Primary efficacy of netakimab, a novel interleukin-17 inhibitor, in the treatment of active ankylosing spondylitis in adults

S. Erdes[1], E. Nasonov[1], E. Kunder[2], A. Pristrom[2], N. Soroka[3], P. Shesternya[4], T. Dubinina[1], S. Smakotina[5], T. Raskina[6], D. Krechikova[7], T. Povarova[8], T. Plaksina[9], I. Gordeev[10], V. Mazurov[11], O. Reshetko[12], E. Zonova[13], A. Eremeeva[14], E. Chernyaeva[14], T. Makulova[15], R. Ivanov[14]

[1]Nasonova Research Institute of Rheumatology, Moscow, Russia; [2]Academy for Postgraduate Education, Minsk, Belarus; [3]Belarus State Medical University, Minsk, Belarus; [4]Krasnoyarsk State Medical University, Krasnoyarsk, Russia; [5]Regional Clinical Hospital, Kemerovo, Russia; [6]Kemerovo State Medical University, Kemerovo, Russia; [7]Regional Clinical Hospital, Smolensk, Russia; [8]Road Clinical Hospital, Saratov, Russia; [9]Clinical Hospital, Nizhniy Novgorod, Russia; [10]City Clinical Hospital no. 15, Moscow, Russia; [11]North-Western State Medical University, St. Petersburg, Russia; [12]Regional Clinical Hospital, Saratov, Russia; [13]Municipal Clinical Inpatient Facility no. 1, Novosibirsk, Russia; [14]JSC BIOCAD, St. Petersburg, Russia; [15]Institute for Medical Research, St. Petersburg, Russia.

Abstract

Objective

Netakimab (NTK) is a humanised monoclonal antibody targeting interleukin-17A, previously investigated in a phase 1 trial in healthy volunteers. Here, we report the results of a phase 2 trial, conducted to assess safety and pharmacokinetics (PK), to establish a therapeutic dose of NTK in a target population of patients with active ankylosing spondylitis (AS).

Methods

89 patients with active AS, despite non-steroidal anti-inflammatory (NSAID) drug treatment, were randomised to receive 40, 80 or 120 mg of subcutaneous NTK or placebo at weeks 0, 1, 2 and q2wk thereafter until week 12. The primary endpoint was to achieve a proportion of patients with ≥20% improvement in Assessment of Spondyloarthritis International Society (ASAS20) response criteria at week 16.

Results

Rates of ASAS20 response at week 16 for NTK with 95%CI for difference in ASAS20 rates NTK vs. placebo were 72.73% [1.69%;58.05%], 81.82% [12.36%;65.56%], 90.91% [23.71%;72.39%] at doses of 40, 80 and 120 mg. The response rate in the placebo arm was 42.86%. The pre-specified margin of clinically non-meaningful difference was 10%. Superiority to placebo was confirmed for doses 80 and 120 mg. The most frequent adverse events (AEs) were lymphocytosis, neutropenia, and asymptomatic bacteriuria. No dose-dependent toxicity or serious adverse events (SAEs) were observed. The most effective dose with the fastest response onset and favourable safety profile was 120 mg.

Conclusion

The data obtained demonstrate the efficacy and favourable safety profile of NTK in active AS. Clinical development of NTK will be continued in a phase 3 trial aimed to evaluate the efficacy of 1-year treatment with NTK 120 mg in patients with AS.

Key words

ankylosing spondylitis, treatment, biologic DMARDs

Shandor Erdes, MD, PhD
Evgeny Nasonov, MD, Prof.
Elena Kunder, MD, Prof.
Andrey Pristrom, MD, Prof.
Nikolay Soroka, MD, Prof.
Pavel Shesternya, MD, PhD
Tatiana Dubinina, MD, PhD
Svetlana Smakotina, MD, PhD
Tatiana Raskina, MD
Diana Krechikova, MD
Tatiana Povarova, MD
Tatyana Plaksina, MD
Ivan Gordeev, MD, PhD
Vadim Mazurov, MD, Prof.
Olga Reshetko, MD, PhD
Elena Zonova, MD, Prof.
Anna Eremeeva, MD, PhD
Ekaterina Chernyaeva, MD
Tatiana Makulova, MD, PhD
Roman Ivanov, MD, PhD

Please address correspondence to:
Dr Anna Eremeeva,
JSC BIOCAD,
Ul. Italianskaya 17-A,
191186 St. Petersburg, Russia.
E-mail: eremeevaav@biocad.ru

Received on October 15, 2018; accepted in revised form on February 25, 2019.

The results of this study were presented at EULAR 2018 Ann Rheum Dis 2018; 77 Suppl.: A64.
doi: 10.1136/annrheumdis-2018-eular.2380.

Funding: this study was supported by JSC BIOCAD.

Competing interests: none declared.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disorder, which mainly involves sacroiliac joints and axial skeleton and may have severe peripheral manifestations. It leads to a decrease in quality of life and functional impairments (1) due to structural damage of the spine (2).

The key drugs for the first-line therapy of AS are non-steroidal anti-inflammatory drugs (NSAIDs). Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) are effective in a variety of joint disorders. However, csDMARDs cannot be considered as a preferred treatment option due to the lack of evidence of improvement in axial symptoms (3). The next therapeutic step in the case of high disease activity despite NSAID treatment is to use biologic DMARDs (bDMARDs).

AS is a multifactorial disease with a defined genetic basis (HLA-B27 genotype). It is characterised by immune disbalance, particularly, an activation of IL-17 axis (4, 5). IL-17 has been previously proved to sustain bone tissue inflammation (6). The number of IL-17-secreting cells was significantly higher in the facet joints of AS patients in comparison with the facet joints of patients with other joint disorders (7). Moreover, increased serum IL-17 was observed in AS compared with healthy volunteers (8, 9). In a model of spontaneous ankylosing enthesitis treatment with anti-IL-17 antibodies had a significant positive impact on disease progression, while prophylactic administration of anti-IL-17 agents in animals prevented the development of ankylosis (10). This resulted in a high level of interest in IL-17 as a potential therapeutic target in AS and led to development of secukinumab, the first approved anti-IL-17 antibody, which is successfully used in patients with AS (11-13).

Netakimab is a recombinant humanised IgG1 anti-IL-17 monoclonal antibody with modified CDR-regions and Fc-fragment. The first step of clinical development of NTK was the phase 1 trial in healthy volunteers. In this trial netakimab was used as a single subcutaneous injection in ascending doses. The drug was well tolerated. Most adverse events were laboratory abnormalities of grade 1 severity. No dose-limiting toxicity was reported. The main PK parameters were evaluated.

Next, the phase 2 trial was performed which aimed to establish therapeutic dosage of NTK was performed. In addition, NTK safety and efficacy in target population were evaluated.

Materials and methods

This is a multicentre randomised double-blind placebo-controlled dose-finding clinical study (ClinicalTrials.gov NCT02763111). The study was conducted in full compliance with the Declaration of Helsinki and ICH GCP at 14 sites in the Russian Federation and the Republic of Belarus. Regulatory and ethical review board approvals from competent authorities in each country were obtained for the study protocol. All patients signed an informed consent document, and the study was conducted in accordance with the Declaration of Helsinki and followed Good Clinical Practice guidelines. After the screening period, 89 patients were randomly assigned in 1:1:1:1 ratio to receive NTK (40, 80 or 120 mg) or placebo. NTK or placebo were administered as subcutaneous injections at weeks 0, 1, 2 (induction) and then q2wk through week 12.

Efficacy, immunogenicity, and safety were assessed throughout the study. Blood samples for PK were collected from baseline up to week 16 from a limited number of patients in each arm (no more than 15 patients in one arm) (Fig. 1).

Patients 18–65 years old were considered eligible in the case of AS according to the modified New York Criteria (1984) for ≥3 months prior to IC signing. Numerical rating scale (NRS) score for spinal pain was ≥4 (range 0–10) in all patients. Disease activity was confirmed with BASDAI ≥4 (range 0–10). All patients had to receive NSAIDs in a stable dose throughout the study. Subjects previously treated with ≤2 anti-TNF-α agents were permitted to participate in the trial if they had an inadequate response defined as a lack of response after ≥3 months of therapy

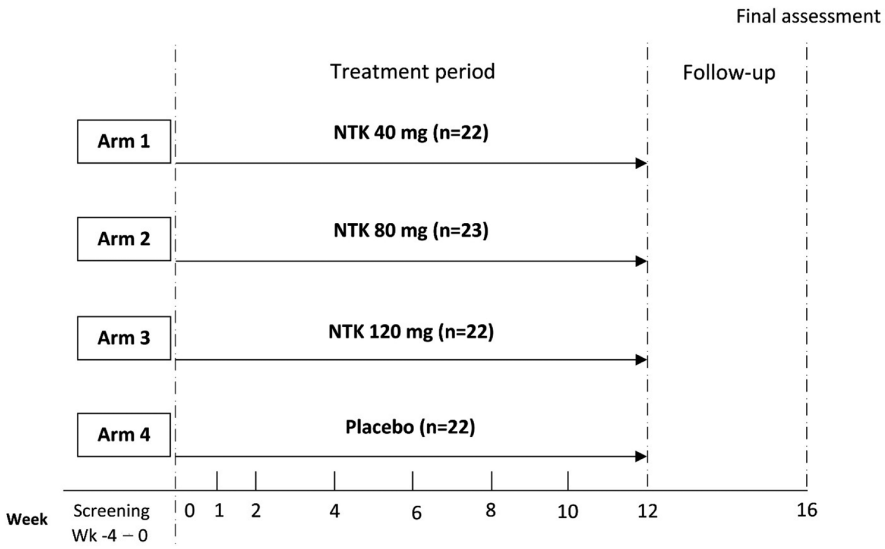

Fig. 1. Study design.

or unacceptable treatment-related side effects. The washout period for anti-TNF-α agents was not less than 12 weeks. Oral glucocorticoids (equivalent to ≤10mg daily prednisolone) and DMARDs were allowed in a stable dose for 4 weeks prior to IC signing.

The main exclusion criteria were total ankylosis of the spine, cancer, tuberculosis (current or in the past) and other systemic infectious diseases, previous treatment with anti-IL-17 and anti-IL-17R agents.

The primary endpoint was to achieve a proportion of patients who met ASAS20 response criteria at week 16 (improvement of ≥20% and an absolute improvement in ≥1 unit on a 0–10 scale in at least three of the four ASAS domains; in the remaining domain, there should be no worsening of 20% and a minimum of 1 unit). Also, the proportion of patients with ASAS20 was assessed at weeks 4, 8, 12.

The secondary endpoints included ASAS40 response (improvement of ≥40% and absolute improvement in ≥2 units on a 0–10 scale in at least three of the four main ASAS domains, with no worsening in the remaining domain), ASAS5/6 response (≥20% improvement in five of the six ASAS domains), and changes in ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score), BASDAI, BASFI (Bath Ankylosing Spondylitis Functional Index), BASMI (Bath Ankylosing Spondylitis Metrology Index), MASES (Maastricht Ankylosing Spondylitis Enthesitis Score), chest expansion, spinal pain, CRP (C-reactive protein) and SF-36 survey. Timepoints for secondary outcome measures assessment were weeks 4, 8, 12, 16.

The safety analysis included all data obtained after the first NTK/placebo injection. Adverse events (AE) were reported according to Common Terminology Criteria for Adverse Events (CTCAE), v. 4.03 (14).

Secondary PK endpoints were C_{min} (minimal serum concentration), AUC_{0-168} (area under the concentration-time curve from 0 to 168 h), $AUC_{0-\infty}$ (area under the time-concentration curve from administration to infinity), C_{max} (maximal serum concentration), T_{max} (time to maximum concentration), T½ (elimination half-life), K_{el} (elimination constant), CL (total clearance). Blood samples for serum NTK assessment were drawn prior to administration and 0.5, 1.5, 4, 8, 24, 48, 72, 144, 168 hours after the first administration, then predose at weeks 2, 4, 6, 8, 10, 12, as well as 336 hours after administration at week 12 and week 16.

Blood samples for immunogenicity (IG) assessment were collected at baseline and weeks 8, 16. Serum samples for the quantitation of NTK and detection of antidrug antibodies (ADA) were analysed using a validated enzyme-linked immunosorbent assay (ELISA).

Statistical analysis

The sample size was calculated on the basis of the literature data on clinical efficacy of IL-17 inhibitors used for the treatment of AS. The purpose of this study was to test the hypothesis of NTK being superior to placebo. The hypothesis was tested with the following error values: 5% type 1 error rate; power of 80%. The 95% two-tailed CI for ASAS20 response in each group were compared with ASAS20 response in the placebo group with pre-defined superiority margin 0.1 (10%). If the entire CI falls to the right of the superiority margin, the hypothesis that NTK is not superior to placebo was rejected.

The statistical analysis was performed using two-tailed hypothesis tests. For efficacy analysis the last observation carried forward method was used to handle any missing data. To compare normally distributed data two-sample Student *t*-test, Welch's test, and ANOVA were used. Non-normally distributed data were compared with the following tests: Mann-Whitney, Wilcoxon, Kruskal-Wallis, and Friedman test. Frequency data were analysed using Fisher's exact test, χ^2 Pearson's test, and Cochran-Mantel-Haenszel test. For multiple comparisons, the Benjamini-Yekutieli procedure was used.

All patients who received at least one dose of NTK or placebo were included in the safety analysis. Efficacy assessment was performed in the same population except for one patient with major protocol violations from the placebo arm. The PK population included data from no more than 15 patients from each arm. Placebo samples were not subject to analysis.

Results

Subjects

From 10th Oct. 2016 to 13th Feb. 2017, 89 patients with active AS were randomised into the study to receive subcutaneous NTK (40, 80 or 120 mg) or placebo. A total of 84 patients completed the study. The reasons of discontinuation were IC withdrawal, AEs and major protocol violation. One patient in the NTK 80 mg arm withdrew IC prior to the first injection and was not included in the study analysis population (Fig. 2).

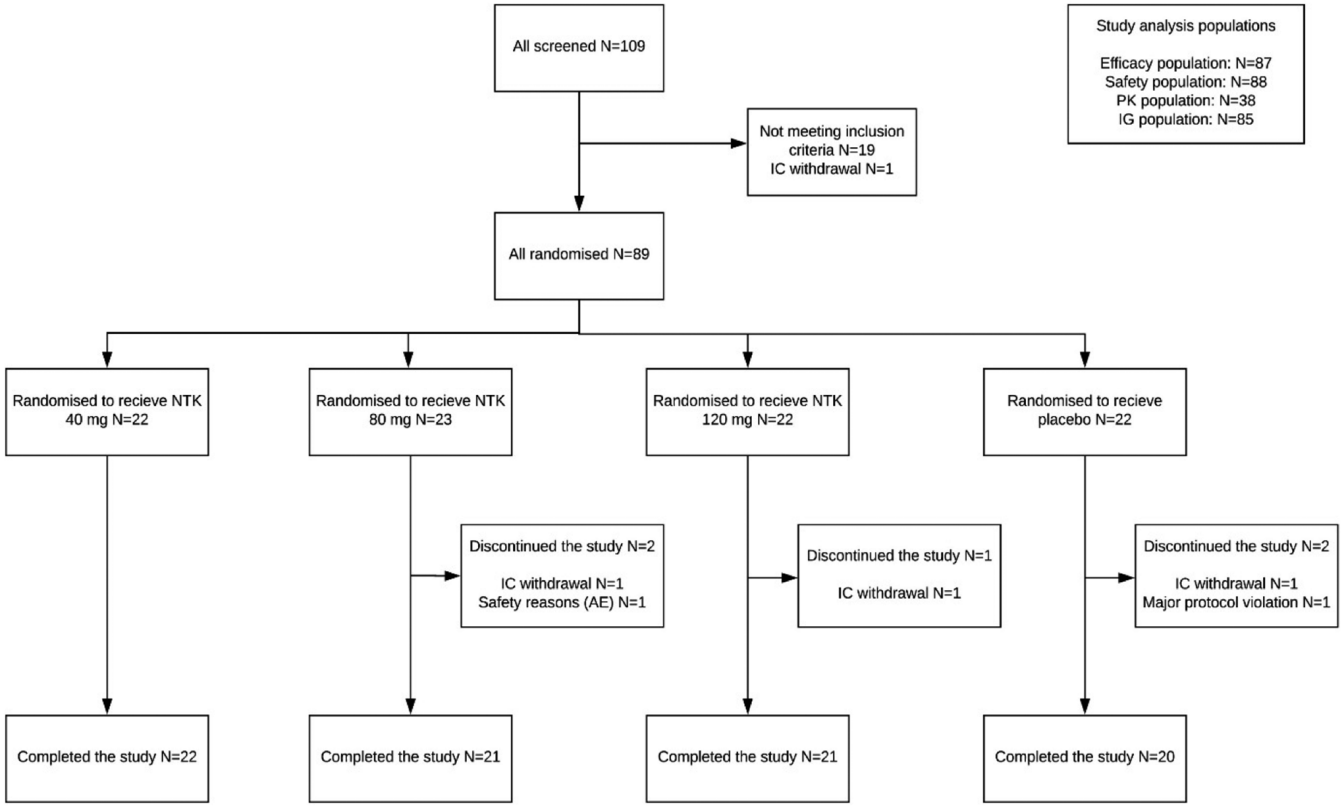

Fig. 2. Patient disposition.

Demographic and baseline AS characteristics did not differ significantly between the arms (Table I). The median total BASDAI score varied from 5.95 to 6.7, spinal pain score was 7.0 to 7.5. From 9.09% up to 18.18% of patients in each arm were previously treated with anti-TNF-α. The number of included males was significantly higher than females. This disproportion was expected due to the known prevalence of male patients in the overall AS population.

Primary endpoint

ASAS20 response at week 16 was achieved by 72.73%, 81.82% and 90.91% patients in the 40, 80 and 120 mg NTK arms, respectively, and in 42.86% patients in the placebo arm.

Table I. Main demographic and baseline AS characteristics (safety population)

Variables	NTK			
	40 mg (n=22)	80 mg (n=22)	120 mg (n=22)	Placebo (n=22)
Age, years	40.0 (33.0-44.0)	34.0 (31.0-36.0)	38.0 (35.0-44.0)	41.0 (32.0-47.0)
Men*	17 (77.27)	19 (86.36)	22 (100.0)	15 (68.18)
Women*	5 (22.73)	3 (13.64)	0	7 (31.82)
Weight, kg	75.5 (61.0-93.0)	79.0 (63.0-86.1)	79.1 (71.5-85.0)	81.3 (75.0-90.0)
AS duration, mo.	26.5 (11-75)	37.5 (20-56)	46.5 (13-96)	26.5 (10-48)
Spinal pain, total score (0-10 scale)	7.5 (6-8)	7 (6-8)	7 (6-8)	7 (6-7)
ASDAS-CRP, total score	4.52 (4.02-4.98)	4.04 (3.16-4.33)	3.67 (3.29-3.9)	3.915 (3.47 4.07)
BASDAI, total score	6.45 (5.4-7.4)	6.7 (5.8-7.1)	6.45 (4.7-7.3)	5.95 (5.1-7)
BASFI, total score	5.9 (4.3-7.2)	5.95 (4.5-6.9)	5.55 (3.9-6.8)	6 (4-6.7)
BASMI, total score	4.65 (3.2-5.2)	4.5 (2.8-5.1)	4.15 (3.5-5.4)	4.55 (3.3-5.1)
MASES, score	2 (0-4)	4 (2-5)	3 (2-3)	3 (0-6)
Chest expansion, cm	3.5 (3-4)	3.5 (2-4)	3 (3-4)	3 (3-5)
CRP, mg/l	43.6 (16-58.6)	18.5 (6.6-34.6)	12.55 (5.8-15.0)	19.95 (9.2-30.5)
Previous use of anti-TNFα*	4 (18.18)	2 (9.09)	3 (13.64)	4 (18.18)

Median and interquartile range are presented except variables marked with *, where no. (%) is presented.
BASDAI: Bath AS Disease Activity Index (scores range from 0 to 10, where 10 indicates the most severe AS activity); BASFI: Bath AS Functional Index (scores range from 0 to 10, where 10 indicates the most severe functional limitation); BASMI: Bath AS Metrology Index (scores range from 0 to 10, where 10 indicates the most severe spinal mobility limitation); MASES: Maastricht Ankylosing Spondylitis Enthesitis Score (scores range from 0 to 13, where 13 indicates the most severe enthesitis), CRP: C-reactive protein.

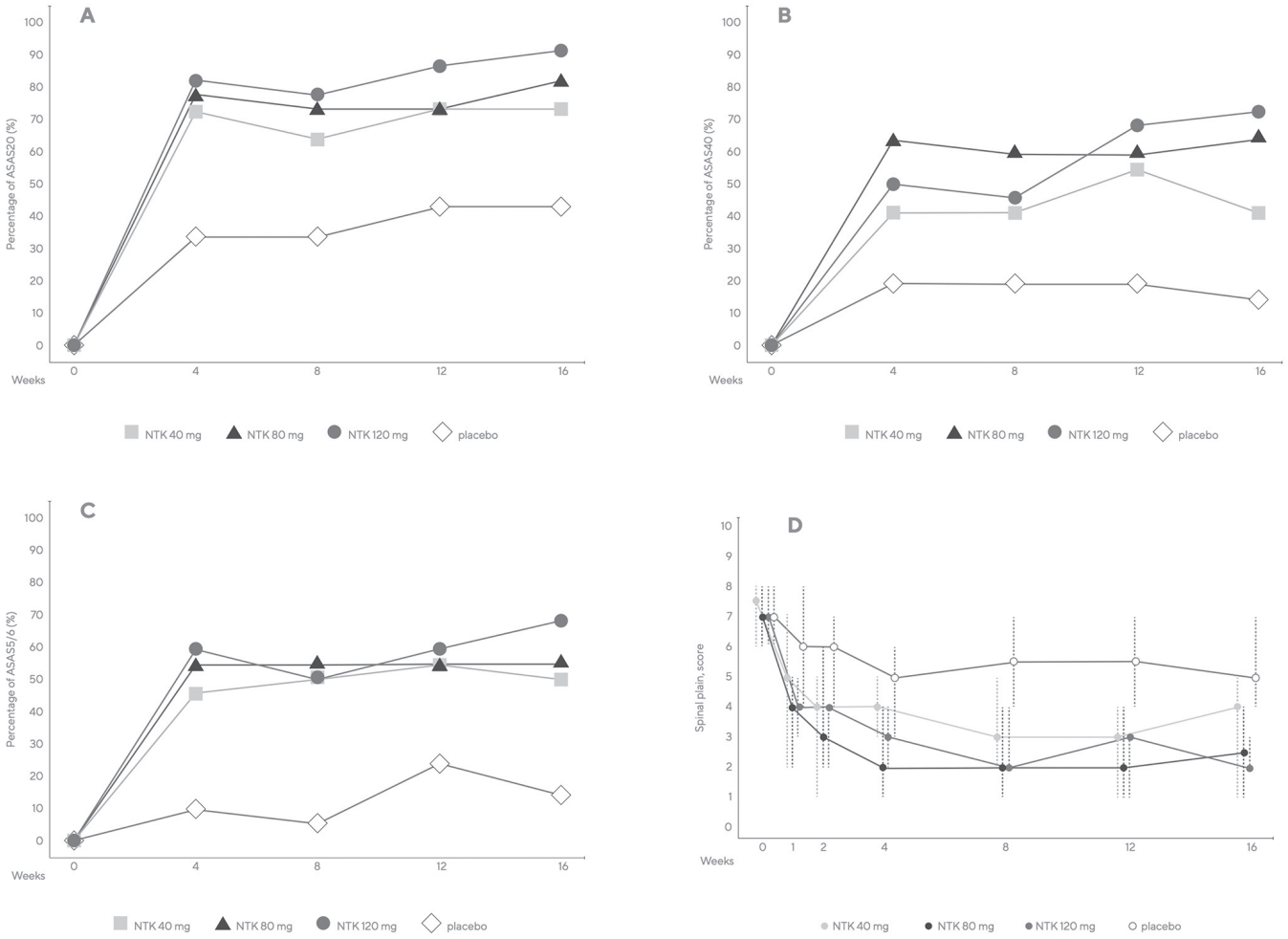

Fig. 3. Data on 16-week efficacy of NTK at doses of 40, 80 and 120 in comparison with placebo.
A: percentage of ASAS20 responders, (%); **B**: percentage of ASAS40 responders, (%); **C**: percentage of ASAS5/6 responders, (%); **D**: spinal pain score dynamics (absolute values, median and interquartile range are presented).

Significant differences between NTK and placebo were revealed for all three groups (p<0.05 for NTK 40 mg *vs*. placebo, p<0.01 for NTK 80 mg *vs*. placebo, p<0.001 for NTK 120 mg *vs*. placebo) (Fig. 3). However, the study hypothesis (superiority to placebo) was confirmed only for doses 80 and 120 mg: 95% CIs for the difference in proportions of ASAS20 rate were [1.69%; 58.05%] for NTK 40 mg *vs*. placebo, [12.36%; 65.56%] for NTK 80 mg *vs*. placebo, [23.71%; 72.39%] for NTK 120 mg *vs*. placebo).

Secondary endpoints

All secondary endpoints demonstrated that throughout the study NTK was superior to placebo in terms of inhibiting AS activity and reducing function impairment. Efficacy of NTK was dose-dependent. The most pronounced changes were observed in the NTK 120 mg arm.

ASAS40 response rates at week 16 were 40.91% (NTK 40 mg), 63.64% (NTK 80 mg), 72.73% (NTK 120 mg) and 14.29% (placebo) (p<0.001). ASAS5/6 response was reported in 50.0% (NTK 40 mg), 54.55% (NTK 80 mg), 68.18% (NTK 120 mg) and 14.29% (placebo) (p<0.01). Rates of ASAS40 and ASAS5/6 responses were significantly higher in the NTK groups throughout the study starting from the first evaluation timepoint (week 4).

Other secondary outcomes also showed an improvement in the NTK arms. Changes from baseline in ASDAS-CRP, BASDAI, BASFI, CRP were significantly greater with NTK compared with placebo (Table II). The NTK arms also showed significant positive intergroup dynamics in BASMI, MASES scores, chest expansion, and SF-36 survey throughout the study. Overall, the most apparent efficacy was detected in the NTK 120 mg group.

Spinal pain dynamics confirmed the fast onset of treatment response. Starting from week 1, NTK 120 mg was superior to placebo in terms of reducing spinal pain (p<0.05). Further assessment confirmed that treatment with NTK leads to a decrease in spinal pain up to full elimination in some patients in NTK arms (minimum spinal pain score was 0) (Fig. 3D).

Safety

The rates of adverse events were similar in all groups and did not differ significantly between NTK and placebo. No dose-depended toxicity was revealed. Moreover, the arm that received the maximum dose of NTK

Table II. Mean changes of secondary outcome measures from baseline (Wk 16).

Secondary outcome measure, mean (SD)	NTK			
	40 mg (n=22)	80 mg (n=22)	120 mg (n=22)	Placebo (n=22)
ASDAS-CRP, score	-2.00 (0.85)‡	-1.80 (1.20)†‡	-1.91 (0.94)†‡	-0.48 (0.86)
BASDAI, score	-2.60 (2.24)‡	-3.52 (2.46)†‡	-3.71 (2.37)†‡	-1.43 (1.61)
BASFI, score	-1.71 (2.62)‡	-2.62 (2.57)‡	-2.70 (2.02)†‡	-0.95 (1.30)
BASMI, score	-0.85 (0.73)‡	-0.61 (0.72)‡	-0.69 (0.75)‡	-0.37 (1.00)
MASES, score	-1.68 (3.17)	-3.19 (2.40)‡	-2.05 (1.07)‡	-2.05 (2.54)
Chest expansion, cm	0.32 (1.27)	0.90 (1.31)	1.17 (1.43)‡	0.45 (1.22)
CRP, mg/l	-36.08 (28.55)†	-23.76 (38.76)†	-16.73 (29.05)†	-6.69 (24.34)
SF-36				
Physical component, score	6.72 (8.88)‡	11.46 (10.01)‡	12.24 (8.52)‡	2.36 (8.30)
Mental component, score	6.98 (11.35)‡	7.66 (9.52)‡	6.96 (9.01)‡	3.28 (11.08)

†$p<0.05$ for the comparison with placebo.
‡$p<0.05$ for the intergroup dymanics (baseline *vs*. Wk16).
SD: standard deviation; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score (maximum score indicates the most severe AS activity); BASDAI: Bath AS Disease Activity Index (scores range from 0 to 10, where 10 indicates the most severe AS activity); BASFI: Bath AS Functional Index (scores range from 0 to 10, where 10 indicates the most severe functional limitation); BASMI: Bath AS Metrology Index (scores range from 0 to 10, where 10 indicates the most severe spinal mobility limitation); MASES: Maastricht Ankylosing Spondylitis Enthesitis Score (scores range from 0 to 13, where 13 indicates the most severe enthesitis); CRP: C-reactive protein.

Table III. Summary of safety data.

Variables	NTK				*p*-value*
	40 mg (n=22)	80 mg (n=22)	120 mg (n=22)	Placebo (n=22)	
Any AE	11 (50.00)	6 (27.27)	4 (18.18)	7 (31.82)	0.183
Therapy related AE	5 (22.73)	4 (18.18)	1 (4.55)	5 (22.73)	0.354
Severe AE	1 (4.55)	2 (9.09)	0	1 (4.55)	0.900
Therapy related severe AE	0	1 (4.55)	0	1 (4.55)	1.00
Serious AE	0	0	0	0	-
Withdrawal due to AE	0	1 (4.55)	0	0	1.00
Death	0	0	0	0	-
Summary of severe AEs					
Anaemia (Grade 3)	0	0	0	1 (4.55)	1.00
Neutropenia (Grade 4)	0	1 (4.55)	0	0	1.00
Erosive colitis (Grade 3)	0	1 (4.55)	0	0	1.00
Episcleritis (Grade 3)	1 (4.55)	0	0	0	1.00
Summary of frequent AEs					
Lymphocytosis (Grade 2)	4 (18.18)	0	2 (9.09)	0	0.051
Neutropenia (Grade 2, 4)	1 (4.55)	2 (9.09)	0	0	0.612
Asymptomatic bacteriuria (Grade 2)	2 (9.09)	0	0	1 (4.55)	0.612
Summary of therapy related AEs					
Diastolic BP increased (Grade 2)	1 (4.55)	0	0	1 (4.55)	1.00
Sinus bradycardia (Grade 1)	0	1 (4.55)	0	1 (4.55)	1.00
Left anterior fascicular block (Grade 1)	1 (4.55)	0	0	0	1.00
Weakness (Grade 1)	0	0	0	1 (4.55)	1.00
Drowsiness (Grade 1)	0	0	0	1 (4.55)	1.00
Anaemia (Grade 3)	0	0	0	1 (4.55)	1.00
Neutropenia (Grade 2, 4)	1 (4.55)	2 (9.09)	0	0	0.612
Thrombocytopenia (Grade 1)	1 (4.55)	0	0	0	1.00
Leucopenia (Grade 1)	1 (4.55)	0	0	0	1.00
ALT increased (Grade 2)	0	0	1 (4.55)	0	1.00
Hyperglycaemia (Grade 1)	1 (4.55)	0	0	0	1.00
Proteinuria (Grade 1)	1 (4.55)	0	0	0	1.00
Maculopapular rash (Grade 2)	0	1 (4.55)	0	0	1.00
Skin itch (Grade 2)	1 (4.55)	0	0	0	1.00
Facial paresthesia (Grade 1)	1 (4.55)	0	0	0	1.00
Sinusitis (Grade 2)	1 (4.55)	0	0	0	1.00

no. (%) is presented. * two-tailed Fisher's exact test.

had the lowest frequency of AEs. The percentage of patients with any AE was 50.0% in NTK 40 mg, 27.27% in NTK 80 mg, 18.18% in NTK 120 mg and 31.82% in placebo (p>0.05) (Table III). Therapy-related AEs were reported in 22.73%, 18.18%, 4.55% and 22.73% patients, respectively, and were mainly presented with blood and lymphatic system disorders (anemia, neutropenia, thrombocytopenia, and leucopenia) (Table III). Cardiac and vascular disorders were less frequent and included increased diastolic blood pressure (Grade 2), sinus bradycardia (Grade 1), and left anterior fascicular block (Grade 1). General disorders and local reactions, related to the study therapy (Grade 1 weakness and drowsiness), were observed only in the placebo arm. Skin disorders were presented with Grade 2 maculopapular rash and skin itching in NTK 40 mg and NTK 80 mg, respectively. One episode of therapy-related infection (sinusitis, Grade 2) occurred in the NTK 80 mg arm. Other infections (viral infection, upper respiratory tract infections) were mild and unrelated to NTK or placebo.

Severe AEs (Grade 3–4) were rare and were reported in all groups except NTK 120 mg. These AEs included anaemia, neutropenia, erosive colitis and episcleritis. Neutropenia (Grade 4, NTK 80 mg) resolved spontaneously by the next visit. Anaemia (Grade 3) developed at week 4 in a patient from the placebo arm, required medication therapy and did not resolve up to completion of the study. Both neutropenia and anaemia were asymptomatic and were only severe AEs related to the study therapy in the opinion of the investigators.

One patient in the NTK 40 mg arm experienced loss of visual acuity, pain and redness of eyes, unrelated to study treatment at week 4. All symptoms resolved without sequelae after standard therapy of episcleritis.

Erosive colitis (Grade 3, NTK 80 mg) was the only AE that led to a patient's withdrawal. The first symptoms appeared before screening and were concealed by the patient. During the active period of the study (at week 1), a colonoscopy was performed (outside the study setting), erosive colitis was established and the patient reported the symptoms and colonoscopy results to the investigator. Taking into account the results of other IL-17 inhibitor clinical studies (*i.e.* cases of inflammatory bowel diseases) and prescribing information of secukinumab and ixekizumab (caution should be exercised when prescribing these drugs to patients with inflammatory bowel disease), it was decided to discontinue the patient from the study. However, neither during the active treatment period nor during the observation period after exclusion, there were no dynamics in the colitis symptoms. Based on these facts the investigator concluded that erosive colitis was a preexisting comorbidity not related to the study treatment.

No local reactions, serious AEs or deaths were observed. No anti-NTK antibodies were detected in all time points.

Table IV. Descriptive statistics for PK parameters in NTK arms.

Variables	NTK			p-value*
	40 mg (n=12)	80 mg (n=14)	120 mg (n=12)	
$AUC_{(0-168)}$	0.627 (0.272-0.698)	1.191 (0.926-1.483)	1.596 (1.288-2.188)	0.0001
C_{max}	0.005 (0.003-0.006)	0.01 (0.008-0.011)	0.013 (0.010-0.016)	0.0001
T_{max}	144 (144-168)	144 (144-168)	144 (144-168)	0.933
$C_{max\ mult}$	0.011 (0.009-0.013)	0.023 (0.015-0.027)	0.032 (0.025-0.038)	0.0001
$T_{max\ mult}$	1680 (1344-2016)	2016 (672-2016)	1680 (1344-2352)	0.599
C_{min}	0.005 (0.003-0.005)	0.009 (0.003-0.0099)	0.013 (0.001-0.013)	0.043

Median and interquartile range are presented. *Kruskal-Wallis test.
$AUC_{(0-168)}$: area under the concentration-time curve from 0 to 168 hours, mg x h/ml; C_{max}: maximum observed serum concentration after single administration, mg/ml; T_{max}: time to maximum observed serum concentration after single administration, h; $C_{max\ mult}$: maximum observed serum concentration after multiple administration, mg/ml; $T_{max\ mult}$: time to maximum observed serum concentration after multiple administration, h; C_{min}: minimum observed serum concentration after multiple administration, mg/ml.

Pharmacokinetics

After a single injection of NTK at doses of 40 mg, 80 mg and 120 mg, the drug concentration changed with time in a similar way for all the doses. The changes in NTK concentration were dose-dependent. Absorption was slow with a gradual linear increase in the serum concentration of NTK with a maximum seen at the end of week 1. Higher doses (80 mg and 120 mg) were characterised by higher C_{max} and AUC as compared to the 40 mg dose. When given as multiple injections, NTK accumulates in the serum and its C_{max} increases. C_{max} differences between the arms remain significant (p=0.001) (Table IV).

Discussion

The aim of this phase 2 double-blind randomised trial was to establish the therapeutic dose of NTK in the target population of patients with active AS.

The hypothesis of NTK superiority over placebo was confirmed for doses of 80 and 120 mg: the 95% CIs for treatment differences were within the predefined superiority margin of 10% (0.10).

The results of the study clearly show that treatment with NTK led to a reduction in AS activity, improvement in functional and metrology indexes, chest expansion, enthesitis score and quality of life. CRP levels significantly reduced by week 4 compared with the baseline and remained at achieved levels up to week 16 in all groups except placebo. In the placebo group no dynamics in CRP were shown throughout the study. To evaluate the timeline of response onset we used the spinal pain score. By the first time of assessment (week 1), *i.e.* after first NTK injection, the spinal pain score decreased in all NTK arms. A further decline in spinal pain was also observed.

Pairwise comparisons of all study arms did not reveal any difference between 40 mg NTK and placebo in some evaluated parameters (BASDAI, BASFI, BASMI). Although significant improvement was observed for

all secondary endpoints in the 80 mg arm, it is worth mentioning that 120 mg showed greater efficacy in terms of all endpoints at week 16. Thus, 120 mg was considered the most effective NTK dose; moreover, NTK efficacy was suggested as dose-dependent.

In general, the results obtained are consistent with the published data on anti-IL-17 efficacy. In MEASURE 1 and MEASURE 2 trials the rate of ASAS20 at week 16 was approximately three times higher in the secukinumab maximum dose group compared to placebo (11).

NTK was well tolerated. Safety profiles of all NTK groups and placebo had no significant differences. The percentage of patients with adverse events, including therapy-related, were comparable in the NTK and placebo arms irrespective of the used dosage. No dose-dependent toxicity was shown. On the contrary, the highest number of patients with AEs was observed in 40 mg NTK arm, the lowest – in 120 mg NTK arm. This difference can be explained by the higher rate of mild (Grade 1) AEs in 40 mg NTK arm. At the same time, the incidence of treatment-related AEs was comparable between 40 mg NTK and placebo arms.

Observed AEs were mostly presented with heart events, blood and lymphatic events, infections and were of mild or moderate severity. Although infections and infestations are known AEs for secukinumab and were expected for NTK, no difference in the incidence of infections was seen in the NTK arms compared with placebo in this study.

Severe AEs were reported in all treatment groups except NTK 120 mg group. Only anaemia and neutropenia (80 mg NTK and placebo arms) were related to study therapy. Erosive colitis (Grade 3, NTK 80 mg) was the only adverse event that led to patient's withdrawal. Despite the fact that inflammatory bowel diseases were previously reported for other anti-IL-17 agents, in this study erosive colitis was considered by the investigator to have no obvious relationship with treatment. However, the frequency of inflammatory bowel disease in NTK treated patients needs to be addressed in the phase 3 study.

No anti-NTK antibodies were detected. Approved anti-IL-17 monoclonal antibodies secukinumab and ixekizumab are known to have low immunogenicity, so this result was expected (11, 15-16). It should also be stated that NTK has optimised CDR regions designed to decrease immunogenicity. On the other hand, formation of anti-NTK antibodies in the case of longer NTK administration cannot be fully excluded and requires further investigation.

NTK pharmacokinetics is linear with gradual elevation of concentrations over the study period. The maximum concentrations after multiple administration were observed at week 10–12. The achieved maximum concentrations remained almost unchanged during the follow-up and showed no significant downward trend. Thus, the obtained data may demonstrate NTK cumulation when used q2wk. This may suggest the possibility of a dosage regimen with less frequent administration.

Conclusion

The results of this clinical study provide preliminary evidence that netakimab as an effective drug with a favourable safety profile, consistent with that of other anti-IL-17 agents. Clinical development of netakimab will be continued with a phase 3 trial in patients with active ankylosing spondylitis, aimed to evaluate therapeutic efficacy of 1-year treatment with netakimab in the dose 120 mg q2wk.

Acknowledgements

The preliminary data were presented at the EULAR 2018 Congress, June 13–16, 2018 (Amsterdam, the Netherlands). The study was supported by JSC BIOCAD. We thank Nikita A Zolkin, an employee of JSC BIOCAD, for processing the statistical data. We would like to acknowledge the collaboration and commitment of all investigators and staff.

References

1. BRAUN J, SIEPER J: Ankylosing spondylitis. *Lancet* 2007; 369: 1379-90.
2. LANDEWÉ R, DOUGADOS M, MIELANTS H *et al*.: Physical function in ankylosing spondylitis is independently determined by both disease activity and radiographic damage of the spine. *Ann Rheum Dis* 2009; 68: 863-7.
3. VAN DER HEIJDE D, RAMIRO S, LANDEWÉ R *et al*.: 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017; 76: 978-91.
4. DE KONING A, SCHOONES JW, VAN DER HEIJDE D, VAN GAALEN FA: Pathophysiology of axial spondyloarthritis: consensus and controversies. *Eur J Clin Invest* 2018; 48: e12913.
5. ZAMBRANO-ZARAGOZA JF, AGRAZ-CIBRIAN JM, GONZALEZ-REYES C *et al*.: Ankylosing Spondylitis: from cells to genes. *Int J Inflam* 2013; 2013: 501653.
6. DI BENEDETTO G, LEMPEREUR L, VALLE D *et al*.: Redundant modulatory effects of pro-inflammatory cytokines in human osteoblastic cells *in vitro*. *Clin Exp Rheumatol* 2018; 36: 959-69.
7. APPEL H, MAIER R, WU P *et al*.: Analysis of IL-17(+) cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response. *Arthritis Res Ther* 2011; 13: R95.
8. MEI Y, PAN F, GAO J *et al*.: Increased serum IL-17 and IL-23 in the patient with ankylosing spondylitis. *Clin Rheumatol* 2011; 30: 269-73.
9. LIU W, WU YH, ZHANG L *et al*.: Elevated serum levels of IL-6 and IL-17 may associate with the development of ankylosing spondylitis. *Int J Clin Exp Med* 2015; 8: 17362-76.
10. EBIHARA S, DATE F, DONG Y, ONO M: Interleukin-17 is a critical target for the treatment of ankylosing enthesitis and psoriasis-like dermatitis in mice. *Autoimmunity* 2015; 48: 259-66.
11. BAETEN D, SIEPER J, BRAUN J *et al*.: Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. *N Engl J Med* 2015; 373: 2534-48.
12. TERENZI R, MONTI S, TESEI G, CARLI L: One year in review 2017: spondyloarthritis. *Clin Exp Rheumatol* 2018; 36: 1-14.
13. BARALIAKOS X, KIVITZ AJ, DEODAR AA *et al*.: Long-term effects of interleukin-17A inhibition with secukinumab in active ankylosing spondylitis: 3-year efficacy and safety results from an extension of the Phase 3 MEASURE 1 trial. *Clin Exp Rheumatol* 2018; 36: 50-55.
14. Common Terminology Criteria for Adverse Events (CTCAE) v4.3, U.S. Department of health and human services, 2010.
15. REICH K, BLAUVELT A, ARMSTRONG A *et al*.: Secukinumab, a fully human anti-interleukin-17A monoclonal antibody, exhibits minimal immunogenicity in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol* 2017; 176: 752-58.
16. SYED YY: Ixekizumab: a review in moderate to severe plaque psoriasis. *Am J Clin Dermatol* 2017; 18: 147-58.