Methods: This phase 3, double-blind, active- and placebo (PBO)-controlled study randomized patients with active RA (3:3:2:3) to FIL 200 mg, FIL 100 mg, active comparator (adalimumab [ADA] 40mg every 2 weeks), or PBO daily for up to 52 weeks; results through week 24 are presented. Patients were also receiving MTX for ≥ 12 weeks with a stable dose of MTX for ≥ 4 weeks before initiation of study drug. Primary efficacy endpoint was proportion of patients achieving ACR20 response at week 12; additional clinical assessments were ACR50 and ACR70 responses, DAS28-CRP score ≤ 3.2 and < 2.6 , van der Heijde modified total Sharp score (mTSS), and patient-reported outcomes were HAQ-DI, SF-36 PCS, and FACIT-Fatigue. Safety endpoints included types and rates of adverse events. Logistic regression adjusting for stratification factors with nonresponder imputation was used for superiority test of FIL vs PBO for ACR response and other binary endpoints. Mixed-effect model adjusting for baseline value, stratification factors, treatment, visit, and treatment by visit interaction as fixed effects with observed cases was used for continuous endpoints. Non-inferiority test of FIL to ADA (preserving $> 50\%$ of ADA response) was performed for DAS28-CRP ≤ 3.2 and < 2.6 .

Results: Of 1,759 patients randomized, 1,755 received study drug and were analyzed, with 475 FIL 200mg; 480 FIL 100mg; 325 ADA; and 475 PBO, of which 89.5%, 90.4%, 88.9%, and 81.3%, respectively, completed week 24 study drug. Most patients (81.8%) were female, mean (standard deviation [SD]) duration of RA was 7.8 (7.6) years, and mean (SD) DAS28-CRP was 5.7 (0.9). At week 12, significantly more patients in the FIL 200mg and 100mg arms achieved an ACR20 response compared to PBO (Table 1). Similarly, compared to PBO, more patients receiving FIL achieved ACR50 and ACR70 responses, DAS28-CRP scores ≤ 3.2 and < 2.6 , had lower radiographic progression, and reported improvements in HAQ-DI, SF-36 PCS, and FACIT-Fatigue scores (Table 1). Non-inferiority of FIL 200mg to ADA was met based on DAS28-CRP ≤ 3.2 . The FIL safety profile was consistent with prior studies through week 24 (Table 2).

Table 1. Efficacy at Week 12 (Primary Analysis) and Week 24*

	FIL 200 mg (N = 475)		FIL 100 mg (N = 480)		ADA 40 mg Q2W (N = 325)		PBO (N = 475)	
	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24
ACR20, %	76.6***	78.1	69.8***	77.7	70.8	74.5	49.9	59.2
ACR50, %	47.2***	57.9	36.3***	52.7	35.1	52.6	19.8	33.3
ACR70, %	26.3***	36.2	18.5***	29.4	14.2	29.5	6.7	14.9
DAS28-CRP ≤ 3.2 , %	49.7***	60.6	38.8***	53.1	43.4	50.5	23.4	33.7
DAS28-CRP < 2.6 , %	33.9***	48.4	23.8***	35.2	23.7	35.7	9.3	16.2
mTSS, mean change from BL	0.08	0.13***	0.11	0.17***	0.13	0.16	0.25	0.38
HAQ-DI, mean change from BL	-0.69***	-0.52	-0.56***	-0.75	-0.61	-0.76	-0.42	-0.62
SF-36 PCS, mean change from BL	9.2***	10.4	8.5***	10.3	8.4	10.4	5.8	7.7
FACIT-Fatigue, mean change from BL	9.2***	10.5	9.1***	10.8	8.8	10.3	6.8	8.4

*All patients who were randomized and received at least 1 dose of study drug were included in efficacy analyses. P-values are shown only for primary time points (all at week 12 except mTSS, which was at week 24).
***P < 0.01 vs PBO; **P < 0.01 vs ADA non-inferiority test; *P < 0.05 vs ADA non-inferiority test. *Comparison not adjusted for multiplicity.
ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; ADA, adalimumab; BL, baseline; DAS28-CRP, Disease Activity Score based on 28 joints with C-reactive protein; FIL, filgrastim; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire Disability Index; mTSS, modified total Sharp score; SD, standard deviation; SF-36 PCS, Short-Form 36 Physical Component Summary; Q2W every 2 weeks.

Table 2. Safety Events of Interest through Week 24

	FIL 200 mg (N = 475)	FIL 100 mg (N = 480)	Q2W (N = 325)	PBO (N = 475)
Patient with event, n (%)				
Serious AEs	21 (4.4)	24 (5.0)	14 (4.3)	20 (4.2)
Serious infections	8 (1.7)	8 (1.7)	8 (2.5)	4 (0.8)
Herpes zoster	2 (0.4)	2 (0.4)	2 (0.6)	2 (0.4)
Adjudicated MACEs	0	1 (0.2)	1 (0.3)	2 (0.4)
Venous thrombotic events	1 (0.2)	0	0	2 (0.4)
Malignancies	0	1 (0.2)	1 (0.3)	3 (0.6)
Deaths	2 (0.4)	1 (0.2)	0	2 (0.4)

AE, adverse event; MACE, major adverse cardiovascular event

Conclusions: The selective JAK1 inhibitor FIL, at doses of 200mg and 100mg led to significant improvement in signs and symptoms of RA, prevented radiographic progression, and improved physical function compared to PBO, and was well tolerated among patients with RA with prior inadequate response to MTX. Efficacy of FIL 200mg was non-inferior to ADA based on DAS28-CRP ≤ 3.2 .

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LB0002

RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE-DOSE, PHASE 2B STUDY TO DEMONSTRATE THE SAFETY AND EFFICACY OF TILDRAKIZUMAB, A HIGH-AFFINITY ANTI-INTERLEUKIN-23P19 MONOCLONAL ANTIBODY, IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS

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Background: Tildrakizumab (TIL), a high-affinity anti-interleukin-23p19 monoclonal antibody, is approved for moderate-to-severe plaque psoriasis treatment and is under investigation for psoriatic arthritis (PsA).

Objectives: To evaluate the 24-week efficacy and safety results from the randomised, double-blind, placebo-controlled, multiple-dose, phase 2b TIL study in patients with active PsA (NCT02980692).

Methods: Patients with active PsA were randomised 1:1:1:1:1 to receive TIL (200 mg once every 4 weeks [Q4W] [n = 78], 200 mg every 12 weeks [Q12W] [n = 79], 100 mg Q12W [n = 77], 20 mg Q12W to week 24 [n = 78]), or placebo (PBO) Q4W to week 24 (n = 79). Stable concomitant methotrexate or leflunomide use was permitted but not mandated. The primary efficacy endpoint was the proportion of patients who achieved a 20% reduction from baseline in American College of Rheumatology response criteria (ACR20) at week 24. Other outcome measurements included proportion of patients achieving ACR50/70 response and Psoriasis Area and Severity Index (PASI) 75, PASI 90, and changes in swollen and

Table 1. Demographics and baseline disease characteristics

	TIL 200 mg Q4W (N = 78)	TIL 200 mg Q12W (N = 79)	TIL 100 mg Q12W (N = 77)	TIL 20 mg Q12W (N = 78)	PBO (N = 79)
Patient demographics					
Age, years, median	50.0	49.0	50.0	47.5	47.0
Female, n (%)	46 (59.0)	37 (46.8)	47 (61.0)	41 (52.6)	44 (55.7)
White, n (%)	76 (97.4)	78 (98.7)	75 (97.4)	75 (96.2)	74 (93.7)
BMI, kg/m ² , median	30.0	29.3	27.8	28.9	27.8
Baseline disease characteristics					
Swollen joint count, median (range)	8.0 (3.0–35)	7.0 (3.0–45)	8.0 (0–38)	8.0 (3.0–38)	8.0 (3.0–42)
Tender joint count, median (range)	13.5 (3.0–64)	15.0 (4.0–63)	19.0 (3.0–59)	14.0 (4.0–54)	15.0 (3.0–64)
BSA $\geq 3\%$, n (%)	53 (67.9)	44 (55.7)	54 (70.1)	41 (52.6)	42 (53.2)
Physician GADA, mean $\pm$ SD	54.0 $\pm$ 16.1	55.4 $\pm$ 16.2	57.3 $\pm$ 17.3	59.4 $\pm$ 14.4	59.5 $\pm$ 15.6
Patient GADA, mean $\pm$ SD	57.8 $\pm$ 18.3	61.1 $\pm$ 20.7	60.3 $\pm$ 20.2	61.9 $\pm$ 17.4	65.2 $\pm$ 18.1
Patient's pain assessment, mean $\pm$ SD	55.4 $\pm$ 19.1	59.6 $\pm$ 23.5	59.2 $\pm$ 22.1	60.9 $\pm$ 19.7	64.2 $\pm$ 20.4

BMI, body mass index; BSA, body surface area; GADA, global assessment of disease activity; Q4W, every 4 weeks; Q12W, every 12 weeks; PBO, placebo; SD, standard deviation; TIL, tildrakizumab.

Table 2. Efficacy endpoints at week 24

	TIL 200 mg Q4W (N = 78)	TIL 200 mg Q12W (N = 79)	TIL 100 mg Q12W (N = 77)	TIL 20 mg Q12W (N = 78)	PBO (N = 79)
PASI 75*, %	64.2***	79.6***	55.6***	46.3*	16.7
PASI 90*, %	47.2***	50.0***	38.9**	36.6*	7.1
Swollen joint count, median change from BL	-6.0*	-6.0	-6.0*	-6.0	-5.0
Tender joint count, median change from BL	-9.0	-10.0*	-11.0*	-10.0	-8.5

*Response rates only calculated in patients with BSA $\geq 3\%$ at baseline, missing responses were imputed as nonresponses. *P < 0.05; **P < 0.001; ***P < 0.0001 vs PBO. BL, baseline; BSA, Body Surface Area; PASI, Psoriasis Area and Severity Index; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.

*P < 0.05; **P < 0.001; ***P < 0.0001 vs PBO. ACR, American College of Rheumatology response criteria; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.

Figure 1. ACR20/50/70 response rates

tender joint count at week 24. Safety assessments included monitoring of treatment-emergent adverse events (TEAEs).

Results: Of 500 patients screened, 391 patients met inclusion criteria (including =18 years old, PsA diagnosis with symptoms for 6 months, and =3 tender and =3 swollen joints). Demographics and baseline disease characteristics are shown in Table 1. There were significantly greater proportions of ACR20/50/70 and PASI 75/90 responders with TIL vs PBO at week 24, and in some cases differences in parameters were noted as early as week 8 (Figure 1 and Table 2).

The most frequent TEAEs through week 24 included nasopharyngitis (pooled TIL arms: 5.4% [17/312]; PBO: 6.3% [5/79]); and diarrhoea (TIL: 1.3% [4/312]; PBO: 0). There were no reports of candidiasis, inflammatory bowel disease, major adverse cardiac events, or malignancy. No patients discontinued treatment due to TEAEs and no deaths were reported. Serious TEAEs occurred in 2.2% (7/312) of TIL-treated patients vs 2.5% (2/79) in PBO-treated patients.

Conclusion: By week 24, TIL was significantly more efficacious than PBO in treatment of joint and skin manifestations of PsA. Furthermore, there was a clear separation between TIL and PBO as early as 8 weeks for ACR20 (TIL 200 mg Q4W and 100 mg) and 12 weeks for ACR50 (all TIL groups). Shortening the dosing interval from Q12W to Q4W for the 200-mg dose did not result in a measurable increase in skin or joint response scores. There was a low rate of TEAEs in the TIL-treated group.

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RA therapy –JAK inhibitors and beyond

OP0023

ACPA-POSITIVE RHEUMATOID ARTHRITIS PATIENTS BENEFITED MORE FROM ADVANCED TREATMENT STRATEGIES THAN ACPA-NEGATIVE RHEUMATOID ARTHRITIS PATIENTS: 25-YEAR RESULTS OF A LONGITUDINAL COHORT STUDY

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Background: Over the last 25 years, treatment of rheumatoid arthritis (RA) has changed considerably, and clinically relevant joint damage and deformations have become infrequent. It is unclear to what extent the long-term outcomes mortality, sustained drug-free remission (DFR) and physical functioning have improved, and whether ACPA+ and ACPA- patients have benefited equally from treatment-improvements.

Objectives: To investigate the influence of treatment strategies that have been improved for 25-years on mortality, DFR and functionality, and whether these effects differed for ACPA+ and ACPA- RA-patients.

Methods: In the Leiden early arthritis cohort, 1291 patients with RA (1987 criteria) were included between 1993-2016. Patients were treated in routine care; initial and subsequent treatment changed over time; divided in 5 inclusion periods. Patients included between 1993-1996 (n=168) received initial NSAIDs and started DMARDs with delay, patients included 1997-2000 (n=185) were treated early with mild DMARDs (e.g. hydroxychloroquine, penicillamine), in 2001-2005 (n=210) patients started early with methotrexate, in 2006-2010 (n=338) early methotrexate was followed by treat to target treatment adjustments; in 2011-2016 (n=390) this was similar and additional efforts were undertaken for very early referral. Patients were followed yearly including assessments of swollen joints, DAS28-ESR and health assessment questionnaires (HAQ). Mortality data were obtained from the civic registry. DFR was defined as the persistent absence of synovitis after cessation of DMARD-therapy during all available follow-up (≥ 1 year). DAS28-ESR and HAQ data were analysed with linear mixed models; mortality and time to DFR with multivariable and univariable Cox regression. Inclusion period 1993-1996 was used as reference. Analyses were stratified for ACPA-status (anti-CCP2).

Results: Baseline age, sex and antibody status did not differ between inclusion periods. With 1993-1996 as reference, the DAS28-ESR decreased in the first year and thereafter remained lower in all inclusion periods (all p<0.05).

Compared to 1993-1996, mortality was decreased in all inclusion periods (1997-2000 HR 0.67 (0.46;0.99); 2001-2005 HR 0.66 (0.45;0.97); 2006-2010 HR 0.64 (0.42;0.98); 2011-2016 HR 0.31 (0.14;0.68)). DFR achievement was faster in 2006-2010 (HR 2.68 (1.68;4.29)) and 2011-2016 (3.37 (1.97;5.74)), compared to 1993-1996. Additionally, HAQ over time was lower in 2006-2010 (-0.25 (-0.36;-0.14)) and 2011-2016 (-0.21 (-0.32;-0.10)).

Stratification for ACPA revealed that ACPA+ patients in the first two inclusion periods remained to have a higher DAS28-ESR over time (1993-1996 β 0.76 (0.42;1.10); 1997-2000 β 0.40 (0.07;0.74)); thereafter there was no difference in DAS28-ESR between ACPA+ and ACPA- patients. The decrease in mortality was similar for ACPA+ and ACPA- patients. The increased rate of DFR was more prominent in ACPA+ patients than ACPA- patients in the two most recent inclusion periods (2006-2010 HR ACPA+: 3.85 (1.25;11.9); ACPA- 2.27 (1.34;3.83); 2011-2016 HR ACPA+: 6.48 (1.89;22.2); ACPA- 3.04 (1.66;5.55)). Within ACPA+ RA, the HAQ over time had improved in 2001-2005 (-0.19 (-0.34;-0.04)), 2006-2010 (-0.35 (-0.49;-0.22)) and 2011-2016 (-0.26 (-0.40;-0.13)), compared to 1993-1996. This effect was absent ACPA- RA.

Figure 1. Disease outcomes over time stratified for inclusion period