Name of Sponsor/Company: Astellas Pharma Europe BV		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: ASP7962		

SYNOPSIS

Title of Study: 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

Coordinating Investigator: [redacted], Kennedy Institute of Rheumatology, University of Oxford, UK.

Study Center(s): The study was conducted at 31 sites in Europe.

Publication Based on the Study: Not applicable

Study Period:

Study Initiation Date (Date of First Enrollment):

16 Feb 2016

Study Completion Date (Date of Last Evaluation):

29 Sep 2017

Phase of Development:

Phase 2

Objectives:

Primary

- Evaluate the analgesic efficacy of ASP7962 relative to placebo

Secondary

- Evaluate the efficacy of ASP7962 relative to placebo on pain on walking, function and stiffness
- Evaluate the time course of efficacy of ASP7962 relative to placebo
- Evaluate the improvement in overall patient status of ASP7962 relative to placebo
- Evaluate the safety and tolerability of ASP7962 relative to placebo

Methodology:

Patients were randomly assigned to receive ASP7962 100 mg BID, placebo or naproxen 500 mg BID in a 2:2:1 ratio. The study consisted of a screening period (up to 3 weeks), a baseline period of 1 week, a double-blind treatment period of 4 weeks, and a follow-up period of 4 weeks.

At the screening visit (visit 1) the index knee was identified and subsequently used for all assessments; furthermore, patients received instructions regarding diary completion and were asked to record daily average knee pain scores on a 0 to 10 numerical rating scale (NRS) in the electronic diary (e-diary) during the screening period. After the screening period, patients who met entry criteria started the 1-week baseline period during which all pain medication was washed out or tapered. With the exception of allowed rescue therapy (tramadol and paracetamol), patients discontinued all pain medications during baseline and treatment periods.

Patients returned to the site for the randomization visit (visit 2) and those fulfilling entry criteria were randomized to treatment. Study drug was administered according to double-dummy regimen. During treatment and follow-up periods, patients recorded a daily average pain NRS score for the index knee in an e-diary. Patients returned to the site for efficacy and safety assessment and collection of blood samples for pharmacokinetic analyses 1 and 2 weeks after randomization and at the end of treatment (EOT) visit.

Additional visits during the follow-up period were scheduled at 2 weeks after the EOT visit and at the end of study (EOS).

Number of Patients (Planned, Enrolled and Analyzed):

The planned sample size was 205 patients who were to be randomized in a 2:2:1 ratio to ASP7692 100 mg BID (82 patients), placebo (82 patients) and naproxen 500 mg BID (41 patients).

417 patients provided informed consent and 215 patients were randomized.

212 patients received at least one dose of study drug and are part of the safety analysis set (SAF). 202 patients were included in the full analysis set (FAS), having taken at least one dose of study drug and had a baseline value and at least one double-blind treatment value for the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale score. The per protocol analysis set (PPS) included 185 patients while the pharmacokinetic data set (PKAS) included 82 patients [Figure 1, Table 1].

Diagnosis and Main Criteria for Inclusion:

Patients aged 18-80 years with a primary diagnosis of OA in the index knee of ≥ 6 months prior to screening were included. Diagnosis had to meet American College of Rheumatology (ACR) clinical classification criteria for OA of the knee and radiographic evidence of OA for index knee with Kellgren-Lawrence grade ≥ 2 at screening (based on central reading). Patients had to have moderate to severe OA pain, defined as pain due to OA of the knee at least 5 days per week for the last 3 months prior to screening based on medical history. Patients had to be ambulant and without orthopedic or prosthetic device in index knee. WOMAC physical function subscale score had to be ≥ 4 at baseline.

Test Product, Dose and Mode of Administration, Batch Numbers:

ASP792 was administered as film-coated tablet of 25 mg strength. Batch numbers used were:

- ASP7962 active treatment kits: [redacted] and [redacted],
- Naproxen active treatment kits: [redacted] and [redacted]
- Placebo kits: [redacted] and [redacted].

Patients in the ASP7962 received matching naproxen placebo, patients in the placebo group received matching ASP7962 and naproxen placebo and patients in the naproxen group received matching ASP7962 placebo.

- ASP7962 100 mg BID: ASP7962 and placebo to match naproxen
- Placebo: placebo BID to match ASP7962 and placebo BID to match naproxen
- Naproxen 500 mg BID: naproxen and placebo to match ASP7962

Doses were taken orally in the morning and evening with or without food (approximately 12 hours apart). In case a patient forgot a dose, the next dose was to be taken as planned (no double dose).

Duration of Treatment (or Duration of Study, if applicable):

Patients received assigned treatment for a period of 4 weeks, including morning dose on day 29.

Reference Product, Dose and Mode of Administration, Batch Numbers:

The test drug ASP7962 was supplied as 25 mg round, light yellowish red film-coated tablets.

Batch numbers for ASP7962 active drug/naproxen placebo kits: [redacted],
[redacted]

Naproxen was administered as 500 mg tablets. Tablets were over encapsulated for blinding purposes.

Batch numbers for naproxen active drug/ASP7962 placebo kits: [redacted],
[redacted]

Matching placebo tablets for ASP7962 25 mg tablets and matching placebo for naproxen 500 mg tablets were supplied.

Batch numbers for ASP7962 and naproxen placebo kits: [redacted],
[redacted].

Criteria for Evaluation:

Primary efficacy endpoint

- Change from baseline to week 4 in WOMAC pain subscale score.

Key secondary efficacy endpoints

- Change from baseline in overall patient improvement assessed by Patient Global Assessment (PGA) at EOT and weeks 1, 2 and 4;
- Proportion of patients who achieved ≥ 30% decrease from baseline to EOT in WOMAC pain subscale score;
- Proportion of patients who achieved ≥ 50% decrease from baseline to EOT in WOMAC pain subscale score.
- Change from baseline to EOT and to weeks 1, 2, 3 and 4 in mean daily average pain score assessed by the numerical rating scale (NRS) in the patient's daily diary.

[redacted]

[redacted]

Safety variables

Safety was assessed based on adverse events (AEs), Clinical laboratory evaluation, vital signs, electrocardiograms, physical examination (including neurological examination), neuropathic pain symptom inventory, Columbia-Suicide severity rating scale and radiographic imaging.

Statistical Methods:

All data processing, descriptive summaries and analyses were performed using [redacted]

Analysis populations

The analysis populations included the full analysis set (FAS) used for demographic and baseline characteristics and all efficacy analyses, the per protocol analysis set (PPS), used for sensitivity analyses of the primary and select secondary efficacy endpoints and the safety analysis set (SAF) used for demographic and baseline characteristics and all safety analyses.

The FAS includes all randomized patients 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. The PPS includes all patients of the FAS who did not meet criteria for PPS exclusion list. The SAF consists of all randomized patients who took at least 1 dose of double blind study drug. The pharmacokinetic analysis set (PKAS) consists of the subset of the SAF for which sufficient pharmacokinetic samples were available to develop a population pharmacokinetic (PPK) model. The PKAS was used for all tables and graphical summaries of the pharmacokinetic data.

Demographic and baseline characteristics

Descriptive statistics were used.

Efficacy analysis for primary endpoint

The hypothesis for comparisons of the primary efficacy endpoint was as follows:

H_0: The mean change from baseline to week 4 in WOMAC pain subscale score for ASP7962 100 mg BID group is the same as the placebo group

H_1: The mean change from baseline to week 4 in WOMAC pain subscale score for ASP7962 100 mg BID group is less than the placebo group.

The change from baseline in WOMAC pain subscale score to weeks 1, 2 and 4 was analyzed using a mixed-effect model repeated measures (MMRM) with treatment group, study site, week and week by treatment group interaction as fixed effects and baseline value and week by baseline interaction as covariates.

The MMRM analysis presented the least square (LS) mean estimate, SE and 2 sided 90% CI for change from baseline to each treatment week within a treatment group (placebo, ASP7962 and naproxen). For comparisons between ASP7962 and placebo, the MMRM analysis presented the difference in LS mean estimates, SE and corresponding 2 sided 90% CI for the change from baseline at each week. The differences in the LS mean estimates were used to obtain 1 sided P values for ASP7962 versus placebo and naproxen versus placebo.

No statistical adjustment for multiplicity was made; nominal P-values are reported.

As a sensitivity analysis, the same analysis of the primary efficacy endpoint as described above was repeated using the PPS.

Subgroup analyses for the primary endpoint were carried out by sex, race and age (< 65 years and ≥ 65 years).

Secondary endpoints

The change from baseline to EOT in WOMAC pain subscale score was analyzed using ANCOVA with treatment group and study site as fixed effects and baseline value as a covariate. The ANCOVA presented LS mean, SE and 2 sided 90% CI for mean changes from baseline within each treatment group (placebo, ASP7962 and naproxen). The difference in LS means between ASP7962 and placebo with corresponding 2 sided 90% CI and the difference in LS means between naproxen and placebo with corresponding 2-sided 80% CI were derived. The differences in the LS mean estimates were used to obtain 1 sided P values for ASP7962 vs placebo and naproxen vs placebo.

The change from baseline to EOT for WOMAC physical function and stiffness subscale scores, WOMAC total score, WOMAC walking pain, mean daily average pain NRS score and PGA was analyzed using the same ANCOVA model as described above for the change from baseline to EOT in WOMAC pain subscale score.

The MMRM analysis as described for the primary efficacy analysis was used to analyze the following secondary efficacy endpoints during the treatment period:

- Change from baseline to weeks 1 and 2 for WOMAC pain subscale score (WOMAC pain subscale scores from the MMRM model with weeks 1, 2 and 4 included),
- Change from baseline to weeks 1, 2 and 4 for WOMAC physical function and stiffness subscale scores, WOMAC total score and WOMAC walking pain,
- Change from baseline to weeks 1, 2, 3 and 4 for mean daily average pain score based on the NRS, and
- Change from baseline to weeks 1, 2 and 4 for PGA.

The proportion of patients who had a ≥ 30% reduction and a ≥ 50% reduction from baseline to EOT in WOMAC pain subscale score (i.e., responders) was summarized for each treatment group, as well as the difference in proportion between ASP7962 and placebo and between naproxen and placebo. The difference in proportion between ASP7962 and placebo and between naproxen and placebo was analyzed using a 1 sided Fisher's exact test.

Safety analysis

AEs were coded using MedDRA v18.1. A TEAE was defined as any AE that started, or worsened, after the first dose of study drug through 30 days after the last dose of study drug. The number and percentage of TEAEs, serious TEAEs, TEAEs leading to discontinuation, and TEAEs related to study drug as assessed by the investigator were summarized by SOC, preferred term and treatment group. In addition, TEAEs were summarized by severity for each treatment group.

Summary of Results/Conclusions:

Demographics:

Demographics were relatively similar across treatment groups Table 2. There were more female patients than male patients included (140 [66.0%]) vs 72 [34.0%]). In the naproxen group, there were approximately 10%

more male patients included as compared to the other treatment groups. Most patients were White (208 [98.1%] patients overall). The mean age across all treatment groups was 64.2 years.

Efficacy Results:

- The mean baseline WOMAC pain subscale scores were somewhat higher in the ASP7962 group than in the placebo and naproxen groups (6.20 vs 5.80 and 5.83). The primary endpoint, mean difference in change from baseline in WOMAC pain subscale score at week 4 between ASP7962 and placebo, was not statistically significant (0.14; 90% 2 sided CI: 0.62, 0.34; P = 0.316). By contrast, the respective mean difference between naproxen and placebo was statistically significant (0.67; 80% 2 sided CI: 1.12, 0.23; P = 0.027) [Table 3].
- There was no statistically significant difference in mean change from baseline between ASP7962 and placebo for the secondary endpoints of mean change from baseline in WOMAC pain, physical function and stiffness subscale scores, WOMAC total score and WOMAC walking pain score [Table 4]; mean change from baseline in daily average NRS pain score; mean change from baseline in PGA; and the proportion of patients who achieved a ≥ 30% decrease and a ≥ 50% decrease from baseline to EOT in WOMAC pain subscale score.
- In conclusion, the 4 week treatment of patients with OA with ASP7962 100 mg BID did not result in a significant improvement in pain measures, physical function or patient global assessment compared with placebo. Assay sensitivity of the trial was confirmed by the statistically significant differences between naproxen and placebo for the majority of efficacy endpoints over time during the double-blind treatment period.

Pharmacokinetic Results:

Total and unbound plasma concentrations of ASP7962 as well as α-1 acid glycoprotein concentrations were assessed during the study. The main findings of the pharmacokinetic analyses are:

- %CV was high (> 80%) for the predose/trough sample concentrations and moderate (between 37% and 59%) for the postdose concentrations.
- Predose concentrations of ASP7962 were relatively constant across the visits indicating that steady state was already attained after 1 week of dosing.
- Unbound exposures were consistent with those previously reported for 100 mg BID administered to healthy subjects.
- No patient exceeded the mean exposure limit based on exposures in the rat 13-week toxicology study.

The pharmacokinetic exposures in this study suggest that, in general, patient treatment compliance for ASP7962 was good, although 3 patients at visits 2 and 2 other patients at visit 4, respectively, had plasma concentrations below the limit of quantification < 0.05 ng/mL; which indicated that these patients did not take ASP7962 for more than 1 day prior to that visit.

Safety Results:

- ASP7962 and naproxen were generally well tolerated with 30.6% and 28.6% of patients reporting a TEAE during the double-blind treatment period in the ASP7962 and naproxen treatment groups, respectively, compared to 22.4% in the placebo group [Table 5]. Most TEAEs were of grade 1 and

grade 2 and 1 patient in the ASP7962 reported with a grade 3 event (posttraumatic headache), not related to study drug.

- The number of patients experiencing a TEAE that led to study drug withdrawal ranged between 3.5% and 4.8%.
- There were no deaths reported during the study.
- There was 1 patient reporting a serious TEAE of arthralgia grade 2 in the ASP7962 group during the double-blind treatment period. This SAE was not considered related to study drug by the investigator.
- Joint-related TEAEs were reported in 1 (1.2%) patient, 3 (3.5%) patients and 2 (4.8%) patients in the placebo, ASP7962 and naproxen groups, respectively. Two joint-related AEs were sent for adjudication to the Osteo IAC which considered the evidence as being consistent with normal progression of OA. RPOA was ruled out in all radiographically assessed patients treated with placebo and ASP7962.
- Autonomic neuropathy events were reported in 1 (1.2%) patient and 3 (3.5%) patients in the placebo and ASP7962 groups, respectively. None of these events were considered related to study drug by the investigator. Peripheral neuropathy events were reported in 1 (1.2%) patient each in the placebo and ASP7962 groups, respectively. One event in the placebo group was considered possibly related to study drug, while the event in the ASP7962 was considered not related to study drug. No neurological-related TEAEs were sent for adjudication to the Neuro IAC.
- Biochemistry parameters showed that neither ASP7962 nor naproxen led to a change in hepatic enzymes (AST, ALT, ALP and TBL) compared to placebo. Variables related to renal function (BUN, creatinine, urate) indicated impaired kidney function in approximately 10% to 20% of patients at baseline. There was a trend towards an increase in mean BUN values over time in patients treated with naproxen, while there was no change in mean BUN values in patients treated with ASP7962 or placebo. During the double-blind period, potentially clinically significant values in liver enzymes and total bilirubin were reported in 2 (2.4%) patients in the ASP7962 group (ALP increased > 1.5 x ULN). During the follow-up period, 1 (1.3%) patient in the placebo group reported with ALT increased > 3 x ULN and 1 (1.2%) patient in the ASP7962 reported with ALP increased > 1.5 ULN. Hepatic-related TEAEs were reported in 1 (2.4%) patient in the naproxen treatment group (worsening of GGT elevation) and was considered possibly related to study drug. Two more patients had hepatic-related events, which were not treatment-emergent.
- Hematology parameters showed a reversible increase in eosinophils in the active treatment groups and a decrease in hemoglobin and erythrocytes values in all treatment groups over time which was most pronounced in the naproxen treatment group. Eosinophilia is a known side effect of naproxen.
- Vital signs showed a trend towards a decrease in mean supine SBP and DBP in all treatment groups. A clinically significant increase in supine SBP (i.e., ≥ 20 mmHg change from baseline) was observed in 8.4%, 10.8% and 9.5% of patients in the placebo, ASP7962 and naproxen group, respectively; while a clinically significant decrease was observed in 2.4%, 6.0% and 11.9% of patients in the placebo, ASP7962 and naproxen group, respectively. Pulse rate showed a decreasing trend in the naproxen group. Orthostatic tests led to clinically significant results or symptoms in 2 patients each in the placebo and ASP7962 groups and in 1 patient in the naproxen group.

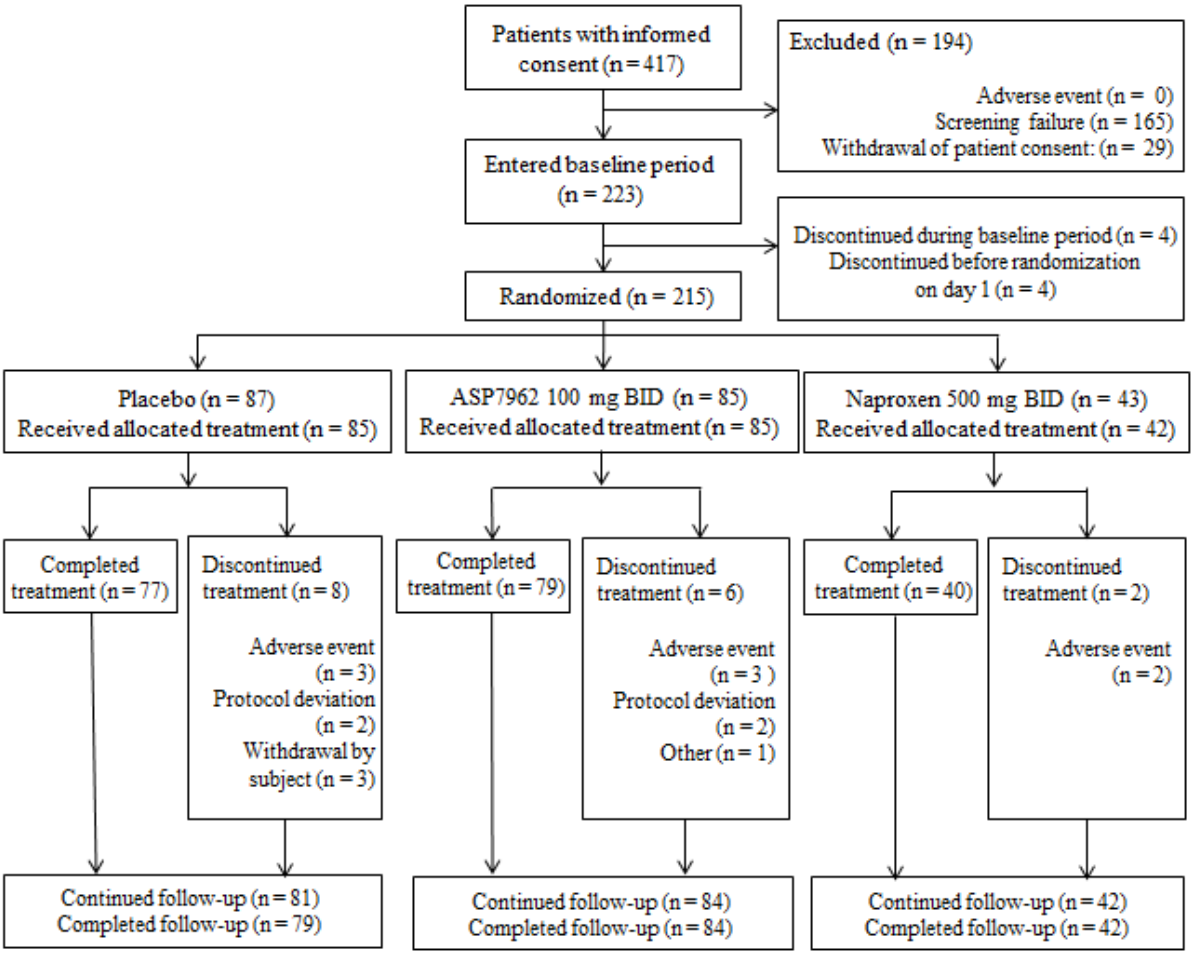
- Abnormalities observed during the 12-lead ECG central reading were similar across treatment groups and over time. A clinically significant abnormal 12-lead ECG result was reported in 1 patient each in the ASP7962 group (QTcF extension) and naproxen group (first-degree AV block) at week 4. During the double-blind treatment period, 4 (4.8%) patients, 5 (6.0%) patients and 3 (7.1%) patients in the placebo, ASP7962 and naproxen group, respectively, had an increase in QTcF of > 30 ms from baseline. No patient had QTcF interval increased by > 60 ms.
- The mean NPSI total score at baseline was comparable across treatment groups. Numerically, the change from baseline observed in the ASP7962 group appeared to be greater than in the placebo group but smaller than in the naproxen group.

CONCLUSIONS:

The primary endpoint, the mean difference in change from baseline in WOMAC pain subscale score at week 4 between ASP7962 and placebo, was not statistically significant. ASP7962 100 mg BID is therefore not considered to have an analgesic effect on OA pain. ASP7962 100 mg BID was shown to be safe and well tolerated.

Date of Report: 28 Mar 2018

Figure 1 Disposition of Subjects



Patients screened twice (following Amendment 3 to the protocol) are counted only once.
Source: Tables 12.1.1.1, 12.1.1.2, 12.1.1.7, 12.1.1.8, 12.1.1.9, 12.1.1.10

Table 1 Analysis Sets (All Randomized Patients)

Analysis Set	Placebo (n = 87)	ASP7962 100 mg BID (n = 85)	Naproxen 500 mg BID (n = 43)	Total (n = 215)
Randomized	87 (100%)	85 (100%)	43 (100%)	215 (100%)
Patients who took study drug	85 (97.7%)	85 (100%)	42 (97.7%)	212 (98.6%)
Patients who did not take study drug	2 (2.3%)	0	1 (2.3%)	3 (1.4%)
Safety analysis set †	85 (97.7%)	85 (100%)	42 (97.7%)	212 (98.6%)
Full analysis set ‡	79 (90.8%)	81 (95.3%)	42 (97.7%)	202 (94.0%)
Per protocol analysis set §	72 (82.8%)	75 (88.2%)	38 (88.4%)	185 (86.0%)
Pharmacokinetic analysis set ¶	0	82 (96.5%)	0	82 (38.1%)

FAS: full analysis set; PPS: per-protocol set; SAF: safety analysis set; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

† All randomized patients who took at least one dose of double-blind study drug.

‡ All randomized patients who took at least one dose of study drug and had a baseline value and at least one double-blind treatment value for the WOMAC pain subscale score.

§ All patients of the FAS who did not meet criteria for PPS exclusion.

¶ Subset of the SAF for which sufficient total and unbound plasma concentration of ASP7962 and α-1 acid glycoprotein concentration are available to facilitate development of the population pharmacokinetic (PPK) model and for whom the time of dosing on the days of pharmacokinetic sampling is known.

Source: Tables 12.1.1.2, 12.4.1.1

Table 2 Demographic and Baseline Characteristics (Safety Analysis Set)

Parameter Category/ Statistics	Placebo (n = 85)	ASP7962 100 mg BID (n = 85)	Naproxen 500 mg BID (n = 42)	Total (n = 212)
Region, n (%) †				
Eastern Europe	34 (40.0)	34 (40.0)	17 (40.5)	85 (40.1)
Western Europe	51 (60.0)	51 (60.0)	25 (59.5)	127 (59.9)
Sex, n (%)				
Male	29 (34.1)	26 (30.6)	17 (40.5)	72 (34.0)
Female	56 (65.9)	59 (69.4)	25 (59.5)	140 (66.0)
Race, n (%)				
White	84 (98.8)	82 (96.5)	42 (100.0)	208 (98.1)
Black or African American	1 (1.2)	1 (1.2)	0	2 (0.9)
Asian	0	1 (1.2)	0	1 (0.5)
Other	0	1 (1.2)	0	1 (0.5)
Age, years				
Mean (SD)	64.0 (8.4)	63.6 (8.4)	65.6 (7.6)	64.2 (8.2)
Median	64.0	64.0	65.5	64.0
Min – Max	38 – 79	35 – 79	48 – 77	35 – 79
Age group, years (%)				
< 65	43 (50.6)	45 (52.9)	19 (45.2)	107 (50.5)
≥ 65 to < 75	33 (38.8)	32 (37.6)	14 (33.3)	79 (37.3)
≥ 75	9 (10.6%)	8 (9.4)	9 (21.4)	26 (12.3)
Weight, kg				
Mean (SD)	82.03 (14.37)	82.08 (15.16)	84.37 (12.33)	82.51 (14.29)
Median	81.0	80.0	82.6	81.1
Min – Max	59.0 – 123	52.0 – 119.0	53.0 – 117.0	52 – 123
Height, cm				
Mean (SD)	166.3 (8.9)	164.9 (9.3)	167.4 (9.3)	165.9 (9.1)
Median	165.0	163.0	166.5	165.0
Min – Max	142.8 – 191.5	150.0 – 191.0	147.0 – 186.0	142.8 – 191.5
BMI, kg/m^2				
Mean (SD)	29.6 (4.0)	30.1 (4.4)	30.1 (3.4)	29.9 (4.0)
Median	29.1	29.6	29.5	29.5
Min – Max	21.8 – 38.3	20.6 – 39.0	24.5 – 36.8	20.6 – 39.0
BMI group, kg/m^2, n (%)				
< 25	11 (12.9)	10 (11.8)	3 (7.1)	24 (11.3)
≥ 25 to < 30	38 (44.7)	34 (40.0)	20 (47.6)	92 (43.4)
≥ 30 to < 35	27 (31.8)	30 (35.3)	14 (33.3)	71 (33.5)
≥ 35	9 (10.6)	11 (12.9)	5 (11.9)	25 (11.8)

BMI: body mass index = weight (kg)/height^2 (m^2); Max: maximum; Min: minimum.

† Eastern Europe: Hungary, Czech Republic. Western Europe: Belgium, Germany, Spain, United Kingdom.

Source: Table 12.1.2.2

Table 3 Repeated Measures Analysis of Change from Baseline at Week 4 in WOMAC Pain Subscale Score (Full Analysis Set)

Visit/Statistic	Placebo (n = 79)	ASP7962 100 mg BID (n = 81)	Naproxen 500 mg BID (n = 42)
Baseline			
n	79	81	42
Mean (SE)	5.80 (0.12)	6.20 (0.14)	5.83 (0.16)
Median (Min to Max)	5.80 (2.6 to 9.0)	6.20 (4.0 to 9.6)	5.70 (4.2 to 7.8)
Week 4			
n	75	77	39
Mean (SE)	4.13 (0.20)	4.21 (0.23)	3.38 (0.34)
Median (Min to Max)	4.20 (0.0 to 7.6)	4.20 (0.0 to 8.8)	3.40 (0.0 to 7.8)
Change from baseline			
n	75	77	39
Mean (SE)	-1.66 (0.20)	-1.98 (0.21)	-2.45 (0.34)
Median (Min to Max)	-1.40 (-6.2 to 2.2)	-1.80 (-7.4 to 1.4)	-2.60 (-7.2 to 1.4)
Adjusted change from baseline			
Mean (SE)	-1.73 (0.21)	-1.87 (0.20)	-2.40 (0.28)
90% 2-sided CI	(-2.07, -1.38)	(-2.20, -1.53)	(-2.87, -1.93)
Difference vs placebo			
Mean (SE)	NA	-0.14 (0.29)	-0.67 (0.35)
90% 2-sided CI	NA	(-0.62, 0.34)	NA
80% 2-sided CI	NA	NA	(-1.12, -0.23)
1-sided P value†	NA	0.316	0.027
P value‡	0.453		

CI: confidence interval; Max; maximum; Min: minimum; NA: not applicable; SE: standard error; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

The FAS includes all randomized patients 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.

Repeated measures analysis was performed using the baseline data and change from baseline data from week 1, 2 and 4 analysis visits.

† P value for pairwise treatment comparison with placebo.

‡ P value for week x treatment interaction.

Source: Table 12.3.1.1.1

Table 4 Adjusted Change from Baseline at EOT in WOMAC Subscale and Total Scores (Full Analysis Set)

Visit/Statistic	Placebo (n = 79)	ASP7962 100 mg BID (n = 81)	Naproxen 500 mg BID (n = 42)
WOMAC pain subscale score			
Adjusted change from baseline			
Mean (SE)	-1.74 (0.20)	-1.91 (0.20)	-2.41 (0.27)
90% 2-sided CI	(-2.07 to -1.42)	(-2.24 to -1.59)	(-2.86,-1.96)
Difference vs placebo			
Mean (SE)	NA	-0.17 (0.28)	-0.66 (0.34)
90% 2-sided CI	NA	(-0.63, 0.30)	NA
80% 2-sided CI	NA	NA	(-1.10, -0.23)
1-sided P value†	NA	0.276	0.025
WOMAC walking pain subscale score			
Adjusted change from baseline			
Mean (SE)	-1.56 (0.22)	-1.82 (0.21)	-2.53 (0.29)
90% 2-sided CI	(-1.92,-1.20)	(-2.17,-1.47)	(-3.01,-2.04)
Difference vs placebo			
Mean (SE)	NA	-0.26 (0.31)	-0.96 (0.37)
90% 2-sided CI	NA	(-0.77, 0.24)	NA
80% 2-sided CI	NA	NA	(-1.44, -0.49)
1-sided P value†	NA	0.197	0.005
WOMAC physical function subscale score			
Adjusted change from baseline			
Mean (SE)	-1.67 (0.19)	-1.81 (0.19)	-2.51 (0.26)
90% 2-sided CI	(-1.99,-1.35)	(-2.12,-1.49)	(-2.95,-2.08)
Difference vs placebo			
Mean (SE)	NA	-0.14 (0.27)	-0.84 (0.33)
90% 2-sided CI	NA	(-0.59, 0.31)	NA
80% 2-sided CI	NA	NA	(-1.26, -0.42)
1-sided P value†	NA	0.306	0.005
WOMAC stiffness subscale score			
Adjusted change from baseline			
Mean (SE)	-1.68 (0.20)	-1.89 (0.20)	-2.82 (0.28)
90% 2-sided CI	(-2.01,-1.35)	(-2.22,-1.56)	(-3.28,-2.37)
Difference vs placebo			
Mean (SE)	NA	-0.21 (0.28)	-1.14 (0.34)
90% 2-sided CI	NA	(-0.68, 0.26)	NA
80% 2-sided CI	NA	NA	(-1.58, -0.70)
1-sided P value†	NA	0.232	0.001
WOMAC total score			
Adjusted change from baseline			
Mean (SE)	-5.07 (0.56)	-5.65 (0.56)	-7.71 (0.77)
90% 2-sided CI	(-6.00,-4.14)	(-6.58,-4.73)	(-8.98,-6.44)
Difference vs placebo			
Mean (SE)	NA	-0.59 (0.80)	-2.64 (0.95)
90% 2-sided CI	NA	(-1.91, 0.74)	NA
80% 2-sided CI	NA	NA	(-3.87, -1.41)
1-sided P value†	NA	0.232	0.003

ANCOVA: analysis of covariance; CI: confidence interval; EOT: end of treatment; NA: not applicable; SE: standard error; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

Footnotes continued on next page

The FAS includes all randomized patients 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.

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

† P value for pairwise treatment comparison with placebo.

Source: Tables 12.3.2.1, 12.3.2.2, 12.3.2.3, 12.3.2.4, 12.3.2.5

Table 5 Overview of Treatment-emergent Adverse Events and Death by Investigational Period (Safety Analysis Set)

	Treatment Period			Follow-up Period†		
n (%)	Placebo (n = 85)	ASP7962 100 mg BID (n = 85)	Naproxen 500 mg BID (n = 42)	Placebo (n = 81)	ASP7962 100 mg BID (n = 84)	Naproxen 500 mg BID (n = 42)
TEAE	19 (22.4)	26 (30.6)	12 (28.6)	10 (12.3)	8 (9.5)	2 (4.8)
Drug-related TEAE‡	10 (11.8)	7 (8.2)	7 (16.7)	0	1 (1.2)	1 (2.4)
Serious TEAE	0	1 (1.2)	0	0	0	0
Drug-related serious TEAE	0	0	0	0	0	0
Deaths§	0	0	0	0	0	0
TEAE leading to withdrawal of treatment	3 (3.5)	3 (3.5)	2 (4.8)	0	0	0
Drug-related TEAE leading to withdrawal of treatment	3 (3.5)	1 (1.2)	2 (4.8)	0	0	0
Joint-related TEAE	1 (1.2)	2 (2.4)	2 (4.8)	0	2 (2.4)	0
Neurological-related TEAE	2 (2.4)	3 (3.5)	0	0	1 (1.2)	0
Hepatic related TEAE	0	0	1 (2.4)	0	0	0

TEAE: treatment emergent adverse event.

† n is the number of patients entering the follow-up period.

‡ Possible or probable, as assessed by the investigator, or records where relationship is missing.

§ All reported deaths after the first study drug administration.

Source: Table 12.6.1.1.2