ORIGINAL INVESTIGATIONS

Effectiveness and safety of levilimab in combination with methotrexate in treatment of patients with active rheumatoid arthritis resistant to methotrexate monotherapy (double-blinded randomized placebo controlled phase III clinical study SOLAR)

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Levilimab is anti-interleukin-6 receptor (IL6R) monoclonal antibody. The article presents data obtained during 24 weeks of the SOLAR phase III study.

Objective: *to confirm efficacy and safety of levilimab in combination with methotrexate (MTX) in patients with methotrexate resistant active rheumatoid arthritis (RA).*

Patients and methods. *154 adult patients, aged ⩾18 years with the diagnosis of RA (ACR/EULAR 2010) and confirmed disease activity at screening despite treatment with MTX for at least 12 weeks (in a stable dose 15-25 mg/week). Patients were randomized 2:1 in levilimab (162 mg once a week, subcutaneously) + MTX (n=102) or placebo + MTX (n=52) group.*

The hypothesis of superiority of levilimab over placebo was tested for two co-primary efficacy endpoints: proportion of subjects who achieved ACR20 at week 12 and proportion of subjects who achieved low disease activity (LDA) of RA (DAS28-CRP <3.2) at week 24. Safety was assessed through monitoring of adverse events (AEs).

Results and discussion. *Seventy (68.6%) subjects who received levilimab and 20 (38.5%) who received placebo achieved ACR20 response at week 12. Fifty three (52%) subjects who received levilimab and 3 (5,8%) subjects who received placebo achieved LDA at week 24. The most common adverse events (reported in ⩾5% of subjects) in levilimab and placebo arms, respectively were (by decreasing frequency): blood c holesterol increase (24% vs 12%), alanine aminotransferase elevation (11% vs 8%), lymphocyte count decrease (9% vs 8%), blood total*

bilirubin increase (11% vs 0%), blood triglycerides increase (10% vs 2%), aspartate aminotransferase elevation (7% vs 4%), positive interferon-gamma release assay (IGRA) with M.tuberculosis antigen blood test (5% vs 6%), absolute neutrophil count decrease (8% vs 0%). No deaths were occurred.

Conclusion. *The study confirmed superior efficacy of levilimab + MTX over placebo + MTX in subjects with MTX resistant active RA. Levilimab showed favorable safety profile and low immunogenicity. No new important safety risks were detected.*

Keywords: *levilimab; monoclonal anti-IL-6 receptor antibody; rheumatoid arthritis.*

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Rheumatoid arthritis (RA) is an immune-mediated inflammatory (autoimmune) rheumatoid disease of unknown origin, associated with chronic erosive arthritis and systemic involvement of internal organs. The disease leads to early disability and a decrease in life expectancy [1, 2]. On average, the prevalence of RA in the world is 51 cases per 10,000 population [3]. Despite the advances in the treatment of RA, a significant number of patients receiving treatment according to current clinical practice guidelines still experience main manifestations of the disease, develop primary drug resistance, or adverse events (AEs) that require therapy discontinuation [4].

Levilimab is an originator belonging to anti-interleukin-6 receptor (IL-6R) monoclonal antibodies. A recent phase II clinical trial (CT) AURORA evaluated the pharmacokinetics, pharmacodynamics, efficacy and safety of levilimab following repeated-dose administration in patients with active RA. Subcutaneous (SC) levilimab 162 mg QW or Q2W has been shown to effectively suppress immune inflammation, have superior clinical efficacy over placebo and a favorable safety profile in MTX-resistant active RA [5]. This article presents the results of the main 24-week double-blind period of the phase III CT SOLAR.

Objective. The study aimed to confirm the efficacy and safety of levilimab in combination with MTX in patients with MTX-resistant active RA.

Patients and methods. SOLAR is an international multicenter comparative randomized double-blind placebo-controlled phase III CT (ClinicalTrials.gov NCT04227366) conducted in compliance with the Declaration of Helsinki of the World Medical Association and the Good Clinical Practice (GCP) in 19 centers in the Russian Federation and 2 centers in the Republic of Belarus.

Eligibility criteria and study design. Males and females aged 18 years and older diagnosed with RA at least 24 weeks before inclusion, who met the ACR/EULAR criteria (American College of Rheumatology/European Alliance of Associations for Rheumatology) 2010 [6], with persisting disease activity for 12 weeks despite MTX monotherapy at a stable dose of 15–25 mg/week for ⩾4 weeks were eligible. Patients with Felty's syndrome and ACR functional class IV (1991) [7], who had significant comorbidity, previously treated with IL-6/IL-6R inhibitors and prednisolone at a dose >10 mg/day, Janus kinase inhibitors, anti-B-cell drugs, leflunomide and tumor necrosis factor-p inhibitors within the last 8 weeks and alkylating agents within the last 12 months before the enrollment were not eligible.

The study design included a screening period (4–6 weeks), a double-blind, placebo-controlled main period (24 weeks), and a follow-up period (weeks 25–56), during which all patients received open-label levilimab. At the time of preparing the manuscript, the main study period was completed, while the follow-up period was ongoing.

Within the screening period, patients received MTX provided by the sponsor, then, if RA activity persisted, they were randomized in a 2:1 ratio to receive either levilimab 162 mg/week SC in combination with MTX or placebo in combination with MTX. A centralized computer system was used to randomize and assign the investigational product (IP). IP was administered at the trial site during the visits (once every 4 weeks) and self-administered by patients between visits.

During the study, patients could continue the use of glucocorticoids (GCs) at a dose of ⩽10 mg/day, as well as non-steroidal anti-inflammatory drugs (NSAIDs) if their dose was stable for ⩾4 weeks. Starting treatment with GCs, disease-modifying antirheumatic drugs (DMARDs), except for MTX, as well as increasing the dose of GCs and NSAIDs during the study was not allowed.

For ethical reasons, patients who did not achieve a ⩾20% reduction in tender/swollen joint count (66/68) at week 12 of treatment received rescue therapy at the discretion of the investigator. A course of GCs, or DMARDs, or NSAIDs were used as rescue therapy. If rescue therapy was used at week 12, all subsequent efficacy assessments for this patient were considered missing.

Assessment parameters. The efficacy, safety, and immunogenicity of levilimab were evaluated over 24 weeks of the main double-blind study period.

Efficacy parameters. The study used two co-primary endpoints:

- proportion of patients who achieved 20% improvement in RA symptoms according to the ACR criteria (ACR20) [8] at week 12
- proportion of patients with low disease activity (LDA) of RA according to the disease activity score for 28 joints (DAS28-CRP <3.2) [9] at week 24

Secondary endpoints:

- proportion of patients with moderate and good response according to the EULAR criteria [10]
- proportion of patients with RA LDA and remission, changes in RA activity according to DAS28, CDAI (Clinical Disease Activity Index), SDAI (Simplified Disease Activity Index) [9]
- changes in ESR and CRP levels relative to baseline values
- changes over time in radiographic joint destruction according to van der Heijde modified total Sharp score (mTSS) [11].

Safety parameters. The safety assessment included vital signs, complete blood count and blood chemistry tests, urinalysis, elec-

trocardiogram, interferon-γ release assay (IGRA) with *M. tuberculosis* antigen, chest radiograph. AE were reported according to CTCAE v. 5.0 (Common Terminology Criteria for Adverse Events). Reported AEs were encoded in accordance with the MedDRA v. 23.1 (Medical Dictionary for Regulatory Activities). Considering the terminology adopted in the ICH E2A (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use), an AE was defined as is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse reaction was defined as an AE related to the study therapy.

Immunogenicity. This parameter was assessed using a validated immunoassay based on the results of a test for binding and, if any, neutralizing anti-drug antibodies at weeks 4, 12 and 24.

At week 24 of the study, after assessing the efficacy, safety and immunogenicity, patients proceeded to the follow-up period and started open-label treatment with levilimab QW without placebo.

Statistical analysis. *Sample size*. The sample size was calculated based on efficacy data for levilimab from the phase II CT AURORA [5] and literature data on the efficacy of biologics with a similar mechanism of action [12, 13]. Based on the expected effect size of 42% for the ACR20 at week 12 and 38% for the DAS28-CRP <3.2 at week 24, the sample size required to provide an 80% statistical power was 52 (26:26) and 62 (31:31) patients, respectively. Thus, to test the hypothesis of superiority for both primary efficacy endpoints, the minimum number of patients in each treatment arm was 31. To ensure sufficient data to assess the safety and exposure required for this, the number of patients in the levilimab arm was increased to 100: it was planned to randomize at least 150 (100:50) patients in levilimab and placebo arms.

Analysis of study data was performed using the SAS v. 9.4 (SAS Institute Inc., Cary, NC, USA).

The main efficacy population was the population of all randomized patients (intention-to-treat, ITT). To replace missing data, we used "non-responder imputation" methods for frequency variables and "baseline observation carried forward" for quantitative variables.

To determine the sensitivity of results to significant study protocol deviations and violations, analysis by primary endpoints was also carried out in the population of patients who completed 24 weeks of the study as per protocol (PP).

The safety population included patients who received at least one IP injection.

The superiority hypothesis was tested using the Pearson's chi-squared test and a one-sided 97.5% confidence interval (CI) according to Wilson's method, applying a continuity correction separately for each of the primary endpoints. To demonstrate the superiority of levilimab over placebo, the lower CI bounds for the difference in proportions between the arms had to be above zero (ε>0) for both primary endpoints.

To compare treatment arms in terms of frequency parameters, the Pearson chi-squared test and Fisher's exact test were used. Parametric (Student's test) and nonparametric (Mann–Whitney test) statistics were used to compare treatment arms in terms of parameters corresponding to quantitative variables. Two-sided hypotheses were tested with a significance level of p=0.05 in all statistical tests, except for the primary efficacy assessment.

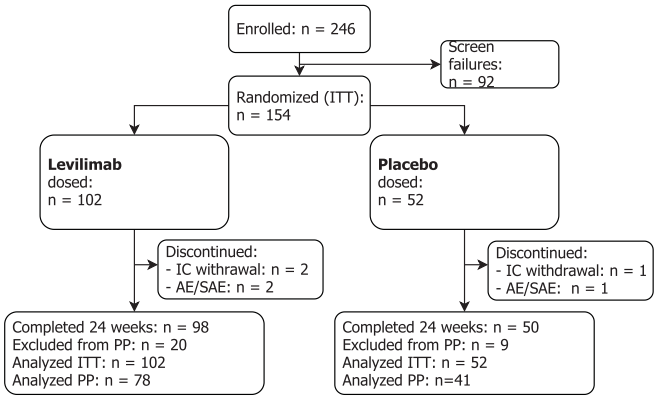

Figure 1. *Distribution of patients by treatment arms. SAE – serious AE; IC – informed consent*

Results

Baseline characteristics. The main period of the study was conducted between November 2019 and January 2021. A total of 246 patients were included in the screening, of which 154 were randomized to receive either levilimab (n=102) or placebo (n=52). All randomized patients received at least one IP injection. Of these, 148 completed the main study period (Fig. 1). 2 (2.0%) patients from the levilimab arm and 1 (1.9%) from the placebo arm withdrew from the study due to AEs. In addition, 2 (2.0%) patients from the levilimab arm and 1 (1.9%) patient from the placebo arm withdrew their consent to participate in the study.

Table 1. Clinical characteristics of patients in the levilimab and placebo arms

Parameter	Levilimab (n=102)	Placebo (n=52)
Demographic characteristics:		
age, years, M ± σ	51.8 ± 10.5	49.7 ± 13.4
females, n (%)	77 (75.5)	34 (65.4)
BMI, kg/m^2, M ± σ	26.9 ± 5.0	26.0 ± 4.6
Baseline characteristics of RA:		
duration of RA, years, M ± σ	7.1 ± 6.7	5.6 ± 4.7
RF seropositivity, n (%)	93 (91.2)	44 (84.6)
ACCPA seropositivity, n (%)	92 (90.2)	46 (88.5)
ESR, mm/h, M ± σ	42.9 ± 20.2	47.4 ± 22.4
C-reactive protein, mg/L, M ± σ	30.9 ± 24.3	39.8 ± 35.4
DAS28-CRP, M ± σ	6.2 ± 0.65	6.3 ± 0.78
DAS28-ESR, M ± σ	6.6 ± 0.72	6.7 ± 0.84
CDAI, M ± σ	39.5 ± 8.7	41.6 ± 10.2
SDAI, M ± σ	42.6 ± 9.0	45.6 ± 11.4
Prior RA treatment:		
NSAIDs, n (%)	89 (87.3)	42 (80.8)
GCs, n (%)	53 (52.0)	30 (57.7)
MTX, n (%)	102 (100)	52 (100)
MTX dose, mg, M ± σ	16.3 ± 2.5	16.7 ± 3.3
csDMARDs, n (%)	19 (18.6)	10 (19.2)
bDMARDs, n (%)	3 (2.9)	2 (3.8)
Questionnaires:		
HAQ-DI, M ± σ	1.6 ± 0.61	1.6 ± 0.65
EQ-5D-3L, M ± σ	0.6 ± 0.2	0.6 ± 0.2
Radiographic features of RA:		
Total mTSS score, M ± σ	118.6 ± 64.1	109.4 ± 51.5

Note. RF – rheumatoid factor; ACCPA – anti-cyclic citrullinated peptide antibodies; BMI – body mass index; csDMARD – conventional synthetic disease-modifying antirheumatic drugs; bDMARDs – biological disease-modifying antirheumatic drugs.

Rescue therapy at week 12 was administered to 9 (8.8%) patients in the levilimab arm and in 9 (17.3%) in the placebo arm.

The study arms were comparable in terms of the main demographic, anthropometric characteristics, and clinical manifesta-

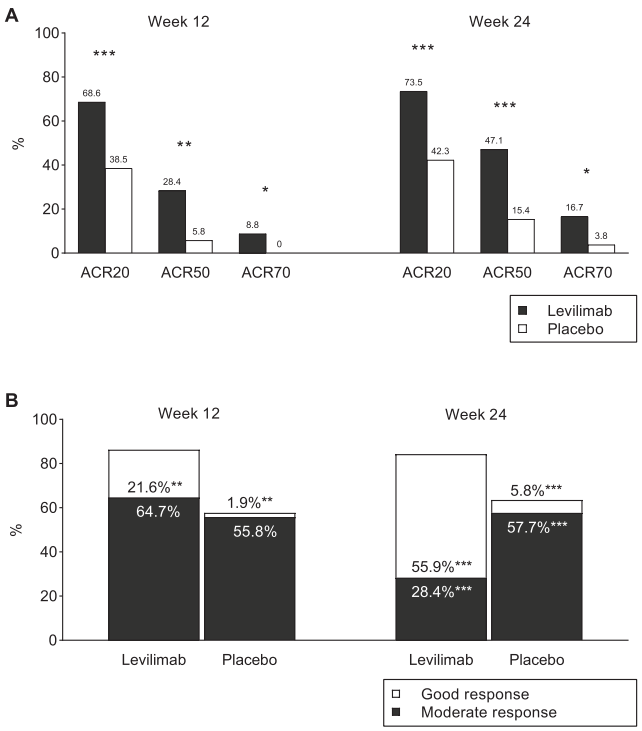

Figure 2. *Efficacy endpoints: ACR20, ACR50 and ACR70 response rates(A); proportion of patients with a moderate and good response according to the EULAR criteria (B). * – p<0.05, ** – p<0.01, *** – p<0.001. Comparisons are shown for patients with a satisfactory and good response to therapy between the levilimab and placebo arms at weeks 12 and 24*

Table 2. Treatment efficacy rates in patients of levilimab and placebo arms, n (%)

Parameter (time point)	Levilimab (n=102)	Placebo (n=52)	p-value
Low RA activity according to DAS28-CRP (<3.2):			
Week 12	21 (20.6)	1 (1.9)	**0.0017***
Week 24	53 (52.0)	3 (5.8)	**<0.0001***
Low RA activity according to DAS28-ESR (<3.2):			
Week 12	41 (40.2)	1 (1.9)	**<0.0001***
Week 24	62 (60.8)	2 (3.8)	**<0.0001***
Low RA activity according to CDAI (≤10):			
Week 12	16 (15.7)	2 (3.8)	**0.0306***
Week 24	36 (35.3)	3 (5.8)	**0.0001***
Low RA activity according to SDAI (≤11):			
Week 12	16 (15.7)	3 (5.8)	0.0768*
Week 24	45 (44.1)	4 (7.7)	**<0.0001***
RA remission according to DAS28-CRP (4) (<2.6):			
Week 12	14 (13.7)	0	**0.0027**[#]
Week 24	23 (22.5)	1 (1.9)	**0.0008***
RA remission according to DAS28-ESR (4) (<2.6):			
Week 12	21 (20.6)	0	**0.0004***
Week 24	43 (42.2)	0	**<0.0001***
RA remission according to CDAI (≤2.8):			
Week 12	6 (5.9)	0	0.0972[#]
Week 24	7 (6.9)	0	0.0960[#]
RA remission according to SDAI (≤3.3):			
Week 12	5 (4.9)	0	0.1679[#]
Week 24	10 (9.8)	0	**0.0167**[#]
RA remission based on ACR/EULAR (2011):			
Week 12	3 (2.9)	0	0.5513[#]
Week 24	7 (6.9)	0	0.0960[#]

* Pearson's chi-squared test; [#] Fisher's exact test.

tions of RA, as well as the comorbidity profile and concomitant medications (Table 1).

Efficacy assessment. Primary efficacy analysis showed superiority of levilimab over placebo for both co-primary endpoints. The superiority for the proportion of patients who achieved ACR20 at week 12 was 30.1% (lower limit of 97.5% CI: 12.5%; p=0.0003; Fig. 2, a).

The superiority for the proportion of patients who achieved RA LDA (DAS28-CRP<3.2) at Week 24 was 46.2% (lower limit of 97.5% CI: 31.2%; p<0.0001; Table 2). The analysis of PP population yielded similar results.

The frequency of achieving 20, 50 and 70% improvement in RA symptoms based on the ACR20/50/70 criteria was significantly higher in the levilimab arm compared with the placebo arm (p<0.05) both at treatment weeks 12 and 24 (see Fig. 2, a). The same was true for the frequency of achieving LDA, which varied depending on the indices used to assess RA activity. Thus, at week 24, LDA rates were 35.3 and 60.8% according to the CDAI and DAS28-ESR criteria, respectively. In the placebo arm, LDA at week 24 was observed in only 3.8% of patients using DAS28-ESR and 7.7% using SDAI (see Table 2).

RA remission rates also varied depending on the RA activity index used. Thus, in the levilimab arm at week 24, RA remission based on CDAI and ACR/EULAR (2011) was reported in 6.9% of cases, while being reported in 42.2% with DAS28-ESR index. In the placebo arm, RA remission was reported in only 1 patient and only based on DAS28-ESR (see Table 2).

In the levilimab arm at week 12 of treatment, 64.7% of patients achieved moderate response to therapy based on the EULAR criteria. At week 24, their number decreased to 55.9% due to the transition to the category of those who achieved good response (see Fig. 2, *b*). In the placebo arm, moderate response rate at weeks 12 and 24 was 55.8 and 57.8% of cases, respectively, while there was no significant increase in the proportion of patients with good response (1.9% at weeks 12 and 5.8% at week 24).

Analysis of RA activity and inflammation markers at weeks 12 and 24 showed a significantly more pronounced (p<0.05) decrease in the levilimab arm compared with the placebo arm (Fig. 3).

In the levilimab arm, there was a decrease in the severity of functional impairment according to the HAQ-DI (Health Assessment Questionnaire-Disability Index) questionnaire over 24 weeks. However, the maximum improvement in HAQ-DI was achieved at week 24 (-0.5±0.5). In the placebo arm, changes over time in this parameter at week 24 were less prominent (-0.3±0.5). At this point in the study, the differences between the arms reached statistical significance (p=0.0275).

Assessment of the quality of life (QoL) in both arms showed an increase in the EQ-5D-3L score, which corresponded to an improvement in QoL. Moreover, QoL was significantly higher in the levilimab arm vs. the placebo arm both at week 12 (0.8±0.1 and 0.7±0.2, respectively; p=0.0025) and week 24 (0.8±0.1 and 0.7±0.2, respectively; p=0.0152).

The results of assessing changes over time in structural joint damage in patients of the compared arms are presented in Table 3.

Safety assessment. AEs were reported in 68 (66.7%) patients in the levilimab arm and in 28 (53.8%) patients in the placebo arm (Table 4). The most common AEs (observed in ⩾5% of

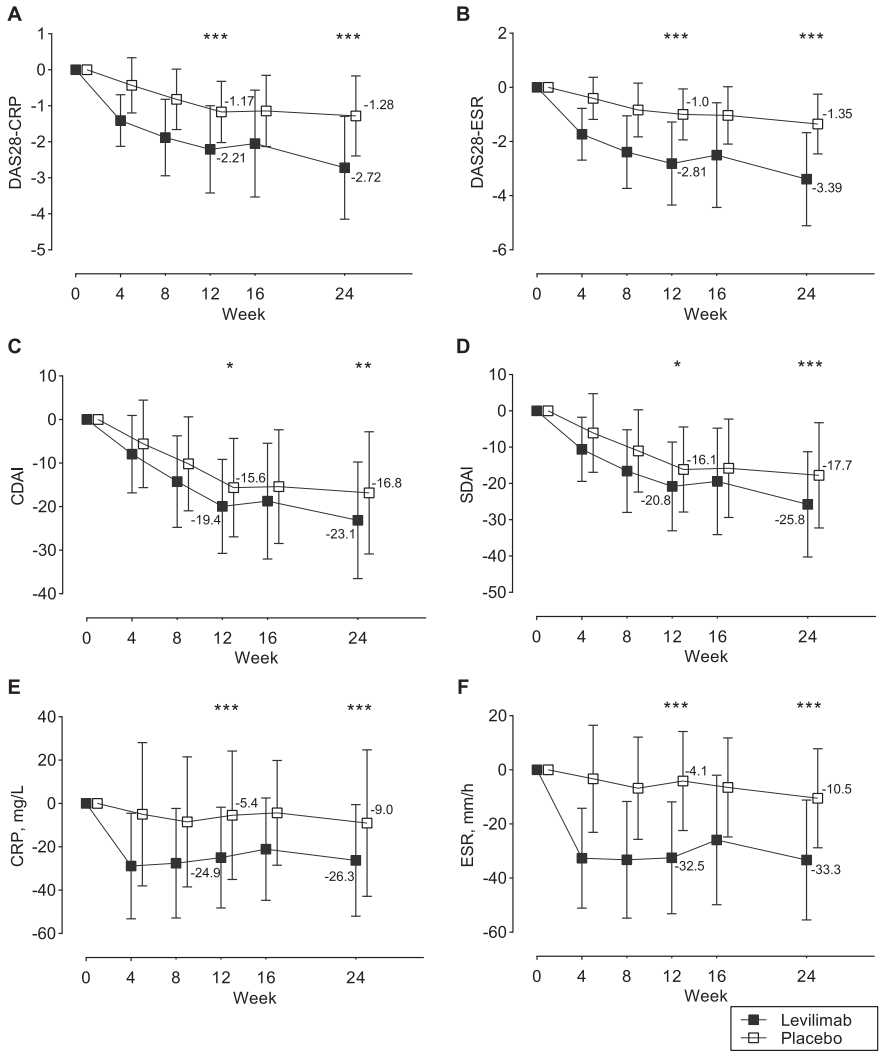

Figure 3. *Dynamics of RA activity indices and inflammation markers: DAS28-CRP (A), DAS28-ESR (B), CDAI (C), SDAI (D), CRP (E), ESR (F)* – p<0.05; ** – p<0.01; *** – p<0.001*

patients) in both arms were laboratory abnormalities (58.8 and 40.4%), as well as infections/infestations (6.9 and 11.5%) and injection site reactions (7.8 and 1.9%).

In the levilimab arm vs. the placebo arm, AEs specific for IL-6R inhibitors and grade 3–4 AEs were reported with higher frequencies (p<0.05). The latter were mainly represented by laboratory abnormalities: increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST), cholesterol/triglycerides, and serum bilirubin. There were no cases of severe leukopenia/neutropenia.

Table 3. Radiological indicators of structural joint damage in patients of the levilimab and placebo arms at 24 weeks compared to baseline, according to the Sharp's method (van der Heijde modification) (mTSS)

Parameter	Levilimab	Placebo	p-value*
Erosions, M ± σ	0.1 ± 0.6	0.2 ± 0.7	0.6114
Joint space narrowing, M ± σ	0.1 ± 0.8	0.2 ± 1.0	1.0000
Total mTSS, M ± σ	0.2 ± 1.4	0.3 ± 1.6	0.8039
Proportion of patients without worsening of structural joint changes, n (%):			
Erosions	84 (82.4)	38 (73.1)	0.1797
Joint space narrowing	84 (82.4)	39 (75.0)	0.2818
Total mTSS	83 (81.4)	38 (73.1)	0.2354

* Pearson's chi-squared test.

One SAE case was reported in each arm. In the levilimab arm, 1 patient was diagnosed with vertebral disk protrusion (grade 3), which required hospitalization. In the opinion of the investigator, this SAE was not related to the therapy, the patient continued to participate in the study. In the placebo arm, 1 patient was diagnosed with a renal cancer (grade 3), which was regarded by the investigator as an AE related to bDMARD (as assessed in a double-blind period). This patient was referred for an examination and treatment to a specialized hospital and was withdrawn from the study.

Along with this, 2 patients from the levilimab arm were prematurely withdrawn from the study due to grade 2 hyperemia at the injection site.

No cases of death were reported during the main study period.

Table 4 shows overall safety data and a list of the most common and severe (grade 3–4) AEs.

Laboratory findings

Complete blood count. The increase in blood hemoglobin level was observed in patients of the levilimab arm: the mean values were 124±13.7 g/L at baseline, reaching 135 ± 13.9 and 136±13.3 g/L at weeks 12 and 24, respectively. No improvement was observed in the placebo arm (Fig. 4, a). In addition, 4 (7.7%) patients from this arm had anemia (grade 1–2), while there were no cases of anemia in the levilimab arm.

A decreased lymphocyte count was observed in 9 (8.8%) patients in the levilimab arm and in 4 (7.7%) patients in the placebo arm. A decreased neutrophil count was detected only in the levilimab arm (7.8%, see Table 4). All cases of decreased lymphocyte and neutrophil counts were of grade 2.

Decreased white blood cell (WBC), lymphocyte, and neutrophil counts in the levilimab arm occurred within the first 4 weeks of therapy, further these parameters did not change significantly until the end of the analyzed period (see Fig. 4, b, c).

Blood chemistry. Increased ALT was reported in 11 (10.8%) patients in the levilimab arm and in 4 (7.7%) patients in the placebo arm. Increase in ALT level reached grade 3 in 5 (4.9%) patients of the levilimab arm. A similar pattern was observed for the AST level (see Table 4, Fig. 4, d).

Eleven (10.8%) patients in the levilimab arm had increased blood bilirubin, with 2 of them having grade 3 increase (see Table 4, Fig. 4, e). There was no increase in total bilirubin in the placebo arm (p<0.05).

Increased blood cholesterol levels were observed in 24 (23.5%) patients in the levilimab arm and 6 (11.5%) in the placebo arm. Most of the cases were grade 2. Grade 3–4 increased cholesterol was reported in isolated cases in patients of the levilimab arm (see Table 4, Fig. 4, f). Increases in blood triglyceride

Table 4. General data on the frequency and nature of AEs in patients of the levilimab and placebo arms, n (%)

Parameter	Levilimab (n=102)	Placebo (n=52)	p-value
Proportion of patients with AEs (including SAEs)	68 (66.7)	28 (53.8)	0.1205*
Proportion of patients with SAEs, *including:*	1 (1.0)	1 (1.9)	1.0000#
grade 3 renal cancer	0	1 (1.9)	0.3377#
grade 3 vertebral disk protrusion	1 (1.0)	0	1.0000#
Proportion of patients with grade 3–4 AEs (CTCAE v.5.0)	15 (14.7)	1 (1.9)	**0.0139***
Proportion of patients with grade 3–4 neutropenia (CTCAE v.5.0)	0	0	1.0000#
Proportion of patients with AEs specific for IL-6R inhibitors in each arm	49 (48.0)	15 (28.8)	**0.0223***
Proportion of patients who were prematurely withdrawn from the study due to AEs/SAEs *including:*	2 (2.0)	1 (1.9)	1.0000#
injection site reaction (grade 2)	2 (2.0)	0	0.5498#
renal cancer (grade 3)	0	1 (1.9)	0.3377#
Proportion of patients with injection site reactions	7 (6.9)	0	0.0960#
Proportion of patients with AEs reported in ≥5% patients			
Increased blood cholesterol *including:*	24 (23.5)	6 (11.5)	0.0756*
Grade 3	1 (1.0)	0	1.0000#
Grade 4	1 (1.0)	0	1.0000#
increased ALT *including:*	11 (10.8)	4 (7.7)	0.5405*
Grade 3	5 (4.9)	0	0.1679#
Decreased lymphocyte count	9 (8.8)	4 (7.7)	1.0000#
Increased blood bilirubin, *including:*	11 (10.8)	0	**0.0163#**
Grade 3	2 (2.0)	0	0.5498#
Increased blood triglycerides, *including:*	10 (9.8)	1 (1.9)	0.0998#
Grade 3	2 (2.0)	0	0.5498#
Grade 4	1 (1.0)	0	1.0000#
Increased AST, *including:*	7 (6.9)	2 (3.8)	0.7187#
Grade 3	2 (2.0)	0	0.5498#
Positive interferon gamma release assay	5 (4.9)	3 (5.8)	1.0000#
Decreased neutrophil count	8 (7.8)	0	0.0519#

* Pearson's chi-squared test; # Fisher's exact test.

levels were also more common in the levilimab arm (9.8%) vs. the placebo arm (1.9%; see Table 4).

It should be noted that AEs related to complete blood count and blood chemistry abnormalities did not require exclusion of patients from the study in any case, and in majority of cases did not require treatment discontinuation or interruption and resolved without sequelae.

Infections and infestations

Tuberculosis. Screening for tuberculosis (TB) at week 24 showed no differences between the arms in the frequency of positive results: the IGRA with M. tuberculosis antigen was positive in 8 (7.8%) patients in the levilimab arm and in 5 (9.6%) in the placebo arm.

The IGRA was positive with the absence of TB signs on a chest radiograph in 5 (4.9%) patients in the levilimab arm and 3 (5.8%) in the placebo arm. The latent TB was diagnosed in 2 (2.0%) patients in the levilimab arm and 2 (3.8%) in the placebo arm, whose IGRA was positive in the absence of TB signs on a chest radiograph. One patient from the levilimab arm with a positive IGRA had signs of pulmonary TB on chest scans and, therefore, he was excluded from the study in the open-label period after Week 24.

Infections. During the study, 2 (2.0%) patients in the levilimab arm and 1 (1.9%) in the placebo arm had pneumonia caused by a novel coronavirus infection (COVID-19) with an improvement/recovery outcome.

Other respiratory viral infections, bronchitis, pharyngitis and acute sinusitis were observed in isolated cases.

Neoplasms. One patient in the placebo arm was diagnosed with renal cancer.

A lung neoplasm was found in 1 patient from the levilimab arm. Based on the investigation, which included follow-up spiral tomography of the lungs and consultation with a thoracic surgeon, the malignant nature of the neoplasm was ruled out, and a lung cyst was diagnosed. The patient continued to participate in the study.

Injection site reactions. In the levilimab arm, 6.9% of cases developed injection site reactions manifested as grade 1 and 2 hyperemia. 2 (2.0%) patients were withdrawn from the study due to these events. No injection site reactions were reported in the placebo arm.

Immunogenicity assessment. In patients of the levilimab arm, binding antibodies against the investigational product were not detected at any of the evaluated time points.

Discussion. Analysis of the efficacy data for the primary endpoints showed that the difference in ACR20 response rates at week 12 between the levilimab and placebo arms was 30.1%, and the difference in LDA rates by DAS28-CRP (<3.2) at week 24 was 46.2%. Since the lower limits of 97.5% CI for the difference in proportions for both primary endpoints is above the prespecified superiority margin (?>0), and the estimated treatment effect size for both endpoints is clinically significant, considering the efficacyq of other approved IL-6R inhibitors [13–15], it was concluded that the hypothesis of the superiority of the investigational product over placebo was confirmed.

Secondary endpoint analysis showed that at week 12 of therapy, the number of patients who achieved the minimal clinical response (20% reduction in the tender/swollen joint count of 66/68) was greater in the levilimab arm compared to the placebo arm. The differences in the number of patients who achieved ACR20 at week 12 were statistically significant and persisted at week 24. In the levilimab arm, significantly more patients achieved ACR50/70 response at both weeks 12 and 24 compared with the placebo arm.

In addition, higher rates of low disease activity and remission of RA based on DAS28-CRP and DAS28-ESR at weeks 12 and 24 and remission of RA based on SDAI at week 24 was reported in patients of levilimab arm, which was also confirmed by the dynamics of RA activity indices and inflammatory markers.

Despite the lack of statistical significance of differences between the levilimab and placebo arms in the number of patients who achieved RA remission based on CDAI and ACR/EULAR criteria (2011), numerically higher rate of remission was reported in the levilimab arm.

Evaluation the dynamics of radiographic signs of joint destruction revealed a decrease in structural progression in

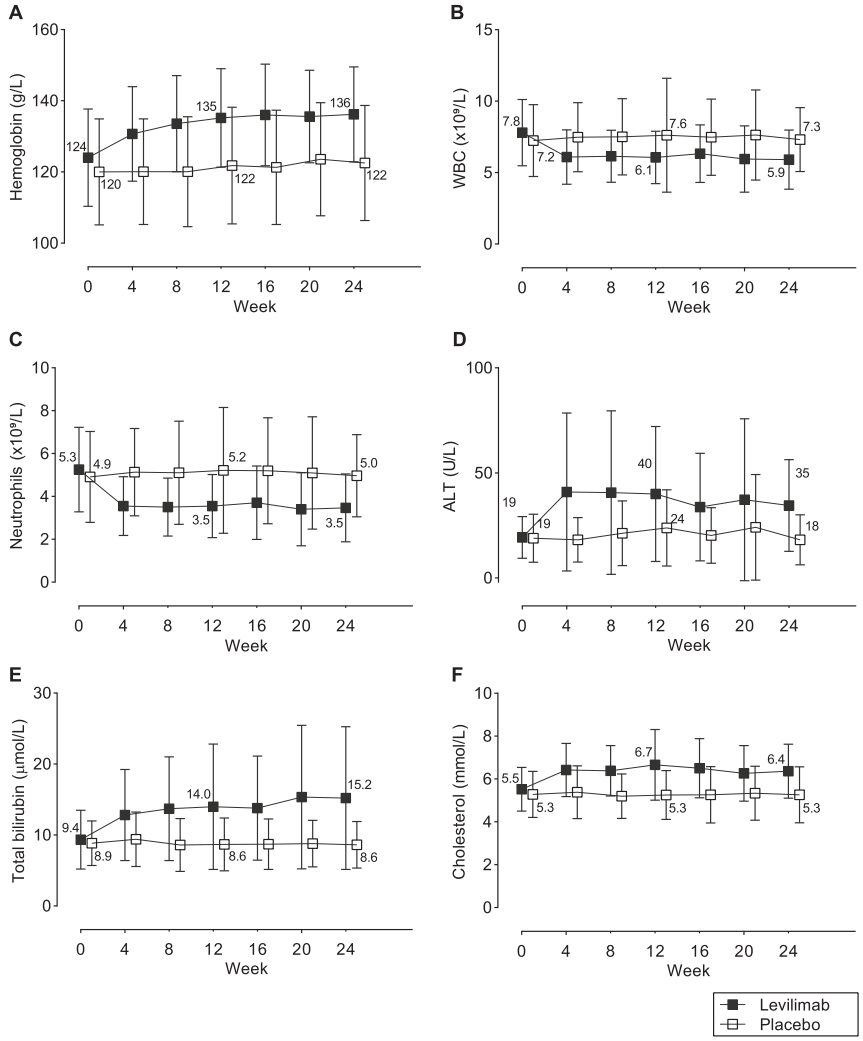

Figure 4. *Dynamics of laboratory parameters: hemoglobin concentration (A), absolute leukocyte count (B), absolute neutrophil count (C), ALT activity (D), total bilirubin concentration (D) and total cholesterol (E)*

patients treated with levilimab compared to placebo. However, these differences did not reach statistical significance during the main double-blind study period.

It can be assumed that the absence of statistically significant differences in individual secondary endpoints between the compared arms is primarily related to early performed efficacy assessment, which does not allow to assess the slowly changing manifestations of RA. Results of open-label follow-up period, will provide more data for an accurate assessment of levilimab efficacy in RA.

The safety analysis showed that the most specific AEs for levilimab are increased liver enzymes, bilirubin, cholesterol and blood triglycerides, as well as a decreased neutrophil count, which are predominantly mild or moderate and do not require treatment discontinuation.

Drug-related AEs reported during the main double-blind study period were predominantly expected, cases of early withdrawal for safety reasons were isolated. Levilimab demonstrated no significant immunogenicity during the analyzed study period.

Conclusion. Results of the main double-blind period of the study indicate the high efficacy of levilimab in combination with MTX in patients with active MTX-resistant RA, which is confirmed by a significant decrease in RA activity, inhibition of structural joints damage progression, and improvement of the patients' QoL. During the analyzed period, levilimab 162 mg QW SC showed a favorable safety profile consistent with the known data on IL-6R inhibitors.

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Supplementary information

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