The efficacy and safety of netakimab in patients with psoriatic arthritis: results from the Phase III clinical study PATERA

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Netakimab is a humanized anti-interleukin-17A (IL-17A) monoclonal antibody approved for the treatment of psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. In this paper, we present the results of a 24-week period of the Phase III clinical study PATERA.

The **objective** of the study was to evaluate the efficacy and safety of netakimab compared to placebo in patients with active psoriatic arthritis.

Patients and methods. 194 patients with active psoriatic arthritis with an inadequate response to previous therapy with nonsteroidal anti-inflammatory drugs, conventional or biological disease-modifying antirheumatic drugs, were randomized in a 1:1 ratio to receive netakimab 120 mg or placebo at weeks 0, 1, 2, 4, 6, 8, 10, 14, 18, 22. At Week 16, ACR20 (20% improvement in the American College of Rheumatology response criteria) non-responders in the placebo group were reassigned to netakimab in a blinded manner. The primary efficacy endpoint was the proportion of patients who achieved ACR20 response at Week 24.

Results. 82.5% of patients in the netakimab group and 9.3% of patients in the placebo group achieved ACR20 response at Week 24 (95% CI 0.63; 0.84, $p<0.0001$). Skin manifestations and axial psoriatic arthritis significantly improved with netakimab therapy. Patients tolerated netakimab well. The safety profile of netakimab was comparable to placebo. The most frequent treatment-related AEs were expected and common for all other IL-17 inhibitors: increased alanine aminotransferase, infections, lymphopenia.

Conclusions. Netakimab 120 mg is significantly superior to placebo in patients with active psoriatic arthritis. The favorable safety profile of netakimab is consistent with other IL-17 inhibitors.

Keywords: netakimab, psoriatic arthritis, interleukin-17 inhibitors.

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ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ НЕТАКИМАБА У ПАЦИЕНТОВ С ПСОРИАТИЧЕСКИМ АРТРИТОМ: РЕЗУЛЬТАТЫ КЛИНИЧЕСКОГО ИССЛЕДОВАНИЯ III ФАЗЫ PATERA

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Нетакимаб – гуманизированное моноклональное антитело против интерлейкина-17 А, разрешенное для применения у пациентов с псориатическим артритом, анкилозирующим спондилитом и бляшечным псориазом. В данной статье представлены результаты 24-недельного периода клинического исследования III фазы PATERA.

Целью исследования PATERA являлась оценка эффективности и безопасности нетакимаба в сравнении с плацебо у пациентов с активным псориатическим артритом.

Пациенты и методы. 194 больных с активным псориатическим артритом с недостаточным ответом на предшествующую терапию, включающую нестероидные противовоспалительные препараты, синтетические базисные противовоспалительные препараты или генно-инженерные биологические препараты, были рандомизированы в соотношении 1:1 в группу нетакимаба 120 мг или группу плацебо. Препараты вводились подкожно на неделях 0, 1, 2, 4, 6, 8, 10, 14, 18, 22. Пациенты группы плацебо, у которых не было зафиксировано 20% улучшения по критериям Американской коллегии ревматологов (ACR20) на неделе 16, были переведены на лечение нетакимабом с сохранением заслепления. Основным показателем эффективности являлась доля пациентов, достигших ACR20 на 24 нед.

Результаты. 82,5% пациентов в группе нетакимаба и 9,3% пациентов в группе плацебо достигли ACR20 на 24 нед. (95% ДИ [0,63; 0,84] ($P < 0,0001$)). На фоне терапии нетакимабом наблюдалось значимое улучшение состояния кожных покровов и снижение выраженности аксиальных проявлений псориатического артрита. Пациенты хорошо переносили нетакимаб. По спектру нежелательных явлений он в целом не отличался от плацебо. Наиболее частые нежелательные явления, связанные с лечением (повышение уровня аланинаминотрансферазы, инфекции, лимфопения), были ожидаемыми и соответствовали данным о безопасности применения других ингибиторов ИЛ-17.

Выводы. Нетакимаб в дозе 120 мг достоверно превосходит по эффективности плацебо при лечении пациентов с активным псориатическим артритом. Показан благоприятный профиль безопасности нетакимаба, соответствующий классу ингибиторов ИЛ-17.

Ключевые слова: нетакимаб, псориатический артрит, ингибиторы интерлейкина-17

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Introduction

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease classified as a spondyloarthriris, which is commonly associated with skin psoriasis. PsA is characterized by the presence of peripheral arthritis, dactylitis, enthesitis, as well as axial manifestations such as spondylitis and sacroiliitis, which are found in 25–70% of patients [1, 2]. The main clinical symptoms of PsA, such as pain, stiffness and joint swelling, can significantly reduce activity of the patient. Depending on the clinical form, PsA can be manifested by asymmetric oligoarthritis (involving ⩽4 joints), a predominant involvement of distal interphalangeal joints, a rheumatoid-like form with symmetric or asymmetric lesions in small joints of the hands (involving ⩾5 joints); less frequently, patients develop arthritis mutilans (about 5%), which is characterized by advanced resorption of the articular surfaces (osteolysis) with shortening of fingers and/or toes. PsA can significantly reduce the quality of life of patients. In addition, high disease activity is associated with progressive joint damage and an increased death rate [2, 3].

The pathogenesis of PsA is still not fully understood. There is evidence of a significant role of IL-17 in the pathogenesis of both psoriasis and PsA. IL-17 demonstrates pronounced pro-inflammatory activity both *in vitro* and *in vivo,* and also affects various cellular targets in the skin and joints, contributing to the development of inflammation and damage to bones and joints. IL-17-producing cells are found in large quantities in serum, synovial fluid, and psoriatic plaques in patients with PsA, and the number of these cells correlates with the severity of the disease [4]. IL-17 inhibition results in a decrease in pro-inflammatory cytokines and slows down bone resorption.

Netakimab (NTK) is an original recombinant humanized monoclonal IgG1 to IL-17A. The main feature of the NTK structure is that it is based on antibodies derived from llama immunoglobulins. The process of humanization included the replacement of all amino acid sequences of the heavy chains with human sequences, with the exception of a few CDR fragments that determine affinity to the antigen. After that, fully human light chains were fused to the modified chains. Thus, the two goals of maintaining high affinity and significantly reducing the potential immunogenicity of the humanized antibody were achieved. To improve the safety profile and pharmacokinetic properties of the drug, the Fc fragment was also modified. The changes aimed at reducing antibody-dependent cytotoxicity led to a decrease of the NTK effects on immune system cells and minimization of possible adverse reactions.

The superiority of NTK at a dose of 120 mg over placebo has been previously confirmed in two Phase III studies in patients with plaque psoriasis (BCD-085-7/PLANETA, NCT03390101) and ankylosing spondylitis (BCD-085-5/ASTERA, NCT03447704) [5–8].

Objective. The objective of the PATERA study was to evaluate the efficacy and safety of netakimab in comparison with placebo in patients with active PsA.

Patients and methods

PATERA is an ongoing international, multicenter, double-blind, randomized, placebo-controlled Phase III clinical trial conducted at 24 study sites in the Russian Federation and the Republic of Belarus in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study was approved by the central regulatory authorities of the Russian Federation and the Republic of Belarus and the ethics committees of each of the participating sites. The study was registered with the US National Institutes of Health (ClinicalTrials.gov; NCT03598751).

In this paper, we present the results of the 24-week double-blind period of the study. It included patients aged 18 years and older who were diagnosed with PsA according to the CASPAR criteria [9] at least 6 months before enrollment, had a tender joint count (TJC) of ⩾3 out of 68 and a swollen joint count (SJC) of ⩾3 out of 66, and had at least one psoriatic plaque ⩾2 cm in diameter and/or nail psoriasis and/or a documented history of plaque psoriasis. The study included patients with an inadequate response to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs), conventional (cDMARDs) or biological (bDMARDs) disease-modifying antirheumatic drugs. During the analyzed period, continued use of NSAIDs, oral glucocorticoids (at a dose of ⩽10 mg in terms of prednisolone) and methotrexate at a stable dose was allowed.

The main exclusion criteria were prior therapy with monoclonal antibodies to IL-17 or its receptor, as well as to IL-12/23, or the use of more than two products of monoclonal antibodies or their fragments. In case of previous use of any other DMARDs, an appropriate washout period was required. Parenteral glucocorticoids and any drugs for intra-articular injections were to be discontinued at least 4 weeks prior to signing the Informed Consent Form (ICF).Topical/oral retinoids, phototherapy, or other topical medications for psoriasis were to be withdrawn after signing the ICF. The use of DMARDs (except for methotrexate) was not allowed from the date of signing the ICF and throughout the study.

Patients who met the inclusion criteria and did not have the exclusion criteria were stratified by the following factors: previous use of bDMARDs (yes/no), current therapy with methotrexate (yes/no). The patients were then randomized in a 1:1 ratio to receive netakimab or placebo.

The main treatment period includes a blinded phase (Weeks 0-24) followed by an open-label period. During the first 3 weeks, all patients received subcutaneous injections of NTK at a dose of 120 mg or placebo once a week (induction phase). Afterwards, patients of the NTK group received it

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at the same dose at Weeks 4, 6, 8, and 10, and then once every 4 weeks starting at Week 14. Patients in the second group received placebo at Weeks 4, 6, 8, 10 and 14. Participants who did not achieve 20% improvement in the ACR criteria (ACR20) by Week 16 were switched to active blinded therapy and received NTK at Weeks 18 and 22. Patients who achieved ACR20 response continued to receive placebo at Weeks 18 and 22. An efficacy analysis was performed at Week 24.

NTK and placebo were supplied in identical pre-filled syringes containing 60 mg of NTK in 1.0 ml or 1.0 ml of placebo in indistinguishable packages. NTK and placebo were administered as two subcutaneous injections of 1.0 ml each. The injections were performed by authorized personnel at the study site. All patients have now completed the double-blind study period.

Assessment parameters

The primary efficacy endpoint was the proportion of patients who achieved ACR20 response at Week 24. Secondary efficacy endpoints included:

- ACR20, 50% (ACR50), and 70% (ACR70) improvements in the ACR criteria;
- response assessed with the **Ps**oriatic **A**rthritis **R**esponse **C**riteria (PsARC);
- minimum disease activity defined by meeting at least 5 of the 7 following criteria: TJC ⩽1, SJC ⩽1, PASI ⩽1 or BSA ⩽3, pain score on a visual analogue scale (VAS) ⩽15 mm, patient global assessment of disease activity on a VAS ⩽20 mm, HAQ-DI ⩽0.5, enthesitis count ⩽1;
- 75% (PASI75), 90% (PASI90) and 100% (PASI100) improvement in the **P**soriasis **A**rea **S**everity **I**ndex (PASI) in patients with a **B**ody **S**urface **A**rea (BSA) ⩾3;
- disease activity assessed with DAS28-CRP(4) and DAPSA (**D**isease **A**ctivity **S**core 28-joint count **C**-reactive protein and **D**isease **A**ctivity in **P**soriatic **A**rthritis);
- assessment of functional activity according to the HAQ-DI score;
- **L**eeds **E**nthesitis **I**ndex (LEI) in patients with LEI >0;
- **L**eeds **D**actylitis **I**ndex (LDI) in patients with LDI >0;
- **N**ail **P**soriasis **S**everity **I**ndex (NAPSI) in patients with NAPSI >0.

AEs were reported according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and summarized using the MedDRA dictionary (version 22.0). In accordance with the ICH E2A terminology, any medically untoward event detected in a patient or clinical trial subject after investigational therapy, which may or may not be causally related to its use, was defined as an AE. An adverse reaction was any negative reaction associated with the study therapy.

Blood samples for immunogenicity analysis were taken before the first dose of NTK/placebo and then at Weeks 2, 12 and 24. Samples were analyzed using a validated enzyme-linked immunosorbent assay (ELISA). The immunogenicity endpoint was the proportion of patients with binding/neutralizing antibodies to the drug.

Sample size

The sample size was calculated using literature data on the clinical efficacy of ixekizumab in patients with active PsA [10]. The efficacy endpoint was the difference between groups in the frequency of ACR20 response at Week 24. As the assumed rates of such a response in the drug and placebo groups were 53% and 19%, respectively, a sample of 176 patients (88 in each group) provides 80% power for evidence of superiority with a preset boundary of 15% and a type I error of 2.5%. With an expected dropout rate of about 10%, the final sample size was 194 patients (97 participants in each group).

Statistical methods

The hypothesis of the study was superiority of the study drug over placebo in terms of the primary efficacy endpoint. The hypothesis was tested by calculating the 95% confidence interval (CI) for the difference in the frequency of ACR20 between the main and control groups. To confirm the correctness of the hypothesis, the lower limit of the calculated 95% CI for the ratio of the number of patients who achieved ACR20 had to exceed the preset limit of clinically insignificant differences, which was 15%.

The efficacy analysis was conducted in the intent-to-treat (ITT) population, which included all randomized patients. Data from placebo-treated patients who were switched to NTK after 16 weeks were processed according to the while-on-treatment strategy: the values obtained at Week 16 were used in the efficacy analysis at Weeks 20 and 24. Categorical data were compared using Fisher's exact test and Pearson's χ^2 test. Patients with missing data or those withdrawing from the study were regarded as non-responders (non-responder imputation). To compare quantitative data, Student's t-test and repeated measures ANOVA were used. Missing values were replaced using the multiple imputation method.

The safety analysis included all patients who received at least one dose of NTK or placebo. The proportions of patients with AEs, serious AEs (SAEs) associated and not associated with the study therapy, the proportion of patients with local reactions, and the proportion of patients withdrawn for safety reasons were assessed in each group. Safety data were analyzed using Fisher's exact test and Pearson's χ^2 test.

Results

Study population

The analyzed period (Weeks 0–24) lasted from July 2018 (the date of the first visit) to June 2019 (the date of the end of the analyzed period for the last participant). A total of 194 patients were randomized into two groups: NTK (n=97) and placebo (n=97); all participants received at least one dose of the study drug or placebo, 2 patients dropped out of the study early due to IC withdrawal and non-compliance (figure 1).

Baseline characteristics

The baseline demographic characteristics of patients and the baseline characteristics of the disease were comparable in the two groups. The average age of patients was 44 and 43 years in the NTK and placebo groups, respectively. Most of the participants were Caucasian. The mean duration of disease was similar. The groups were comparable in baseline disease activity, which was assessed by DAPSA and DAS28-CRP (4), as well as in previous therapy for PsA (Table 1). 85.6% of participants were receiving methotrexate at the time of signing the IC, and 20.1% of participants in the entire population reported prior treatment with tumor necrosis factor (TNF) inhibitors. Only 13 patients receiving placebo had an ACR20 response at Week 16. They continued to receive placebo until Week 24.

Primary efficacy endpoint

82.5% of patients from the NTK group and 9.3% of patients from the placebo group achieved ACR20 at Week 24. The 95% CI for the difference in rates of achieving ACR20 was [0.63;

0.84] (p <0.0001). The lower limit of the 95% CI is above the pre-specified superiority margin (δ=0.15). Thus, the superiority of NTK over placebo was confirmed.

Secondary efficacy endpoints

As early as in the first Week of treatment, a significant difference was noted between the NTK and placebo groups in respect of almost all efficacy parameters.

The proportion of patients who achieved ACR20 was significantly higher in the NTK group as early as at Week 1 (p= 0.0013). The ACR50 and ACR70 response rate was also significantly higher in patients treated with NTK compared with placebo, starting at Weeks 2 and 4, respectively, with maintaining superiority up to Week 24 (p <0.05) (fig. 2).

86.6% of patients in the NTK group and 28.9% of patients in the placebo group achieved a PsARC response at Week 24 (p<0.0001).

The NTK group was characterized by a significant decrease in disease activity according to DAS28-CRP(4) and DAPSA, as well as an improvement in functional status, as assessed by HAQ-DI, starting from Week 1. Mean changes in DAS28-CRP(4), DAPSA and HAQ-DI scores relative to the baseline were significantly different between the NTK and placebo groups at Week 24 and were –2.1 and –0.3; –22.7 and –3.8; –0.6 and –0.1, respectively (p<0.0001). 42.3% of patients in the NTK group and 1.0% in the placebo group (p<0.0001) met the criteria for minimal disease activity at Week 24.

On NTK therapy, a pronounced decrease in the intensity of axial symptoms was observed. The evaluation was performed in patients with inflammatory back pain at baseline. The mean change in ASDAS-CRP score at Week 24 was –1.6 and –0.1 for NTK and placebo, respectively (p <0.0001). Similar results were obtained for BASDAI, with a mean change at week 24 of –2.8 and –0.2, respectively (p <0.0001).

The majority of patients with baseline BSA ⩾3 experienced a decrease in the psoriasis area and severity over 24 weeks of NTK treatment. Significant differences between the treatment groups were observed as early as at Week 4. PASI75 response at Week 24 was recorded in 82.9% of patients in the NTK group and in 11.1% of patients in the placebo group (p <0.0001). The proportions of patients with PASI90 and PASI100 responses were significantly higher in the NTK group than in the placebo group (fig. 2). Among patients with nail psoriasis at baseline, a NAPSI score of 0 at Week 24 was noted in 31.5% of patients in the NTK group and in 5.3% of patients in the placebo group (p <0.0001).

At Week 24, the resolution of baseline enthesitis (LEI=0) was recorded significantly more frequently in patients treated with NTK than in patients treated with placebo (63.0 vs. 4.2%, p<0.0001), a significantly higher proportion of patients with the baseline LDI score >0 reached LDI =0 by the same time point (76.7 vs 9.7% in the NTK and placebo groups, respectively, p<0.0001) (Table 2).

Safety

The paper presents the results obtained during the blinded study period. Participants randomized to placebo, who did not achieve ACR20 at Week 16, were switched to active therapy and received the first dose of NTK at Week 18. The safety profile in these patients was assessed separately (hereinafter – placebo NTK group).

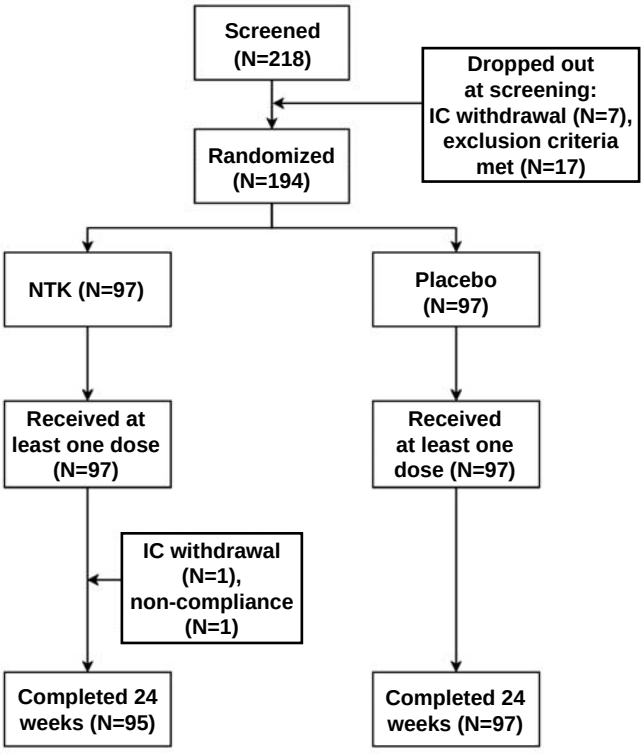

Figure 1. Patient disposition
Note: IC, informed consent; NTK, netakimab.

Table 1. Patient characteristics

Parameter	NTK (n=97)	Placebo (n=97)
Age, years, M±δ	44.0±11.7	43.1±11.9
Race, n (%)		
Caucasian*	96 (99)	96 (99)
Asian*	1 (1)	1 (1)
Males, n (%)	52 (53.6)	50 (51.6)
Disease duration, years, M±δ	5.3±6.1	5.7±6.5
BMI, kg/m^2, M±δ	28.5±5.4	27.7±5.4
DAPSA, M±δ	32.2±12.2	33.5±16.0
DAS28-CRP(4), M±δ	4.6±1.0	4.4±1.0
HAQ-DI, M±δ	1.2±0.6	1.2±0.6
TJC (66/68), M±δ	12.9±10.0	12.0±9.9
SJC (66/68), M±δ	7.0±4.9	7.2±7.2
BSA≥3%, n (%)	76 (78.4)	72 (74.2)
PASI*, M±δ	14.6±11.4	12.3±10.0
Dactylitis, n (%)	30 (30.9)	31 (32.0)
Enthesitis, n (%)	46 (47.2)	48 (49.5)
NAPSI, n (%)	73 (75.3)	76 (78.4)
Inflammatory back pain, n (%)	54 (55.7)	50 (51.5)
PsA treatment		
Current methotrexate treatment, n (%)	83 (85.6)	83 (85.6)
Duration of methotrexate use, years, M±δ	2.2±4.4	2.1±2.9
Current glucocorticoid treatment, n (%)	7 (7.2)	13 (13.4)
TNF inhibitor treatment, n (%)	22 (22.7)	17 (17.5)

Note: * patients with baseline BSA ≥3; BMI – body mass index; TJC – tender joint count; SJC – swollen joint count; TNF – tumor necrosis factor.

Over the analyzed period, no SAEs, cases of early withdrawal from the study for safety reasons, and local reactions were recorded. There were no deaths.

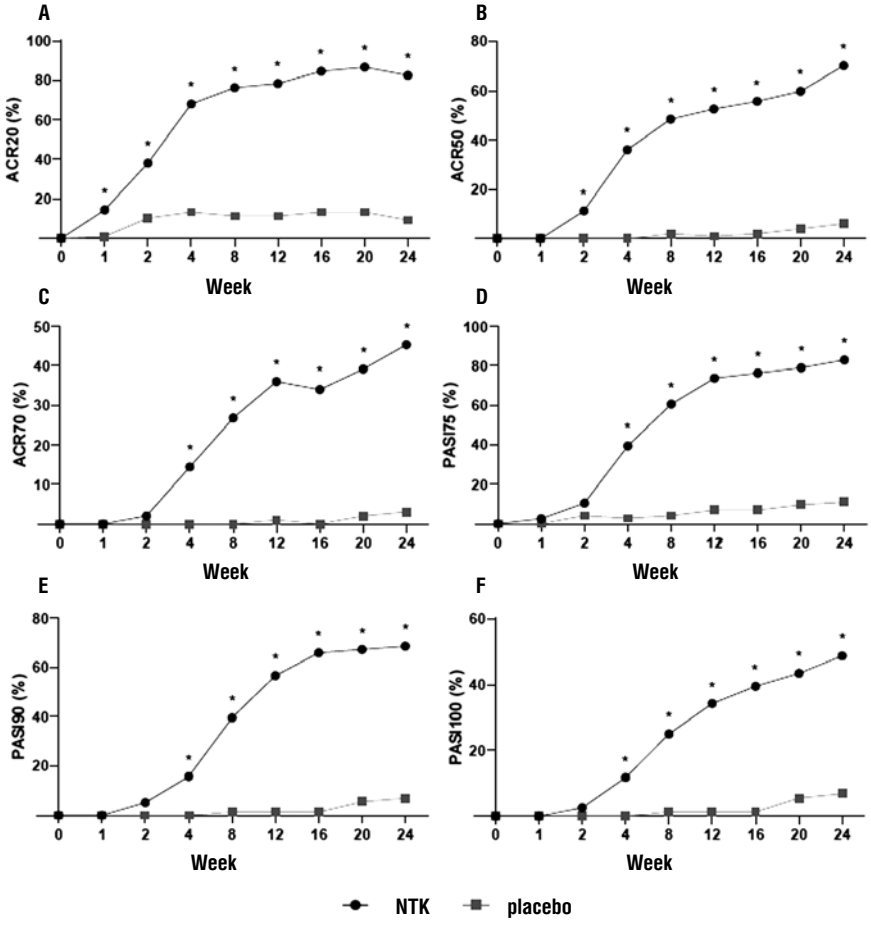

Figure 2. The therapy efficacy over 24 weeks of the study (efficacy parameter rates at different follow-up periods)
Note. * NTK versus placebo, p <0.05.

Table 2. Efficacy assessment at Week 24

Parameter	NTK (n=97)	Placebo (n=97)	p
Efficacy parameter rate, n (%)			
ACR20	80 (82.5)	9 (9.3)	<0.0001
ACR50	68 (70.1)	6 (6.2)	<0.0001
ACR70	44 (45.4)	3 (3.1)	<0.0001
PsARC	84 (86.6)	28 (28.9)	<0.0001
Minimal disease activity	41 (42.3)	1 (1.0)	<0.0001
PASI75 †	63 (82.9)	8 (11.1)	<0.0001
PASI90 †	52 (68.4)	5 (6.9)	<0.0001
PASI100 †	37 (48.7)	5 (6.9)	<0.0001
NAPSI 0 ‡	23 (31.5)	4 (5.3)	<0.0001
LEI 0 §	29 (63.0)	2 (4.2)	<0.0001
LDI 0 ¶	23 (76.7)	3 (9.7)	<0.0001
Change from the baseline values, M±δ			
DAS28-CRP(4)	-2.1±1.0	-0.3±0.9	<0.0001
HAQ-DI	-0.6±0.5	-0.1±0.5	<0.0001
DAPSA	-22.7±12.2	-3.8±11.8	<0.0001
PASI †	-87.5±32.8	-4.4±63.5	<0.0001
ASDAS-CRP ††	-1.6±1.1	-0.1±1.0	<0.0001
BASDAI ††	-2.8±2.2	-0.2±1.7	<0.0001

Note. † patients with baseline BSA score ≥3; ‡ patients with baseline NAPSI score >0; § patients with baseline LEI score >0; ¶ patients with baseline LDI score >0; †† patients with inflammatory back pain at baseline.

Safety analysis in the NTK and placebo groups (0–24 weeks)

In the NTK group, significantly more patients experienced at least one AE. The proportion of patients with AEs was 41.2% and 24.7% in the NTK and placebo groups, respectively (p=0.0146). Most AEs were mild to moderate. The most common AEs (reported in more than 3% of patients) were lymphopenia (grade 2–3), neutropenia (grade 2–3), hypercholesterolemia (grade 1–3), increased ALT levels (grade 1–2), infection (grade 1–2). A significant difference between the two groups was recorded only for the incidence of hypercholesterolemia. It was noted in 12.4% of patients from the NTK group and in 1.0% from the placebo group (p=0.0025). These differences appear to be due to significantly higher cholesterol levels at the baseline in patients randomized to the NTK group (p=0.0487). Infectious AEs were represented by two cases of grade 1–2 upper respiratory tract infections (one in each group) and one case of latent tuberculosis, confirmed by a positive T-SPOT.TB test, in the NTK group. The patient was prescribed isoniazid and pyrazinamide and continued the participation in the clinical study. Further follow-up did not reveal active tuberculosis infection.

The incidence of treatment-related AEs was comparable in both groups. At least one treatment-related AE was reported in 12.4% and 7.2% of participants treated with NTK and placebo, respectively. The most common of these were elevated ALT levels, infections, lymphopenia, and mild to moderate hyperbilirubinemia.

Treatment-related severe (grade 3) AEs were rare, with one case in the NTK group (increased blood pressure) and two cases (lymphopenia) in the placebo group.

Safety assessment in the placebo/NTK group

After switching to NTK (18–24 weeks), at least one AE was reported in 13.1% of patients from the placebo/NTK group. All AEs were unrelated to study therapy.

Most AEs were mild to moderate (grade 1–2). Isolated cases of severe AEs (grade 3) were presented by cases of periodontitis, angioedema and metrorrhagia. Angioedema and metrorrhagia required hospitalization and were SAEs not related to treatment. The most common AE was hypercholesterolemia (3.6%). Other AEs were reported in isolated cases (Table 3).

Table 3. Safety summary

Parameter	NTK (*n*=97)		Placebo (*n*=97)		Placebo/NTK (*n*=84)	
	n (%)	Frequency/100 patient-years	*n* (%)	Frequency/100 patient-years	*n* (%)	Frequency/100 patient-years
	0–24 weeks				**18–24 weeks**	
AEs*	40 (41.2)	90.1	24 (24.7)	53.1	11 (13.1)	112.7
Severe AEs	4 (4.1)	9.0	4 (4.1)	8.8	2 (2.4)	20.5
Treatment-related AEs	12 (12.4)	27.0	2 (7.2)	4.4	0	-
Severe treatment-related AEs	1 (1.0)	2.3	2 (2.1)	4.4	0	-
Treatment-related SAEs	0	-	0	-	0	-
Premature withdrawal from the study due to AE	0	-	0	-	0	-
	Most common AEs (≥3%)					
Lymphopenia	4 (4.1)	9.0	5 (5.2)	11.1	-	-
Neutropenia	6 (6.2)	13.5	2 (2.1)	4.4	-	-
Hypercholesterolemia*	12 (12.4)	27.0	1 (1.0)	2.2	-	-
Increased ALT	6 (6.2)	13.5	3 (3.1)	6.6	-	-
Infections	11 (11.3)	24.8	6 (6.2)	13.3	-	-
Systolic BP increased	4 (4.1)	9.0	1 (1.0)	2.2	-	-
Hyperglycemia	3 (3.1)	6.8	1 (1.0)	2.2	-	-
Hyperbilirubinemia	3 (3.1)	6.8	1 (1.0)	2.2	-	-
	Severe AEs					
Neutropenia (grade 3)	2 (2.1)	4.5	1 (1.0)	2.2	-	-
Lymphopenia (grade 3)	0		2 (2.1)	4.4	-	-
Increased BP (grade 3)	1 (1.0)	2.3	0	-	-	-
Hypercholesterolemia (grade 3)	1 (1.0)	2.3	0	-	-	-
Angiodema (grade 3)	-	-	-	-	1 (1.2)	10.2
Metrorrhagia (grade 3)	-	-	-	-	1 (1.2)	10.2
Periodontitis	-	-	-	-	1 (1.2)	10.2
	Treatment-related AEs					
Neutropenia (grade 2)	1 (1.0)	2.3	1 (1.0)	2.2	-	-
Leucopenia (grade 2)	1 (1.0)	2.3	1 (1.0)	2.2	-	-
Lymphopenia (grade 2–3)	2 (2.1)	4.5	3 (3.1)	6.6	-	-
Lymphocytosis (grade 2)	1 (1.0)	2.3	0		-	-
Infections (grade 2)	2 (2.1)	4.5	1 (1.0)	2.2	-	-
Hyperbilirubinemia (grades 1–2)	3 (3.1)	6.8	0		-	-
Increased AST (grades 1–2)	1 (1.0)	2.3	1 (1.0)	2.2	-	-
Increased ALT (grades 1–2)	3 (3.1)	6.8	2 (2.1)	4.4	-	-
Hypercholesterolemia (grade 2)	1 (1.0)	2.3	0	-	-	-
Increased BP (grade 3)	1 (1.0)	2.3	0	-	-	-
Systolic BP increased (grade 2)	1 (1.0)	2.3	0	-	-	-
Diastolic BP increased (grade 2)	1 (1.0)	2.3	0	-	-	-

Note: * $p<0.05$, NTK versus placebo. AE – adverse event; SAE – serious adverse event, ALT – alanine aminotransferase, AST – aspartate aminotransferase, BP – blood pressure.

Immunogenicity

The immunogenicity analysis included 96 patients in the NTK group and 97 in the placebo group. Anti-drug antibodies were not detected.

Discussion

The main period of the PATERA study was conducted to assess the efficacy and safety of NTK versus placebo in patients with PsA.

The findings indicate the superiority of NTK over placebo and confirm that inhibition of the IL-17 signaling pathway by NTK leads to a significant decrease in PsA activity. Thus, during the 24 Weeks of the PATERA study, a significant reduction in arthritis symptoms was observed with NTK. A pronounced improvement in the skin condition and a decrease in the intensity of axial symptoms in patients treated with NTK were demonstrated. In addition, in the NTK group, a significant proportion of study participants who had nail lesions, dactylitis and enthesitis at baseline, achieved zero NAPSI, LDI and LEI scores at Week 24. For most efficacy endpoints, the response to treatment was observed as early as at Week 1.

In the NTK group, the ACR20 response rate at Week 24 was 82.5%, which is 20–30% higher than that in the studies of secukinumab and ixekizumab. The ACR20 response rate with IL-17 inhibitors at Week 24 in patients with PsA varies from

42.0% to 62.1%, depending on the dose and treatment regimen [10–14].

The PATERA study population mainly consisted of bDMARDs-naive patients. About 80% of patients included in the study were anti-TNF-naive. In addition, the patients had a short duration of the disease. Thus, it can be assumed that the early initiation of NTK as the first bDMARD in PsA results in a significant improvement in the condition of patients.

It is necessary to separately discuss the effect of NTK on the axial symptoms. The presence of inflammatory back pain is associated with high disease activity and severe skin lesions [15]. The baseline characteristics of PsA in patients enrolled in the PATERA study confirm the literature data on the prevalence of axial symptoms in this disease. Thus, the proportion of patients with clinical manifestations of spondylitis at the baseline was approximately 50%. According to the current guidelines for the treatment of PsA, bDMARDs are indicated to patients with axial symptoms and failure of NSAIDs. The drugs of choice are IL-17A inhibitors [16]. Despite the fact that axial symptoms in PsA are quite common, there is limited data on the effect of bDMARDs on these manifestations in clinical studies in PsA.

By Week 24, a decrease in the BASDAI and ASDAS-CRP in the NTK group was −2.8 and −1.6 points, respectively, while in the placebo group, there were virtually no changes in these parameters over time. Thus, NTK provided a significant reduction in inflammatory back pain and may become the drug of choice for patients with axial symptoms, i.e. in a significant part of patients with PsA.

The patients tolerated NTK well. Its safety profile in patients with PsA was consistent with that in previous clinical studies of NTK in plaque psoriasis and ankylosing spondylitis [5, 7]. The most frequent treatment-related AEs were expected and consistent with frequent AEs for other IL-17 inhibitors: increased ALT levels, infections, lymphopenia. Also, cases of upper respiratory tract infections were previously reported with secukinumab and ixekizumab [10, 11, 13, 14, 17].

During the analyzed period of the PATERA study, infectious AEs were represented by mild to moderate upper respiratory tract infections and one case of a positive test for tuberculosis (T-SPOT.TB test), which was interpreted as latent tuberculosis. For ixekizumab or secukinumab, no cases of latent tuberculosis have been reported; however, there have been AEs of positive TB test results [17]. When discussing a case of latent TB, several factors should be taken into account. Tuberculosis is currently widespread in the Russian Federation [18]. Despite a decrease in the overall incidence of tuberculosis over the past decade, the observed annual incidence rate is about 35%. The published data describe both an increased risk of tuberculosis reactivation in patients treated with bDMARDs and a risk of false-negative diagnostic results at screening due to previous long-term immunosuppressive therapy.

Thus, NTK showed a favorable safety profile. Most cases of AEs were mild to moderate. In combination with low immunogenicity and high efficacy, the good tolerability of the drug suggests long-term treatment adherence and, accordingly, no need to change the bDMARD.

Conclusions

In patients with PsA, NTK demonstrates a high clinical response rate as early as in the first weeks of treatment and a favorable safety profile. The study is ongoing. Follow-up is aimed at obtaining data on the long-term efficacy and safety of NTK.

Additional information

A.V. Eremeeva, M.A. Morozova are employees of JSC BIOCAD.

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Conflicts of interest

T.V. Korotaeva received grants from pharmaceutical companies Pfizer LLC, JSC Biocad, Janssen, pharmaceutical division of Johnson & Johnson LLC, USB Pharma LLC, AbbVe LLC, Novartis Pharma LLC, Lilly Pharma LLC.

V.I. Mazurov, A.M. Lila, I.Z. Gaydukova, A.L. Bakulev, A.V. Samtsov, V.R. Khairutdinov declare no conflicts of interest to disclose, related to this article.

A.V. Eremeeva, M.A. Morozova are employees of JSC BIOCAD.

Study transparency

The study was sponsored by JSC BIOCAD. The authors did not receive any funding for this study. The authors are solely responsible for submitting the final version of the manuscript to print. The results of the study were presented as orally at the meeting of the European League Against Rheumatism (e-EULAR 2020), June 3-6, Frankfurt, Germany.

Declaration of financial and other relationships

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