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Efficacy and safety of intra-articular injection of tropomyosin receptor kinase A inhibitor in painful knee osteoarthritis: a randomized, double-blind and placebo-controlled study

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SUMMARY

Objective: This trial evaluated the efficacy and safety of GZ389988A, a tropomyosin receptor kinase A (TrkA) inhibitor, in subjects with painful knee osteoarthritis (OA).
Method: In this single center, double-blind, placebo-controlled and randomized trial, 104 subjects with moderate-to-severe knee OA pain were enrolled to receive a single intra-articular (IA) injection of either GZ389988A or placebo. Efficacy measures were assessed over 12 weeks and included walking pain (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] A1), overall knee pain, WOMAC A, B, C and total score, Patient Global Impression of Change (PGIC), OMERACT-OARSI responder rate and rescue medication use. Adverse events (AEs) were monitored up to 24 weeks.
Results: The primary efficacy endpoint was met with a between-group difference of −7.49 (VAS 0–100) on WOMAC A1 changes over 4 weeks ($P < 0.05$ favoring GZ389988A). The secondary outcome on WOMAC A1 changes over 12 weeks had a between-group difference of −6.78 ($P = 0.064$). Among weekly assessments, statistically significant greater improvement in the GZ389988A group was observed in WOMAC A1, overall knee pain and/or WOMAC A at weeks 2–5. Although not statistically significant, improvements over placebo on pain and WOMAC C persisted over 12 weeks. Greater AE incidence was observed in the GZ389988A group including transient and self-limited injection joint inflammatory reactions with a spike of acetaminophen intake within the first week post-injection.
Conclusion: IA injection of TrkA inhibitor GZ389988A in knee OA subjects reduced pain with a numerically functional gain and an acceptable safety profile. (ClinicalTrials.gov, NCT02845271).

Introduction

Globally osteoarthritis affects about 302 million patients, knee osteoarthritis accounts for 263 million[1] and ranks the highest in disability and pain compared to OA of other joints. Women tend to be more frequently affected than men[2,3]. Prevalence estimates for symptomatic knee OA are 12–30% among adults ≥65 years[3–7].

Pharmacologic treatment for knee OA may include oral NSAIDs, capsaicin, duloxetine, acetaminophen, topical nonsteroidal anti-inflammatory drugs and intra-articular (IA) corticosteroids[8]. However, uncertain appropriateness and no clear consensus exist regarding other treatment modalities[9–11]. IA corticosteroids are generally effective for only a short time (effect sizes decrease rapidly by 4 weeks)[12,13] and carry potential safety risks with frequent joint injections[12]. IA hyaluronic acid injections showed inconsistent efficacy data across studies[12,13]. NSAIDs and acetaminophen are associated with potential safety risks and are inadequate for many patients[11,14–16]. Total knee replacement is associated with chronic postoperative pain in approximately 15% of OA patients[17,18]. Thus, an unmet need exists for effective and tolerable long-duration treatments for OA[19].

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Nerve growth factor (NGF) in adults mediates pain sensitization to noxious stimuli. NGF binds to the tropomyosin receptor kinase A (TrkA) and the p75 neurotrophin receptors on the distal ends of axons that innervate the targets[20]. In man, the levels of NGF are elevated in serum, synovial fluid, cerebrospinal fluid, and tissue specimens in a variety of pain conditions, including OA[21–23]. Systemically delivered NGF antibodies (blocking both TrkA and p75 receptors) have shown beneficial effect in OA and other pain conditions in multiple clinical trials, though associated with serious adverse events (SAEs) including rapidly progressive OA[24]. Human genetic mutations of TrkA are linked to congenital pain insensitivity[25]. Taken together, these findings suggest that TrkA receptors may play a major role in mediating NGF-induced pain signaling.

GZ389988 (and its monohydrate form GZ389988A) is a small molecule inhibitor of TrkA. The IC_{50} of GZ389988 for TrkA, TrkB, TrkC and colony stimulating factor 1 (CSF1R) receptors are 0.89 nM, 0.38 nM, 0.5 nM and 1.3 nM, respectively. This high potency indicates that a low drug concentration may be sufficient to activate the targets. Inhibition of TrkB, TrkC and CSF1R may confer additional benefits in the treatment of OA[26,27]. GZ389988A is insoluble in water and has been formulated as an aqueous suspension for intra-articular (IA) injection, aiming at sustaining pain reduction and reducing systemic exposure. In rat models of OA and joint pain, GZ389988 showed a significant relief of local knee pain[28].

The current study is designed to assess the efficacy and safety of a single IA injection of GZ389988A suspension in subjects with moderate to severe painful knee OA. As we know, this is the first report of an intra-articular injection of TrkA receptor inhibitor in knee OA subjects.

Subjects and methods

Study design and study participants

This was a single-center, double-blind, randomized (1:1 allocation ratio), placebo-controlled, parallel-group study to assess the efficacy and safety of a single IA dose of GZ389988A compared to placebo in subjects with moderate to severe knee OA (ClinicalTrials.gov, NCT02845271).

This proof-of-concept study included a screening phase, baseline pain assessment, a dosing day (day 1), office visits on days 2, 7, 14, 21, 28, 42, 56, and 70 and an end-of-study (EOS) visit on day 84. For collection of potential serious AEs, safety follow-ups (post EOS visit) by phone were conducted every 4 weeks for 12 additional weeks.

Eligibility criteria included: male and female subjects of 40–80 years of age with primary knee OA fulfilling the American College of Rheumatology Clinical and Radiographic criteria[29]; Kellgren and Lawrence (KL) grade 2 to 4; and being symptomatic for more than 6 months. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) A1 pain (walking pain) was between 40 and 90 inclusive (VAS 0–100 with 100 being the most painful) over the last 48 h in the target knee and $\leq$30 in the contralateral knee at screening. Following the washout phase, the average baseline pain (WOMAC A1 from eDiary) was between 50 and 90 (inclusive) between day −5 and day −1 in the target knee. Subjects were ambulatory with an active lifestyle and in good general health. Women of child bearing potential were excluded.

Neuropathic pain components from OA or other sources associate with greater central sensitization, and may mask the treatment effect of potential therapeutics administered by local (intra-articular) route. Thus, stratification accordingly is recommended in knee OA trials[30]. The painDETECT questionnaire (PD-Q)[31] was used at the screening visit to exclude the subjects with PD-Q score >18 (neuropathic pain likely, >90% possibility). The inclusion of subjects with a PD-Q score of 13–18 (possible neuropathic pain components) was limited to a maximum of 30% of the study population.

In order to exclude potential non-responders and/or high placebo responders, subjects with moderately severe or severe depression and/or with severe anxiety were excluded per Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder 7 (GAD-7) scale. To identify any features with a potential link to rapidly progressive osteoarthritis (RPOA), central reading of the magnetic resonance imaging (MRI) scans of the target knee was conducted at baseline and follow-up. This assessment was based on an imaging overview relevant to anti-NGF compounds[32], as GZ389988A is an inhibitor of the main receptor (TrkA) for NGF. Subjects with such features were excluded at baseline.

Furthermore, subjects with one of the following conditions were notably excluded: ipsilateral hip osteoarthritis, prior history of osteonecrosis and/or rapidly progressive OA, intra-articular injection within 3 months prior to inclusion, or other unstable medical conditions that might interfere with the evaluation of the study drug.

The study protocol complied with the recommendations of the eighteenth World Health Congress (Helsinki, 1964) and all applicable amendments, and any applicable country-specific laws, regulations and guidelines. It was approved by the local ethics committee. All subjects provided written informed consent prior to study procedures.

Eligible subjects were administered with GZ389988A (formulation in 3-mL IA injection vehicle) or placebo (vehicle: 2% povidone K17 [polyvinylpyrrolidone] + 4.5% sorbitol in 10 mM phosphate buffer at pH 7.4, 3 mL). The appearance of the GZ389988A suspension was different from the placebo. The drug was prepared by an independent pharmacist and transported in a closed box by an unblinded nurse to the unblinded injector. Subjects' vision was blocked from seeing the injection products. The study participant and medical staff including the Investigator were blinded to the investigational medicinal products. The unblinded injector and the unblinded nurse, both of whom were not otherwise involved in the study and were instructed to maintain the double-blind conditions. Only blinded people (study participant, investigator, study nurse, etc.) were allowed for the outcome assessment. All injections were performed according to a standardized IA injection protocol in a sterile manner. Prior to injection the position of the needle in the synovial cavity was confirmed by ultrasound and/or aspiration of synovial fluid.

Study participants were asked to washout pain medications other than acetaminophen (capped at 4 g/day as rescue medication) for at least 2 weeks prior to entry into the study. Subjects may continue glucosamine, chondroitin sulfate, diacerhein, and/or oral vocado/soya extracts, provided these were started at least 2 months prior to enrollment without substantial change during the study. The Investigator considered the use of other rescue medication (i.e., codeine or tramadol) on a case-by-case basis in a tiered manner. Pain medication use for OA pain and/or any other reasons were recorded in an electronic diary (eDiary). It was recommended to avoid the intake of rescue medication within the 48 h before office visits.

Assessments

GZ389988 was tested in animal OA models, and a 4-week efficacy was observed (the entire observation period due to limitations of animal models[28]). With this, it was predicted hypothetically that the duration of efficacy in humans could be around 2.5 months. Based on the observed animal data, the primary efficacy endpoint

was designated as the change from baseline averaged over 4 weeks in weekly mean score of daily WOMAC A1 (walking pain). The main secondary efficacy endpoint was the change from baseline averaged over 12 weeks in weekly mean score of daily WOMAC A1. Other secondary efficacy outcomes included the change from baseline in weekly mean score of daily overall knee pain and the WOMAC (0–100 VAS, WOMAC Osteoarthritis Index VAS 3.1 version) for pain (WOMAC A), stiffness (WOMAC B), and physical function (WOMAC C) over the last 48 h prior to office visits. Patient Global Impression of Change (PGIC) was evaluated at day 28 (1–4 weeks), day 56 (1–8 weeks), and day 84 (1–12 weeks). The OMERACT-OARSI responder rates[33] at day 28, day 56, and day 84 were also assessed.

The incidence of adverse events (AEs), treatment-emergent AEs (TEAEs) defined in the period from the time of injection up to the end-of-study visit, and SAEs up to 24 weeks were monitored.

Statistical analysis

Sample size was targeted to demonstrate the superiority of GZ389988A vs placebo for this proof-of-concept and non-pivotal study. Given the proven pathway by NGF-antibodies trials, the sponsor decided to take a pre-defined one-way test at $\alpha = 5\%$ level to reduce subject exposure to this novel compound at the early stage of development. A sample size of 94 study participants was calculated to provide 85% power to detect a true treatment difference equal to 14 (on VAS 0–100) between GZ389988A and placebo in weekly mean score of WOMAC A1 (walking pain) over 4 weeks. This was assuming the common SD equal to 25 on VAS 0–100 (effect size = −0.56), with a one-sided test at significance level of 5% (sample size calculations based on the two samples *t*-test). Assuming 10% exclusion rate from per protocol population, a total of 104 subjects (52 subjects per treatment group) was planned.

Efficacy outcomes were analyzed in the modified intent-to-treat (mITT) population, including all randomized subjects who were exposed to the study treatment without major/critical deviations, and when WOMAC A1 (e-Diary) were evaluable at baseline and had at least one post-baseline assessment. Primary analysis for the primary endpoint, main secondary endpoint and all other secondary endpoints were performed using a mixed model with repeated measures (MMRM) approach under the "missing at random" framework. The model included treatment, week, week-by-treatment interaction and gender as fixed terms and the baseline score as a covariate (using SAS® PROC MIXED, version 9.4). The errors were modeled using a heterogeneous compound symmetry variance–covariance structure. Estimates and 90% confidence intervals (CIs) for the difference between GZ3889988A and placebo were calculated within the linear mixed-effect model framework. Estimates and 90% CIs of the mean change from baseline for each treatment were also provided. All pairwise comparisons were one-sided at significance level of 5%. Number and percentage of responders according to OMERACT-OARSI criteria were summarized by treatment group. PGIC was also summarized using descriptive statistics. The number and percentage of subjects who used rescue medications were summarized by treatment, week and overall. Efficacy data in the text and tables are presented as least square means ± standard error if not specified otherwise.

Safety outcomes were analyzed in all randomized subjects who were exposed to study treatment, regardless of the amount of treatment administered. TEAEs were summarized by primary System Organ Class (SOC) and Preferred Term (PT) for each treatment group.

Results

Subject disposition and baseline characteristics

A total of 104 subjects were randomized to placebo (n = 52) or GZ389988A (n = 52) groups; all subjects were treated per randomization. All subjects completed follow-up without early termination (Fig. 1).

Baseline characteristics were similar between groups (Table I), with an overall mean age of 63.1 years. Male and female subjects were evenly distributed. All had radiographically confirmed knee OA and 47.1% had contralateral knee OA. 62.5% had KL grade 2, 34.6% had KL-3 and KL-4 accounted for 2.9% at screening. Mean baseline pain intensity was moderate: WOMAC A1 pain scores at baseline were 63.97 ± 8.6 and 68.09 ± 9.99 (mean ± SD) in placebo and GZ389988A groups, respectively (Table I). Among the screened subjects (Fig. 1), eight subjects were excluded due to PD-Q score >18. The overall mean PD-Q score in the total of 104 subjects was 6.7. The pain was mainly nociceptive in nature (87.5% with PD-Q score ≤12; mean score of 5.4), some subjects scored between 13 and 18 (12.5%; mean score of 15.5) may have had neuropathic pain components. Among 217 subjects who had MRI at screening, 60 subjects with the features of potential risk for RPOA were excluded, mainly including severe meniscal extrusion (n = 27), meniscal posterior root tear (n = 11), subchondral insufficiency fracture (n = 9), severe meniscal extrusion with meniscal posterior root tear (n = 6) and stress fracture (n = 2). Three subjects were excluded for depression. All enrolled subjects were free of depression or anxiety at inclusion except one subject who had non-severe anxiety in the GZ389988A group.

Walking pain and overall knee pain

WOMAC A1 scores from eDiary statistically significantly improved from baseline at each time point since week 2 in both groups ($P < 0.0001$). GZ389988A treatment resulted in statistically greater pain relief than placebo with between-group difference of −7.49 ± 4.35 (mean ± SE, one-sided $P = 0.044$ and one-sided upper 95% confidence bound = −0.27) over the first 4 weeks (met the primary endpoint), as well as over 6 weeks ($\delta = -7.58 \pm 4.32$; one-sided $P = 0.041$) and over 8 weeks ($\delta = -7.23 \pm 4.33$; one-sided $P = 0.049$). Such improvement was statistically significant (δ range of -10.50 ± 4.82 to -8.54 ± 4.52; one-sided $P < 0.05$) compared to placebo at each week from weeks 2–5 (Fig. 2). Over 12 weeks, GZ389988A treatment brought in numerically greater pain improvement over placebo with a difference of -6.78 ± 4.41 (one-sided $P = 0.064$).

Like-wise, overall knee pain from daily eDiary showed a significant improvement from baseline at every time point since week 2 ($P < 0.0001$) in both groups (Fig. 3). GZ389988A treatment showed statistically a significant pain relief over placebo at weeks 2, 4 and 5 (one-sided $P < 0.05$, one-sided upper 95% confidence bound of −1.10, −1.57 and −0.79, respectively). Over 4 and 12 weeks, numerically greater pain improvement from GZ389988A was observed ($\delta = -6.86 \pm 4.53$, -6.09 ± 4.63, one-sided $P = 0.067$ and 0.096, respectively).

WOMAC Pain, Function, PGIC and OMERACT-OARSI Responder Rate

WOMAC A pain and WOMAC C function [Fig. 4(A) and (B)] also were significantly improved from baseline at every time point in both groups ($P < 0.0001$), exceeding minimal clinically meaningful improvement threshold of 20% since week 1. Statistically significant pain relief (WOMAC A) favoring GZ389988A over placebo was achieved at Weeks 2–4 (one-sided $P < 0.05$). Over 4 and 12 weeks,

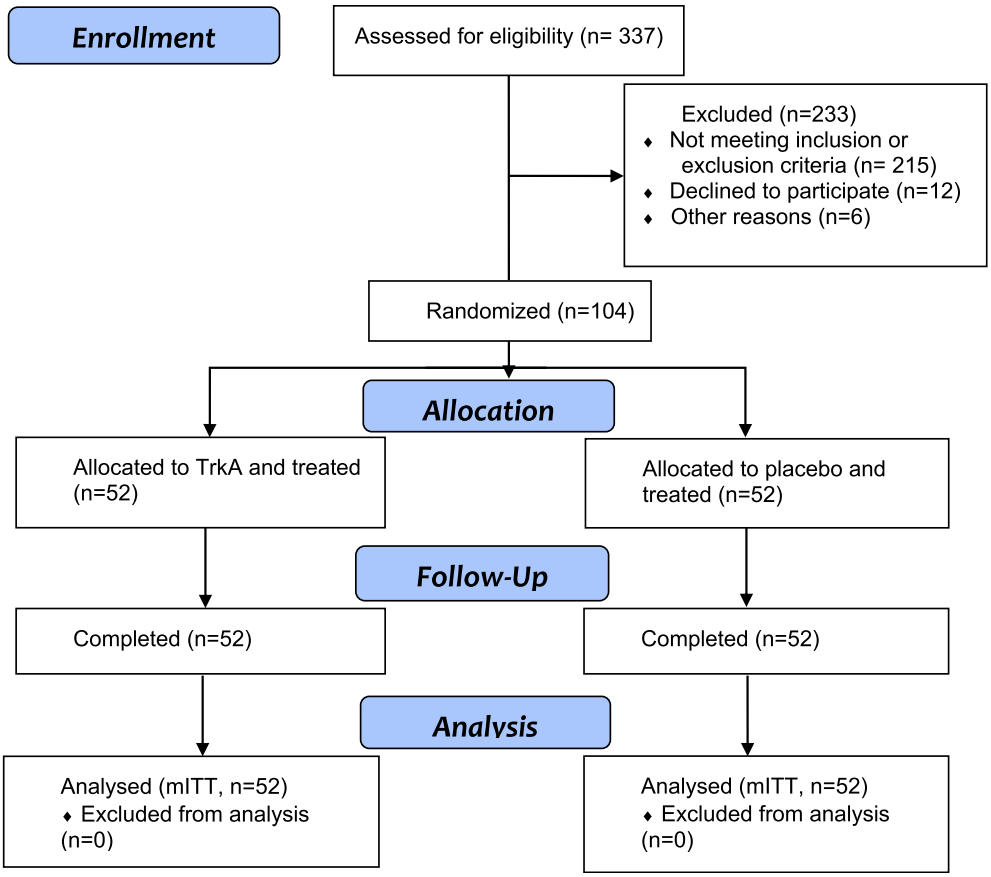


Fig. 1. Subject disposition.

Table I
Subject demographics and baseline characteristics

	Placebo (N = 52)	GZ389988A (N = 52)	All (N = 104)
Age (years), mean (SD)	64.1 (8.1)	62.1 (9.4)	63.1 (8.8)
Male, n (%)	27 (51.9)	26 (50.0)	53 (51.0)
Race, n (%)			
White	50 (96.2)	52 (100)	102 (98.1)
Asian	1 (1.9)	0	1 (1.0)
Other	1 (1.9)	0	1 (1.0)
BMI (kg/m^2), Mean (SD)	27.85 (3.48)	28.94 (4.22)	28.40 (3.89)
PD-Q score (categories)			
<=12, n (%)	46 (88.5)	45 (86.5)	91 (87.5)
[13–18], n (%)	6 (11.5)	7 (13.5)	13 (12.5)
PHQ-9 score, Mean (SD)	2.9 (2.9)	1.9 (2.1)	2.4 (2.5)
GAD-7 score, Mean (SD)	2.2 (2.6)	1.2 (1.5)	1.7 (2.2)
Kellgren and Lawrence grade			
GRADE II, n (%)	32 (61.5)	33 (63.5)	65 (62.5)
GRADE III, n (%)	18 (34.6)	18 (34.6)	36 (34.6)
GRADE IV, n (%)	2 (3.8)	1 (1.9)	3 (2.9)
OA (years), mean (SD)	7.83 (7.06)	7.28 (6.77)	7.55 (6.89)
Contralateral knee OA, n (%)	30 (57.7)	19 (36.5)	49 (47.1)
Baseline WOMAC A1 (VAS), mean (SD)	63.97 (8.6)	68.09 (9.99)	66.03 (9.5)

the between-group difference favoring GZ389988A was −7.15 ± 4.13 and −6.30 ± 4.24 with one-sided $P = 0.043$ and 0.070, respectively.

A numerical difference for WOMAC C favoring GZ389988A was most apparent at Weeks 3 and 4 where the estimated mean differences were −6.34 ± 4.08 and −6.06 ± 4.34, with no significant statistical difference (one-sided $P = 0.062$ and 0.083, respectively). This trend was observed over all other weeks as well.

Improvements from baseline in WOMAC B stiffness scores were observed over all weeks in the placebo and GZ389988A treatment arms, with the changes being numerically greater in the GZ389988A arm but not statistically significant.

Improvements from baseline in WOMAC total scores were observed over all weeks in both groups, with numerically greater magnitude in the GZ389988A group. At Week 3 this difference was

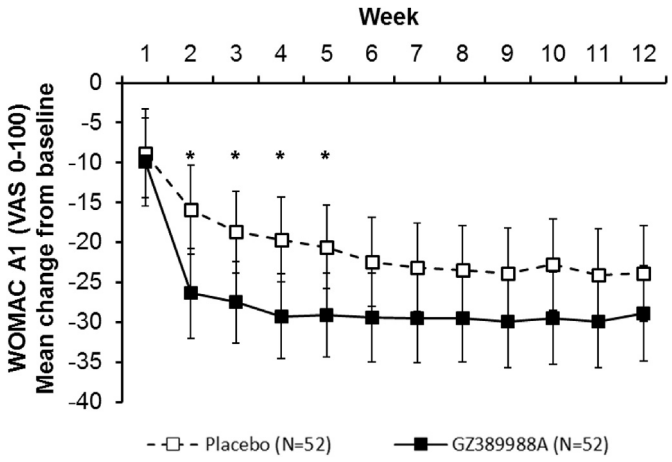


Fig. 2. WOMAC A1 (from eDiary) mean change from baseline. Data are presented as weekly least squares means ± 90% confidence intervals, *one-sided $P < 0.05$ vs placebo.

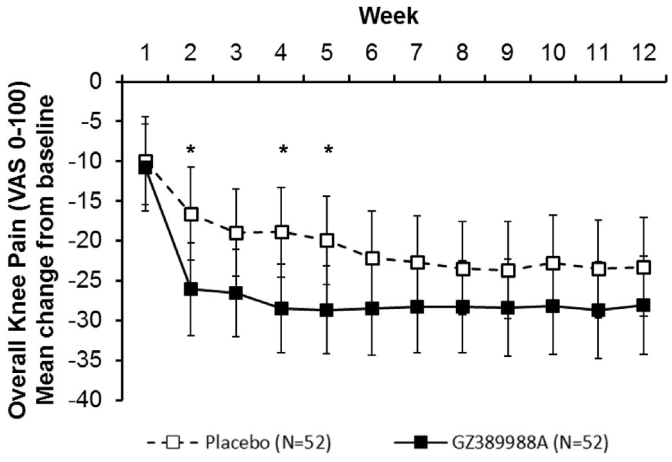
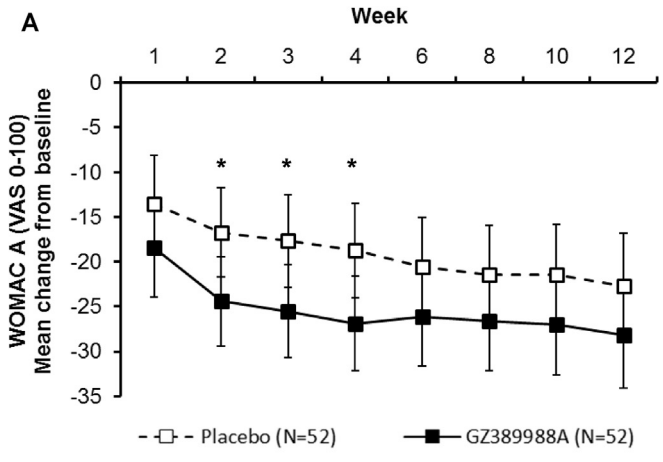


Fig. 3. Overall Knee Pain (from eDiary) mean change from baseline. Data are presented as weekly least squares means ± 90% confidence intervals, *one-sided. $P < 0.05$ vs placebo.



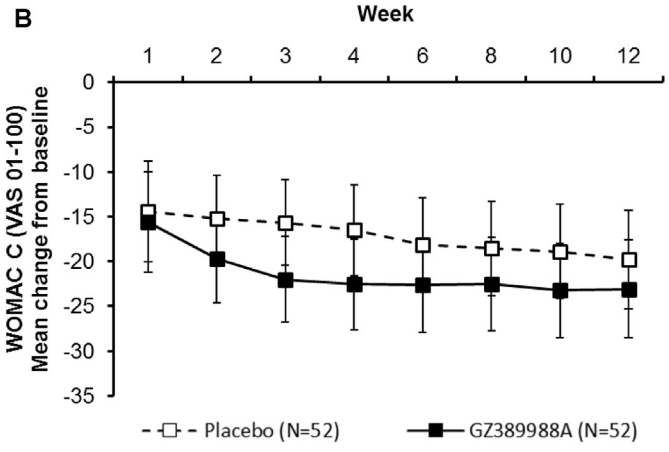


Fig. 4. Mean change from baseline in WOMAC A (A) and WOMAC C (B). Data are presented as weekly least squares means ± 90% confidence intervals, *one-sided. $P < 0.05$ vs placebo.

statistically significant ($\delta = -6.74 \pm 4.03$; one sided $P = 0.049$), but not at any other time.

There was no between-group difference in PGIC (Table II). Numerically, the average score over 12 weeks was below scale 4 corresponding to "somewhat better, but the change has not made any real difference" in the placebo group; while this score was above scale 4 in GZ389988A group. The proportion of subjects considered responders based upon the OMERACT-OARSI criteria was approximately 10% more in the GZ389988A group, compared to the placebo group at weeks 4, 8, and 12 (Table II).

Use of rescue medication

Over 12 weeks, a total of 32 (61.5%) and 19 (36.5%) subjects in the GZ389988A and placebo groups took rescue medications, respectively. Acetaminophen was the primary rescue medication used; acetaminophen and codeine in combination was taken by 3 subjects in the GZ389988A group but not in the placebo group. The rescue medications were mainly taken during the first week post-injection [Fig. 5(A)] with greater percentage in the GZ389988A group. This was most likely due to injection site joint inflammation which occurred only in the GZ389988A group [Fig. 5(B)]. Despite the post-injection joint inflammation, the mean daily acetaminophen intake was approximately one tablet (~427 mg) or one half of a tablet (~272.3 mg) more in GZ389988A arm than in placebo in the first week or over 12 weeks, respectively.

Subgroup analysis was conducted to assess the impact of rescue medication use on walking pain (WOMAC A1) reported on eDiary. By removing pain scores collected on the day of taking rescue medication and on the following day, the between-group differences of pain relief favoring GZ389988A were -8.91 ± 4.31 and -7.41 ± 4.44 with 90% CI of (-16.210 to -1.618) and (-14.780 to -0.034) over 4 and 12 weeks, respectively. Rescue medication use was prohibited 48 h prior to office visits, thus WOMAC scores were not impacted by rescue medication use.

Safety and tolerability

Overall 75% subjects in the placebo group and 94.2% subjects in the GZ389988A group reported TEAEs (Table III). Two subjects reported SAEs, which were not considered as related to GZ389988A. The most frequent TEAEs were injection joint inflammatory reaction (IJIR). It occurred in 67.3% of subjects treated with GZ389988A but none in the placebo arm. Such subjects presented with moderate to severe post-injection joint pain starting a few hours following injection and lasting for a few hours. It occurred in 16 out of 17 subjects (94.1%) who had effusion prior to injection and in 19 out of 35 subjects (54.3%) who had no effusion prior to injection. As

Table II
Patient global impression of change (PGIC) and OMERACT-OARSI responder rate

Week	PGIC* Mean ± SE		OMERACT-OARSI responder rate n (%)	
	Placebo (N = 52)	GZ389988A (N = 52)	Placebo (N = 52)	GZ389988A (N = 52)
Week 4	3.7 ± 0.23	4.4 ± 0.25	29 (55.8%)	35 (67.3%)
Week 8	3.8 ± 0.25	4.1 ± 0.25	30 (57.7%)	34 (65.4%)
Week 12	3.8 ± 0.25	4.3 ± 0.25	29 (55.8%)	34 (65.4%)

*Scale 1–7: 1 – no change (or condition has got worse); 2 – almost the same, hardly any change at all; 3 – a little better, but no noticeable change; 4 – somewhat better, but the change has not made any real difference; 5 – moderately better, and a slight but noticeable change; 6 – better, and a definite improvement that has made a real and worthwhile difference; 7 – a great deal better, and a considerable improvement that has made all the difference.

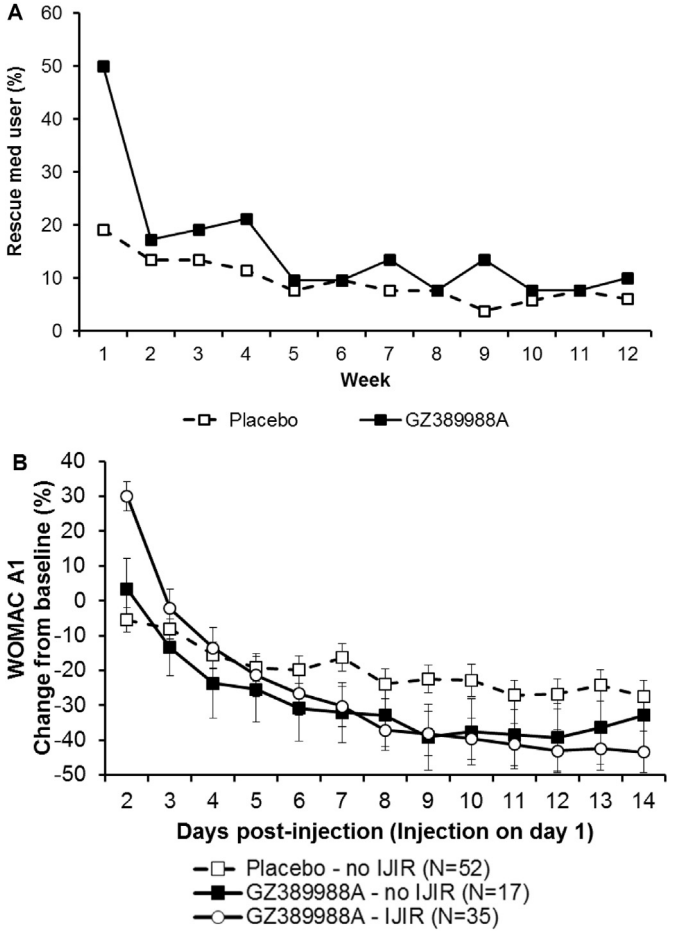


Fig. 5. Percentage of subjects taking rescue medications post-injection (A) and Relative change from baseline in WOMAC A 1 (from eDiary) in subjects with or without injection joint inflammatory reaction (IJIR) (B, Mean ± S.E.M.).

quantitated in Fig. 5(B), subjects with IJIR had approximately 30% increase of their baseline pain score within the first 24 h post-injection (reported on day 2 morning). The pain intensity recovered to baseline within the second 24 h (reported on day 3 morning) with or without rest, cold pack and/or acetaminophen. The IJIR was accompanied with at least a 2-fold elevation of high-sensitivity C-reactive protein (hsCRP) and some subjects also had mild elevation in neutrophils and monocytes (not lymphocytes); all generally recovered to normal by day 7. No neurosensory events have been reported in the GZ389988A arm.

No changes from baseline in the MRI assessment of the knee were reported 12 weeks following the single IA injection of the study drug, except one subject in the GZ389988A group. This study participant was a 74-year-old male and had a stress fracture at the medial tibial plateau of the injected knee without associated symptoms. This finding was reported as a mild nonserious TEAE and was considered not related to the study drug. The event was resolved without corrective treatment or therapy after 4 months.

Discussion

This first report on IA injection of a small molecule TrkA inhibitor demonstrated that a single administration of GZ389988A statistically relieved knee OA pain vs placebo over the first 4 weeks (primary endpoint), and lasting 8 weeks. The difference in pain relief favoring GZ389988A was observed over 12 weeks across all pain measures though not statistically significant. Numerically greater functional improvement favoring GZ389988A was noted over 12 weeks, but not statistically significant. So was PGIC or OMERACT-OARSI responder rate.

This trial proved the clinical concept that locally IA-delivered TrkA inhibitor GZ389988A suspension provided persistent clinical benefits over placebo in knee OA subjects. In both groups, the magnitude of pain and functional relief exceeded minimally clinical important improvement defined as 9–12 (on VAS 0–100) and/or 20% improvement from baseline[34,35]. To illustrate, weekly mean changes from baseline on WOMAC A1 and overall knee pain (eDiary) were ≤ -26.13 and ≤ -26.55 respectively at each week of weeks 2–12; and mean changes from baseline on WOMAC A and C were ≤ -18.88 and ≤ -16.05 respectively at each office visit during weeks 1–12. The onset of effect was quick. Improvement from baseline in walking pain was observed since day 4 and exceeded 30% by the end of first week [Fig. 5(B)]. The between-group differences of pain improvement from baseline of the primary efficacy measure WOMAC A1 from weeks 2–5 (δ of approximately 10 in VAS 0–100) was comparable with those of NGF antibody phase 3 trials[36,37]. This similarity in magnitude is probably determined by blocking the common pain pathway incurred by NGF, despite IA placebo had greater effect than systemically-delivered placebo[38]. However, this magnitude of efficacy was not maintained in the later weeks of the trial. This presumably is due to the diminishing drug amount within the joint space over time.

The occurrence of TEAEs was greater in the GZ389988A group compared with placebo, mainly due to the transient IJIR. This adverse reaction was likely an innate immune response to foreign particles as it is accompanied with hsCRP elevation and mild neutrophils and monocytes increases in some study participants[39]. This reaction could be mitigated with rest, cold pack and/or acetaminophen treatment. A similar reaction up to 26% incidence rate was observed with insoluble corticosteroid crystals injected intra-articularly for OA[40]. Considering that patients usually have background treatments with NSAIDs and/or oral opioids for OA pain management, the transient inflammatory reaction could be ameliorated or masked in the real world. Furthermore, lidocaine is

Table III
Number (%) of subjects with TEAE(s) (≥2%) by primary SOC and PT – safety population

Primary system organ class Preferred term [n (%)]	Placebo (N = 52)	GZ389988A (N = 52)
Any class	39 (75.0)	49 (94.2)
Infections and infestations	14 (26.9)	20 (38.5)
Viral upper respiratory tract infection	11 (21.2)	17 (32.7)
Rhinitis	2 (3.8)	1 (1.9)
Nervous system disorders	23 (44.2)	15 (28.8)
Headache	21 (40.4)	14 (26.9)
Dizziness	2 (3.8)	4 (7.7)
Vascular disorders	0	6 (11.5)
Orthostatic hypotension	0	4 (7.7)
Hematoma	0	2 (3.8)
Gastrointestinal disorders	3 (5.8)	7 (13.5)
Nausea	1 (1.9)	3 (5.8)
Vomiting	0	3 (5.8)
Skin and subcutaneous tissue disorders	1 (1.9)	3 (5.8)
Hyperhidrosis	0	2 (3.8)
Musculoskeletal and connective tissue disorders	17 (32.7)	18 (34.6)
Arthralgia	8 (15.4)	10 (19.2)
Back pain	7 (13.5)	3 (5.8)
Joint effusion	2 (3.8)	2 (3.8)
Joint warmth	3 (5.8)	2 (3.8)
Musculoskeletal pain	1 (1.9)	2 (3.8)
General disorders and administration site conditions	11 (21.2)	42 (80.8)
Injection site joint inflammation	0	35 (67.3)
Injection site edema	4 (7.7)	13 (25.0)
Injection site pain	7 (13.5)	13 (25.0)
Feeling cold	0	11 (21.2)
Influenza like illness	0	4 (7.7)
Injection site hematoma	3 (5.8)	2 (3.8)
Injury, poisoning and procedural complications	2 (3.8)	6 (11.5)
Fall	0	2 (3.8)

TEAE: treatment emergent adverse event, SOC: system organ class, PT: preferred term MedDRA 20.0.
n (%) = number and % of subjects with at least one TEAE in each category.
An adverse event is considered as treatment emergent if it occurred from the time of the first investigational medicinal product (IMP) administration up to the end of study visit (included).

usually used to numb the path of needle insertion; this could further reduce procedure pain.

Despite the fact that standard IA steroids can reliably reduce pain only for 1–3 weeks[12], it is still the only IA injection therapeutics recommended by treatment guidelines[9,10], and its chronic use may be associated with cartilage damage[41]. More recently, a novel, microsphere-based, extended-release steroid formulation showed a prolonged pain relief for 12 weeks following a single IA injection in study participants with painful knee OA[42] and it is currently indicated for single use. So, there is an urgent need for effective and safe alternative IA injection treatments to fill in the chronic journey of OA patients. Since no treatment-related structural damage in the knee has been observed, GZ389988A may be worth testing for chronic and repeat use.

GZ389988A has high affinity with CSF1R and thus theoretically blocks monocyte activation. This property may enable it to reduce OA inflammation and cartilage degradation. Antibody against CSF1R is in clinical trial for erosive hand OA (web post in clinicaltrial.gov).

The current trial has its limitations for generalizing conclusions. It was a single-center study with limited subject sampling in such a heterogeneous population of patients. The duration of effect in the subpopulation with or without knee effusion remains to be further studied. The pharmacokinetics inside joint and in plasma should also be explored further. The safety profile remains to be cautiously assessed, particularly with the shadow of NGF-antibody-induced RPOA under systemic delivery. It is now established that high dose of NGF-antibodies and/or long-term simultaneous intake of NSAIDs are associated with the increased incidence of RPOA[43,44]. Besides the local delivery of GZ389988A to mitigate potential systemic risk, a theoretical advantage is that the specific inhibition of NGF-TrkA pathway could keep the NGF-p75 pathway intact, which mediates homeostatic cellular responses[45]. By sparing p75 receptors, GZ389988A may avoid NGF-antibodies-associated RPOA and abnormal sensation, which were not encountered during the early clinical development.

In conclusion, this single center trial demonstrated that a single intra-articular injection of TrkA inhibitor, GZ389988A suspension, resulted in a sustained pain improvement and was associated with a numerically functional gain over placebo with an acceptable safety profile.

Author contributions

All authors contributed to the design, acquisition, analysis, or interpretation of data and the drafting and/or critical revision of the manuscript. All authors take responsibility for the integrity of the work as a whole from inception to finished article.

Conflict interest statement

Guang-Liang Jiang was employed by Sanofi up to the completion of the first draft of the manuscript and continued in the collaboration up to the final version with Emmanuel Krupka and Christelle Jan, who are employees of Sanofi.

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