Clinical trial results:
A Phase 2a, Randomized, Double-blind, Placebo- and Naproxen-controlled, Parallel-group Study to Assess the Analgesic Efficacy of ASP7962 in Patients With Pain Due to Osteoarthritis of the Knee

Summary

EudraCT number	2014-004996-22
Trial protocol	BE HU GB CZ ES
Global end of trial date	29 September 2017

Results information

Result version number	v1
This version publication date	20 June 2018
First version publication date	20 June 2018

Trial information

Trial identification

Sponsor protocol code	7962-CL-0022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02611466
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe B.V.
Sponsor organisation address	Sylviusweg 62, Leiden, Netherlands, 2333 BE
Public contact	Clinical Trial Disclosure, Astellas Pharma Europe B.V., Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe B.V., Astellas.resultsdisclosure@astellas.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	29 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study, conducted in participants with pain due to osteoarthritis (OA) of the knee, was to evaluate the analgesic efficacy of ASP7962 relative to placebo. The study consisted of a screening period (up to 3 weeks), a 1-week baseline period, a 4-week double-blind treatment period and a 4-week follow-up period.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czech Republic: 20
Country: Number of subjects enrolled	Germany: 64
Country: Number of subjects enrolled	Hungary: 67
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	215
EEA total number of subjects	215

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)	108
From 65 to 84 years	107
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with pain due to OA of the knee were enrolled in sites in Western and Eastern Europe.

Pre-assignment

Screening details:

Participants who met the screening criteria entered a washout of all pain medication for at least 7 days and recorded daily average pain ratings for at least 5 days in an e-diary. After entry criteria were reassessed, eligible participants were randomized to receive ASP7962, placebo or naproxen treatment in a ratio of 2:2:1.

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	Investigator, Monitor, Subject, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo orally twice daily for a period of 4 weeks.

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

Dosage and administration details:

Participants received matching placebo orally twice daily, in the morning and evening with or without food (approximately 12 hours).

Arm title	ASP7962

Arm description:

Participants received 100 mg of ASP7962 orally twice daily for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	ASP7962
Investigational medicinal product code	ASP7962
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received ASP7962 100 mg orally twice daily, in the morning and evening with or without food (approximately 12 hours).

Arm title	Naproxen

Arm description:

Participants received 500 mg of Naproxen orally twice daily for 4 weeks.

Arm type	Active comparator

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

Dosage and administration details:

Participants received naproxen 500 mg orally twice daily, in the morning and evening with or without food (approximately 12 hours).

Number of subjects in period 1	Placebo	ASP7962	Naproxen
Started	87	85	43
Completed	77	79	40
Not completed	10	6	3
Did Not Receive Study Drug	2	-	1
Adverse Event	3	3	2
Protocol Deviation	2	2	-
Miscellaneous	-	1	-
Withdrawal by Subject	3	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo orally twice daily for a period of 4 weeks.	
Reporting group title	ASP7962
Reporting group description:	
Participants received 100 mg of ASP7962 orally twice daily for 4 weeks.	
Reporting group title	Naproxen
Reporting group description:	
Participants received 500 mg of Naproxen orally twice daily for 4 weeks.	

Reporting group values	Placebo	ASP7962	Naproxen
Number of subjects	87	85	43
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.0	63.6	65.7
standard deviation	± 8.4	± 8.4	± 7.5
Gender categorical Units:			
Male	29	26	17
Female	58	59	26
Race Units: Subjects			
White	86	82	43
Black or African American	1	1	0
Asian	0	1	0
Other	0	1	0
Index Knee Location Units: Subjects			
Right	46	39	22
Left	41	46	21
Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain Subscale Score			
WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee.			
Units: units on a scale			
arithmetic mean	5.63	6.08	5.83
standard deviation	± 1.33	± 1.37	± 1.04
WOMAC Stiffness Subscale Score			
WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or			

hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The stiffness subscale contains two questions that ask about stiffness during the last 48 hours caused by the arthritis.			
Units: units on a scale			
arithmetic mean	5.78	6.20	5.88
standard deviation	± 1.71	± 1.72	± 1.76
WOMAC Physical Function Subscale Score			
WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The physical function subscale contains 17 questions that ask about the difficulty following daily physical activities.			
Units: units on a scale			
arithmetic mean	5.82	6.27	5.99
standard deviation	± 1.37	± 1.40	± 0.99
WOMAC Walking Pain Score			
WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The walking pain score is based on question 1 of the questionnaire on pain when walking on a flat surface.			
Units: units on a scale			
arithmetic mean	5.54	6.12	6.02
standard deviation	± 1.50	± 1.61	± 1.41
WOMAC Total Score			
WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The total score is the sum of scores from pain, physical function and stiffness subscales. Total score ranges from 0 to 30.			
Units: units on a scale			
arithmetic mean	17.22	18.54	17.71
standard deviation	± 4.07	± 4.05	± 3.36
Mean Daily Average Numerical Rating Scale (NRS) Pain Score: Index Knee			
The NRS is an 11-point scale used to capture the participant’s average pain in the last 24 hours on a daily basis. This scale is composed of a single question and the score ranges from 0 to 10, where 0 anchors “no pain” and 10 anchors “pain as bad as you can imagine." The mean daily average NRS pain score was derived from the daily index knee pain ratings recorded by participants in an electronic diary (e-diary) on the last 4 days prior to randomization. Data only available for 214 participants [86, 85 43].			
Units: units on a scale			
arithmetic mean	6.15	6.26	6.40
standard deviation	± 1.39	± 1.57	± 1.29
Patient Global Assessment Score			
The PGA is an 11-point NRS scale used to capture the participant’s overall impression at the time of the assessment in the index knee. This is a single question and the score ranges from 0 to 10, where 0 anchors “very good” and 10 anchors “very poor.” Data only available for 211 participants [84, 84 43].			
Units: units on a scale			
arithmetic mean	5.98	6.36	6.23
standard deviation	± 1.69	± 1.71	± 1.57

Reporting group values	Total		
Number of subjects	215		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units:			
Male	72		
Female	143		
Race Units: Subjects			
White	211		
Black or African American	2		
Asian	1		
Other	1		
Index Knee Location Units: Subjects			
Right	107		
Left	108		
Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain Subscale Score			
WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee.			
Units: units on a scale arithmetic mean standard deviation	- -		
WOMAC Stiffness Subscale Score			
WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The stiffness subscale contains two questions that ask about stiffness during the last 48 hours caused by the arthritis.			
Units: units on a scale arithmetic mean standard deviation	- -		
WOMAC Physical Function Subscale Score			
WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The physical function subscale contains 17 questions that ask about the difficulty following daily physical activities.			
Units: units on a scale arithmetic mean standard deviation	- -		
WOMAC Walking Pain Score			
WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or			

hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The walking pain score is based on question 1 of the questionnaire on pain when walking on a flat surface.			
Units: units on a scale arithmetic mean standard deviation	- 		
WOMAC Total Score			
WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The total score is the sum of scores from pain, physical function and stiffness subscales. Total score ranges from 0 to 30.			
Units: units on a scale arithmetic mean standard deviation	- 		
Mean Daily Average Numerical Rating Scale (NRS) Pain Score: Index Knee			
The NRS is an 11-point scale used to capture the participant's average pain in the last 24 hours on a daily basis. This scale is composed of a single question and the score ranges from 0 to 10, where 0 anchors "no pain" and 10 anchors "pain as bad as you can imagine." The mean daily average NRS pain score was derived from the daily index knee pain ratings recorded by participants in an electronic diary (e-diary) on the last 4 days prior to randomization. Data only available for 214 participants [86, 85 43].			
Units: units on a scale arithmetic mean standard deviation	- 		
Patient Global Assessment Score			
The PGA is an 11-point NRS scale used to capture the participant's overall impression at the time of the assessment in the index knee. This is a single question and the score ranges from 0 to 10, where 0 anchors "very good" and 10 anchors "very poor." Data only available for 211 participants [84, 84 43].			
Units: units on a scale arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo orally twice daily for a period of 4 weeks.	
Reporting group title	ASP7962
Reporting group description:	
Participants received 100 mg of ASP7962 orally twice daily for 4 weeks.	
Reporting group title	Naproxen
Reporting group description:	
Participants received 500 mg of Naproxen orally twice daily for 4 weeks.	

Primary: Change from Baseline to Week 4 in Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain Subscale Score

End point title	Change from Baseline to Week 4 in Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain Subscale Score

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. A negative change indicated a reduction/improvement from baseline. The analysis population was the full analysis set (FAS), which included all randomized participants who took at least 1 dose of study drug and who had a baseline and at least 1 double-blind treatment value for the WOMAC pain subscale score. Only participants with data available at baseline and at each timepoint were included.

End point type	Primary

End point timeframe:

Baseline and week 4

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	77	39	
Units: units on a scale				
least squares mean (standard error)	-1.73 (± 0.21)	-1.87 (± 0.20)	-2.40 (± 0.28)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 and 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline and week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean

of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.316 [1]
Method	Mixed-effect model, Repeated measures
Parameter estimate	Least Squares Mean (LSM) Difference
Point estimate	-0.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.62
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:

[1] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 and 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline and week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 [2]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.67
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.12
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.35

Notes:

[2] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline to End of Treatment (EOT) in WOMAC Pain Subscale Score

End point title	Change from Baseline to End of Treatment (EOT) in WOMAC Pain Subscale Score

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using

11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. The EOT value was defined as the last available postbaseline measurement within the treatment period.

End point type	Secondary

End point timeframe:

Baseline and EOT (up to 4 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)	-1.74 (± 0.20)	-1.91 (± 0.20)	-2.41 (± 0.27)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo

Statistical analysis description:

Analysis of covariance (ANCOVA) model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276 [3]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.63
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.28

Notes:

[3] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v Naproxen

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025 [4]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.66
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.1
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.34

Notes:

[4] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline to EOT in WOMAC Physical Function Subscale Score

End point title	Change from Baseline to EOT in WOMAC Physical Function Subscale Score

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The physical function subscale contains 17 questions that ask about the difficulty following daily physical activities. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. The EOT value was defined as the last available postbaseline measurement within the treatment period.

End point type	Secondary

End point timeframe:

Baseline and EOT (up to 4 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)	-1.67 (± 0.19)	-1.81 (± 0.19)	-2.51 (± 0.26)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v ASP7962

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.306 [5]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.59
upper limit	0.31
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[5] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [6]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.84
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.26
upper limit	-0.42
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[6] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline to EOT in WOMAC Stiffness Subscale Score

End point title	Change from Baseline to EOT in WOMAC Stiffness Subscale Score

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The stiffness subscale contains two questions that ask about stiffness during the last 48 hours caused by the arthritis. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. The EOT value was defined as the last available postbaseline measurement within the treatment period.

End point type	Secondary

End point timeframe:

Baseline and EOT (up to 4 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)	-1.68 (± 0.20)	-1.89 (± 0.20)	-2.82 (± 0.28)	

Statistical analyses

Statistical analysis title	Difference ASP7962 vs. Placebo

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.232 [7]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.68
upper limit	0.26
Variability estimate	Standard error of the mean
Dispersion value	0.28

Notes:

[7] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [8]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-1.14

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.58
upper limit	-0.7
Variability estimate	Standard error of the mean
Dispersion value	0.34

Notes:

[8] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline to EOT in WOMAC Total Score

End point title	Change from Baseline to EOT in WOMAC Total Score

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The total score is the sum of scores from pain, physical function and stiffness subscales. Total score ranges from 0 to 30. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. The EOT value was defined as the last available postbaseline measurement within the treatment period.

End point type	Secondary

End point timeframe:

Baseline and EOT (up to 4 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)	-5.07 (± 0.56)	-5.65 (± 0.56)	-7.71 (± 0.77)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.232 [9]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.59

Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.91
upper limit	0.74
Variability estimate	Standard error of the mean
Dispersion value	0.8

Notes:

[9] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [10]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-2.64
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.87
upper limit	-1.41
Variability estimate	Standard error of the mean
Dispersion value	0.95

Notes:

[10] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline to EOT in WOMAC Walking Pain Score

End point title	Change from Baseline to EOT in WOMAC Walking Pain Score

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The walking pain score is based on question 1 of the questionnaire on pain when walking on a flat surface. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. The EOT value was defined as the last available postbaseline measurement within the treatment period.

End point type	Secondary

End point timeframe:

Baseline and EOT (up to 4 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)	-1.56 (± 0.22)	-1.82 (± 0.21)	-2.53 (± 0.29)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.197 [11]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.26
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.77
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.31

Notes:

[11] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [12]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.96
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.44
upper limit	-0.49

Variability estimate	Standard error of the mean
Dispersion value	0.37

Notes:

[12] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline to Weeks 1 and 2 in WOMAC Pain Subscale Score

End point title	Change from Baseline to Weeks 1 and 2 in WOMAC Pain Subscale Score

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1 and 2

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)				
Week 1 [N=76, 79, 42]	-1.13 (± 0.17)	-1.12 (± 0.17)	-1.90 (± 0.23)	
Week 2 [N=75, 80, 41]	-1.19 (± 0.19)	-1.49 (± 0.18)	-1.83 (± 0.25)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.516 [13]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	0.01

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.38
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[13] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [14]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.77
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.13
upper limit	-0.41
Variability estimate	Standard error of the mean
Dispersion value	0.28

Notes:

[14] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.122 [15]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.31

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.74
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[15] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [16]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.64
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.05
upper limit	-0.24
Variability estimate	Standard error of the mean
Dispersion value	0.31

Notes:

[16] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline to Weeks 1, 2 and 4 in WOMAC Physical Function Subscale Score

End point title	Change from Baseline to Weeks 1, 2 and 4 in WOMAC Physical Function Subscale Score

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The physical function subscale contains 17 questions that ask about the difficulty following daily physical activities. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, and 4

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)				
Week 1 [N=76, 79, 42]	-1.00 (± 0.16)	-1.07 (± 0.16)	-1.87 (± 0.21)	
Week 2 [N=75, 80, 41]	-1.14 (± 0.18)	-1.42 (± 0.18)	-1.92 (± 0.24)	
Week 4 [N=75, 77, 39]	-1.65 (± 0.20)	-1.77 (± 0.20)	-2.48 (± 0.27)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.375 [17]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.44
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[17] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [18]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.88
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.21
upper limit	-0.54
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[18] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132 [19]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.28
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.69
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[19] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.005 [20]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.77
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.16
upper limit	-0.39
Variability estimate	Standard error of the mean
Dispersion value	0.3

Notes:

[20] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.335 [21]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.12
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.58
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.28

Notes:

[21] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [22]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.83
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.26
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[22] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline to Weeks 1, 2 and 4 in WOMAC Stiffness Subscale Score

End point title	Change from Baseline to Weeks 1, 2 and 4 in WOMAC Stiffness Subscale Score

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The stiffness subscale contains two questions that ask about stiffness during the last 48 hours caused by the arthritis. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, and 4

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)				
Week 1 [N=76, 79, 42]	-1.20 (± 0.18)	-1.24 (± 0.18)	-2.11 (± 0.25)	
Week 2 [N=75, 80, 41]	-1.32 (± 0.19)	-1.52 (± 0.19)	-2.39 (± 0.26)	
Week 4 [N=75, 77, 39]	-1.66 (± 0.20)	-1.83 (± 0.20)	-2.81 (± 0.28)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment

group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.439 [23]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.46
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[23] - One-sided P-value for pairwise treatment comparison with placebo..

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [24]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.9
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.3
upper limit	-0.51
Variability estimate	Standard error of the mean
Dispersion value	0.3

Notes:

[24] - One-sided P-value for pairwise treatment comparison with placebo..

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo

from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.217 [25]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.65
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[25] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [26]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-1.08
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.49
upper limit	-0.67
Variability estimate	Standard error of the mean
Dispersion value	0.32

Notes:

[26] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.278 [27]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.64
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.28

Notes:

[27] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [28]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-1.16
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.6
upper limit	-0.71
Variability estimate	Standard error of the mean
Dispersion value	0.34

Notes:

[28] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline to Weeks 1, 2 and 4 in WOMAC Total Score

End point title	Change from Baseline to Weeks 1, 2 and 4 in WOMAC Total Score

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The total score is the sum of scores from pain, physical function and stiffness subscales. Total score ranges from 0 to 30. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, and 4

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)				
Week 1 [N=76, 79, 42]	-3.30 (± 0.48)	-3.50 (± 0.47)	-5.84 (± 0.64)	
Week 2 [N=75, 80, 41]	-3.63 (± 0.52)	-4.50 (± 0.52)	-6.11 (± 0.71)	
Week 4 [N=75, 77, 39]	-5.02 (± 0.58)	-5.54 (± 0.57)	-7.66 (± 0.79)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.379 [29]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.3
upper limit	0.89
Variability estimate	Standard error of the mean
Dispersion value	0.66

Notes:

[29] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [30]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-2.54
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.56
upper limit	-1.53
Variability estimate	Standard error of the mean
Dispersion value	0.79

Notes:

[30] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.117 [31]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.88
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.09
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.73

Notes:

[31] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [32]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-2.48
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.61
upper limit	-1.36
Variability estimate	Standard error of the mean
Dispersion value	0.87

Notes:

[32] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.261 [33]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.52
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.86
upper limit	0.82
Variability estimate	Standard error of the mean
Dispersion value	0.81

Notes:

[33] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [34]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-2.64
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.89
upper limit	-1.39
Variability estimate	Standard error of the mean
Dispersion value	0.97

Notes:

[34] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline to Weeks 1, 2 and 4 in WOMAC Walking Pain Score

End point title	Change from Baseline to Weeks 1, 2 and 4 in WOMAC Walking Pain Score

End point description:

WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The walking pain score is based on question 1 of the questionnaire on pain when walking on a flat surface. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, and 4

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)				
Week 1 [N=76, 79, 42]	-0.91 (± 0.20)	-0.90 (± 0.19)	-1.80 (± 0.26)	
Week 2 [N=75, 80, 41]	-0.95 (± 0.21)	-1.33 (± 0.21)	-1.92 (± 0.28)	
Week 4 [N=75, 77, 39]	-1.56 (± 0.23)	-1.78 (± 0.22)	-2.52 (± 0.31)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment

group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.518 [35]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.44
upper limit	0.46
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[35] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [36]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.89
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.31
upper limit	-0.48
Variability estimate	Standard error of the mean
Dispersion value	0.32

Notes:

[36] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo

from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.101 [37]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.38
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.86
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:

[37] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [38]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.97
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.42
upper limit	-0.52
Variability estimate	Standard error of the mean
Dispersion value	0.35

Notes:

[38] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.243 [39]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.74
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.32

Notes:

[39] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [40]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.96
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.45
upper limit	-0.47
Variability estimate	Standard error of the mean
Dispersion value	0.38

Notes:

[40] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline to Weeks 1, 2, 3, 4 and EOT in Mean Daily Average Pain Score Assessed by the Numerical Rating Scale

End point title	Change from Baseline to Weeks 1, 2, 3, 4 and EOT in Mean Daily Average Pain Score Assessed by the Numerical Rating Scale

End point description:

The NRS is an 11-point scale used to capture the participant’s average pain in the last 24 hours on a daily basis. This scale is composed of a single question and the score ranges from 0 to 10, where 0 anchors “no pain” and 10 anchors “pain as bad as you can imagine." The mean daily average NRS pain score was derived from the daily index knee pain ratings recorded by participants in an electronic diary (e-diary) on the last 4 days prior to randomization. A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of

participants with data available at baseline and at each time point that were included in the analysis. The EOT value was defined as the last available postbaseline measurement within the treatment period.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4 and EOT (up to 4 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)				
Week 1 [N=78, 81, 42]	-0.61 (± 0.15)	-0.58 (± 0.15)	-1.38 (± 0.21)	
Week 2 [N=77, 81, 42]	-1.17 (± 0.17)	-0.96 (± 0.17)	-1.96 (± 0.23)	
Week 3 [N=77, 80, 41]	-1.40 (± 0.19)	-1.20 (± 0.19)	-2.22 (± 0.26)	
Week 4 [N=77, 80, 40]	-1.59 (± 0.20)	-1.42 (± 0.19)	-2.26 (± 0.27)	
EOT [N=78, 81, 42]	-1.60 (± 0.19)	-1.49 (± 0.19)	-2.30 (± 0.26)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.555 [41]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	0.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.32
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.21

Notes:

[41] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment

group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [42]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.77
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.1
upper limit	-0.44
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[42] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.807 [43]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	0.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.19
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

[43] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo

from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [44]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.79
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.16
upper limit	-0.42
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:

[44] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 3)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.775 [45]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	0.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.24
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[45] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 3)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [46]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.83
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.24
upper limit	-0.42
Variability estimate	Standard error of the mean
Dispersion value	0.32

Notes:

[46] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.734 [47]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	0.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.28
upper limit	0.63
Variability estimate	Standard error of the mean
Dispersion value	0.28

Notes:

[47] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023 [48]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.67
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.1
upper limit	-0.24
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[48] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (EOT)

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number analyzed is calculated incorrectly due to system limitation.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.653 [49]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	0.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.34
upper limit	0.55
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[49] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (EOT)

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number analyzed is calculated incorrectly due to system limitation.

Comparison groups	Placebo v Naproxen

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [50]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.71
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.13
upper limit	-0.29
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[50] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Change from Baseline Patient Global Assessment (PGA) at Weeks 1, 2, 4 and EOT

End point title	Change from Baseline Patient Global Assessment (PGA) at Weeks 1, 2, 4 and EOT

End point description:

The PGA is an 11-point NRS scale used to capture the participant's overall impression at the time of the assessment in the index knee. This is a single question and the score ranges from 0 to 10, where 0 anchors "very good" and 10 anchors "very poor." A negative change indicated a reduction/improvement from baseline. The analysis population was the FAS. N is the number of participants with data available at baseline and at each time point that were included in the analysis. The EOT value was defined as the last available postbaseline measurement within the treatment period.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 4 and EOT (up to 4 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: units on a scale				
least squares mean (standard error)				
Week 1 [N=75, 79, 42]	-1.15 (± 0.20)	-1.27 (± 0.19)	-1.71 (± 0.26)	
Week 2 [N=74, 80, 41]	-1.25 (± 0.21)	-1.55 (± 0.20)	-2.02 (± 0.28)	
Week 4 [N=73, 77, 39]	-1.57 (± 0.24)	-1.97 (± 0.23)	-2.43 (± 0.32)	
EOT [N=78, 81, 42]	-1.56 (± 0.23)	-1.99 (± 0.22)	-2.48 (± 0.31)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline

interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.324 [51]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.13
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.58
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[51] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 1)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042 [52]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.57
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.98
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[52] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.148 [53]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.78
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.29

Notes:

[53] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 2)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [54]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.77
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.22
upper limit	-0.33
Variability estimate	Standard error of the mean
Dispersion value	0.35

Notes:

[54] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v ASP7962

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.112 [55]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.95
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[55] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (Week 4)

Statistical analysis description:

MMRM analysis was performed using change from baseline (week 1, 2 & 4) as response and treatment group, study site, week, week x treatment group interaction as fixed effects, baseline & week x baseline interaction as covariates. Unstructured covariance structure was used among the within-participant results. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number is incorrect due to system limit.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 [56]
Method	Mixed-effect model, Repeated measures
Parameter estimate	LSM Difference
Point estimate	-0.87
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.38
upper limit	-0.36
Variability estimate	Standard error of the mean
Dispersion value	0.4

Notes:

[56] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: ASP7962 vs. Placebo (EOT)

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number analyzed is calculated incorrectly due to system limitation.

Comparison groups	Placebo v ASP7962

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088 [57]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.44
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.97
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.32

Notes:

[57] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo (EOT)

Statistical analysis description:

ANCOVA model was performed with change from baseline at the EOT timepoint as response and terms for baseline, treatment and study site. Differences of the adjusted means were calculated by subtracting the adjusted mean of placebo from the adjusted mean of treatment group. The subject number analyzed is calculated incorrectly due to system limitation.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [58]
Method	ANCOVA
Parameter estimate	LSM Difference
Point estimate	-0.92
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.42
upper limit	-0.42
Variability estimate	Standard error of the mean
Dispersion value	0.39

Notes:

[58] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Percentage of Participants who Achieved ≥ 30% Decrease from Baseline to EOT in WOMAC Pain Subscale Score

End point title	Percentage of Participants who Achieved ≥ 30% Decrease from Baseline to EOT in WOMAC Pain Subscale Score

End point description:

Percentage of participants who had a reduction from baseline to EOT in WOMAC pain subscale score of ≥ 30% is reported. WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. The analysis population was the FAS. Only participants with data at baseline or EOT were included

in the analysis. The EOT value was defined as the last available postbaseline measurement within the treatment period.

End point type	Secondary

End point timeframe:

Baseline and EOT (up to 4 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: percentage of participants				
number (confidence interval 90%)	43 (33.6 to 52.9)	53.1 (43.4 to 62.6)	64.3 (50.5 to 76.5)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo

Statistical analysis description:

Differences of the percentages were calculated by subtracting the percentage of placebo group from the percentage of the active treatment group. Confidence interval for each treatment group and the difference of the percentage was an exact unconditional confidence interval based on Santner-Snell approach.

Comparison groups	Placebo v ASP7962
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.133 [59]
Method	Fisher exact
Parameter estimate	Percentage Difference
Point estimate	10
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.2
upper limit	23.2

Notes:

[59] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo

Statistical analysis description:

Differences of the percentages were calculated by subtracting the percentage of placebo group from the percentage of the active treatment group. Confidence interval for each treatment group and the difference of the percentage was an exact unconditional confidence interval based on Santner-Snell approach.

Comparison groups	Placebo v Naproxen

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 [60]
Method	Fisher exact
Parameter estimate	Percentage Difference
Point estimate	21.2
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	8.8
upper limit	33.1

Notes:

[60] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Percentage of Participants who Achieved ≥ 50% Decrease from Baseline to EOT in WOMAC Pain Subscale Score

End point title	Percentage of Participants who Achieved ≥ 50% Decrease from Baseline to EOT in WOMAC Pain Subscale Score

End point description:

Percentage of participants who had a reduction from baseline to EOT in WOMAC pain subscale score of ≥ 50% is reported. WOMAC is a tri-dimensional, self-administered, patient-centered health status questionnaire designed to capture the elements of pain, stiffness and physical function in participants with OA of the knee and/or hip joints. The questionnaire consists of 24 questions, which are divided into three subscales: pain (5 questions), stiffness (2 questions) and physical function (17 questions). Each question is scored using 11-point NRS scale ranging from 0 (none) to 10 (extreme). The pain subscale contains five questions that ask about pain during the last 48 hours caused by arthritis in the index knee. The analysis population was the FAS. Only participants with data at baseline or EOT were included in the analysis. The EOT value was defined as the last available postbaseline measurement within the treatment period.

End point type	Secondary

End point timeframe:

Baseline and EOT (up to 4 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	81	42	
Units: percentage of participants				
number (confidence interval 90%)	22.8 (15.3 to 31.9)	32.1 (23.6 to 41.7)	45.2 (32.0 to 59.0)	

Statistical analyses

Statistical analysis title	Difference: ASP7962 vs. Placebo

Statistical analysis description:

Differences of the percentages were calculated by subtracting the percentage of placebo group from the percentage of the active treatment group. Confidence interval for each treatment group and the difference of the percentage was an exact unconditional confidence interval based on Santner-Snell approach.

Comparison groups	Placebo v ASP7962

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127 [61]
Method	Fisher exact
Parameter estimate	Percentage Difference
Point estimate	9.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.7
upper limit	22.2

Notes:

[61] - One-sided P-value for pairwise treatment comparison with placebo.

Statistical analysis title	Difference: Naproxen vs. Placebo

Statistical analysis description:

Differences of the percentages were calculated by subtracting the percentage of placebo group from the percentage of the active treatment group. Confidence interval for each treatment group and the difference of the percentage was an exact unconditional confidence interval based on Santner-Snell approach.

Comparison groups	Placebo v Naproxen
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [62]
Method	Fisher exact
Parameter estimate	Percentage Difference
Point estimate	22.5
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	10.1
upper limit	34.3

Notes:

[62] - One-sided P-value for pairwise treatment comparison with placebo.

Secondary: Number of Participants with Treatment-Emergent Adverse Events

End point title	Number of Participants with Treatment-Emergent Adverse Events

End point description:

A TEAE was defined as an adverse event (AE) which started or worsened after the first dose of study drug until 30 days after taking the last dose of study drug. This included abnormal laboratory tests, vital signs or electrocardiogram data that were defined as AEs if the abnormality induced clinical signs or symptoms, required active intervention, interruption or discontinuation of study drug or was clinically significant in the investigator's opinion. The analysis population was the safety analysis set (SAF), which consisted of all randomized participants who took at least 1 dose of double-blind study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug up to 30 days after last dose of study drug (up to 8 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	85	42	
Units: participants				
TEAE	24	31	13	
Drug-related TEAE	10	8	7	
Serious TEAE	0	1	0	
Drug-related serious TEAE	0	0	0	
Deaths	0	0	0	
TEAE leading to withdrawal of treatment	3	3	2	
Drug-related TEAE leading to treatment withdrawal	3	1	2	
Joint-related TEAE	1	3	2	
Neurological-related TEAE	2	4	0	
Hepatic-related TEAE	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Affirmative Response in Columbia – Suicide Severity Rating Scale (C-SSRS): Suicidal Ideation

End point title	Number of Participants with an Affirmative Response in Columbia – Suicide Severity Rating Scale (C-SSRS): Suicidal Ideation

End point description:

C-SSRS is a questionnaire used for suicide assessment. The data presented are the number of participants with an affirmative ("YES") response to questions: (1) Wish to be dead; (2) Non-specific active suicidal thoughts; (3) Active suicidal ideation with any methods (not plan) without intent to act; (4) Active suicidal ideation with some intent to act, without specific plan; and (5) Active suicidal ideation with specific plan and intent. The participant’s worst finding in the treatment period or follow-up period is reported. The analysis population was the SAF. N is the number of participants with data available at each time point.

End point type	Secondary

End point timeframe:

From first dose of study drug up to end of study (up to 8 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	85	42	
Units: participants				
Treatment period [N=79, 82, 42]	0	0	0	
Follow-up period [N=77, 81, 42]	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Affirmative Response in C-SSRS: Suicidal Behavior

End point title	Number of Participants with an Affirmative Response in C-SSRS: Suicidal Behavior

End point description:

C-SSRS is a questionnaire used for suicide assessment. The data presented are the number of participants with an affirmative ("YES") response to questions: (1) Preparatory acts or behavior; (2) Aborted attempt; (3) Interrupted attempt; (4) Actual attempt; and (5) Completed suicide. The participant's worst finding in the treatment period or follow-up period is reported. The analysis population was the SAF. N is the number of participants with data available at each time point.

End point type	Secondary

End point timeframe:

From first dose of study drug up to end of study (up to 8 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	85	42	
Units: participants				
Treatment period [N=79, 82, 42]	0	0	0	
Follow-up period [N=77, 81, 42]	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Affirmative Response in C-SSRS: Suicidal Ideation or Behavior

End point title	Number of Participants with an Affirmative Response in C-SSRS: Suicidal Ideation or Behavior

End point description:

C-SSRS is a questionnaire used for suicide assessment. The data presented are the number of participants with an affirmative ("YES") response to any one of the ten suicidal ideation and behavior questions. The participant's worst finding in the treatment period or follow-up period is reported. The analysis population was the SAF. N is the number of participants with data available at each time point.

End point type	Secondary

End point timeframe:

From first dose of study drug up to end of study (up to 8 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	85	42	
Units: participants				
Treatment period [N=79, 82, 42]	0	0	0	
Follow-up period [N=77, 81, 42]	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Affirmative Response in C-SSRS: Self-injurious Behavior without Suicidal Intent

End point title	Number of Participants with an Affirmative Response in C-SSRS: Self-injurious Behavior without Suicidal Intent

End point description:

C-SSRS is a questionnaire used for suicide assessment. The data presented are the number of participants with an affirmative ("YES") response to the question "Has subject engaged in Non-Suicidal Self-Injurious Behavior?" The participant's worst finding in the treatment period or follow-up period is reported. The analysis population was the SAF. N is the number of participants with data available at each time point.

End point type	Secondary

End point timeframe:

From first dose of study drug up to end of study (up to 8 weeks)

End point values	Placebo	ASP7962	Naproxen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	85	42	
Units: participants				
Treatment period [N=79, 82, 42]	0	1	0	
Follow-up period [N=77, 81, 42]	0	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug up to 30 days after last dose of study drug (up to 8 weeks)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo orally twice daily for a period of 4 weeks.	
Reporting group title	ASP7962
Reporting group description:	
Participants received 100 mg of ASP7962 orally twice daily for 4 weeks.	
Reporting group title	Naproxen
Reporting group description:	
Participants received 500 mg of Naproxen orally twice daily for 4 weeks.	

Serious adverse events	Placebo	ASP7962	Naproxen
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 85 (0.00%)	1 / 85 (1.18%)	0 / 42 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 85 (0.00%)	1 / 85 (1.18%)	0 / 42 (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

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Placebo	ASP7962	Naproxen
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 85 (9.41%)	8 / 85 (9.41%)	5 / 42 (11.90%)
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	4 / 85 (4.71%)	4 / 85 (4.71%)	0 / 42 (0.00%)
occurrences (all)	9	4	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 85 (0.00%)	0 / 85 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	1 / 85 (1.18%)	2 / 85 (2.35%)	2 / 42 (4.76%)
occurrences (all)	1	2	2
Constipation			
subjects affected / exposed	0 / 85 (0.00%)	0 / 85 (0.00%)	2 / 42 (4.76%)
occurrences (all)	0	0	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 85 (4.71%)	3 / 85 (3.53%)	0 / 42 (0.00%)
occurrences (all)	4	3	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2015	The substantial changes include: 1) The procedure for obtaining radiographic images was changed. A radiograph image of the index knee was added to the follow-up period to assess for potential changes in the index knee poststudy drug treatment. The requirement for a lateral view of hips was removed because it was considered not essential to the assessment of the progression of hip OA. 2) Inclusion Criteria 12 and 14 were revised. The list of highly effective forms of birth control was updated, and Inclusion Criteria 12 and 14 were updated to reflect current recommendations by the Clinical Trials Facilitation Group related to contraception in clinical trials. 3) The gastrointestinal protective strategy was expanded, adding explicit language to state that gastroprotective agents could be used at the investigators' discretion, considering the risk of serious gastrointestinal toxicity of naproxen, especially in older adults and patients treated with low dose aspirin for cardioprophylaxis. 4) Text was added regarding the absence of any evaluation of the test drug's phototoxic potential because specific phototoxicity studies have not been conducted for ASP7962. Although ASP7962 did not contain typical phototoxic structural moieties and the nonclinical data did not indicate a photosafety concern, based on the absorption peak at 305 nm, a phototoxicity potential for ASP7962 could not be excluded. Nonsubstantial changes were made: 1) To update Sponsor contact information 2) To update footnote in schedule of assessments 3) To update Appendix 12.6.
26 July 2016	The substantial changes include: (continued from above) 5) Specification for exclusion of participants with severe knee malalignment or another jointrelated condition was updated. Due to the change of Inclusion Criterion 4, it was considered relevant to add severe malalignment to the exclusion criteria. Although malalignment does not appear to be an independent risk factor for RPOA, out of an abundance of caution, the Osteo IAC members recommended that patients with severe malalignment be excluded from the study. This was assessed through centrally read radiographs as well as clinical evaluation of the participant. It was recommended that, in case of acute subchondral insufficiency fracture, additional medical evaluation would be required before considering a participant for enrollment into this study. 6) The specification for exclusion of participants with specific shoulder medical history was updated. Based on a few cases of RPOA of the shoulder reported in the anti-NGF programs, there was a theoretical concern of RPOA of the shoulder. However, there is a lack of evidence to indicate which participants this might affect. As a history of conditions, such as rotator cuff diseases, was expected to be common among the patients, these types of condition were not to prohibit enrollment. 7) Exclusion Criterion12 was revised, stating that participants with intolerance or hypersensitivity to tramadol were allowed to enter the study if the participants accepted to limiting rescue medication to paracetamol. 8) Exclusion Criterion 17 was revised to allow the enrollment of participants with a history of cardiovascular disease whose condition was stable. Unexplained syncope was removed from the exclusion criterion. PR interval was increased from 210 to 240 ms.

26 July 2016	The substantial changes include: (continued from above) 9) Exclusion Criterion 21 was revised, removing hepatitis B core antibodies (anti-HBc) test result from the exclusion criterion. HBsAg was considered a sufficient serologic test to assess presence of infection. A positive test result for anti-HBc in the presence of negative HBsAg suggests immunity due to natural infection. Active disease would be associated with increased liver tests and would be excluded due to Exclusion Criterion 19. 10) Exclusion Criterion 23 was revised, limiting the exclusion of participants having previously received antibodies to NGF to 3 months prior to screening. A 3-month washout was considered sufficient not to interfere with any study endpoints or cause any safety concerns. 11) Exclusion Criterion 23 and Prohibited Medications and Nonmedication Therapies were revised, reducing the use of intraarticular local anesthetics from 12 months to 3 months before screening. The reason was that there is no evidence that participants undergoing local anesthetic injection, such as lidocaine during a related single injection procedure, are at high risk of presentation of clinical chondral toxicity. 12) The strength and use of cytochrome P450 inducers were specified, adding "strong" to cytochrome P450 inducers and "regularly" to be consistent with the wording of Exclusion Criterion 32. 13) Study design was slightly revised, adding a section to allow reevaluation of participants who were not eligible under Version 2.0 of the protocol, but would be eligible based on the revised inclusion and exclusion criteria in Version 3.0 of the protocol. In case new radiographic assessments were deemed inappropriate, this was to be discussed first with the Medical Monitor. 14) Laboratory assessments were modified, deleting benzodiazepines from drug and alcohol urine screening. Assessment of benzodiazepine use was not considered to impact participant safety or adherence to the protocol.
26 July 2016	Nonsubstantial changes were made: (continued from above) 1) To update the contact details of key study personnel 2) To update the abbreviations list 3) To extend the planned study period 4) To update the planned number of study centers 5) To clarify the process for radiographic imaging 6) To update the order of the secondary safety endpoints 7) To update the statistical presentation of treatment-emergent adverse events (TEAEs) 8) To add text regarding educational material for participants 9) To update the schedule of assessments 10) To update the Hospital Anxiety and Depression Scale (HADS) 11) To update the physical examination section 12) To update the Neuropathic Pain Symptom Inventory (NPSI) 13) To update the reporting of serious adverse events (SAEs) 14) To update the analysis of exploratory endpoints 15) To update the statistical section on physical examination 16) To delete a reference 17) To update the table of questionnaires 18) To include minor administrative-type changes.

26 July 2016	The substantial changes include: 1) Inclusion Criterion 2 was revised, increasing the upper age limit from 75 to 80 years to allow participants aged 76 to 80 years to be entered in the study. The reason was that OA becomes increasingly prevalent with aging, and symptomatic OA affects many in their eighth decade. There was no evidence that ASP7962 should benefit older individuals to a lesser extent than those who are younger. 2) Inclusion Criterion 8 was removed. This inclusion criterion required participants to have a mean daily index knee average pain score between ≥ 4 and ≤ 9 (on a 0 to10 NRS). Pain criteria to enter the study were thus limited to the well-established WOMAC criteria for pain that are the standard for OA pain studies. 3) Inclusion Criterion 6 was revised. The Kellgren-Lawrence grade at screening (based on central reading) was increased such that participants with Kellgren-Lawrence grade 4 were included as well. After a review of publically available information from the anti-NGF monoclonal antibody programs and discussion with external experts and key opinion leaders (with expertise in rheumatology, radiology and RPOA), the exclusion of Kellgren-Lawrence grade 4 was considered unnecessary as there was no evidence suggesting an increased risk of RPOA with Kellgren-Lawrence grade 4. 4) Exclusion Criterion 4 was revised. If a participant was stable, treated and not experiencing clinical signs of concomitant diseases, the participant could be suitable as this should not impact safety or assessments within the study. For participants with diabetes mellitus, attaining a target HbA1c of < 6.5% to 7% can be challenging. For some participants the risks of intensive glycemic control may have outweighed the benefits and a less strict HbA1c cutoff seemed reasonable provided that, in the investigator's judgment, the participant was clinically stable. HbA1c was increased from 7.1% to 8.0% to allow a less strict surrogate for diabetes control.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported