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Tropomyosin-related kinase A (TrkA) inhibition for the treatment of painful knee osteoarthritis: results from a randomized controlled phase 2a trial

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SUMMARY

Objective: To investigate the TrkA inhibitor, ASP7962, for treatment of painful knee osteoarthritis.
Design: Phase 2a, double-blind, placebo- and naproxen-controlled, double-dummy, parallel-group study. Adults with knee osteoarthritis were randomized (2:2:1) to ASP7962 (100 mg), placebo, or naproxen (500 mg) twice daily (BID) for 4 weeks. Primary endpoint: change from baseline to Week 4 in Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale score. Secondary endpoints: change from baseline to Weeks 1, 2, and End of Treatment (EoT) in WOMAC pain subscale score; change from baseline to Weeks 1, 2, 4, and EoT in WOMAC physical function and stiffness subscales, walking pain and WOMAC total scores; and change from baseline in daily average pain score.
Results: 215 participants were randomized (ASP7962 100 mg BID, $n = 85$; placebo, $n = 87$; naproxen 500 mg BID, $n = 43$). No significant difference was observed between ASP7962 and placebo in change from baseline to Week 4 in WOMAC pain subscale score (−0.14; 90% 2-sided CI: −0.62, 0.34; $P = 0.316$); a significant difference was observed between naproxen and placebo (−0.67; 80% 2-sided CI: −1.12, −0.23; $P = 0.027$). No differences were observed between ASP7962 and placebo in change from baseline in any WOMAC subscale score; statistically significant changes were observed between naproxen and placebo ($P \leq 0.01$, all time points for all WOMAC endpoints). ASP7962 was safe and well-tolerated.
Conclusions: Four-week treatment with ASP7962 (100 mg BID) did not improve pain or physical function in individuals with painful knee osteoarthritis.
ClinicalTrials.gov, NCT02611466; EudraCT Number, 2014-004996-22.

Introduction

Osteoarthritis (OA) affects ~27 million people in the US and contributes to the recent increased rates of knee arthroplasty[1]. Common symptoms include pain, stiffness, and function loss, and can affect an individual's ability to carry out normal daily activities and diminish overall quality of life. Risk factors include increasing age, genetic predisposition, and obesity; women have a higher risk of developing OA and typically suffer more severe symptoms[2,3]. Treatment of knee OA aims at reducing pain and stiffness and improving long-term physical function. Non-pharmacological interventions such as exercise[4] and weight loss[5] are common, and pharmacological interventions include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and in more severe cases, opioid analgesics[3,6]. However, NSAIDs and opioids are associated with numerous side effects and often contraindicated in patients with co-morbidities, and non-pharmacological treatment often

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yields insufficient efficacy when used alone. Therefore, there is an unmet need for new drugs for knee OA pain with improved efficacy and safety profiles.

In vivo studies demonstrate that exogenous nerve growth factor (NGF) has a role in nociception, inducing hyperalgesia[7,8], and suggest that blocking NGF may represent a novel target for the treatment of painful chronic conditions including OA. NGF is a neurotrophin that binds to the p75 neurotrophin receptor (p75NTR) with low affinity, and to the tropomyosin-related kinase A (TrkA) receptor with high affinity[9]. The actions of NGF on pain appear to be mediated by TrkA as p75NTR-knockout mice show similar NGF-induced hyperalgesia to wild-type mice[7]. TrkA is expressed on the surface of nociceptors and in the dorsal root ganglion; the binding of NGF to TrkA initiates the nociceptive signal[7,10]. The expression of NGF and TrkA is increased in the serum and synovial fluid of individuals with painful conditions including OA[11], and inhibition of NGF by tanezumab and other monoclonal antibodies (mAbs) to NGF is effective in reducing knee pain in subjects with moderate-to-severe OA[12–16]. However, rapidly progressive OA (RPOA) and other joint-related adverse events (AEs) in non-target joints have been observed in clinical trials of mAbs to NGF[17,18]. Other options to block the NGF/TrkA signaling pathway include mAbs to TrkA, such as MNAC13[19], and small-molecule TrkA inhibitors, such as AR786[20]. Both strategies have the advantage that, by specifically blocking TrkA, they should not affect NGF signaling via p75NTR. Moreover, compared with mAbs, non-biological TrkA inhibitors offer the advantage of being orally available, having shorter half-lives, and being easier to manufacture[21].

ASP7962 is a novel, oral, selective inhibitor of human TrkA that was investigated for the treatment of OA. *In vitro* studies found that ASP7962 inhibited ATP-induced substrate phosphorylation of human TrkA, B, and C kinase with 50% inhibitory (IC50) value of 0.155 μmol/L, 1.41 μmol/L, and 1.09 μmol/L, respectively. Dosing and toxicity studies in pre-clinical models and subsequent phase 1 human studies supported the choice of the 100 mg BID human dose as the optimum therapeutic dose (data on file). Phase 1 studies (NCT01981928 and NCT02136316) assessing the safety and tolerability of ASP7962 demonstrated a favorable safety profile for single doses up to 240 mg and multiple doses up to 200 mg twice daily (BID) in healthy subjects. This proof-of-concept phase 2a study investigated the efficacy of a 4-week administration of 100 mg ASP7962 BID for the treatment of pain associated with knee OA and compared it with placebo. Naproxen, an NSAID approved for the treatment of OA, was utilized as an active control to test assay sensitivity.

Methods

Study design

The 7962-CL-0022 study was a phase 2a, double-blind, randomized, placebo- and naproxen-controlled, parallel-group study (ClinicalTrials.gov, NCT02611466; EudraCT Number, 2014-004996-22) conducted at 31 sites (Western Europe: Spain, Germany, United Kingdom, and Belgium; and Eastern Europe: Hungary and Czech Republic) from February 2016 to September 2017. The study comprised screening (Day −28 through Day −7), baseline (Day −7 through Day −1), treatment (Day 1 through Day 29), and follow-up (Day 30 through Day 57) periods [Fig. 1(A)]. At screening, the index knee was identified and used for all subsequent assessments. If both knees were affected, the more painful one was selected as the index knee. Radiographic images of both knees (semi-flexed standing views) were evaluated to assess participants' eligibility. At the end of the screening period, eligible participants entered the baseline period where washout of all pain medications was conducted. Participants returned to the study site on Day 1 and were reassessed for eligibility and randomized 2:2:1 to one of the following double-dummy regimens: 1) ASP7962 (100 mg) BID and naproxen-matched placebo BID (hence referred to as ASP7962 or treatment arm; 2) ASP7962-matched placebo BID and naproxen-matched placebo BID (hence referred to as placebo arm); or 3) naproxen (500 mg) BID and ASP7962-matched placebo BID (hence referred to as the naproxen arm). Participants continued treatment for 4 weeks and returned to the study site for safety and efficacy assessments at 1, 2, and 4 weeks after Day 1 and during follow-up at 2 and 4 weeks after the last treatment. Participants were trained to use an electronic diary to record their index knee daily average pain scores on a 0–10 numerical rating scale (NRS) every evening during the treatment and follow-up periods. Participants who discontinued the study during the treatment period were asked to complete the End of Treatment (EoT) and follow-up visits. If patients withdrew during the follow-up period, they were asked to complete an End of Study visit.

Throughout the study, safety was evaluated by a neurological Independent Adjudication Committee (IAC), which assessed neurological events, and by an Osteo IAC, which monitored the risk for RPOA. This study also had an Independent Data Monitoring Committee for safety surveillance. Due to the 2:2:1 design, the number of participants randomized to naproxen was intentionally lower than that for placebo and ASP7962; naproxen was included as an active control to confirm that the study was properly designed to detect treatment efficacy (i.e., assay sensitivity). The dose of ASP7962 (100 mg BID) was based on pre-clinical toxicity data where 100 mg was the highest dose for which safety assessments were available in healthy adults at the time this study was initiated (data on file). The BID regimen of dosing was chosen based on the half-life of ASP7962 (8 h).

This study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization, and applicable local laws and regulations. Independent Ethics Committees in each country reviewed and approved the study protocol and documentation, including participant informed consent forms.

Population and eligibility criteria

Participants were men and women aged 18–80 years who had a primary diagnosis of knee OA, with symptoms persisting for ≥6 months before screening. Inclusion criteria were the American College of Rheumatology clinical diagnostic criteria for knee OA[22]; radiographic OA of the index knee (Kellgren and Lawrence grade ≥2)[23] at screening and Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain and physical function subscale scores ≥4 at baseline; participants needed to be ambulatory with no orthopedic and/or prosthetic device with moderate-to-severe index knee pain (≥5 days per week for 3 months before screening); patients also had to be willing to discontinue all current pain medications after signing informed consent, upon starting the baseline period. Rescue therapy for intolerable pain experienced during baseline and the treatment period included ice packs, paracetamol (up to 3000 mg/day, 5 days per week), and tramadol (up to 200 mg/day, three times per week), and was recorded in their electronic diary. Key exclusion criteria included a history of suicidal behavior; current or prior clinically significant psychiatric disorder; neurological disease; uncontrolled musculoskeletal disorder, cardiovascular (e.g., symptomatic orthostatic hypotension), gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, dermatologic, renal and/or other major disease; malignancy in the last 5 years; a history of inflammatory arthritis; RPOA or increased risk of RPOA;

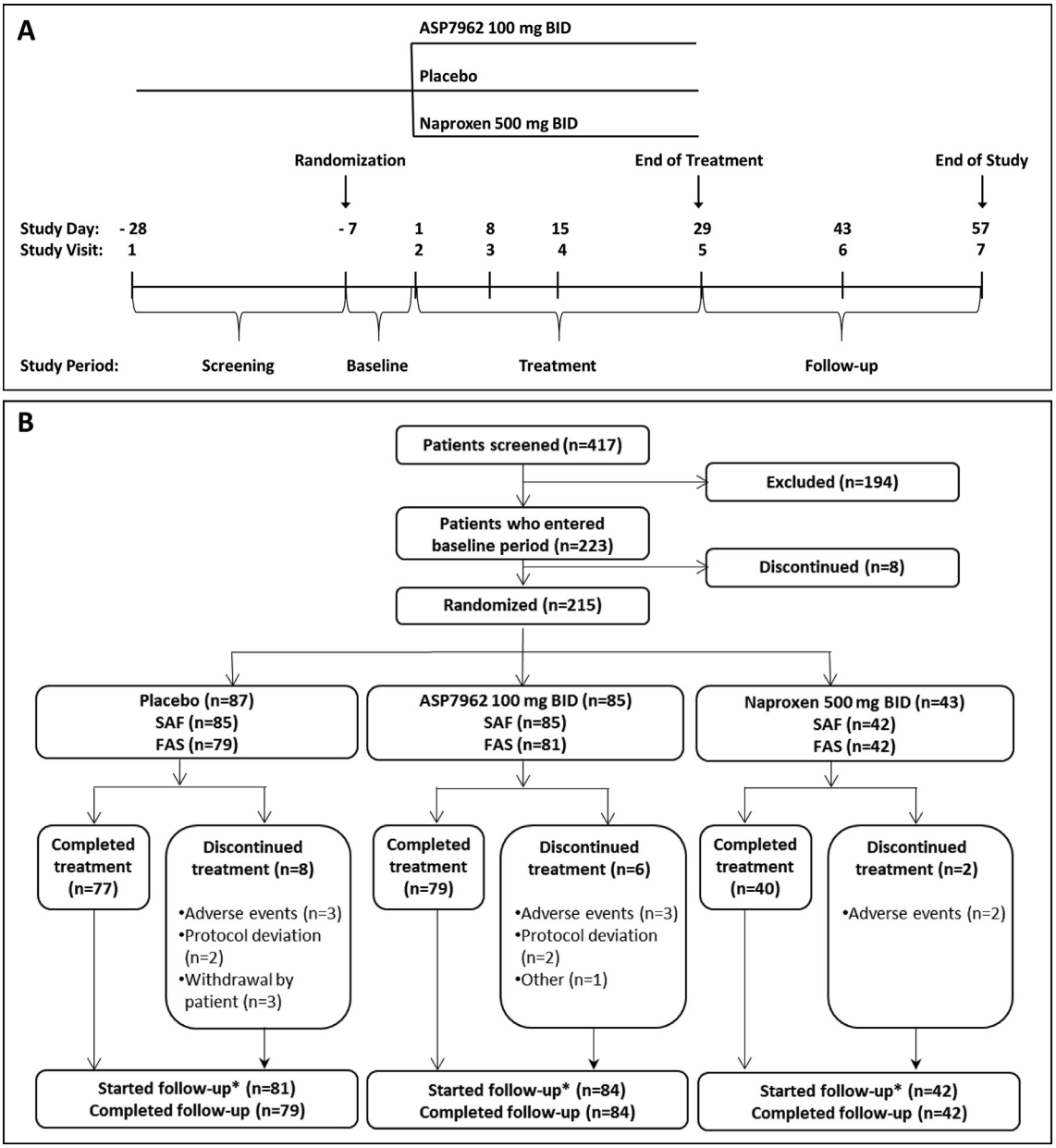

Fig. 1. Flow Chart (A) and Participant Disposition (B). Abbreviations: BID, twice daily; FAS, full analysis set; SAF, safety analysis set. *Subjects who discontinued the study during the treatment period could enter the follow-up period.

abnormality on 12-lead electrocardiogram (ECG); any cause for knee pain other than OA (e.g., radiculopathy); any painful condition syndrome (e.g., neuropathy, fibromyalgia); or body mass index >39 kg/m^2. Full inclusion and exclusion criteria can be found in the Supplementary materials.

Endpoints

The primary endpoint was change from baseline to Week 4 in WOMAC pain subscale score. Secondary endpoints included change from baseline to Weeks 1 and 2, and EoT in WOMAC pain subscale score; change from baseline to Weeks 1, 2, 4, and EoT in WOMAC physical function and stiffness subscale scores, WOMAC total score, and WOMAC walking pain; change from baseline to Weeks 1, 2, 3, 4, and EoT in mean daily average pain score; change from baseline to Weeks 4 and EoT in overall patient improvement assessed by Patient Global Assessment (PGA); and proportion of participants who achieved a ≥30% and ≥50% decrease from baseline to EoT in WOMAC pain subscale score[24]. Safety was assessed by monitoring AEs; vital signs (including orthostatic challenge test to assess autonomic risks); 12-lead ECG; and physical examinations (including neurological examination).

Assessments

The WOMAC Index is a self-administered 24-item questionnaire comprising pain (five items), stiffness (two items), and physical function (17 items) subscales. The first item of the pain subscale assesses walking pain. Each item is scored on a 0–10 NRS, with total score calculated from the three subscale scores[25]. The PGA is a single question to rate patients' overall impression in the index knee on a 0–10 NRS (0, very good; 10, very poor). Standardized

radiographic images of the knees were obtained at the End of Study visit.

Statistical methods

Sample size

A total of 205 participants were planned (ASP7962, $n = 82$; placebo, $n = 82$; and naproxen, $n = 41$). A sample size of 78 participants in the ASP7962 and placebo groups would be able to detect a difference of 1.2 in the WOMAC pain subscale score between the treatment groups with 80% power, assuming a standard deviation (SD) of 3.0 and using a 2-group *t*-test at a 1-sided alpha level of 0.05. The difference of 1.2 between treatment groups and the SD of 3.0 were selected based on meta-analysis of the tanezumab studies (data on file). The sample size of 82 participants for each group was chosen under the assumption that there was no on-treatment measure of WOMAC pain subscale scores for 5% of participants. Since naproxen was included solely to test the assay sensitivity, a smaller sample size was chosen for this group, which would reduce the power to detect a difference between treatment groups. A sample size of 41 participants in the naproxen group would be able to detect a 1.2 difference in the WOMAC pain subscale score between naproxen and placebo with 77% power, using a 2-group *t*-test at a 1-sided alpha level of 0.10. This was intentionally different from the more stringent comparison between ASP7962 and placebo that was made using a 1-sided test at the 0.05 significance level, as the efficacy of naproxen in this setting is well-established[26,27]. Assignment of participants was performed at the study site using a block randomization schedule that was computer-generated via interactive response technology and was based on balanced sets of latin squares generated with different permutations of the treatment arms. Patients, investigators, the sponsor's study management team, and clinical staff were blind to treatment, and ASP7962, naproxen, and placebo were undistinguishable in appearance.

Analysis populations

The full analysis set included all participants who took ≥1 dose of ASP7962 and had ≥1 double-blind treatment value for the WOMAC pain subscale scores and was used to summarize all efficacy analyses. The safety analysis set, used to summarize demographic and baseline characteristics and all safety analyses, included all randomized participants who took ≥1 dose of ASP7962.

Statistical analysis

A mixed-effect model repeated measures (MMRM), which is a statistical model that contains both fixed and random effects, was used to analyze the change from baseline in WOMAC pain subscale score to Weeks 1, 2, and 4. Treatment group, study site, week, and week by treatment group interaction were used as fixed effects, and baseline value and week by baseline interaction were used as covariates. The treatment group contrasts for the change from baseline to Week 4 was the primary statistical inference obtained from the model. For each treatment group, least square (LS) mean, standard error (SE), and 2-sided 90% confidence interval (CI) were reported for the change from baseline to Weeks 1, 2, and 4. To compare treatment groups, the difference in LS means, SE, and the corresponding 2-sided 90% CI for ASP7962 vs placebo and 2-sided 80% CI for naproxen vs placebo were reported. The 1-sided *P* values for the comparison between ASP7962 and placebo and between naproxen and placebo were calculated using the differences in LS mean. MMRM analysis was also used to analyze the change from baseline to Weeks 1, 2, and 4 for PGA, WOMAC physical function and stiffness subscale scores, WOMAC total score, and WOMAC walking pain, and the change from baseline to Weeks 1, 2, 3, and 4 for mean daily average pain score. The change from baseline to EoT in the WOMAC pain subscale score was analyzed by analysis of covariance (ANCOVA), with the treatment group and study site as fixed effects and baseline value as a covariate. The differences in the LS means were used to obtain 1-sided *P* values for ASP7962 vs placebo and naproxen vs placebo. The same ANCOVA model was used to analyze the change from baseline to EoT for the WOMAC physical function and stiffness subscale scores, WOMAC total score, WOMAC walking pain, mean daily average pain NRS score, and PGA.

Results

Participant disposition

Of 417 participants who provided informed consent, 165 failed screening and 29 withdrew before entering the baseline period (Supplementary Table S1). Of 223 participants who entered the baseline period, eight discontinued due to failure to meet randomization criteria ($n = 4$), screening failure ($n = 3$), and AE ($n = 1$), and 215 were randomized to ASP7962 100 mg BID ($n = 85$), placebo ($n = 87$), and naproxen 500 mg BID ($n = 43$). Ten patients were randomized in addition to the 205 planned participants, due to above-expected eligibility rates in those completing screening. Two hundred twelve (98.6%) and 202 (94%) participants were included in the safety analysis set and full analysis set, respectively. One hundred ninety-six (91.2%) participants completed the treatment period and 205 (95.3%) participants completed the follow-up period [Fig. 1(B)].

Overall, there were more female ($n = 140$, 66.0%) than male ($n = 72$, 34.0%) participants and most were Caucasian ($n = 208$, 98.1%). Participants were from Eastern ($n = 85$; 40.1%) or Western ($n = 127$; 59.9%) Europe. The mean time from diagnosis was approximately 7 years, and 158 (74.5%) participants also had OA in their non-index knee. Demographics and baseline characteristics were similar among groups; however, slightly higher WOMAC pain subscale and total scores were observed in the ASP7962 group compared with the placebo and the naproxen groups (Table I). A total of 44 (20.8%) patients (placebo, $n = 16$ [18.8%]; ASP7962, $n = 17$ [20.0%]; naproxen, $n = 11$ [26.2%]) were previously receiving NSAIDs for OA pain that were subsequently washed out during the baseline period.

Efficacy of ASP7962

Adjusted mean changes from baseline to Week 1, 2, and 4 in WOMAC pain subscale scores are shown in Fig. 2. The mean difference in change from baseline to Week 4 in WOMAC pain subscale scores between ASP7962 ($n = 77$) and placebo ($n = 75$) was not statistically significant (−0.14; 90% 2-sided CI: −0.62, 0.34; $P = 0.316$), whereas a statistically significant difference was observed between naproxen ($n = 39$) and placebo ($n = 75$) (−0.67; 80% 2-sided CI: −1.12, −0.23; $P = 0.027$) (Fig. 2; Supplementary Table S2).

Analysis of the secondary endpoints showed no statistically significant differences between ASP7962 and placebo in the change from baseline to Week 1, 2, or 4 in any of the WOMAC subscale scores, walking pain score, or total score (Fig. 3). The adjusted mean differences between ASP7962 and placebo in the change from baseline to Week 4 were: physical function, −0.12 (90% 2-sided CI: −0.58, 0.34; $P = 0.335$; Supplementary Table S3); stiffness, −0.17, (90% 2-sided CI: −0.64, 0.30; $P = 0.278$); walking pain, −0.22 (90% 2-sided CI: −0.74, 0.30; $P = 0.243$); and WOMAC total score, −0.52 (90% 2-sided CI: −1.86, 0.82; $P = 0.261$). Similarly, there were no

Table I
Demographic and baseline characteristics

Parameter	Placebo $N = 85$	ASP7962 100 mg BID $N = 85$	Naproxen 500 mg BID $N = 42$	Total $N = 212$
Age (years)				
Mean (SD)	64.0 (8.4)	63.6 (8.4)	65.6 (7.6)	64.2 (8.2)
Sex, *n* (%)				
Female	56 (65.9)	59 (69.4)	25 (59.5)	140 (66.0)
BMI (kg/m^2)				
Mean (SD)	29.6 (4.0)	30.1 (4.4)	30.1 (3.4)	29.9 (4.0)
Index knee location, *n* (%)				
Right	46 (54.1)	39 (45.9)	22 (52.4)	107 (50.5)
Kellgren–Lawrence grade, index knee, *n* (%)				
Grade 1	1 (1.2)	0	0	1 (0.5)
Grade 2	17 (20.0)	18 (21.2)	11 (26.2)	46 (21.7)
Grade 3	44 (51.8)	41 (48.2)	18 (42.9)	103 (48.6)
Grade 4	23 (27.1)	26 (30.6)	13 (31.0)	62 (29.2)
OA pain present, *n* (%)				
Index knee only	21 (24.7)	17 (20.0)	9 (21.4)	47 (22.2)
Index knee + 1 joint	48 (56.5)	48 (56.5)	26 (61.9)	122 (57.5)
Index knee + 2 joints	3 (3.5)	6 (7.1)	4 (9.5)	13 (6.1)
Index knee + 3 joints	13 (15.3)	14 (16.5)	3 (7.1)	30 (14.2)
WOMAC pain subscale score				
Mean (SD)	5.67 (1.29)	6.08 (1.37)	5.83 (1.05)	5.86 (1.29)
WOMAC walking pain score				
Mean (SD)	5.61 (1.44)	6.12 (1.61)	6.02 (1.42)	5.90 (1.52)
WOMAC stiffness subscale score				
Mean (SD)	5.84 (1.66)	6.20 (1.72)	5.88 (1.78)	5.99 (1.71)
WOMAC physical function				
Mean (SD)	5.84 (1.36)	6.27 (1.40)	6.00 (1.00)	6.04 (1.32)
WOMAC total score				
Mean (SD)	17.35 (3.95)	18.54 (4.05)	17.71 (3.4)	17.90 (3.91)

Abbreviations: BMI, body mass index; Max, maximum; Min, minimum; OA, osteoarthritis; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

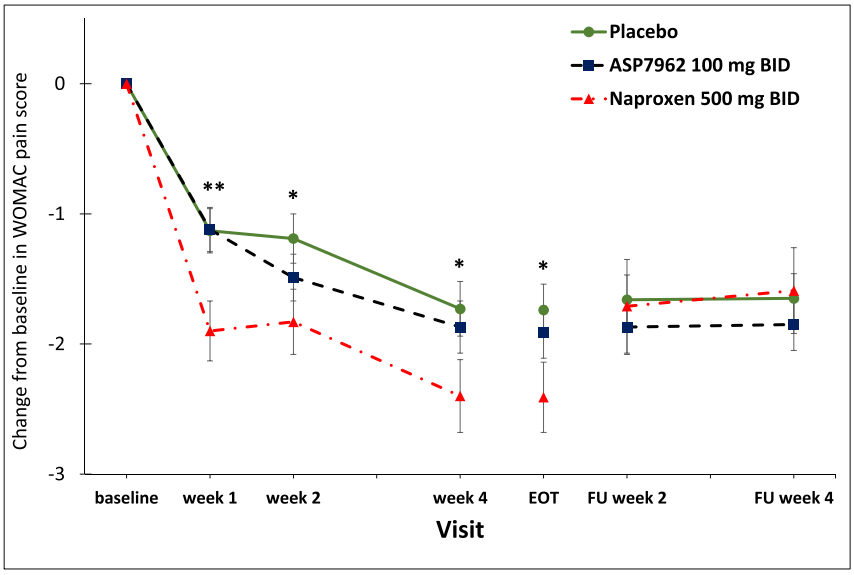

Fig. 2. Change From Baseline and Follow-up in WOMAC Pain Subscale Score in the Index Knee. Data are presented as mean (SE). Abbreviations: EoT, end of treatment; FU, follow-up; SE, standard error. EoT results include all participants who completed the 4-week treatment and those who discontinued the study before Week 4. The change from baseline to Weeks 1, 2, and 4 results are based on repeated measures analysis, with treatment group, study site, week, and week by treatment group interaction as fixed effects and baseline and week by baseline interaction as covariates. The change from baseline to EoT result is based on an analysis of covariance with treatment group and study site as fixed effects and baseline value as a covariate. Results for the FU visits are based on descriptive statistics. $^*P \leq 0.05$, $^{**}P \leq 0.01$, between naproxen and placebo.

statistically significant differences between placebo and ASP7962 in the adjusted mean changes from baseline to EoT in WOMAC pain (placebo, −1.74; ASP7962, −1.91; $P = 0.276$), physical function (placebo, −1.67; ASP7962, −1.81; $P = 0.306$; Supplementary Table S3), and stiffness (placebo, −1.68; ASP7962, −1.89; $P = 0.232$) subscale scores, walking pain score (placebo, −1.56; ASP7962, −1.82; $P = 0.197$), and WOMAC total score (placebo, −5.07; ASP7962, −5.65; $P = 0.232$). Conversely, statistically significant differences in the adjusted mean changes from baseline to EoT were observed in all WOMAC subscale scores between naproxen and placebo (pain, naproxen, −2.41, $P = 0.025$; physical function, naproxen, −2.51, $P = 0.005$; stiffness, naproxen, −2.82, $P = 0.001$), walking pain score (naproxen, −2.53, $P = 0.005$), and WOMAC total score (naproxen, −7.71, $P = 0.003$), as expected.

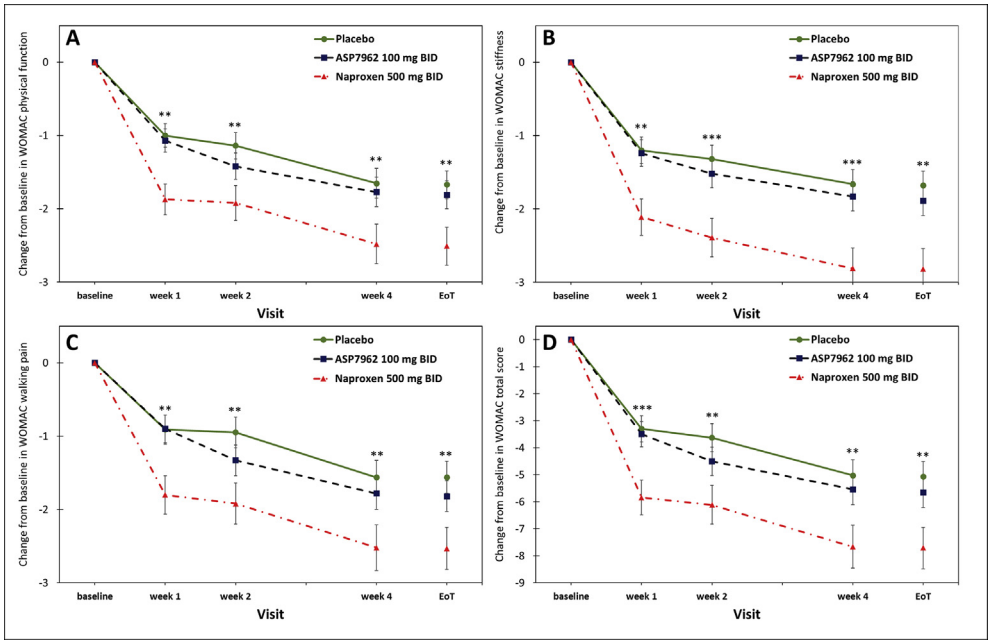

Fig. 3. Changes From Baseline in WOMAC Subscales (A–B), Walking Pain (C), and Total (D) Scores. Abbreviation: EoT, end of treatment. Data are presented as adjusted mean (SE). EoT results include all participants who completed the 4-week treatment and those who discontinued the study before Week 4. The change from baseline to Weeks 1, 2, and 4 results are based on repeated measures analysis, with treatment group, study site, week, and week by treatment group interaction as fixed effects and baseline and week by baseline interaction as covariates. The change from baseline to EoT results are based on an analysis of covariance with treatment group and study site as fixed effects and baseline value as a covariate. $^{**}P \leq 0.01$, $^{***}P \leq 0.001$, between naproxen and placebo.

The mean daily average pain scores were similar among treatment groups at baseline (ASP7962, 6.37; placebo, 6.26; naproxen, 6.42), and there was no statistically significant difference between ASP7962 and placebo in mean change from baseline to Week 4 (0.17; 90% 2-sided CI: −0.28, 0.63; $P = 0.734$) or EoT (0.11; 90% 2-sided CI: −0.34, 0.55; $P = 0.653$) (Fig. 4). Conversely, there was a statistically significant difference between naproxen and placebo in mean change from baseline to Week 4 (−0.67; 80% 2-sided CI: −1.10, −0.24; $P = 0.023$) and EoT (−0.71; 80% 2-sided CI: −1.13, −0.29; $P = 0.016$).

The mean (SE) baseline PGA score was slightly higher in the ASP7962 group (6.48 [0.17]) than in the placebo (6.17 [0.18]) and naproxen (6.24 [0.25]) groups. There was no statistically significant difference between ASP7962 and placebo in the mean change of PGA score from baseline to EoT (−0.44; 90% 2-sided CI: −0.97, 0.10; $P = 0.088$) or Week 4 (−0.40; 90% 2-sided CI: −0.95, 0.14; $P = 0.112$)

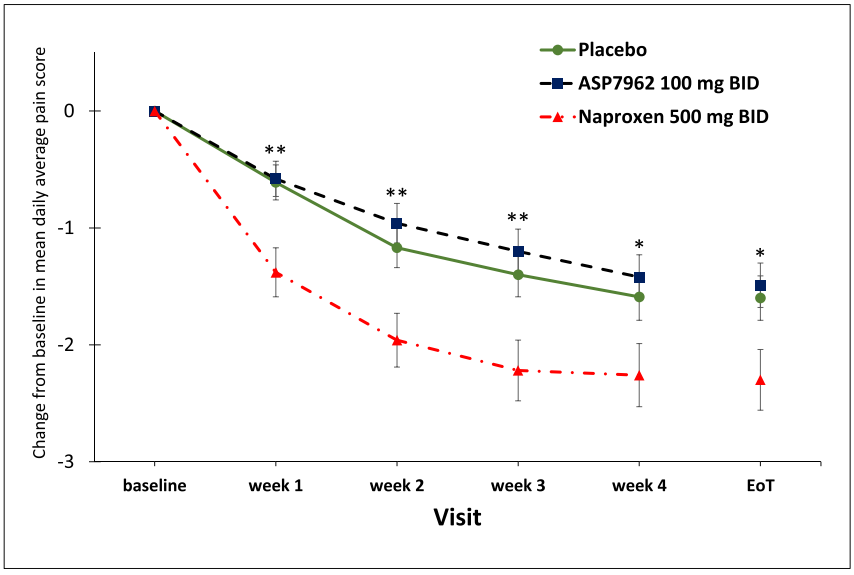

Fig. 4. Change From Baseline in Mean Daily Average Pain Score in the Index Knee. Abbreviations: EoT, end of treatment; NRS, numerical rating scale. NRS was recorded daily on the patient's electronic diary device; the score ranges from 0–10 (0, "no pain"; 10, "pain as bad as you can imagine"). Data are presented as mean (SE). The change from baseline to Weeks 1, 2, and 4 results are based on repeated measures analysis, with treatment group, study site, week, and week by treatment group interaction as fixed effects and baseline and week by baseline interaction as covariates. The change from baseline to EoT result is based on an analysis of covariance with treatment group and study site as fixed effects and baseline value as a covariate. $^{*}P \leq 0.05$, $^{**}P \leq 0.01$, between naproxen and placebo.

(Supplementary Table S4). In contrast, a significant difference in PGA score was observed between placebo and naproxen at EoT (−0.92; 80% 2-sided CI: −1.42, −0.42; $P = 0.009$) and at Week 4 (Supplementary Table S4). There was no statistically significant difference between ASP7962 and placebo in the proportion of participants who showed a decrease from baseline to EoT in the WOMAC pain subscale score of ≥30% (ASP7962, $n = 43/81$ [53.1%]; placebo, $n = 34/79$ [43.0%]; $P = 0.133$) or ≥50% (ASP7962, $n = 26/81$ [32.1%]; placebo, $n = 18/79$ [22.8%]; $P = 0.127$). A statistically significant difference in the proportion of responders was observed between naproxen and placebo for both the ≥30% (naproxen, $n = 27/42$ [64.3%]; $P = 0.021$) and ≥50% (naproxen, $n = 19/42$ [45.2%]; $P = 0.01$) decrease in the WOMAC pain subscale score. During the treatment period, a total of 63 patients (placebo, $n = 21$ [27%]; ASP7962, $n = 30$ [30%]; naproxen, $n = 12$ [28%]) used rescue medication (paracetamol and/or tramadol) for any reason; 51 patients (placebo, $n = 16$ [20%]; ASP7962, $n = 25$ [31%]; naproxen, $n = 10$ [24%]) used rescue medication specifically for OA pain.

Safety

The proportion of participants reporting treatment-emergent adverse events (TEAEs) in any treatment group ranged between 22.4% and 30.6% during the treatment period and between 4.8% and 12.3% during follow-up (Table II). The proportion of participants who withdrew from treatment due to a TEAE was 3.5%, 3.5%, and 4.8% in the ASP7962, placebo, and naproxen groups, respectively. No deaths occurred in any treatment group. The most frequent TEAEs were vertigo (ASP7962, $n = 4$ [4.7%]; placebo, $n = 4$ [4.7%]) and nasopharyngitis (ASP7962, $n = 3$ [3.5%]; placebo, $n = 4$ [4.7%]). Joint-related TEAEs were of special interest and included arthralgia (ASP7962, $n = 3$ [3.5%]; placebo, $n = 1$ [1.2%]), other musculoskeletal pain (naproxen, $n = 1$ [2.4%]) and spinal osteoarthritis (naproxen, $n = 1$ [2.4%]). In the ASP7962 group, one participant reported a serious joint-related TEAE of arthralgia in the right hip, which was not considered by the investigator to be drug related. This event and one AE of suspected RPOA in the right knee that occurred 63 days after the last dose of naproxen, were sent for adjudication to the Osteo IAC and were determined to be consistent with normal progression of OA based on the radiographic evidence. No new radiological events in the index knee were observed in any participants at the End of Study visit.

Although no neurologic events were adjudicated, autonomic events considered of special interest included dizziness (placebo, $n = 1$ [1.2%]; ASP7962, $n = 1$ [1.2%]), fall (ASP7962, $n = 1$ [1.2%]), and syncope (ASP7962, $n = 1$ [1.2%]), and were not considered to be drug related. Peripheral neurological events including paresthesia (placebo, $n = 1$ [1.2%]) and sensory disturbance (ASP7962, $n = 1$ [1.2%]) were reported, neither of which were serious, led to treatment withdrawal, or met criteria for adjudication. One non-serious hepatic TEAE (gamma-glutamyl transferase increased) was reported with naproxen and did not lead to withdrawal of the study drug.

Discussion

This study suggests that blocking the NGF/TrkA pathway with the oral small-molecule TrkA inhibitor ASP7962 does not reduce pain in patients with knee OA. The primary outcome was not achieved as there was no significant difference in the change from baseline to Week 4 in the WOMAC pain subscale scores between the ASP7962 and placebo groups. In contrast, a significant difference was observed between naproxen and placebo, confirming that the study design was appropriate to detect treatment efficacy. There were no statistically significant differences in the change from baseline to EoT between the ASP7962 and placebo treatment groups in the WOMAC pain, physical function, or stiffness subscale scores, in walking pain, or in the WOMAC total score, whereas naproxen resulted in an improvement in all WOMAC subscale scores and in the walking pain score and total score. No differences were observed for the index knee in the mean daily average pain scores between placebo and ASP7962 at any point. No effect of ASP7962 was observed on changes from baseline in PGA, and the proportion of participants who achieved ≥30% and ≥50% decrease from baseline to EoT in the WOMAC pain subscale score were similar between placebo and ASP7962.

Our findings contrast with phase 2 studies demonstrating that NGF inhibition with the NGF mAbs tanezumab[12–14], fasinumab[15], and fulranumab[16] were effective in reducing pain in patients with knee OA. It is possible that a higher dose of ASP7962 may have a greater pharmacological effect, but this would need to be balanced with a potentially higher toxicity risk. The 100 mg BID dose of ASP7962 used in this study yielded plasma drug levels that were well above the IC50 reported in pre-clinical models. The mean (SD) peak plasma concentrations were expected to be reached between 0.5 and 2 h postdose, and were 2866.53 (1344.44) ng/mL and 248.91 (146.84) for total and unbound ASP7962 concentrations, respectively, whereas the mean (SD) trough concentration at Week 2 was 920.06 (958.87) ng/mL and 44.46 (71.31) ng/mL for total and unbound ASP7962 concentrations, respectively. Individuals with mutations of the TrkA receptor, either in humans or in pre-clinical models, have insensitivity to pain, suggesting that TrkA is a valid analgesic target. However, it may be that the more complete and longer-lasting blockade of NGF signaling exerted by a mAb than that by a small molecule is necessary to achieve a clinical effect. However, this is not supported by pre-clinical evidence from NGF receptor knockouts[7]. Also, the slightly higher baseline WOMAC pain subscale and total scores observed in the ASP7962 group than the

Table II
Treatment-emergent adverse events by investigational period

N (%)	Treatment period			Follow-up period		
	Placebo $N = 85$	ASP7962 100 mg BID ($N = 85$)	Naproxen 500 mg BID ($N = 42$)	Placebo $N = 85$	ASP7962 100 mg BID ($N = 85$)	Naproxen 500 mg BID ($N = 42$)
TEAEs	19 (22.4)	26 (30.6)	12 (28.6)	10 (12.3)	8 (9.5)	2 (4.8)
Drug-related TEAEs	10 (11.8)	7 (8.2)	7 (16.7)	0	1 (1.2)	1 (2.4)
Serious TEAEs	0	1 (1.2)	0	0	0	0
Drug-related serious TEAEs	0	0	0	0	0	0
TEAEs leading to withdrawal of treatment	3 (3.5)	3 (3.5)	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

Abbreviations: BID, twice daily; TEAE, treatment-emergent adverse event.
A TEAE is any adverse event which started, or worsened, after the first dose of study drug through 30 days after the last dose of study drug.

placebo group might have contributed to the lack of a significant effect of ASP7962. Furthermore, although ASP7962 showed potent and reproducible effects on pain outcome measures in pre-clinical studies in well-validated models of acute and chronic joint pain, such as the rat mono-iodoacetate model, these may not be optimal models for translation to human chronic OA pain due to various reasons, including multiple OA phenotypes and risk factors (e.g., age, sex, and weight), and the limited structural assessments that are performed in animal models[28–30].

The stringent eligibility criteria required by the Food and Drug Administration (FDA, United States) as part of a mitigation strategy for trials of anti-NGF therapeutics were one of the reasons for the high screen failure (202/417, 48%) and is typical of clinical trials of investigational medicinal products in OA[31]. The population investigated in this study, and in other similar OA studies, is therefore not fully generalizable to the overall population with knee OA, given that many patients with commonly associated co-morbidities were excluded[32]. Patients in this study had high levels of persistent daily pain, had failed to respond adequately to other analgesics (WOMAC pain subscale score in the index knee $\geq$4 at baseline), and had symptoms for an average of 7 years, often with OA in multiple joints. As with many knee OA studies, only patients with advanced structural radiographic disease were included[12,33]. Whether a greater effect would have been detectable in those with earlier disease or less severe pain of shorter duration is unknown. In addition, washing out all analgesics may have caused flare symptoms which were less responsive to the study drug than chronic pain symptoms. However, the statistically significant effect of naproxen affirms a well-designed study, capable of detecting a clinically significant effect of an analgesic in OA. It is noteworthy that only ~20% of patients were washed out of NSAIDs for OA pain during the baseline period, likely avoiding a substantial bias towards a positive or negative response to NSAIDs.

A further strength of this study was the ability to examine the real-time pain rating of daily average pain by electronic diary prior to, and for the duration of, the study. This is important given that day-to-day OA pain can vary substantially and patients often find recall of average pain over longer periods challenging[34]. The use of this technology to measure pain, and the lack of effect detected using this measure, lend further support for the true lack of effect.

Overall, oral administration of the TrkA inhibitor ASP7962 100 mg BID did not result in any improvement of pain measures or physical function in subjects with painful radiographic knee OA but appeared to be well tolerated and safe for the duration of the study.

Author contributions

1) Conception and design: NEL, HJ, AF, FEW, MBB, 2) Acquisition of data: FEW, RS, 3) Analysis and interpretation of the data: NEL, HJ, AF, FEW, MBB, RS, 4) Drafting of the article: All authors, 5) Critical revision of the article for important intellectual content: All authors, 6) Final approval of the article: All authors.

Conflict of interest

MB Blauwet, A Fakhoury, and R Smulders are employed by Astellas. H Jacobs was employed by Astellas until October 2018. FE Watt received funding from Astellas for site activity for this study and for serving as international coordinating investigator of the study. In the past she has also received funding from Pfizer for site activity relating to a study in this therapeutic area. She is supported in part by the Centre for Osteoarthritis Pathogenesis Versus Arthritis (20205 and 21621) and the National Institute for Health Research (NIHR, United Kingdom) Oxford Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the charity, the National Health Service (NHS, United Kingdom), the NIHR, or the Department of Health. NE Lane has nothing to disclose.

Role of the funding source

The funder of the study had a role in the design of the study and was responsible for collection, analysis, and interpretation of the data, all of which was confirmed by the clinical expert authors. The funder also had a role in writing the report, under guidance of the authors.

Data statement

Access to anonymized individual participant level data collected during the trial, in addition to supporting clinical documentation, is planned for trials conducted with approved product indications and formulations, as well as compounds terminated during development. Conditions and exceptions are described under the Sponsor Specific Details for Astellas on www.clinicalstudydatarequest.com. Study-related supporting documentation is redacted and provided if available, such as the protocol and amendments, statistical analysis plan, and clinical study report. Access to participant level data is offered to researchers after publication of the primary manuscript (if applicable) and is available as long as Astellas has legal authority to provide the data. Researchers must submit a proposal to conduct a scientifically relevant analysis of the study data. The research proposal is reviewed by an Independent Research Panel. If the proposal is approved, access to the study data is provided in a secure data sharing environment after receipt of a signed Data Sharing Agreement.

As required by EU regulations, the data presented from this study have been posted on the EU Clinical Trials Register in June of 2018.

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Supplementary data

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