower limit	-46.0989
upper limit	37.9609

Statistical analysis title	Up to Day 84: GZ389988A Dose 1 vs Placebo

Statistical analysis description:

Analysis was performed using linear mixed effect model with corresponding baseline as covariate and dose, week, week-by-dose interaction and gender as fixed effects.

Comparison groups	Part 1: GZ389988A Dose 1 v Part 1: Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares mean difference
Point estimate	13.5698
Confidence interval	
level	90 %
sides	2-sided
lower limit	-20.9287
upper limit	48.0684

Statistical analysis title	Up to Day 84: GZ389988A Dose 2 vs Placebo

Statistical analysis description:

Analysis was performed using linear mixed effect model with corresponding baseline as covariate and dose, week, week-by-dose interaction and gender as fixed effects.

Comparison groups	Part 1: GZ389988A Dose 2 v Part 1: Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares mean difference
Point estimate	22.9246
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.8893
upper limit	58.7384

Statistical analysis title	Up to Day 84: GZ389988A Dose 3 vs Placebo
Statistical analysis description:	
Analysis was performed using linear mixed effect model with corresponding baseline as covariate and dose, week, week-by-dose interaction and gender as fixed effects.	
Comparison groups	Part 1: GZ389988A Dose 3 v Part 1: Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares mean difference
Point estimate	-15.5315
Confidence interval	
level	90 %
sides	2-sided
lower limit	-43.306
upper limit	12.2429

Statistical analysis title	Up to Day 84: GZ389988A Dose 4 vs Placebo
Statistical analysis description:	
Analysis was performed using linear mixed effect model with corresponding baseline as covariate and dose, week, week-by-dose interaction and gender as fixed effects.	
Comparison groups	Part 1: GZ389988A Dose 4 v Part 1: Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares mean difference
Point estimate	3.8271
Confidence interval	
level	90 %
sides	2-sided
lower limit	-24.334
upper limit	31.9882

Statistical analysis title	Up to Day 84: GZ389988A Dose 5 vs Placebo
Statistical analysis description:	
Analysis was performed using linear mixed effect model with corresponding baseline as covariate and dose, week, week-by-dose interaction and gender as fixed effects.	
Comparison groups	Part 1: GZ389988A Dose 5 v Part 1: Placebo
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least squares mean difference
Point estimate	3.0649

Confidence interval	
level	90 %
sides	2-sided
lower limit	-38.7884
upper limit	44.9183

Secondary: Part 1: Change From Baseline in WOMAC Stiffness Sub-score at Day 7, 14, 21, 28, 42, 56, 70 and 84

End point title	Part 1: Change From Baseline in WOMAC Stiffness Sub-score at Day 7, 14, 21, 28, 42, 56, 70 and 84[19]

End point description:

WOMAC index is health status measure questionnaire of twenty-four questions comprising 3 sub-scales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question was measured on a 100-mm VAS ranging from 0=no pain to 100=maximal pain. Stiffness was defined as a sensation of decreased ease of movement in the index joint. WOMAC stiffness sub-score was sum of 2 questions with score ranging from 0 to 200 mm, where higher score indicated higher level of stiffness. The change from baseline in WOMAC stiffness sub-score was calculated at each specified visit (Day 7, 14, 21, 28, 42, 56, 70, and 84). Analysis was performed on PD population.

End point type	Secondary

End point timeframe:

Baseline, Day 7, 14, 21, 28, 42, 56, 70 and 84

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 1 only.

End point values	Part 1: Placebo	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	3	6
Units: millimeter				
arithmetic mean (standard deviation)				
Day 7	-79.7 (± 58.9)	-55.3 (± 54)	2.7 (± 14.2)	-87.7 (± 46.2)
Day 14	-72 (± 69.1)	-56 (± 70.4)	16.7 (± 26)	-96.3 (± 43.2)
Day 21	-73.3 (± 61.2)	-48.3 (± 69.3)	6.3 (± 17.5)	-96 (± 56.5)
Day 28	-74.4 (± 67.9)	-46.7 (± 73.2)	-6.7 (± 1.5)	-90.8 (± 74.9)
Day 42	-79 (± 60.4)	-39 (± 63.5)	0.7 (± 15.3)	-87.7 (± 67.4)
Day 56	-77 (± 63.9)	-44 (± 66.7)	-19.3 (± 9.9)	-87.8 (± 66.1)
Day 70	-84.6 (± 57.7)	-44.3 (± 70.8)	-13 (± 12.5)	-81.5 (± 66.5)
Day 84	-82.3 (± 57.4)	-43.7 (± 67.2)	-19.3 (± 15.3)	-63.2 (± 64.6)

End point values	Part 1: GZ389988A Dose 4	Part 1: GZ389988A Dose 5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	2		
Units: millimeter				
arithmetic mean (standard deviation)				

Day 7	-56.5 (± 57.1)	-78 (± 70.7)		
Day 14	-62 (± 56.9)	-97 (± 75)		
Day 21	-56 (± 59.6)	-98.5 (± 67.2)		
Day 28	-58.2 (± 65.1)	-86.5 (± 62.9)		
Day 42	-62.2 (± 65.5)	-75.5 (± 85.6)		
Day 56	-66 (± 64.3)	-77.5 (± 98.3)		
Day 70	-71 (± 65.5)	-60 (± 86.3)		
Day 84	-69.7 (± 67)	-46.5 (± 68.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Change From Baseline in WOMAC Physical Function Sub-score at Day 7, 14, 21, 28, 42, 56, 70 and 84

End point title	Part 1: Change From Baseline in WOMAC Physical Function Sub-score at Day 7, 14, 21, 28, 42, 56, 70 and 84[20]

End point description:

WOMAC index is health status measure questionnaire of twenty-four questions comprising of 3 sub-scales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question was measured on a 100-mm VAS ranging from 0=no pain to 100=maximal pain. WOMAC physical function sub-score was sum of 17 questions with score ranging from 0 to 1700 mm, where higher score indicated higher level of physical function. The change from baseline in WOMAC physical sub-score was calculated at each specified visit (Day 7, 14, 21, 28, 42, 56, 70, and 84). Analysis was performed on PD population.

End point type	Secondary

End point timeframe:

Baseline, Day 7, 14, 21, 28, 42, 56, 70 and 84

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 1 only.

End point values	Part 1: Placebo	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2	Part 1: GZ389988A Dose 3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	3	6
Units: millimeter				
arithmetic mean (standard deviation)				
Day 7	-720.1 (± 503.8)	-587.3 (± 577.3)	-24.3 (± 16.8)	-807.3 (± 469)
Day 14	-628.4 (± 586.4)	-460.3 (± 521.4)	35.3 (± 258)	-875.8 (± 411.2)
Day 21	-672.1 (± 561.9)	-387.7 (± 495.9)	-102.7 (± 138.4)	-853.8 (± 496.9)
Day 28	-631.9 (± 573.5)	-342.3 (± 515.4)	-110 (± 118.6)	-736.8 (± 605.6)
Day 42	-730.7 (± 493.2)	-336.7 (± 511.7)	-101 (± 91.1)	-759.5 (± 632.4)
Day 56	-725.6 (± 524.9)	-376.7 (± 557.5)	-179.7 (± 105)	-748 (± 575.3)
Day 70	-730.3 (± 495.2)	-332 (± 540.7)	-161.3 (± 115.7)	-718.5 (± 569.4)

Day 84	-718.9 (± 500.5)	-357 (± 535.5)	-226.7 (± 153.4)	-547.7 (± 531.4)

End point values	Part 1: GZ389988A Dose 4	Part 1: GZ389988A Dose 5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	2		
Units: millimeter				
arithmetic mean (standard deviation)				
Day 7	-460.2 (± 444.4)	-725.5 (± 634.3)		
Day 14	-561 (± 474.5)	-876 (± 596.8)		
Day 21	-552.5 (± 484.3)	-880.5 (± 539.5)		
Day 28	-565.3 (± 523.8)	-685 (± 547.3)		
Day 42	-541 (± 504.5)	-691 (± 767.9)		
Day 56	-579.7 (± 495.5)	-645.5 (± 785.6)		
Day 70	-606.8 (± 512.5)	-479 (± 646.3)		
Day 84	-605.3 (± 498)	-357.5 (± 354.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Change From Baseline Average Over 12 Weeks (up to Day 84) in Weekly Mean score of WOMAC A1 Pain Subscore (Walking Pain) Collected Daily in the Target Knee

End point title	Part 2: Change From Baseline Average Over 12 Weeks (up to Day 84) in Weekly Mean score of WOMAC A1 Pain Subscore (Walking Pain) Collected Daily in the Target Knee[21]

End point description:

WOMAC A1 (Question 1 of the pain sub-scale of WOMAC index) was used to measure the amount of pain in the target knee while walking on a flat surface during last 24 hours. It was measured daily on a 0-100 VAS ranging from 0=no pain to 100=maximal pain, where higher score indicated the higher intensity of pain. The weekly mean score of WOMAC A1 pain subscore, defined as average of daily measurements over the week were calculated for each week. The statistical analysis was done on the change from baseline score calculated at each week. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Days 1 to 84

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on a Scale				
least squares mean (standard error)	-20.6174 (± 3.0805)	-27.3981 (± 3.0790)		

Statistical analyses

Statistical analysis title	Over 12 weeks: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0636 [22]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.7807
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.1019
upper limit	0.5405
Variability estimate	Standard error of the mean
Dispersion value	4.4096

Notes:

[22] - Specified one-sided P-value.

Secondary: Part2:Change From Baseline Average Over Days 1to7(1 Week),1to14(2 Weeks),1to21(3 Weeks),1to42(6 Weeks),1to56(8 Weeks), and 1to70(10 Weeks) in Weekly Mean Score of WOMAC A1 Pain Subscore (Walking Pain) Collected Daily in the Target Knee

End point title	Part2:Change From Baseline Average Over Days 1to7(1 Week),1to14(2 Weeks),1to21(3 Weeks),1to42(6 Weeks),1to56(8 Weeks), and 1to70(10 Weeks) in Weekly Mean Score of WOMAC A1 Pain Subscore (Walking Pain) Collected Daily in the Target Knee[23]

End point description:

WOMAC A1 (Question 1 of the pain sub-scale of WOMAC index) was used to measure the amount of pain in the target knee while walking on a flat surface during last 24 hours. It was measured daily on a 0-100 VAS ranging from 0=no pain to 100=maximal pain, where higher score indicated the higher intensity of pain. The weekly mean score of WOMAC A1 pain subscore, defined as average of daily measurements over the week were calculated for each week. The statistical analysis was done on the change from baseline score calculated at each week. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Days 1 to 7, 1 to 14, 1 to 21, 1 to 42, 1 to 56, and 1 to 70

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on a Scale				
least squares mean (standard error)				
Days 1 to 7	-8.8568 (± 3.3391)	-9.9056 (± 3.3378)		
Days 1 to 14	-12.3714 (± 3.2149)	-18.1451 (± 3.2135)		
Days 1 to 21	-14.4834 (± 3.0802)	-21.2600 (± 3.0787)		
Days 1 to 42	-17.6864 (± 3.0139)	-25.2616 (± 3.0125)		
Days 1 to 56	-19.0908 (± 3.0223)	-26.3236 (± 3.0208)		
Days 1 to 70	-19.9442 (± 3.0493)	-27.0007 (± 3.0478)		

Statistical analyses

Statistical analysis title	Over Days 1 to 7: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4133 [24]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-1.0488
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.9906
upper limit	6.8929
Variability estimate	Standard error of the mean
Dispersion value	4.7714

Notes:

[24] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 14: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1062 [25]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.7737
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.4134
upper limit	1.866
Variability estimate	Standard error of the mean
Dispersion value	4.5975

Notes:

[25] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 21: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0638 [26]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.7766
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.1001
upper limit	0.5469
Variability estimate	Standard error of the mean
Dispersion value	4.4092

Notes:

[26] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 42: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0412 [27]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-7.5751
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.7424
upper limit	-0.4079
Variability estimate	Standard error of the mean
Dispersion value	4.3167

Notes:

[27] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 56: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0489 [28]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-7.2329
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.4193
upper limit	-0.0464
Variability estimate	Standard error of the mean
Dispersion value	4.3284

Notes:

[28] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 70: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0546 [29]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-7.0565

Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.3054
upper limit	0.1923
Variability estimate	Standard error of the mean
Dispersion value	4.366

Notes:

[29] - Specified one-sided P-value.

Secondary: Part2:Change From Baseline at Day 7(Week 1),14(Week 2),21(Week 3),28(Week 4),35(Week 5),42(Week 6),49(Week 7),56(Week 8),63(Week 9),70(Week 10),77(Week 11) and 84(Week 12) in Weekly Mean WOMAC A1 Pain Subscore (Walking Pain) Collected Daily in Target Knee

End point title	Part2:Change From Baseline at Day 7(Week 1),14(Week 2),21(Week 3),28(Week 4),35(Week 5),42(Week 6),49(Week 7),56(Week 8),63(Week 9),70(Week 10),77(Week 11) and 84(Week 12) in Weekly Mean WOMAC A1 Pain Subscore (Walking Pain) Collected Daily in Target Knee[30]

End point description:

WOMAC A1 (Question 1 of the pain sub-scale of WOMAC index) was used to measure the amount of pain in the target knee while walking on a flat surface during last 24 hours. It was measured daily on a 0-100 VAS ranging from 0=no pain to 100=maximal pain, where higher score indicated the higher intensity of pain. The weekly mean score of WOMAC A1 pain subscore, defined as average of daily measurements over the week were calculated for each week. The statistical analysis was done on the change from baseline score calculated at each week. Analysis was performed on mITT population. Here, "Number analyzed"(n)=number of subjects with available data at specified time point for each dose respectively.

End point type	Secondary

End point timeframe:

Baseline, Day 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on a Scale				
least squares mean (standard error)				
Day 7 (n= 52, 52)	-8.8568 (± 3.3391)	-9.9056 (± 3.3378)		
Day 14 (n= 52, 52)	-15.8860 (± 3.3768)	-26.3846 (± 3.3755)		
Day 21 (n= 52, 52)	-18.7074 (± 3.0849)	-27.4899 (± 3.0835)		
Day 28 (n= 52, 52)	-19.6397 (± 3.1821)	-29.2558 (± 3.1807)		
Day 35 (n= 52, 52)	-20.5792 (± 3.1606)	-29.1186 (± 3.1591)		
Day 42 (n= 52, 52)	-22.4494 (± 3.3453)	-29.4149 (± 3.3440)		
Day 49 (n= 52, 52)	-23.1269 (± 3.3366)	-29.5587 (± 3.3353)		

Day 56 (n= 52, 52)	-23.4806 (± 3.3393)	-29.4609 (± 3.3380)		
Day 63 (n= 52, 52)	-23.9254 (± 3.4491)	-29.9304 (± 3.4478)		
Day 70 (n= 52, 52)	-22.7903 (± 3.4670)	-29.4876 (± 3.4657)		
Day 77 (n= 52, 52)	-24.0650 (± 3.4885)	-29.8836 (± 3.4872)		
Day 84 (n= 52, 51)	-23.9020 (± 3.6026)	-28.8869 (± 3.6072)		

Statistical analyses

Statistical analysis title	At Day 7: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4133 [31]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-1.0488
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.9906
upper limit	6.8929
Variability estimate	Standard error of the mean
Dispersion value	4.7714

Notes:

[31] - Specified one-sided P-value.

Statistical analysis title	At Day 14: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [32]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-10.4986

Confidence interval	
level	90 %
sides	2-sided
lower limit	-18.5104
upper limit	-2.4867
Variability estimate	Standard error of the mean
Dispersion value	4.8241

Notes:

[32] - Specified one-sided P-value.

Statistical analysis title	At Day 21: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0247 [33]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-8.7824
Confidence interval	
level	90 %
sides	2-sided
lower limit	-16.1122
upper limit	-1.4527
Variability estimate	Standard error of the mean
Dispersion value	4.4159

Notes:

[33] - Specified one-sided P-value.

Statistical analysis title	At Day 28: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0185 [34]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-9.6161
Confidence interval	
level	90 %
sides	2-sided
lower limit	-17.1703
upper limit	-2.062
Variability estimate	Standard error of the mean
Dispersion value	4.5517

Notes:

[34] - Specified one-sided P-value.

Statistical analysis title	At Day 35: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0308 [35]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-8.5393
Confidence interval	
level	90 %
sides	2-sided
lower limit	-16.0423
upper limit	-1.0363
Variability estimate	Standard error of the mean
Dispersion value	4.5216

Notes:

[35] - Specified one-sided P-value.

Statistical analysis title	At Day 42: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.074 [36]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.9655
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.8971
upper limit	0.9661
Variability estimate	Standard error of the mean
Dispersion value	4.78

Notes:

[36] - Specified one-sided P-value.

Statistical analysis title	At Day 49: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0901 [37]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.4318
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.3434
upper limit	1.4798
Variability estimate	Standard error of the mean
Dispersion value	4.7678

Notes:

[37] - Specified one-sided P-value.

Statistical analysis title	At Day 56: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1064 [38]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.9804
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.8986
upper limit	1.9379
Variability estimate	Standard error of the mean
Dispersion value	4.7717

Notes:

[38] - Specified one-sided P-value.

Statistical analysis title	At Day 63: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1127 [39]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.005
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.1785
upper limit	2.1685
Variability estimate	Standard error of the mean
Dispersion value	4.9253

Notes:

[39] - Specified one-sided P-value.

Statistical analysis title	At Day 70: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0895 [40]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.6973
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.9124
upper limit	1.5179
Variability estimate	Standard error of the mean
Dispersion value	4.9504

Notes:

[40] - Specified one-sided P-value.

Statistical analysis title	At Day 77: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1227 [41]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.8185

Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.0838
upper limit	2.4468
Variability estimate	Standard error of the mean
Dispersion value	4.9805

Notes:

[41] - Specified one-sided P-value.

Statistical analysis title	At Day 84: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1674 [42]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.9849
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.5217
upper limit	3.5519
Variability estimate	Standard error of the mean
Dispersion value	5.144

Notes:

[42] - Specified one-sided P-value.

Secondary: Part2:Change From Baseline Average Over Days 1to7(1 Week),1to14(2 Weeks),1to21(3 Weeks), 1to28(4 Weeks),1to42(6 Weeks),1to56(8 Weeks),1to70(10 Weeks) and 1to84(12 Weeks) in Weekly Mean Overall Knee Pain Scores Collected Daily in Target Knee

End point title	Part2:Change From Baseline Average Over Days 1to7(1 Week),1to14(2 Weeks),1to21(3 Weeks), 1to28(4 Weeks),1to42(6 Weeks),1to56(8 Weeks),1to70(10 Weeks) and 1to84(12 Weeks) in Weekly Mean Overall Knee Pain Scores Collected Daily in Target Knee[43]

End point description:

Overall knee pain was measured daily in target knee on a 0-100 VAS ranging from 0=no pain to 100=maximal pain, where higher score indicated the higher level of pain. The weekly mean score of overall Knee pain score, defined as average of daily measurements over the week were calculated for each week. The statistical analysis was done on the change from baseline score calculated at each week. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Days 1 to 7, 1 to 14, 1 to 21, 1 to 28, 1 to 42, 1 to 56, 1 to 70, and 1 to 84

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on a Scale				
least squares mean (standard error)				
Days 1 to 7	-9.9274 (± 3.3127)	-10.7946 (± 3.3118)		
Days 1 to 14	-13.2629 (± 3.2686)	-18.4167 (± 3.2676)		
Days 1 to 21	-15.1501 (± 3.1853)	-21.1158 (± 3.1843)		
Days 1 to 28	-16.0917 (± 3.1581)	-22.9558 (± 3.1570)		
Days 1 to 42	-17.7356 (± 3.1494)	-24.8351 (± 3.1484)		
Days 1 to 56	-19.0673 (± 3.1611)	-25.6929 (± 3.1601)		
Days 1 to 70	-19.9019 (± 3.1966)	-26.2116 (± 3.1955)		
Days 1 to 84	-20.4833 (± 3.2299)	-26.5761 (± 3.2289)		

Statistical analyses

Statistical analysis title	Over Days 1 to 7: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4278 [44]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-0.8672
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.7645
upper limit	7.0301
Variability estimate	Standard error of the mean
Dispersion value	4.7477

Notes:

[44] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 14: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1371 [45]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.1538
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.9374
upper limit	2.6299
Variability estimate	Standard error of the mean
Dispersion value	4.686

Notes:

[45] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 21: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0974 [46]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.9658
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.554
upper limit	1.6224
Variability estimate	Standard error of the mean
Dispersion value	4.5699

Notes:

[46] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 28: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0665 [47]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.8641
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.3885
upper limit	0.6603
Variability estimate	Standard error of the mean
Dispersion value	4.5319

Notes:

[47] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 42: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0597 [48]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-7.0995
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.6032
upper limit	0.4041
Variability estimate	Standard error of the mean
Dispersion value	4.5199

Notes:

[48] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 56: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0736 [49]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.6255
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.1561
upper limit	0.9051
Variability estimate	Standard error of the mean
Dispersion value	4.5362

Notes:

[49] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 70: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0859 [50]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.3097
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.9222
upper limit	1.3027
Variability estimate	Standard error of the mean
Dispersion value	4.5856

Notes:

[50] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 84: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0957 [51]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.0927

Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.7823
upper limit	1.5969
Variability estimate	Standard error of the mean
Dispersion value	4.6321

Notes:

[51] - Specified one-sided P-value.

Secondary: Part2:Change From Baseline at Day 7(Week 1),14(Week 2),21(Week 3),28(Week 4),35(Week 5),42(Week 6),49(Week 7),56(Week 8),63(Week 9),70(Week 10),77(Week 11) and 84(Week 12) in Weekly Mean Score of Overall Knee Pain Collected Daily

End point title	Part2:Change From Baseline at Day 7(Week 1),14(Week 2),21(Week 3),28(Week 4),35(Week 5),42(Week 6),49(Week 7),56(Week 8),63(Week 9),70(Week 10),77(Week 11) and 84(Week 12) in Weekly Mean Score of Overall Knee Pain Collected Daily[52]

End point description:

Overall knee pain was measured daily on a 0-100 VAS ranging from 0=no pain to 100=maximal pain, where higher score indicated the higher level of pain. The weekly mean score of Overall knee pain, defined as average of daily measurements over the week were calculated for each week. The statistical analysis was done on the change from baseline score calculated at each week. Analysis was performed on mITT population. Here, "n"= number of subjects with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Day 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on a Scale				
least squares mean (standard error)				
Day 7 (n= 52, 52)	-9.9274 (± 3.3127)	-10.7946 (± 3.3118)		
Day 14 (n= 52, 52)	-16.5985 (± 3.5081)	-26.0388 (± 3.5072)		
Day 21 (n= 52, 52)	-18.9243 (± 3.3007)	-26.5141 (± 3.2997)		
Day 28 (n= 52, 52)	-18.9167 (± 3.3622)	-28.4757 (± 3.3612)		
Day 35 (n= 52, 52)	-19.9309 (± 3.3408)	-28.6657 (± 3.3399)		
Day 42 (n= 52, 52)	-22.1158 (± 3.5050)	-28.5219 (± 3.5041)		
Day 49 (n= 52, 52)	-22.6754 (± 3.4793)	-28.2430 (± 3.4784)		
Day 56 (n= 52, 52)	-23.4499 (± 3.5077)	-28.2891 (± 3.5068)		

Day 63 (n= 52, 52)	-23.6896 (± 3.6526)	-28.3854 (± 3.6517)		
Day 70 (n= 52, 52)	-22.7903 (± 3.6445)	-28.1876 (± 3.6437)		
Day 77 (n= 52, 52)	-23.5177 (± 3.6836)	-28.7047 (± 3.6827)		
Day 84 (n= 52, 51)	-23.2638 (± 3.7426)	-28.0923 (± 3.7481)		

Statistical analyses

Statistical analysis title	At Day 7: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4278 [53]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-0.8672
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.7645
upper limit	7.0301
Variability estimate	Standard error of the mean
Dispersion value	4.7477

Notes:

[53] - Specified one-sided P-value.

Statistical analysis title	At Day 14: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0315 [54]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-9.4404
Confidence interval	
level	90 %
sides	2-sided
lower limit	-17.7768
upper limit	-1.1039

Variability estimate	Standard error of the mean
Dispersion value	5.0205

Notes:

[54] - Specified one-sided P-value.

Statistical analysis title	At Day 21: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0559 [55]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-7.5898
Confidence interval	
level	90 %
sides	2-sided
lower limit	-15.442
upper limit	0.2623
Variability estimate	Standard error of the mean
Dispersion value	4.7309

Notes:

[55] - Specified one-sided P-value.

Statistical analysis title	At Day 28: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0249 [56]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-9.559
Confidence interval	
level	90 %
sides	2-sided
lower limit	-17.5526
upper limit	-1.5655
Variability estimate	Standard error of the mean
Dispersion value	4.8167

Notes:

[56] - Specified one-sided P-value.

Statistical analysis title	At Day 35: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0354 [57]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-8.7348
Confidence interval	
level	90 %
sides	2-sided
lower limit	-16.6783
upper limit	-0.7912
Variability estimate	Standard error of the mean
Dispersion value	4.7869

Notes:

[57] - Specified one-sided P-value.

Statistical analysis title	At Day 42: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1022 [58]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.4061
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.7298
upper limit	1.9176
Variability estimate	Standard error of the mean
Dispersion value	5.0162

Notes:

[58] - Specified one-sided P-value.

Statistical analysis title	At Day 49: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1331 [59]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.5676
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.8315
upper limit	2.6962
Variability estimate	Standard error of the mean
Dispersion value	4.9802

Notes:

[59] - Specified one-sided P-value.

Statistical analysis title	At Day 56: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1686 [60]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.8392
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.169
upper limit	3.4906
Variability estimate	Standard error of the mean
Dispersion value	5.02

Notes:

[60] - Specified one-sided P-value.

Statistical analysis title	At Day 63: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1853 [61]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.6959

Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.3618
upper limit	3.9701
Variability estimate	Standard error of the mean
Dispersion value	5.2226

Notes:

[61] - Specified one-sided P-value.

Statistical analysis title	At Day 70: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1514 [62]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.3973
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.0448
upper limit	3.2501
Variability estimate	Standard error of the mean
Dispersion value	5.2113

Notes:

[62] - Specified one-sided P-value.

Statistical analysis title	At Day 77: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1634 [63]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.187
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.925
upper limit	3.551
Variability estimate	Standard error of the mean
Dispersion value	5.2659

Notes:

[63] - Specified one-sided P-value.

Statistical analysis title	At Day 84: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1845 [64]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.8286
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.7105
upper limit	4.0534
Variability estimate	Standard error of the mean
Dispersion value	5.3526

Notes:

[64] - Specified one-sided P-value.

Secondary: Part 2: Change From Baseline Average Over Days 1to7(1 Week),1to14(2 Weeks),1to21(3 Weeks), 1to28(4 Weeks),1to42(6 Weeks),1to56(8 Weeks),1to70(10 Weeks) and 1to84(12 Weeks) in WOMAC A1 Pain Subscore (Walking Pain) Over Last 48 Hours (hrs) at Each Visit

End point title	Part 2: Change From Baseline Average Over Days 1to7(1 Week),1to14(2 Weeks),1to21(3 Weeks), 1to28(4 Weeks),1to42(6 Weeks),1to56(8 Weeks),1to70(10 Weeks) and 1to84(12 Weeks) in WOMAC A1 Pain Subscore (Walking Pain) Over Last 48 Hours (hrs) at Each Visit[65]

End point description:

WOMAC A1 (Question 1 of the pain sub-scale of WOMAC index) was used to measure the amount of pain in the target knee while walking on a flat surface during last 48 hours. It was measured daily on a 0-100 VAS ranging from 0=no pain to 100=maximal pain, where higher score indicated the higher intensity of pain. The statistical analysis was done on the change from baseline score (calculated as average of daily measurements over the week) for each week. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Days 1 to 7, 1 to 14, 1 to 21, 1 to 28, 1 to 42, 1 to 56, 1 to 70, and 1 to 84

Notes:

[65] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on Scale				
least squares mean (standard error)				
Days 1 to 7	-15.4217 (± 3.4624)	-20.4256 (± 3.4613)		
Days 1 to 14	-18.0488 (± 3.3113)	-23.7308 (± 3.3103)		
Days 1 to 21	-19.5463 (± 3.2320)	-25.6484 (± 3.2323)		
Days 1 to 28	-20.4634 (± 3.2113)	-26.6924 (± 3.2113)		
Days 1 to 42	-21.5405 (± 3.2292)	-27.3880 (± 3.2289)		
Days 1 to 56	-22.4092 (± 3.2288)	-27.8870 (± 3.2284)		
Days 1 to 70	-22.9995 (± 3.2364)	-28.3369 (± 3.2360)		
Days 1 to 84	-23.6827 (± 3.2759)	-28.8040 (± 3.2754)		

Statistical analyses

Statistical analysis title	Over Days 1 to 7: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1572 [66]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.0039
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.2235
upper limit	3.2156
Variability estimate	Standard error of the mean
Dispersion value	4.9481

Notes:

[66] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 14: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1166 [67]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.6819
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.5459
upper limit	2.1821
Variability estimate	Standard error of the mean
Dispersion value	4.7369

Notes:

[67] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 21: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0951 [68]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.1021
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.7836
upper limit	1.5795
Variability estimate	Standard error of the mean
Dispersion value	4.6273

Notes:

[68] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 28: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0893 [69]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.229
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.8622
upper limit	1.4042
Variability estimate	Standard error of the mean
Dispersion value	4.5981

Notes:

[69] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 42: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1044 [70]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.8475
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.5218
upper limit	1.8268
Variability estimate	Standard error of the mean
Dispersion value	4.6229

Notes:

[70] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 56: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1194 [71]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.4778

Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.1512
upper limit	2.1956
Variability estimate	Standard error of the mean
Dispersion value	4.6222

Notes:

[71] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 70: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.126 [72]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.3373
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.0285
upper limit	2.3538
Variability estimate	Standard error of the mean
Dispersion value	4.6328

Notes:

[72] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 84: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1386 [73]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.1214
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.9041
upper limit	2.6613
Variability estimate	Standard error of the mean
Dispersion value	4.6879

Notes:

[73] - Specified one-sided P-value.

Secondary: Part2:Change From Baseline in WOMAC A1 Pain Subscore (Walking Pain) at Days 7(Week 1),14(Week 2),21(Week 3),28(Week 4),42(Week 6),56(Week 8),70(Week 10) and 84(Week 12) as Measured by the VAS 0-100 Over the Last 48 Hours at Each Visit

End point title	Part2:Change From Baseline in WOMAC A1 Pain Subscore (Walking Pain) at Days 7(Week 1),14(Week 2),21(Week 3),28(Week 4),42(Week 6),56(Week 8),70(Week 10) and 84(Week 12) as Measured by the VAS 0-100 Over the Last 48 Hours at Each Visit[74]

End point description:

WOMAC A1 (Question 1 of the pain sub-scale of WOMAC index) was used to measure the amount of pain in the target knee while walking on a flat surface during last 48 hours. It was measured daily on a 0-100 VAS ranging from 0=no pain to 100=maximal pain, where higher score indicated the higher intensity of pain. The change from baseline in WOMAC A1 Pain sub-score was calculated at each specified visit (Day 7, 14, 21, 28, 42, 56, 70, and 84). Analysis was performed on mITT population. Here, "n" = number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Day 7, 14, 21, 28, 42, 56, 70, and 84

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on a Scale				
least squares mean (standard error)				
Day 7 (n= 51, 51)	-15.4217 (± 3.4624)	-20.4256 (± 3.4613)		
Day 14 (n= 52, 52)	-20.6760 (± 3.5315)	-27.0359 (± 3.5308)		
Day 21 (n= 52, 51)	-22.5414 (± 3.4460)	-29.4838 (± 3.4541)		
Day 28 (n= 52, 52)	-23.2144 (± 3.5295)	-29.8243 (± 3.5289)		
Day 42 (n= 52, 52)	-25.8491 (± 3.6966)	-30.1705 (± 3.6960)		
Day 56 (n= 52, 52)	-26.7529 (± 3.6175)	-30.3820 (± 3.6169)		
Day 70 (n= 52, 52)	-26.5414 (± 3.6795)	-31.0359 (± 3.6789)		
Day 84 (n= 52, 52)	-28.4644 (± 3.9791)	-32.0743 (± 3.9785)		

Statistical analyses

Statistical analysis title	At Day 7: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1572 [75]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.0039
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.2235
upper limit	3.2156
Variability estimate	Standard error of the mean
Dispersion value	4.9481

Notes:

[75] - Specified one-sided P-value.

Statistical analysis title	At Day 14: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1052 [76]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.3599
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.7348
upper limit	2.015
Variability estimate	Standard error of the mean
Dispersion value	5.0453

Notes:

[76] - Specified one-sided P-value.

Statistical analysis title	At Day 21: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0811 [77]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.9424
Confidence interval	
level	90 %
sides	2-sided
lower limit	-15.1275
upper limit	1.2426
Variability estimate	Standard error of the mean
Dispersion value	4.9325

Notes:

[77] - Specified one-sided P-value.

Statistical analysis title	At Day 28: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0964 [78]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.6099
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.9774
upper limit	1.7575
Variability estimate	Standard error of the mean
Dispersion value	5.0425

Notes:

[78] - Specified one-sided P-value.

Statistical analysis title	At Day 42: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2073 [79]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.3214

Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.0767
upper limit	4.4338
Variability estimate	Standard error of the mean
Dispersion value	5.2765

Notes:

[79] - Specified one-sided P-value.

Statistical analysis title	At Day 56: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2419 [80]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.6291
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.201
upper limit	4.9428
Variability estimate	Standard error of the mean
Dispersion value	5.1657

Notes:

[80] - Specified one-sided P-value.

Statistical analysis title	At Day 70: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1971 [81]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.4945
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.2108
upper limit	4.2217
Variability estimate	Standard error of the mean
Dispersion value	5.2526

Notes:

[81] - Specified one-sided P-value.

Statistical analysis title	At Day 84: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.263 [82]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.6099
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.0243
upper limit	5.8045
Variability estimate	Standard error of the mean
Dispersion value	5.6726

Notes:

[82] - Specified one-sided P-value.

Secondary: Part2:Change From Baseline Average Over Days1to7(1Week),1to14(2Weeks),1to21(3Weeks), 1to28(4Weeks),1to42(6Weeks),1to56(8Weeks),1to70(10Weeks),1to84(12Weeks)in WOMAC Index total,Pain,Stiffness,Physical Function Subscale Scores Over Last

End point title	Part2:Change From Baseline Average Over Days1to7(1Week),1to14(2Weeks),1to21(3Weeks), 1to28(4Weeks),1to42(6Weeks),1to56(8Weeks),1to70(10Weeks),1to84(12Weeks)in WOMAC Index total,Pain,Stiffness,Physical Function Subscale Scores Over Last 48hrs at Each Visit[83]

End point description:

WOMAC index is health status measure questionnaire of twenty-four questions comprising of 3 subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question was measured on a 0-100 VAS ranging from 0=minimum to 100=maximum during last 48 hours. Higher score= higher intensity of pain, worse physical function and higher level of stiffness respectively. A total WOMAC index score and a WOMAC sub-score for each dimension were calculated as an average of each item concerned. The statistical analysis was done on the change from baseline score (calculated as average of daily measurements over the week), for each week. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Days 1 to 7, 1 to 14, 1 to 21 , 1 to 28, 1 to 42, 1 to 56, 1 to 70, and 1 to 84

Notes:

[83] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on a Scale				
least squares mean (standard error)				
WOMAC index total score: Days 1 to 7	-13.9536 (± 3.2157)	-16.2722 (± 3.2156)		
WOMAC index total score: Days 1 to 14	-14.6039 (± 2.8898)	-18.4564 (± 2.8897)		
WOMAC index total score: Days 1 to 21	-15.0071 (± 2.7805)	-19.8222 (± 2.7811)		
WOMAC index total score: Days 1 to 28	-15.4475 (± 2.7629)	-20.6935 (± 2.7632)		
WOMAC index total score: Days 1 to 42	-16.0557 (± 2.7745)	-21.2131 (± 2.7747)		
WOMAC index total score: Days 1 to 56	-16.5502 (± 2.7821)	-21.5489 (± 2.7822)		
WOMAC index total score: Days 1 to 70	-16.9351 (± 2.7917)	-21.8778 (± 2.7917)		
WOMAC index total score: Days 1 to 84	-17.3448 (± 2.8144)	-22.1534 (± 2.8145)		
WOMAC pain: Days 1 to 7	-13.5225 (± 3.2676)	-18.4672 (± 3.2677)		
WOMAC pain: Days 1 to 14	-15.1259 (± 2.9754)	-21.4359 (± 2.9755)		
WOMAC pain: Days 1 to 21	-15.9809 (± 2.9200)	-22.8014 (± 2.9208)		
WOMAC pain: Days 1 to 28	-16.6680 (± 2.9075)	-23.8205 (± 2.9079)		
WOMAC pain: Days 1 to 42	-17.4526 (± 2.9282)	-24.2865 (± 2.9285)		
WOMAC pain: Days 1 to 56	-18.1224 (± 2.9414)	-24.6728 (± 2.9416)		
WOMAC pain: Days 1 to 70	-18.5926 (± 2.9533)	-25.0136 (± 2.9534)		
WOMAC pain: Days 1 to 84	-19.1073 (± 2.9844)	-25.4106 (± 2.9846)		
WOMAC stiffness: Days 1 to 7	-12.5795 (± 3.1733)	-15.2077 (± 3.1730)		
WOMAC stiffness: Days 1 to 14	-12.7060 (± 2.8869)	-16.6392 (± 2.8865)		
WOMAC stiffness: Days 1 to 21	-13.0431 (± 2.8011)	-17.3458 (± 2.8016)		
WOMAC stiffness: Days 1 to 28	-13.6227 (± 2.7517)	-17.8996 (± 2.7518)		
WOMAC stiffness: Days 1 to 42	-14.3493 (± 2.7603)	-18.3973 (± 2.7602)		
WOMAC stiffness: Days 1 to 56	-14.9539 (± 2.7693)	-18.6249 (± 2.7691)		
WOMAC stiffness: Days 1 to 70	-15.4091 (± 2.7859)	-18.8163 (± 2.7857)		
WOMAC stiffness: Days 1 to 84	-15.7973 (± 2.8181)	-19.1306 (± 2.8178)		
WOMAC physical function: Days 1 to 7	-14.3938 (± 3.3808)	-15.6007 (± 3.3805)		
WOMAC physical function: Days 1 to 14	-14.8167 (± 3.0225)	-17.6462 (± 3.0222)		

WOMAC physical function: Days 1 to 21	-15.0919 (± 2.8798)	-19.0910 (± 2.8802)		
WOMAC physical function: Days 1 to 28	-15.4419 (± 2.8524)	-19.9566 (± 2.8525)		
WOMAC physical function: Days 1 to 42	-15.9833 (± 2.8539)	-20.4948 (± 2.8538)		
WOMAC physical function: Days 1 to 56	-16.4127 (± 2.8536)	-20.8287 (± 2.8534)		
WOMAC physical function: Days 1 to 70	-16.7638 (± 2.8571)	-21.1705 (± 2.8568)		
WOMAC physical function: Days 1 to 84	-17.1449 (± 2.8742)	-21.4059 (± 2.8740)		

Statistical analyses

Statistical analysis title	Days1 to 7:WOMAC index-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3059 [84]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-2.3186
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.8826
upper limit	5.2454
Variability estimate	Standard error of the mean
Dispersion value	4.5517

Notes:

[84] - Specified one-sided P-value.

Statistical analysis title	Days1to14:WOMAC index-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1743 [85]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.8525

Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.6463
upper limit	2.9413
Variability estimate	Standard error of the mean
Dispersion value	4.0913

Notes:

[85] - Specified one-sided P-value.

Statistical analysis title	Days1to21:WOMAC index-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1121 [86]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.8151
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.3523
upper limit	1.7221
Variability estimate	Standard error of the mean
Dispersion value	3.9374

Notes:

[86] - Specified one-sided P-value.

Statistical analysis title	Days1to28:WOMAC index-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0915 [87]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.246
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.7414
upper limit	1.2494
Variability estimate	Standard error of the mean
Dispersion value	3.9124

Notes:

[87] - Specified one-sided P-value.

Statistical analysis title	Days1to42:WOMAC index-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0961 [88]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.1574
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.6798
upper limit	1.365
Variability estimate	Standard error of the mean
Dispersion value	3.9286

Notes:

[88] - Specified one-sided P-value.

Statistical analysis title	Days1to56:WOMAC index-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1037 [89]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.9987
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.5389
upper limit	1.5414
Variability estimate	Standard error of the mean
Dispersion value	3.9393

Notes:

[89] - Specified one-sided P-value.

Statistical analysis title	Days1to70:WOMAC index-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.107 [90]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.9427
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.5054
upper limit	1.62
Variability estimate	Standard error of the mean
Dispersion value	3.9528

Notes:

[90] - Specified one-sided P-value.

Statistical analysis title	Days1to84:WOMAC index-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1152 [91]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.8086
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.4247
upper limit	1.8076
Variability estimate	Standard error of the mean
Dispersion value	3.9849

Notes:

[91] - Specified one-sided P-value.

Statistical analysis title	Days1to7:WOMAC pain-GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1446 [92]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.9447
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.6514
upper limit	2.762
Variability estimate	Standard error of the mean
Dispersion value	4.6389

Notes:

[92] - Specified one-sided P-value.

Statistical analysis title	Days1to14:WOMAC pain-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0694 [93]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.31
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.3288
upper limit	0.7089
Variability estimate	Standard error of the mean
Dispersion value	4.2274

Notes:

[93] - Specified one-sided P-value.

Statistical analysis title	Days1to21:WOMAC pain-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0517 [94]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.8205

Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.7103
upper limit	0.0692
Variability estimate	Standard error of the mean
Dispersion value	4.15

Notes:

[94] - Specified one-sided P-value.

Statistical analysis title	Days1to28:WOMAC pain-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0433 [95]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-7.1525
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.0125
upper limit	-0.2924
Variability estimate	Standard error of the mean
Dispersion value	4.1321

Notes:

[95] - Specified one-sided P-value.

Statistical analysis title	Days1to42:WOMAC pain-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0518 [96]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.8339
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.7423
upper limit	0.0745
Variability estimate	Standard error of the mean
Dispersion value	4.1612

Notes:

[96] - Specified one-sided P-value.

Statistical analysis title	Days1to56:WOMAC pain-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0601 [97]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.5504
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.4896
upper limit	0.3888
Variability estimate	Standard error of the mean
Dispersion value	4.1796

Notes:

[97] - Specified one-sided P-value.

Statistical analysis title	Days1to70:WOMAC pain-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0646 [98]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.421
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.3882
upper limit	0.5461
Variability estimate	Standard error of the mean
Dispersion value	4.1964

Notes:

[98] - Specified one-sided P-value.

Statistical analysis title	Days1to84:WOMAC pain-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0701 [99]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.3033
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.3433
upper limit	0.7368
Variability estimate	Standard error of the mean
Dispersion value	4.2402

Notes:

[99] - Specified one-sided P-value.

Statistical analysis title	Days1to7:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2799
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-2.6283
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.0893
upper limit	4.8328
Variability estimate	Standard error of the mean
Dispersion value	4.4902

Statistical analysis title	Day1to14:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.169 [100]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.9332
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.7165
upper limit	2.8502
Variability estimate	Standard error of the mean
Dispersion value	4.0855

Notes:

[100] - Specified one-sided P-value.

Statistical analysis title	Day1to21:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1402 [101]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.3027
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.8849
upper limit	2.2795
Variability estimate	Standard error of the mean
Dispersion value	3.9648

Notes:

[101] - Specified one-sided P-value.

Statistical analysis title	Day1to28:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1374 [102]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.277

Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.7429
upper limit	2.189
Variability estimate	Standard error of the mean
Dispersion value	3.8948

Notes:

[102] - Specified one-sided P-value.

Statistical analysis title	Day1to42:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1513 [103]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.048
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.5339
upper limit	2.4379
Variability estimate	Standard error of the mean
Dispersion value	3.9068

Notes:

[103] - Specified one-sided P-value.

Statistical analysis title	Day1to56:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1756 [104]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.6711
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.1782
upper limit	2.8361
Variability estimate	Standard error of the mean
Dispersion value	3.9195

Notes:

[104] - Specified one-sided P-value.

Statistical analysis title	Day1to70:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1948 [105]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.4073
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.9535
upper limit	3.139
Variability estimate	Standard error of the mean
Dispersion value	3.9429

Notes:

[105] - Specified one-sided P-value.

Statistical analysis title	Day1to84:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2026 [106]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.3333
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.9551
upper limit	3.2886
Variability estimate	Standard error of the mean
Dispersion value	3.9883

Notes:

[106] - Specified one-sided P-value.

Statistical analysis title	Day1to7:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4007 [107]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-1.2069
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.1559
upper limit	6.742
Variability estimate	Standard error of the mean
Dispersion value	4.7829

Notes:

[107] - Specified one-sided P-value.

Statistical analysis title	Day1to14:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2549 [108]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-2.8295
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.9312
upper limit	4.2721
Variability estimate	Standard error of the mean
Dispersion value	4.2764

Notes:

[108] - Specified one-sided P-value.

Statistical analysis title	Day1to21:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1644 [109]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.9991
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.7655
upper limit	2.7673
Variability estimate	Standard error of the mean
Dispersion value	4.0753

Notes:

[109] - Specified one-sided P-value.

Statistical analysis title	Day1to28:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.133 [110]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.5148
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.2162
upper limit	2.1867
Variability estimate	Standard error of the mean
Dispersion value	4.0364

Notes:

[110] - Specified one-sided P-value.

Statistical analysis title	Day1to42:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1333 [111]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.5115

Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.2161
upper limit	2.1931
Variability estimate	Standard error of the mean
Dispersion value	4.0383

Notes:

[111] - Specified one-sided P-value.

Statistical analysis title	Day1to56:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1384 [112]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.416
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.12
upper limit	2.2879
Variability estimate	Standard error of the mean
Dispersion value	4.0379

Notes:

[112] - Specified one-sided P-value.

Statistical analysis title	Day1to70:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1392 [113]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.4066
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.1187
upper limit	2.3054
Variability estimate	Standard error of the mean
Dispersion value	4.0427

Notes:

[113] - Specified one-sided P-value.

Statistical analysis title	Day1to84:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1487 [114]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.261
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.0134
upper limit	2.4914
Variability estimate	Standard error of the mean
Dispersion value	4.067

Notes:

[114] - Specified one-sided P-value.

Secondary: Part2:Change From Baseline at Days 7(Week 1),14(Week 2),21(Week 3),28(Week 4),42(Week 6),56(Week 8),70(Week 10) and 84(Week 12) in WOMAC Index Total, Pain, Stiffness, and Physical Function Subscores Over the Last 48 Hours at Each Visit

End point title	Part2:Change From Baseline at Days 7(Week 1),14(Week 2),21(Week 3),28(Week 4),42(Week 6),56(Week 8),70(Week 10) and 84(Week 12) in WOMAC Index Total, Pain, Stiffness, and Physical Function Subscores Over the Last 48 Hours at Each Visit[115]

End point description:

WOMAC index is health status measure questionnaire of twenty-four questions comprising of 3 subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question was measured on a 0-100 VAS ranging from 0=minimum to 100=maximum over last 48 hours. A total WOMAC index score and a WOMAC sub-score for each dimension were calculated as an average of each item concerned. The change from baseline in all sub-scores were calculated at each specified visit (Day 7, 14, 21, 28, 42, 56, 70, and 84). Analysis was performed on mITT population. Here, "n" = number of subjects with available data at specified time-points.

End point type	Secondary

End point timeframe:

Baseline, Days 7, 14, 21, 28, 42, 56, 70, and 84

Notes:

[115] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on a Scale				
least squares mean (standard error)				
WOMAC index total score: Day 7 (n= 51, 51)	-13.9536 (± 3.2157)	-16.2722 (± 3.2156)		
WOMAC index total score: Day 14 (n= 52, 52)	-15.2543 (± 2.8562)	-20.6406 (± 2.8561)		
WOMAC index total score: Day 21 (n= 52, 51)	-15.8136 (± 2.8464)	-22.5539 (± 2.8524)		
WOMAC index total score: Day 28 (n= 52, 52)	-16.7687 (± 3.0042)	-23.3073 (± 3.0041)		
WOMAC index total score: Day 42 (n= 52, 52)	-18.4882 (± 3.1248)	-23.2913 (± 3.1247)		
WOMAC index total score: Day 56 (n= 52, 52)	-19.0227 (± 3.1251)	-23.2280 (± 3.1251)		
WOMAC index total score: Day 70 (n= 52, 52)	-19.2446 (± 3.1578)	-23.8514 (± 3.1578)		
WOMAC index total score: Day 84 (n= 52, 52)	-20.2126 (± 3.2945)	-24.0822 (± 3.2944)		
WOMAC pain: Day 7 (n= 51, 51)	-13.5225 (± 3.2676)	-18.4672 (± 3.2677)		
WOMAC pain: Day 14 (n= 52, 52)	-16.7293 (± 2.9820)	-24.4045 (± 2.9820)		
WOMAC pain: Day 21 (n= 52, 51)	-17.6908 (± 3.1114)	-25.5325 (± 3.1180)		
WOMAC pain: Day 28 (n= 52, 52)	-18.7293 (± 3.1775)	-26.8776 (± 3.1775)		
WOMAC pain: Day 42 (n= 52, 52)	-20.5908 (± 3.3318)	-26.1507 (± 3.3318)		
WOMAC pain: Day 56 (n= 52, 52)	-21.4716 (± 3.3291)	-26.6045 (± 3.3291)		
WOMAC pain: Day 70 (n= 52, 52)	-21.4139 (± 3.3493)	-27.0584 (± 3.3493)		
WOMAC pain: Day 84 (n= 52, 52)	-22.7101 (± 3.5443)	-28.1891 (± 3.5443)		
WOMAC stiffness: Day 7 (n= 51, 51)	-12.5795 (± 3.1733)	-15.2077 (± 3.1730)		
WOMAC stiffness: Day 14 (n= 52, 52)	-12.8326 (± 2.9546)	-18.0707 (± 2.9542)		
WOMAC stiffness: Day 21 (n= 52, 51)	-13.7172 (± 2.9834)	-18.7590 (± 2.9905)		
WOMAC stiffness: Day 28 (n= 52, 52)	-15.3614 (± 2.9550)	-19.5611 (± 2.9546)		
WOMAC stiffness: Day 42 (n= 52, 52)	-17.2557 (± 3.1652)	-20.3880 (± 3.1648)		
WOMAC stiffness: Day 56 (n= 52, 52)	-17.9768 (± 3.1887)	-19.7630 (± 3.1884)		
WOMAC stiffness: Day 70 (n= 52, 52)	-18.1403 (± 3.2690)	-19.9649 (± 3.2686)		
WOMAC stiffness: Day 84 (n= 52, 52)	-18.5153 (± 3.4455)	-21.3303 (± 3.4452)		
WOMAC physical function: Day 7 (n= 51, 51)	-14.3938 (± 3.3808)	-15.6007 (± 3.3805)		
WOMAC physical function: Day 14 (n= 52, 52)	-15.2395 (± 2.9659)	-19.6916 (± 2.9656)		

WOMAC physical function: Day 21 (n= 52, 51)	-15.6423 (± 2.8821)	-21.9805 (± 2.8879)		
WOMAC physical function: Day 28 (n= 52, 52)	-16.4918 (± 3.0682)	-22.5536 (± 3.0678)		
WOMAC physical function: Day 42 (n= 52, 52)	-18.1491 (± 3.1651)	-22.6475 (± 3.1648)		
WOMAC physical function: Day 56 (n= 52, 52)	-18.5597 (± 3.1579)	-22.4982 (± 3.1576)		
WOMAC physical function: Day 70 (n= 52, 52)	-18.8708 (± 3.1861)	-23.2211 (± 3.1858)		
WOMAC physical function: Day 84 (n= 52, 52)	-19.8119 (± 3.3138)	-23.0536 (± 3.3135)		

Statistical analyses

Statistical analysis title	At Day 7: WOMAC index- GZ389988A Dose 4 vs Placebo
Statistical analysis description:	
The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.	
Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3059
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-2.3186
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.8826
upper limit	5.2454
Variability estimate	Standard error of the mean
Dispersion value	4.5517

Statistical analysis title	At Day 14:WOMAC index- GZ389988A Dose4 vs Placebo
Statistical analysis description:	
The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.	
Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0929
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.3864

Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.1001
upper limit	1.3274
Variability estimate	Standard error of the mean
Dispersion value	4.0438

Statistical analysis title	At Day 21:WOMAC index- GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0489
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.7403
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.4366
upper limit	-0.044
Variability estimate	Standard error of the mean
Dispersion value	4.0344

Statistical analysis title	At Day 28:WOMAC index- GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0636
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.5386
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.5968
upper limit	0.5195
Variability estimate	Standard error of the mean
Dispersion value	4.2529

Statistical analysis title	At Day 42:WOMAC index- GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.8031
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.1439
upper limit	2.5378
Variability estimate	Standard error of the mean
Dispersion value	4.4233

Statistical analysis title	At Day 56:WOMAC index- GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.172
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.2053
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.5475
upper limit	3.1369
Variability estimate	Standard error of the mean
Dispersion value	4.4238

Statistical analysis title	At Day 70:WOMAC index- GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1526
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.6067
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.0255
upper limit	2.8121
Variability estimate	Standard error of the mean
Dispersion value	4.47

Statistical analysis title	At Day 84:WOMAC index- GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2043
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.8696
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.6091
upper limit	3.87
Variability estimate	Standard error of the mean
Dispersion value	4.663

Statistical analysis title	At Day 7:WOMAC pain-GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1446
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.9447
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.6514
upper limit	2.762
Variability estimate	Standard error of the mean
Dispersion value	4.6389

Statistical analysis title	At Day 14:WOMAC pain-GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0365
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-7.6752
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.7089
upper limit	-0.6415
Variability estimate	Standard error of the mean
Dispersion value	4.2368

Statistical analysis title	At Day 21:WOMAC pain-GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0396
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-7.8417

Confidence interval	
level	90 %
sides	2-sided
lower limit	-15.1836
upper limit	-0.4998
Variability estimate	Standard error of the mean
Dispersion value	4.4236

Statistical analysis title	At Day 28:WOMAC pain-GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0369
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-8.1483
Confidence interval	
level	90 %
sides	2-sided
lower limit	-15.6366
upper limit	-0.6601
Variability estimate	Standard error of the mean
Dispersion value	4.512

Statistical analysis title	At Day 42:WOMAC pain-GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1212
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.5599
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.4087
upper limit	2.289
Variability estimate	Standard error of the mean
Dispersion value	4.7293

Statistical analysis title	At Day 56:WOMAC pain-GZ389988A Dose 4 vs Placebo
Statistical analysis description: The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects	
Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.1329
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.9761
upper limit	2.7103
Variability estimate	Standard error of the mean
Dispersion value	4.7255

Statistical analysis title	At Day 70:WOMAC pain-GZ389988A Dose 4 vs Placebo
Statistical analysis description: The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects	
Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1189
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.6445
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.5353
upper limit	2.2464
Variability estimate	Standard error of the mean
Dispersion value	4.7541

Statistical analysis title	At Day 84:WOMAC pain-GZ389988A Dose 4 vs Placebo
Statistical analysis description: The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects	

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1392
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.4791
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.826
upper limit	2.8679
Variability estimate	Standard error of the mean
Dispersion value	5.0288

Statistical analysis title	At Day7:WOMAC stiffness-GZ389988A Dose4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2799
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-2.6283
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.0893
upper limit	4.8328
Variability estimate	Standard error of the mean
Dispersion value	4.4902

Statistical analysis title	At Day14:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1066
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.2381
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.1806
upper limit	1.7044
Variability estimate	Standard error of the mean
Dispersion value	4.1812

Statistical analysis title	At Day21:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1179
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.0418
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.0581
upper limit	1.9744
Variability estimate	Standard error of the mean
Dispersion value	4.2272

Statistical analysis title	At Day28:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1588
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.1996

Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.1391
upper limit	2.7398
Variability estimate	Standard error of the mean
Dispersion value	4.1817

Statistical analysis title	At Day42:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: Placebo v Part 2: GZ389988A Dose 4 from Part 1
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2429
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.1323
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.5647
upper limit	4.3
Variability estimate	Standard error of the mean
Dispersion value	4.4787

Statistical analysis title	At Day56:WOMAC stiffness-GZ389988A Dose4vsPlacebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3465
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-1.7862
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.2753
upper limit	5.7029
Variability estimate	Standard error of the mean
Dispersion value	4.5121

Statistical analysis title	At Day70:WOMAC stiffness-GZ389988A Dose4vsPlacebo
Statistical analysis description: The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects	
Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.347
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-1.8246
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.5019
upper limit	5.8526
Variability estimate	Standard error of the mean
Dispersion value	4.6255

Statistical analysis title	At Day84:WOMAC stiffness-GZ389988A Dose4vsPlacebo
Statistical analysis description: The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects	
Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2825
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-2.815
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.9068
upper limit	5.2767
Variability estimate	Standard error of the mean
Dispersion value	4.875

Statistical analysis title	At Day7:WOMAC physical function-GZ389988A/Placebo
Statistical analysis description: The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects	

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4007
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-1.2069
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.1559
upper limit	6.742
Variability estimate	Standard error of the mean
Dispersion value	4.7829

Statistical analysis title	Day14:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1456
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.4521
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.4195
upper limit	2.5153
Variability estimate	Standard error of the mean
Dispersion value	4.1965

Statistical analysis title	Day21:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0618
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.3382
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.1144
upper limit	0.4379
Variability estimate	Standard error of the mean
Dispersion value	4.0825

Statistical analysis title	Day28:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0828
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.0618
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.2662
upper limit	1.1425
Variability estimate	Standard error of the mean
Dispersion value	4.341

Statistical analysis title	Day42:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1587
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.4985

Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.9303
upper limit	2.9334
Variability estimate	Standard error of the mean
Dispersion value	4.4781

Statistical analysis title	Day56:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.9385
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.3538
upper limit	3.4768
Variability estimate	Standard error of the mean
Dispersion value	4.4678

Statistical analysis title	Day70:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1684
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.3503
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.8315
upper limit	3.131
Variability estimate	Standard error of the mean
Dispersion value	4.5077

Statistical analysis title	Day84:WOMAC physical function-GZ389988A/Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2454
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.2417
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.0232
upper limit	4.5398
Variability estimate	Standard error of the mean
Dispersion value	4.6883

Secondary: Part 2: Change From Baseline in Patient Global Assessment (PGA) of Disease Status Average Over Days 1 to 7 (1 Week), 1 to 14 (2 Weeks), 1 to 21 (3 Weeks), 1 to 28 (4 Weeks), 1 to 42 (6 Weeks), 1 to 56 (8 Weeks), 1 to 70 (10 Weeks) and 1 to 84 (12 Weeks)

End point title	Part 2: Change From Baseline in Patient Global Assessment (PGA) of Disease Status Average Over Days 1 to 7 (1 Week), 1 to 14 (2 Weeks), 1 to 21 (3 Weeks), 1 to 28 (4 Weeks), 1 to 42 (6 Weeks), 1 to 56 (8 Weeks), 1 to 70 (10 Weeks) and 1 to 84 (12 Weeks)[116]

End point description:

The PGA was used by subjects to rate the disease (osteoarthritis) status of the target knee. Subjects provided their response on a 0-100 VAS ranging from 0 (very well) to 100 (very poor), where higher scores indicated very poor condition of the knee. The statistical analysis was done on the change from baseline score (calculated as average of daily measurements over the week) for each week. Analysis was performed on mITT population. Here, "number of subjects analysed"= subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Days 1 to 7, 1 to 14, 1 to 21, 1 to 28, 1 to 42, 1 to 56, 1 to 70, and 1 to 84

Notes:

[116] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	50		
Units: Units on a Scale				
least squares mean (standard error)				
Days 1 to 7	-14.1316 (± 3.3297)	-15.2721 (± 3.3621)		
Days 1 to 14	-13.8982 (± 2.9877)	-17.0106 (± 3.0163)		
Days 1 to 21	-14.3368 (± 2.8826)	-18.7073 (± 2.9113)		
Days 1 to 28	-14.7325 (± 2.8647)	-19.7327 (± 2.8927)		
Days 1 to 42	-15.6194 (± 2.8508)	-20.0680 (± 2.8780)		
Days 1 to 56	-15.9930 (± 2.8412)	-20.1116 (± 2.8683)		
Days 1 to 70	-16.0358 (± 2.8573)	-20.2284 (± 2.8846)		
Days 1 to 84	-16.3448 (± 2.8734)	-20.5685 (± 2.9008)		

Statistical analyses

Statistical analysis title	Over Days 1 to 7: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4051 [117]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-1.1405
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.0084
upper limit	6.7274
Variability estimate	Standard error of the mean
Dispersion value	4.7344

Notes:

[117] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 14: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2328 [118]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-3.1124
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.1667
upper limit	3.9419
Variability estimate	Standard error of the mean
Dispersion value	4.2484

Notes:

[118] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 21: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1445 [119]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.3705
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.178
upper limit	2.437
Variability estimate	Standard error of the mean
Dispersion value	4.0999

Notes:

[119] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 28: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1113 [120]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.0002
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.7651
upper limit	1.7647
Variability estimate	Standard error of the mean
Dispersion value	4.0742

Notes:

[120] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 42: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1376 [121]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.4486
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.1802
upper limit	2.283
Variability estimate	Standard error of the mean
Dispersion value	4.0539

Notes:

[121] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 56: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1553 [122]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.1185

Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.8277
upper limit	2.5906
Variability estimate	Standard error of the mean
Dispersion value	4.0402

Notes:

[122] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 70: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1523 [123]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.1926
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.94
upper limit	2.5549
Variability estimate	Standard error of the mean
Dispersion value	4.0631

Notes:

[123] - Specified one-sided P-value.

Statistical analysis title	Over Days 1 to 84: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1519 [124]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.2237
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.0094
upper limit	2.5621
Variability estimate	Standard error of the mean
Dispersion value	4.086

Notes:

[124] - Specified one-sided P-value.

Secondary: Part 2: Change From Baseline in PGA of Disease Status at Each Visit (Days 7, 14, 21, 28, 42, 56, 70 and 84)

End point title	Part 2: Change From Baseline in PGA of Disease Status at Each Visit (Days 7, 14, 21, 28, 42, 56, 70 and 84)[125]

End point description:

The PGA was used by subjects to rate the disease (osteoarthritis) status of the target knee. Subjects provided their response on a 0-100 VAS ranging from 0 (very well) to 100 (very poor), where higher scores indicated very poor condition of the knee. The change from baseline in all sub-scores were calculated at each specified visit (Day 7, 14, 21, 28, 42, 56, 70, and 84). Analysis was performed on mITT population. Here, "n" = number of subjects with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Day 7, 14, 21, 28, 42, 56, 70, and 84

Notes:

[125] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on a Scale				
least squares mean (standard error)				
Day 7 (n= 50, 49)	-14.1316 (± 3.3297)	-15.2721 (± 3.3621)		
Day 14 (n= 51, 50)	-13.6649 (± 3.0777)	-18.7492 (± 3.1072)		
Day 21 (n= 51, 49)	-15.2139 (± 3.1048)	-22.1005 (± 3.1442)		
Day 28 (n= 51, 50)	-15.9198 (± 3.2593)	-22.8092 (± 3.2907)		
Day 42 (n= 50, 50)	-19.1669 (± 3.2510)	-21.4092 (± 3.2726)		
Day 56 (n= 51, 50)	-17.8610 (± 3.2428)	-20.3292 (± 3.2740)		
Day 70 (n= 51, 50)	-16.2923 (± 3.4257)	-20.9292 (± 3.4588)		
Day 84 (n= 51, 50)	-18.5080 (± 3.4637)	-22.9492 (± 3.4972)		

Statistical analyses

Statistical analysis title	At Day 7: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4051 [126]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-1.1405
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.0084
upper limit	6.7274
Variability estimate	Standard error of the mean
Dispersion value	4.7344

Notes:

[126] - Specified one-sided P-value.

Statistical analysis title	At Day 14: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1241 [127]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-5.0843
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.3511
upper limit	2.1825
Variability estimate	Standard error of the mean
Dispersion value	4.3762

Notes:

[127] - Specified one-sided P-value.

Statistical analysis title	At Day 21: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0612 [128]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.8866

Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.2264
upper limit	0.4532
Variability estimate	Standard error of the mean
Dispersion value	4.4216

Notes:

[128] - Specified one-sided P-value.

Statistical analysis title	At Day 28: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0701 [129]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-6.8894
Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.581
upper limit	0.8022
Variability estimate	Standard error of the mean
Dispersion value	4.6342

Notes:

[129] - Specified one-sided P-value.

Statistical analysis title	At Day 42: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3141 [130]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-2.2422
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.9037
upper limit	5.4192
Variability estimate	Standard error of the mean
Dispersion value	4.6156

Notes:

[130] - Specified one-sided P-value.

Statistical analysis title	At Day 56: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2968 [131]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-2.4682
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.1217
upper limit	5.1853
Variability estimate	Standard error of the mean
Dispersion value	4.6108

Notes:

[131] - Specified one-sided P-value.

Statistical analysis title	At Day 70: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1717 [132]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.6369
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.7232
upper limit	3.4495
Variability estimate	Standard error of the mean
Dispersion value	4.8706

Notes:

[132] - Specified one-sided P-value.

Statistical analysis title	At Day 84: GZ389988A Dose 4 vs Placebo

Statistical analysis description:

The linear mixed effect model included the corresponding baseline as covariate and treatment, week, week-by-treatment interaction and gender as fixed effects.

Comparison groups	Part 2: GZ389988A Dose 4 from Part 1 v Part 2: Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1847 [133]
Method	Linear Mixed Effect Model
Parameter estimate	Least squares mean difference
Point estimate	-4.4412
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.6177
upper limit	3.7354
Variability estimate	Standard error of the mean
Dispersion value	4.9246

Notes:

[133] - Specified one-sided P-value.

Secondary: Part 2: Patient Global Impression of Change (PGIC) Score at Day 28 (Over First Four Weeks), 56 (Over First Eight Weeks) and 84 (Over Twelve Weeks)

End point title	Part 2: Patient Global Impression of Change (PGIC) Score at Day 28 (Over First Four Weeks), 56 (Over First Eight Weeks) and 84 (Over Twelve Weeks)[134]

End point description:

PGIC scale is an instrument to measure the change in subject's overall health status for the duration of last 4 week at each specified visit (Day 28, 56 and 84). It was rated on a scale ranging from 1(no change or worse) to 7 (a great deal better, and a considerable improvement), where higher score indicates better condition (health status). Analysis was performed on mITT population. Here, "n" = number of subjects with available data at specified time points for each dose respectively.

End point type	Secondary

End point timeframe:

Day 28, 56, and 84

Notes:

[134] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: scores on scale				
arithmetic mean (standard deviation)				
Day 28 (n= 52, 52)	3.7 (± 1.7)	4.4 (± 1.8)		
Day 56 (n= 51, 52)	3.8 (± 1.8)	4.1 (± 1.8)		
Day 84 (n= 52, 52)	3.8 (± 1.8)	4.3 (± 1.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Patient Global Response to Therapy (PGART) Score Over the Last Four Weeks at Day 28 (4 Weeks), 56 (8 Weeks) and 84 (12 Weeks)

End point title	Part 2: Patient Global Response to Therapy (PGART) Score Over the Last Four Weeks at Day 28 (4 Weeks), 56 (8 Weeks) and 84 (12 Weeks)[135]

End point description:

PGART was an instrument to measure the subjects' s assessment of response of OA to study treatment over the last 4 weeks at each specified visit (Day 28, 56 and 84) on 0-100 VAS ranging from 0 (none) to 100 (excellent), where higher score indicated better response to treatment. Analysis was performed on mITT population. Here, "n" = number of subjects with available data at specified time point.

End point type	Secondary

End point timeframe:

Day 28, 56, and 84

Notes:

[135] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Day 28 (n= 52, 52)	41.0 (± 27.4)	53.9 (± 29.4)		
Day 56 (n= 51, 52)	44.2 (± 27.0)	52.5 (± 28.9)		
Day 84 (n= 52, 52)	42.5 (± 29.4)	52.1 (± 29.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects With Response to Therapy Based on Outcome Measures in Rheumatology Committee and the Osteoarthritis Research Society International (OMERACT-OARSI) Criteria

End point title	Part 2: Percentage of Subjects With Response to Therapy Based on Outcome Measures in Rheumatology Committee and the Osteoarthritis Research Society International (OMERACT-OARSI) Criteria[136]

End point description:

The OMERACT-OARSI criteria was used to determine whether subjects maybe considered responders to treatment. OMERACT-OARSI responder was a subject who had better response on the WOMAC pain subscale score, a better response on the WOMAC physical function subscale score or improvement on atleast 2 of the 3 domains:WOMAC pain subscale score(overall score range of 0[no pain] to 100[maximal pain],higher scores indicating higher intensity of pain),WOMAC physical function subscale score(overall score range of 0[minimum] to 100[maximum],higher scores indicating worse physical function)and PGA of arthritic condition score(overall score range of 0(very well) to 100(very poor),where higher scores indicated very poor condition of the knee). Subscore was calculated as average of each item specific of each dimension. Subjects were classified as responder or not responder to OMERACT-OARSI criteria. The endpoint value is the percentage of responder subjects. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Week 4, 8, and 12

Notes:

[136] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Percentage of Subjects				
number (not applicable)				
Week 4	55.8	67.3		
Week 8	57.7	65.4		
Week 12	55.8	65.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects With Reduction in WOMAC A1 Pain Intensity of at Least 30% and 50%

End point title	Part 2: Percentage of Subjects With Reduction in WOMAC A1 Pain Intensity of at Least 30% and 50%[137]

End point description:

Percentage of subjects with reduction in WOMAC A1 pain intensity of at least 30% and 50% at Days 7, 14, 21, 28, 42, 56, 70 and 84 compared to baseline were classified as responder to WOMAC A1 and are reported here. WOMAC A1 (Question 1 of the pain sub-scale of WOMAC index) was used to measure the amount of pain in the target knee while walking on a flat surface during last 24 hours. It was measured daily on a 0-100 VAS ranging from 0=no pain to 100=maximal pain, where higher score indicated the higher intensity of pain. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Days 7, 14, 21, 28, 42, 56, 70, and 84

Notes:

[137] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: percentage of subjects				
number (not applicable)				
Day 7: At least 30% reduction	15.4	26.9		

Day 7: At least 50% reduction	9.6	15.4		
Day 14: At least 30% reduction	36.5	50.0		
Day 14: At least 50% reduction	21.2	36.5		
Day 21: At least 30% reduction	44.2	53.8		
Day 21: At least 50% reduction	28.8	44.2		
Day 28: At least 30% reduction	46.2	55.8		
Day 28: At least 50% reduction	36.5	51.9		
Day 42: At least 30% reduction	48.1	59.6		
Day 42: At least 50% reduction	42.3	50.0		
Day 56: At least 30% reduction	51.9	57.7		
Day 56: At least 50% reduction	38.5	46.2		
Day 70: At least 30% reduction	48.1	57.7		
Day 70: At least 50% reduction	42.3	48.1		
Day 84: At least 30% reduction	51.9	52.9		
Day 84: At least 50% reduction	42.3	45.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Time to First WOMAC A1 Response for >=30% and >=50% Reductions in Pain Intensity

End point title	Part 2: Time to First WOMAC A1 Response for >=30% and >=50% Reductions in Pain Intensity[138]

End point description:

Time to first WOMAC A1 response was defined as the time from first study drug injection to first response to reduction in pain intensity of >=30% or >=50%. WOMAC A1 (Question 1 of the pain sub-scale of WOMAC index) was used to measure the amount of pain in the target knee while walking on a flat surface during last 24 hours. It was measured daily on a 0-100 VAS ranging from 0=no pain to 100=maximal pain, where higher score indicated the higher intensity of pain. For the time from the IMP injection to first response of reduction of at least 30% and 50% compared to baseline for weekly mean score WOMAC A1 pain subscore (walking pain) collected daily - The median ”survival” in weeks and the confidences intervals at 95% were estimated using Kaplan-Meier estimates. Analysis was performed on mITT population. Here, 99999 represents that data was not calculated since very few subjects had event between the median time survival and the censored time at 12 weeks.

End point type	Secondary

End point timeframe:

Baseline to Week 12

Notes:

[138] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: weeks				
median (confidence interval 95%)				
Reduction in pain intensity of at least 30%	4.5 (3.00 to 99999)	2.0 (2.00 to 4.00)		

Reduction in pain intensity of at least 50%	9.0 (4.00 to 99999)	4.0 (3.00 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Amount of Rescue Medication Used by the Subjects

End point title	Part 2: Amount of Rescue Medication Used by the Subjects[139]

End point description:

Rescue medication was administered on an as-needed basis in a tiered manner: paracetamol/acetaminophen, paracetamol/codeine, or paracetamol/tramadol. Analysis was performed on mITT population. Here, "n" = number of subjects with available data at specified time point.

End point type	Secondary

End point timeframe:

Week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12

Notes:

[139] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: milligram				
arithmetic mean (standard deviation)				
Week 1 (n= 10, 26)	900.0 (± 459.5)	2365.4 (± 1763.8)		
Week 2 (n= 7, 9)	1285.7 (± 1318.4)	1944.4 (± 1550.1)		
Week 3 (n= 7, 10)	1000.0 (± 500.0)	2000.0 (± 1699.7)		
Week 4 (n= 6, 11)	1083.3 (± 491.6)	1772.7 (± 1722.8)		
Week 5 (n= 4, 5)	875.0 (± 750.0)	2000.0 (± 1172.6)		
Week 6 (n= 5, 5)	700.0 (± 447.2)	1900.0 (± 741.6)		
Week 7 (n= 4, 7)	1500.0 (± 1080.1)	1285.7 (± 698.6)		
Week 8 (n= 4, 4)	1500.0 (± 912.9)	2125.0 (± 250.0)		
Week 9 (n= 2, 7)	1750.0 (± 353.6)	1071.4 (± 534.5)		
Week 10 (n= 3, 4)	2500.0 (± 1322.9)	2125.0 (± 1315.0)		
Week 11 (n= 4, 4)	1500.0 (± 1154.7)	1375.0 (± 750.0)		
Week 12 (n= 3, 5)	1666.7 (± 1607.3)	700.0 (± 273.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number of Days Subjects Used the Rescue Medication

End point title	Part 2: Number of Days Subjects Used the Rescue

End point description:

Rescue medication was administered on an as-needed basis in a tiered manner: paracetamol/acetaminophen, paracetamol/codeine, or paracetamol/tramadol. The number of days for which the subjects used the rescue medication were reported. Analysis was performed on mITT population. Here, "n" = number of subjects with available data at specified time points.

End point type	Secondary

End point timeframe:

Week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12

Notes:

[140] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: days				
arithmetic mean (standard deviation)				
Week 1 (n= 10, 26)	1.4 (± 0.5)	2.3 (± 1.6)		
Week 2 (n= 7, 9)	1.6 (± 1.1)	2.6 (± 2.0)		
Week 3 (n= 7, 10)	1.3 (± 0.5)	2.5 (± 2.2)		
Week 4 (n= 6, 11)	1.5 (± 0.8)	2.1 (± 1.8)		
Week 5 (n= 4, 5)	1.8 (± 1.5)	2.4 (± 1.7)		
Week 6 (n= 5, 5)	1.4 (± 0.9)	2.0 (± 0.7)		
Week 7 (n= 4, 7)	2.3 (± 1.5)	1.7 (± 1.1)		
Week 8 (n= 4, 4)	2.3 (± 1.5)	3.0 (± 0.8)		
Week 9 (n= 2, 7)	2.5 (± 0.7)	1.6 (± 0.8)		
Week 10 (n= 3, 4)	3.3 (± 1.2)	2.3 (± 1.0)		
Week 11 (n= 4, 4)	2.8 (± 2.1)	1.8 (± 1.0)		
Week 12 (n= 3, 5)	2.0 (± 1.0)	1.0 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Time From IMP Injection to First Rescue Medication Intake

End point title	Part 2: Time From IMP Injection to First Rescue Medication Intake[141]

End point description:

Rescue medication was administered on an as-needed basis in a tiered manner: paracetamol/acetaminophen, paracetamol/codeine, or paracetamol/tramadol. The median ”survival” in weeks and the confidences intervals at 95% for the time from IMP injection to the first rescue medication intake were estimated using Kaplan-Meier estimates. Analysis was performed on mITT population. Here, 99999 represents that data was not calculated since very few subjects had event over 12 weeks.

End point type	Secondary

End point timeframe:

Baseline to Week 12

Notes:

[141] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)	1.5 (1.00 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects Taking Rescue Medication by Medication Type

End point title	Part 2: Percentage of Subjects Taking Rescue Medication by Medication Type[142]

End point description:

Rescue medication was administered on an as-needed basis in a tiered manner: paracetamol/acetaminophen, paracetamol/codeine, or paracetamol/tramadol. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12

Notes:

[142] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Part 2 only.

End point values	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: percentage of subjects				
number (not applicable)				
Week 1: Paracetamol/Acetaminophen	19.2	48.1		
Week 1: Paracetamol/Codein	0.0	1.9		
Week 1: Tramadol	0.0	0.0		
Week 2: Paracetamol/Acetaminophen	13.5	13.5		
Week 2: Paracetamol/Codein	0.0	3.8		
Week 2: Tramadol	0.0	0.0		
Week 3: Paracetamol/Acetaminophen	13.5	17.3		
Week 3: Paracetamol/Codein	0.0	3.8		
Week 3: Tramadol	0.0	0.0		
Week 4: Paracetamol/Acetaminophen	11.5	21.2		
Week 4: Paracetamol/Codein	0.0	0.0		
Week 4: Tramadol	0.0	0.0		
Week 5: Paracetamol/Acetaminophen	7.7	9.6		
Week 5: Paracetamol/Codein	0.0	0.0		
Week 5: Tramadol	0.0	0.0		
Week 6: Paracetamol/Acetaminophen	9.6	9.6		
Week 6: Paracetamol/Codein	0.0	0.0		
Week 6: Tramadol	0.0	0.0		
Week 7: Paracetamol/Acetaminophen	7.7	13.5		
Week 7: Paracetamol/Codein	0.0	0.0		
Week 7: Tramadol	0.0	0.0		
Week 8: Paracetamol/Acetaminophen	7.7	7.7		
Week 8: Paracetamol/Codein	0.0	0.0		
Week 8: Tramadol	0.0	0.0		
Week 9: Paracetamol/Acetaminophen	3.8	13.5		
Week 9: Paracetamol/Codein	0.0	1.9		
Week 9: Tramadol	0.0	0.0		
Week 10: Paracetamol/Acetaminophen	5.8	7.7		
Week 10: Paracetamol/Codein	0.0	1.9		
Week 10: Tramadol	0.0	0.0		
Week 11: Paracetamol/Acetaminophen	7.7	7.7		
Week 11: Paracetamol/Codein	0.0	1.9		
Week 11: Tramadol	0.0	0.0		
Week 12: Paracetamol/Acetaminophen	5.8	7.8		
Week 12: Paracetamol/Codein	0.0	2.0		
Week 12: Tramadol	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from signature of informed consent form up to end of study visit (Day 84 for both Part 1 and Part 2) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are TEAEs that is AEs that developed/worsened during the 'on treatment period' (time from the first dose of study medication administration up to EOS visit).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Part 1: Placebo

Reporting group description:

Subjects received single dose of placebo (matched to GZ389988A) IA injection on Day 1. Data was pooled for all subjects who received placebo in Part1 and reported in this arm.

Reporting group title	Part 1: GZ389988A Dose 1

Reporting group description:

Subjects received single dose of GZ389988A dose 1 IA injection on Day 1.

Reporting group title	Part 1: GZ389988A Dose 2

Reporting group description:

Subjects received single dose of GZ389988A dose 2 IA injection on Day 1.

Reporting group title	Part 1: GZ389988A Dose 3

Reporting group description:

Subjects received single dose of GZ389988A dose 3 IA injection on Day 1.

Reporting group title	Part 1: GZ389988A Dose 4

Reporting group description:

Subjects received single dose of GZ389988A dose 4 IA injection on Day 1.

Reporting group title	Part 1: GZ389988A Dose 5

Reporting group description:

Subjects received single dose of GZ389988A dose 5 IA injection on Day 1.

Reporting group title	Part 2: Placebo

Reporting group description:

Subjects received single IA dose of placebo (matched to GZ389988A) injection on Day 1.

Reporting group title	Part 2: GZ389988A Dose 4 from Part 1

Reporting group description:

Subjects received single IA dose of GZ389988A on Day 1 at Dose 4.

Serious adverse events	Part 1: Placebo	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic Dissection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 1: GZ389988A Dose 3	Part 1: GZ389988A Dose 4	Part 1: GZ389988A Dose 5
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic Dissection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	2 / 52 (3.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Dissection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
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: 5 %

Non-serious adverse events	Part 1: Placebo	Part 1: GZ389988A Dose 1	Part 1: GZ389988A Dose 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
Orthostatic Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dizziness Postural			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	3 / 7 (42.86%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	8	7	2
Sciatica			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Catheter Site Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Feeling Cold			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Influenza Like Illness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection Site Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection Site Joint Inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection Site Oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Injection Site Pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	3 / 7 (42.86%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	3	1	3
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	2	0	2
Arthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Back Pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Joint Effusion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Joint Swelling			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Joint Warmth			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Limb Discomfort			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	1	1	1
Muscle Spasms			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal Pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	1	0	3
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 1: GZ389988A Dose 3	Part 1: GZ389988A Dose 4	Part 1: GZ389988A Dose 5
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	5 / 6 (83.33%)	3 / 3 (100.00%)
Vascular disorders			
Orthostatic Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dizziness Postural			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	1	1	1
Sciatica			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Catheter Site Haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Feeling Cold			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Influenza Like Illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection Site Haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection Site Joint Inflammation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection Site Oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection Site Pain			

subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Pain			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	2 / 3 (66.67%)
occurrences (all)	2	3	3
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
Arthritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Back Pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Joint Effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Joint Swelling			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 3 (66.67%)
occurrences (all)	0	1	2
Joint Warmth			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Limb Discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Muscle Spasms			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Musculoskeletal Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	2 / 3 (66.67%)
occurrences (all)	0	2	2
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 2: Placebo	Part 2: GZ389988A Dose 4 from Part 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 52 (71.15%)	48 / 52 (92.31%)	
Vascular disorders			
Orthostatic Hypotension			
subjects affected / exposed	0 / 52 (0.00%)	4 / 52 (7.69%)	
occurrences (all)	0	4	
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 52 (3.85%)	4 / 52 (7.69%)	
occurrences (all)	2	4	
Dizziness Postural			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	21 / 52 (40.38%)	14 / 52 (26.92%)	
occurrences (all)	35	24	
Sciatica			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Catheter Site Haematoma			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
occurrences (all)	0	0	
Feeling Cold			
subjects affected / exposed	0 / 52 (0.00%)	11 / 52 (21.15%)	
occurrences (all)	0	11	
Influenza Like Illness			
subjects affected / exposed	0 / 52 (0.00%)	4 / 52 (7.69%)	
occurrences (all)	0	4	
Injection Site Haematoma			
subjects affected / exposed	3 / 52 (5.77%)	2 / 52 (3.85%)	
occurrences (all)	3	2	
Injection Site Joint Inflammation			
subjects affected / exposed	0 / 52 (0.00%)	35 / 52 (67.31%)	
occurrences (all)	0	35	
Injection Site Oedema			
subjects affected / exposed	4 / 52 (7.69%)	13 / 52 (25.00%)	
occurrences (all)	4	13	
Injection Site Pain			

subjects affected / exposed	7 / 52 (13.46%)	13 / 52 (25.00%)	
occurrences (all)	7	13	
Pain			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	1 / 52 (1.92%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Vomiting			
subjects affected / exposed	0 / 52 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 52 (15.38%)	10 / 52 (19.23%)	
occurrences (all)	8	10	
Arthritis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Back Pain			
subjects affected / exposed	7 / 52 (13.46%)	3 / 52 (5.77%)	
occurrences (all)	7	4	
Joint Effusion			
subjects affected / exposed	2 / 52 (3.85%)	2 / 52 (3.85%)	
occurrences (all)	3	2	
Joint Swelling			

subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Joint Warmth			
subjects affected / exposed	3 / 52 (5.77%)	2 / 52 (3.85%)	
occurrences (all)	3	2	
Limb Discomfort			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
occurrences (all)	0	0	
Muscle Spasms			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Musculoskeletal Pain			
subjects affected / exposed	1 / 52 (1.92%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
occurrences (all)	0	0	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	11 / 52 (21.15%)	17 / 52 (32.69%)	
occurrences (all)	11	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2015	- A change was made to the staggered dosing and the method of dose escalation, in order to increase the chance of detecting possible undesirable effects of GZ389988A; - Additional time points for laboratory test, body weight, blood pressure, and heart rate measurements were included; - The stopping rules were changed, and the criteria of severe reactions at the injection site were updated to state that they will be considered based on the common terminology criteria for adverse events (CTCAE) Version 4.0; - An additional safety investigation of an Magnetic Resonance Imaging (MRI) was added; - An additional inclusion criterion was added; - Additional options as rescue medication were added; - Details surrounding the neurological examinations were clarified.
23 June 2015	Part 1 only: - Clarification around the MRI to be performed on back-up subjects was added. - The number of additional subjects as back-ups for each cohort was defined.
19 November 2015	- The number of subjects to be included in Part 1 was redefined.
28 January 2016	- The use of synovial fluid samples was added/clarified.
01 June 2016	- Implementation of an electronic diary for collection of continuous and accurate self-reported pain as a daily efficacy assessment. - Update to inclusion/exclusion criteria based on electronic diary use. - Update to inclusion/exclusion criteria based on the use of (Patient Health Questionnaire-9) PHQ-9, Generalized Anxiety Disorder 7 (GAD-7) and painDETECT questionnaire (PD-Q) questionnaires and pre-existing findings on MRI of Rapidly progressive osteoarthritis (RPOA). - Addition of PD-Q questionnaire performed at screening. - Determination of ratio in the study population based on painDETECT score. - Amendment of dose rationale. - Update of primary and secondary efficacy endpoints. - Addition of follow-up visit on Day 2. - Updated assessment schedule for PK plasma samples. - Updated statistical considerations for efficacy. - Screening period changed to 21 days. - Clarification of MRI procedure at baseline. - Addition of preliminary data from TDU13828 and implementation of a new Adverse Event of Special Interest (AESI) based on findings. - Clarification on optional interim analysis. - Update of method of assigning subjects to treatment group for the Part 2 - ACT13830 - Clarification on code breaking during the study. - Clarification on allowed/not allowed concomitant treatment. - Implementation of central reading of MRI of the target knee. - Update of aliquots of serum and urine for archival samples. - Addition of exploratory efficacy endpoint.
02 August 2016	- Addition of an X-ray of target knee at screening if not available from the last 6 months. - Removal of optional drug metabolizing enzymes Deoxyribonucleic acid (DNA) samples. - Update on randomization lists. - Update on information entered in the electronic Case Report Form (eCRF), rescue medication now entered in electronic diary. - Correction to type of alcohol test from Amendment 05.
18 November 2016	Addition of a second site in the same country (unapproved).

12 January 2017	- Addition of a second site in the same country. - Considerations for communication of safety data between Sponsor and investigators.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported