SUPPLEMENTARY MATERIAL

Supplementary table 1 Demographics and patient characteristics at entry into the open-label extension, by original randomisation group

	Open-label extension		
		Sarilumab q2w + MTX	
Parameter at open-label extension baseline	**Placebo + MTX (N=307)**	**150 mg (N=300)**	**200 mg (N=294)**
Female, n (%)	246 (80)	241 (80)	246 (84)
Age, mean (SD), years	51.8 (10.7)	51.3 (11.8)	51.2 (11.6)
Weight, mean (SD), kg	75.3 (17.4)	75.5 (18.4)	76.4 (19.5)
Body mass index, mean (SD), kg/m^2	28.6 (6.0)	28.6 (6.3)	29.2 (6.5)
Region, n (%)*			
Region 1	45 (15)	55 (18)	52 (18)
Region 2	129 (42)	126 (42)	119 (41)
Region 3	133 (43)	119 (40)	123 (42)
Smoking status, n (%)			
Never	229 (75)	225 (75)	225 (77)
Former	39 (13)	30 (10)	33 (11)
Current	37 (12)	45 (15)	35 (12)
Alcohol habits			
Never	241 (79)	237 (79)	245 (84)
At least monthly	41 (13)	38 (13)	33 (11)
At least weekly	21 (7)	22 (7)	14 (5)
At least daily	3 (1)	3 (1)	1 (0.3)

*Region 1: Austria, Australia, Belgium, Canada, Czech Republic, Finland, Germany, Greece, Hungary, Italy, Israel, The Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, United Kingdom, USA; Region 2: Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru; Region 3: Belarus , Estonia, India , Lithuania, Malaysia , Philippines , Poland, Romania, Russia, South Africa, South Korea, Ukraine, Taiwan, Thailand, Turkey.

Supplementary table 2 Duration of sarilumab treatment

	Sarilumab + methotrexate		
Sarilumab treatment	**150 mg initial dose (n=400)**	**200 mg initial dose* (n=735)**	**Any dose† (n=1135)**
Cumulative exposure to treatment, PY	346.1	2050.4	3766.5
Number of patients with duration of study treatment by category (%)			
≥1 day	400 (100)	735 (100)	1135 (100)
>12 weeks	368 (92.0)	665 (90.5)	1050 (92.5)
>24 weeks	308 (77.0)	629 (85.6)	1003 (88.4)
>48 weeks	274 (68.5)	537 (73.1)	900 (79.3)
>96 weeks	7 (1.8)	416 (56.6)	768 (67.7)
>144 weeks	6 (1.5)	363 (49.4)	702 (61.9)
>192 weeks	6 (1.5)	336 (45.7)	653 (57.5)
>240 weeks	5 (1.3)	218 (29.7)	476 (41.9)

*Including placebo patients from the double-blind phase who switched to sarilumab 200 mg in the open-label extension.

†Any dose includes exposure on all sarilumab doses.

PY, patient-years

Supplementary table 3 Investigator-reported treatment-emergent AEs of special interest

AEs of special interest	n_E (n_E/100 PY)		
	Sarilumab 150 mg initial dose + MTX	**Sarilumab 200 mg initial dose*+ MTX**	**Any sarilumab dose† + MTX**
Cumulative total AE observation period, PY	355.5	2082.5	3826.0
Infections	289 (81.3)	1128 (54.2)	2109 (55.1)
Serious infections	14 (3.9)	82 (3.9)	148 (3.9)
Opportunistic infections	2 (0.6)	20 (1.0)	37 (1.0)
Herpes zoster‡	1 (0.3)	13 (0.6)	20 (0.5)
Tuberculosis§	0	0	1 (<0.1)
Leucopenia	88 (24.8)	343 (16.5)	676 (17.7)
Thrombocytopenia	5 (1.4)	26 (1.2)	54 (1.4)
Hepatic disorders	66 (18.6)	199 (9.6)	372 (9.7)
Confirmed GI perforation‖	1 (0.3)	3 (0.1)	5 (0.1)
Upper	1 (0.3)	1 (<0.1)	2 (<0.1)
Lower	0	2 (<0.1)	3 (<0.1)
GI ulcerations	7 (2.0)	7 (0.3)	18 (0.5)
Elevation in lipids	19 (5.3)	134 (6.4)	215 (5.6)
Hypersensitivity	36 (10.1)	89 (4.3)	189 (4.9)
Anaphylaxis	0	0	0
Injection-site reactions	124 (34.9)	456 (21.9)	828 (21.6)
Malignancy	4 (1.1)	16 (0.8)	24 (0.6)
Malignancy excluding NMSC	4 (1.1)	10 (0.5)	18 (0.5)
MACE	2 (0.6)	7 (0.3)	13 (0.3)
Lupus-like syndrome	1 (0.3)	1 (0.0)	2 (0.1)
Demyelinating disorders	0	0	0

Investigator-reported treatment-emergent AEs of special interest are presented for the entire 5-year period.

*Including placebo patients from the double-blind phase who switched to sarilumab 200 mg in the open-label extension.

†Any dose includes exposure on all sarilumab doses.

‡Herpes zoster was reported as an opportunistic infection per protocol requirement; all cases of herpes zoster were localised.

§All cases of tuberculosis were reported as opportunistic infections.

‖Cases were medically reviewed.

AE, adverse event; GI, gastrointestinal; MACE, major adverse cardiovascular events; MTX, methotrexate; n_E, number of events; n_E/100 PY, number of events per 100 PY; NMSC, nonmelanoma skin cancer; PY, patient-years.

Supplementary table 4 Laboratory abnormalities over 5 years of follow-up

Laboratory parameter	Sarilumab + methotrexate, n (%)		
	150 mg initial dose (n=400)	**200 mg initial dose* (n=735)**	**Any dose† (n=1135)**
ANC			
Patients with ANC <1000 cells/mm^3	24 (6.0)	86 (11.7)	143 (12.6)
Normalised on treatment‡	15 (3.8)	41 (5.6)	104 (9.2)
Normalised after the last dose	5 (1.3)	13 (1.8)	27 (2.4)
Did not normalise after the last episode	4 (1.0)	32 (4.4)	12 (1.1)
Treatment continuing§	3 (0.8)	29 (4.0)	3 (0.3)
Treatment discontinued – last value available	1 (0.3)	3 (0.4)	9 (0.8)
Grade 1: ≥1500 cells/mm^3	0	0	0
Grade 2: ≥1000–<1500 cells/mm^3	0	2 (0.3)	5 (0.4)
Grade 3/4: <1000 cells/mm^3	1 (0.3)	1 (0.1)	4 (0.4)
ALT			
Patients with ALT >3× ULN	39 (9.8)	87 (11.9)	158 (14.0)
Normalised on treatment‡	19 (4.8)	28 (3.8)	84 (7.4)
Normalised after the last dose	8 (2.0)	19 (2.6)	33 (2.9)
Did not normalise after the last episode	12 (3.0)	40 (5.5)	41 (3.6)
Treatment continuing§	6 (1.5)	24 (3.3)	12 (1.1)
Treatment discontinued – last value available	6 (1.5)	16 (2.2)	29 (2.6)
ALT: 1–1.5× ULN	2 (0.5)	5 (0.7)	12 (1.1)
ALT: 1.5–3× ULN	3 (0.8)	8 (1.1)	13 (1.1)
ALT: >3× ULN	1 (0.3)	3 (0.4)	4 (0.4)
Platelet count			
Patients with platelet count <100 x 10^9 cells/L	4 (1.0)	18 (2.5)	33 (2.9)
Normalised on treatment‡	2 (0.5)	12 (1.6)	20 (1.8)
Normalised after the last dose	1 (0.3)	2 (0.3)	6 (0.5)
Did not normalise after the last episode	1 (0.3)	4 (0.5)	7 (0.6)
Treatment continuing§	0	2 (0.3)	4 (0.4)

Treatment discontinued – last value available	1 (0.3)	2 (0.3)	3 (0.3)
Platelet count ≥50–100 x 10^9 cells/L	1 (0.3)	1 (0.1)	2 (0.2)
Platelet count <50 x 10^9 cells/L	0	0	0

Laboratory abnormalities are presented for the entire 5-year period.

*Including placebo patients from the double-blind phase who switched to sarilumab 200 mg in the open-label extension.

†Any dose includes exposure on all sarilumab doses.

‡End of treatment defined as ≤17 days after date of last dose of investigational medicinal product.

§Patient was still in the study at time of data extraction

ALT, alanine aminotransferase; ANC, absolute neutrophil count; ULN, upper limit of normal.

Supplementary table 5 Incidence of infection and serious infection by lowest on-study ANC

Lowest on-study ANC (neutropenia grade)	Sarilumab + methotrexate, n_i/n_c (%)		
	150 mg initial dose (n=400)	200 mg initial dose* (n=735)	Any dose† (n=1135)
Any infection			
≥LLN	115/267 (43.1)	200/339 (59.0)	322/529 (60.9)
<LLN	55/133 (41.4)	214/393 (54.5)	386/603 (64.0)
≥1500 cells/mm^3 – LLN (grade 1)	22/54 (40.7)	88/152 (57.9)	145/218 (66.5)
≥1000–<1500 cells/mm^3 (grade 2)	23/55 (41.8)	92/155 (59.4)	156/242 (64.5)
≥500–<1000 cells/mm^3 (grade 3)	10/20 (50.0)	30/80 (37.5)	78/128 (60.9)
<500 cells/mm^3 (grade 4)	0/4 (0)	4/6 (66.7)	7/15 (46.7)
Serious infection			
≥LLN	7/267 (2.6)	28/339 (8.3)	52/529 (9.8)
<LLN	4/133 (3.0)	41/393 (10.4)	66/603 (10.9)
≥1500 cells/mm^3 – LLN (grade 1)	3/54 (5.6)	20/152 (13.2)	32/218 (14.7)
≥1000–<1500 cells/mm^3 (grade 2)	1/55 (1.8)	18/155 (11.6)	26/242 (10.7)
≥500–<1000 cells/mm^3 (grade 3)	0/20	3/80 (3.8)	7/128 (5.5)
<500 cells/mm^3 (grade 4)	0/4	0/6	1/15 (6.7)

Incidence of infection and serious infection by lowest on-study ANC are presented for the entire 5-year period.

*Including placebo patients from the double-blind phase who switched to sarilumab 200 mg in the open-label extension.

†Any dose includes exposure on all sarilumab doses.

ANC, absolute neutrophil count; LLN, lower limit of normal; n_c, number of patients in ANC category; n_i, number of patients with infection.

Supplementary table 6 Number of infections and serious infections within 12 weeks after an ANC assessment

Number of infections within 12 weeks after an ANC assessment	**Sarilumab + MTX (3826.0 PY), n_E (n_E/100 PY)**
All infections	1879 (49.1)
≥LLN	1652 (43.2)
≥1500 cells/mm^3 – LLN (grade 1)	152 (4.0)
≥1000–<1500 cells/mm^3 (grade 2)	66 (1.7)
≥500–<1000 cells/mm^3 (grade 3)	7 (0.2)
<500 cells/mm^3 (grade 4)	2 (<0.1)
Serious infections	130 (3.4)
≥LLN	125 (3.3)
≥1500 cells/mm^3 – LLN (grade 1)	3 (<0.1)
≥1000–<1500 cells/mm^3 (grade 2)	0
≥500–<1000 cells/mm^3 (grade 3)	1 (<0.1)
<500 cells/mm^3 (grade 4)	1 (<0.1)

ANC category represents most recent ANC value before onset of infection.

ANC, absolute neutrophil count; LLN, lower limit of normal; n_E, number of events; n_E/100 PY, number of events per 100 PY; PY, patient-years.

Supplementary table 7 ANC and ALT following dose reduction

	Before dose reduction*	Time after dose reduction, months†		
		≤1	2–3	4–6
Lowest ANC value (neutropenia grade), n (%)				
No. of patients‡	108	75	88	101
>LLN	5 (4.6)	27 (36.0)	39 (44.3)	50 (49.5)
≥1500 cells/mm^3–LLN (grade 1)	13 (12.0)	13 (17.3)	16 (18.2)	20 (19.8)
≥1000 and <1500 cells/mm^3 (grade 2)	30 (27.8)	24 (32.0)	25 (28.4)	25 (24.8)
≥500 and <1000 cells/mm^3 (grade 3)	60 (55.6)	10 (13.3)	8 (9.1)	6 (5.9)
<500 cells/mm^3 (grade 4)	0	1 (1.3)	0	0
Maximum ALT value, n (%)				
No. of patients§	44	25	37	38
≤ULN	1 (2.3)	4 (16.0)	7 (18.9)	13 (34.2)
>1× and ≤1.5× ULN	1 (2.3)	5 (20.0)	10 (27.0)	8 (21.1)
>1.5× and ≤3× ULN	6 (13.6)	9 (36.0)	19 (51.4)	15 (39.5)
>3× and ≤5× ULN	34 (77.3)	6 (24.0)	1 (2.7)	2 (5.3)
>5× and ≤10× ULN	2 (4.5)	1 (4.0)	0	0
>10× ULN	0	0	0	0

*Reason for dose reduction for ANC was ANC ≥500–<1000 cells/mm^3 or precautionary measure to avoid ANC <1000 cells/mm^3, and for ALT was ALT increase to >3× and ≤5× ULN or precautionary measure to avoid ALT increase >3× ULN.

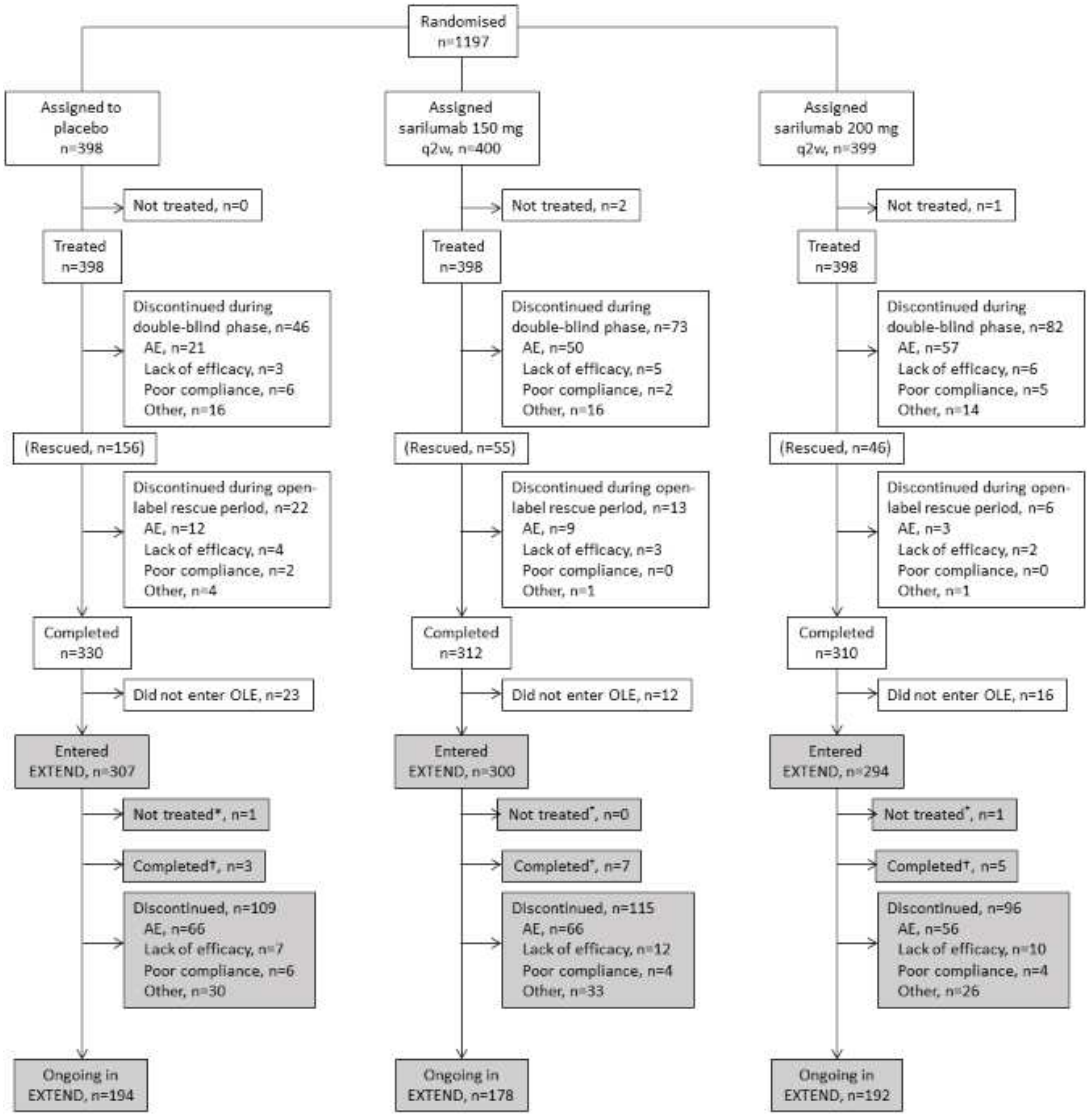
†≤1 month = ≤30 days; 2–3 months = 31–90 days; 4–6 months = 91–180 days.

‡The number of patients who reduced their dose due to ANC reduction and had their ANC measured during the specified period.

§The number of patients who reduced their dose due to ALT increase and had their ALT measured during the specified period.

ALT, alanine aminotransferase; ANC, absolute neutrophil count; LLN, lower limit of normal; ULN, upper limit of normal.

Supplementary figure 1 Flowchart of patient disposition in the double-blind study and the open-label extension.



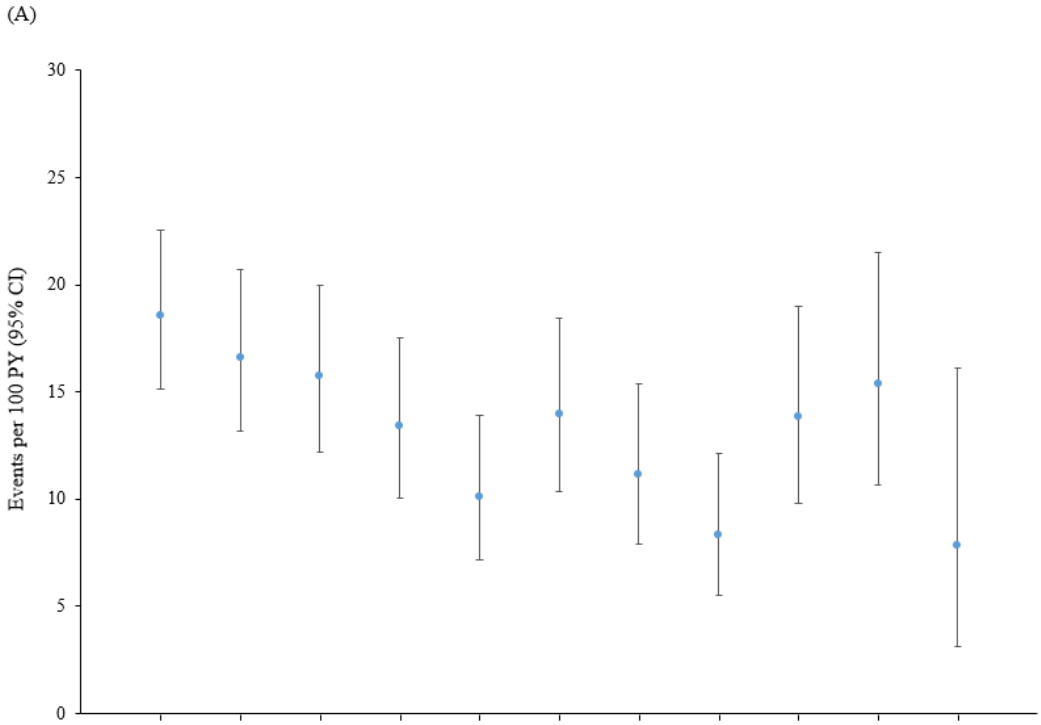
*Two patients discontinued the study without treatment due to personal reason and AE reason.

†Patients switched to commercially available sarilumab.

AE, adverse event; OLE, open-label extension; q2w, every 2 weeks.

Supplementary figure 2 Incidence of selected adverse events by 6-month interval (either dose of sarilumab + methotrexate).

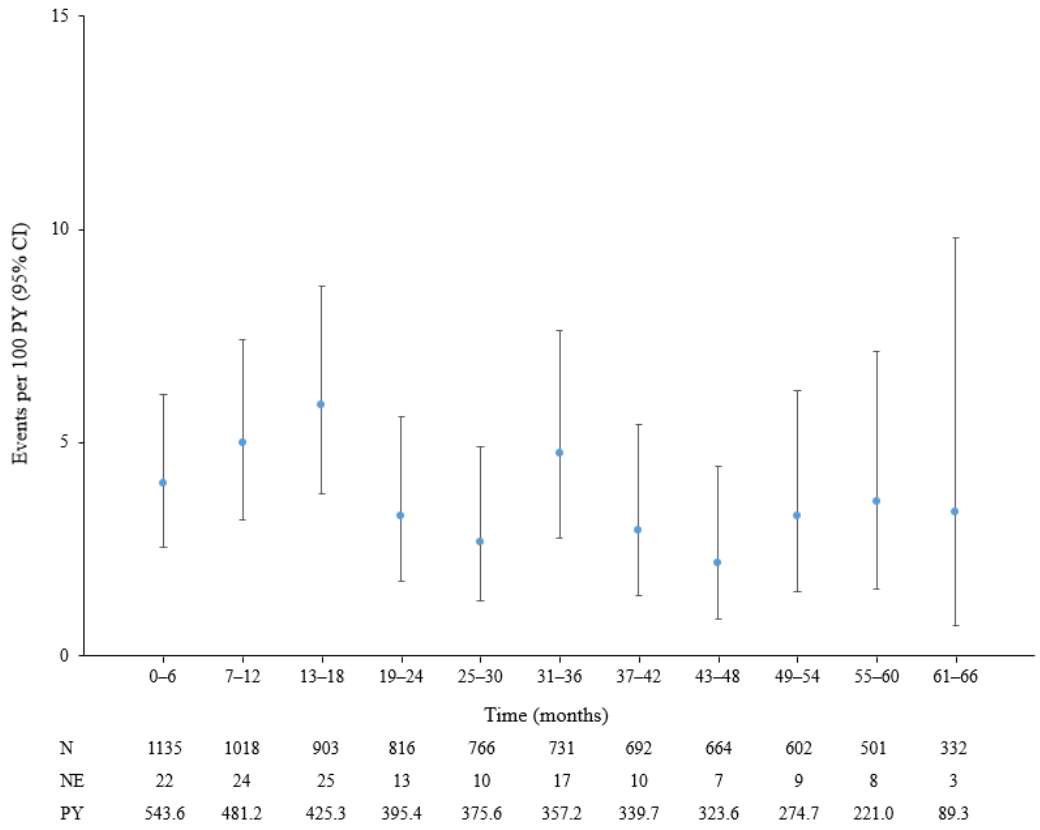
Serious adverse events



	0–6	7–12	13–18	19–24	25–30	31–36	37–42	43–48	49–54	55–60	61–66
N	1135	1018	903	816	766	731	692	664	602	501	332
NE	101	80	67	53	38	50	38	27	38	34	7
PY	543.6	481.2	425.3	395.4	375.6	357.2	339.7	323.6	274.7	221.0	89.3

Serious infections

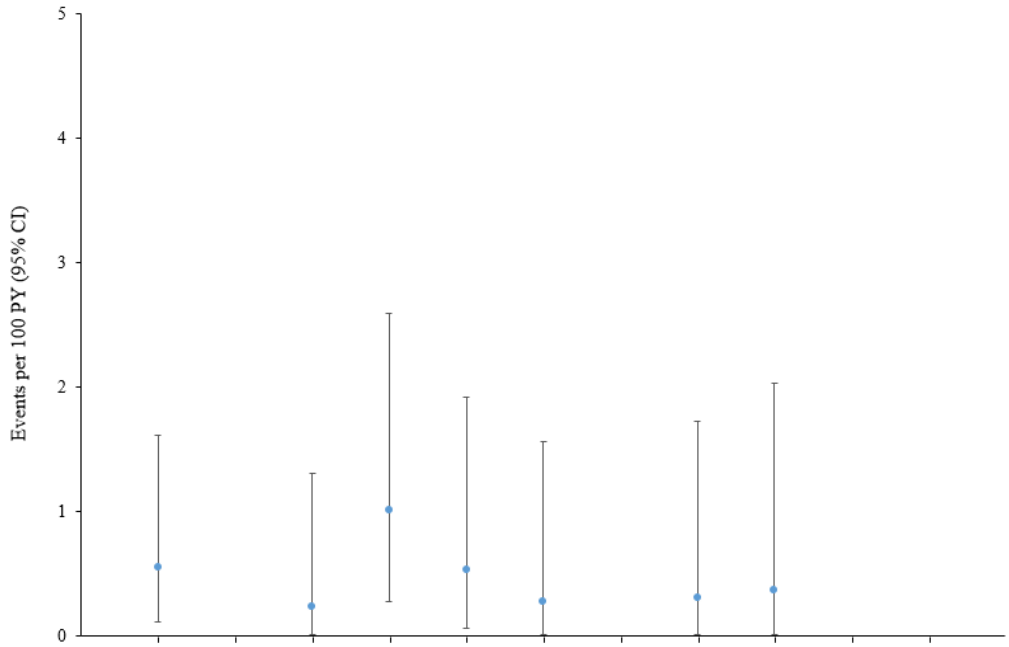
(B)



	0–6	7–12	13–18	19–24	25–30	31–36	37–42	43–48	49–54	55–60	61–66
N	1135	1018	903	816	766	731	692	664	602	501	332
NE	22	24	25	13	10	17	10	7	9	8	3
PY	543.6	481.2	425.3	395.4	375.6	357.2	339.7	323.6	274.7	221.0	89.3

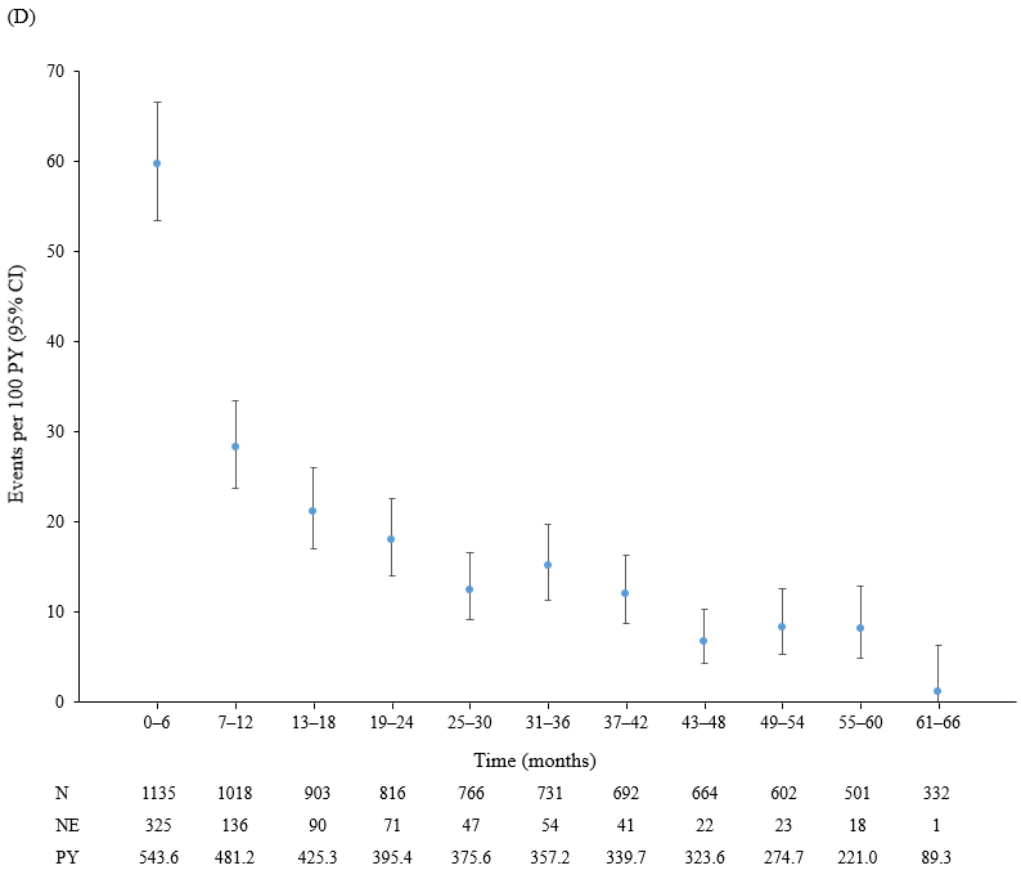
MACE

(C)



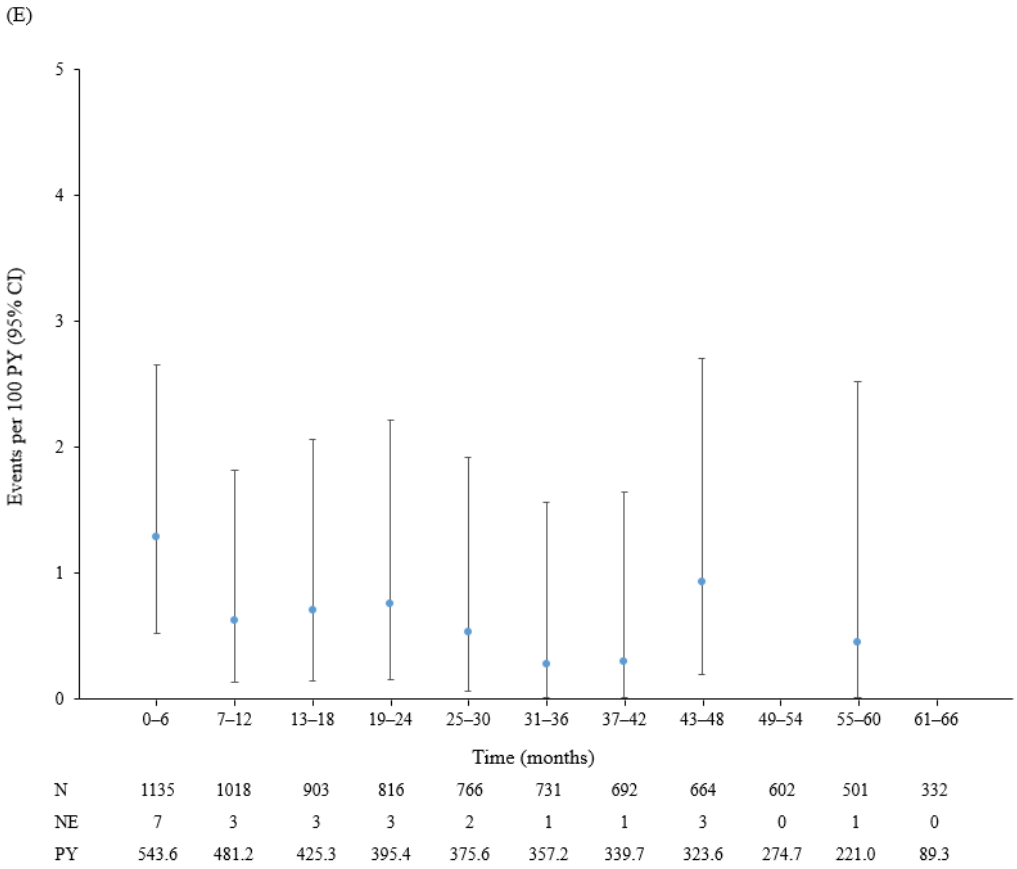
	0–6	7–12	13–18	19–24	25–30	31–36	37–42	43–48	49–54	55–60	61–66
N	1135	1018	903	816	766	731	692	664	602	501	332
NE	3	0	1	4	2	1	0	1	1	0	0
PY	543.6	481.2	425.3	395.4	375.6	357.2	339.7	323.6	274.7	221.0	89.3

Injection-site reactions



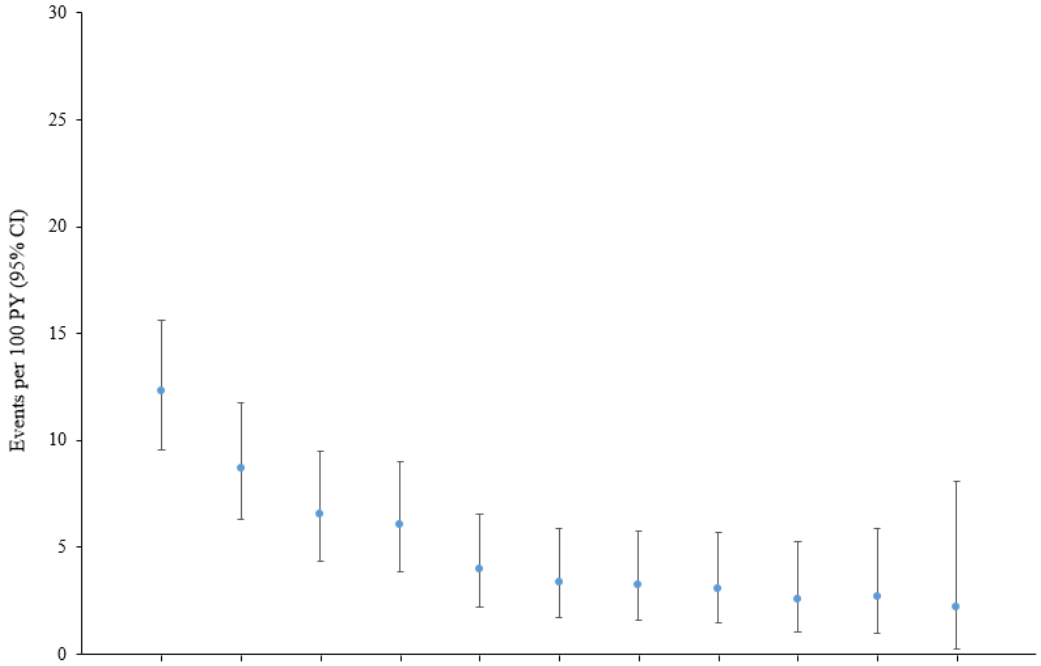
	0–6	7–12	13–18	19–24	25–30	31–36	37–42	43–48	49–54	55–60	61–66
N	1135	1018	903	816	766	731	692	664	602	501	332
NE	325	136	90	71	47	54	41	22	23	18	1
PY	543.6	481.2	425.3	395.4	375.6	357.2	339.7	323.6	274.7	221.0	89.3

Malignancy


(E)
Events per 100 PY (95% CI)
0
1
2
3
4
5
0–6
7–12
13–18
19–24
25–30
31–36
37–42
43–48
49–54
55–60
61–66
Time (months)
N 1135 1018 903 816 766 731 692 664 602 501 332
NE 7 3 3 3 2 1 1 3 0 1 0
PY 543.6 481.2 425.3 395.4 375.6 357.2 339.7 323.6 274.7 221.0 89.3

ANC <1000 cells/mm^3

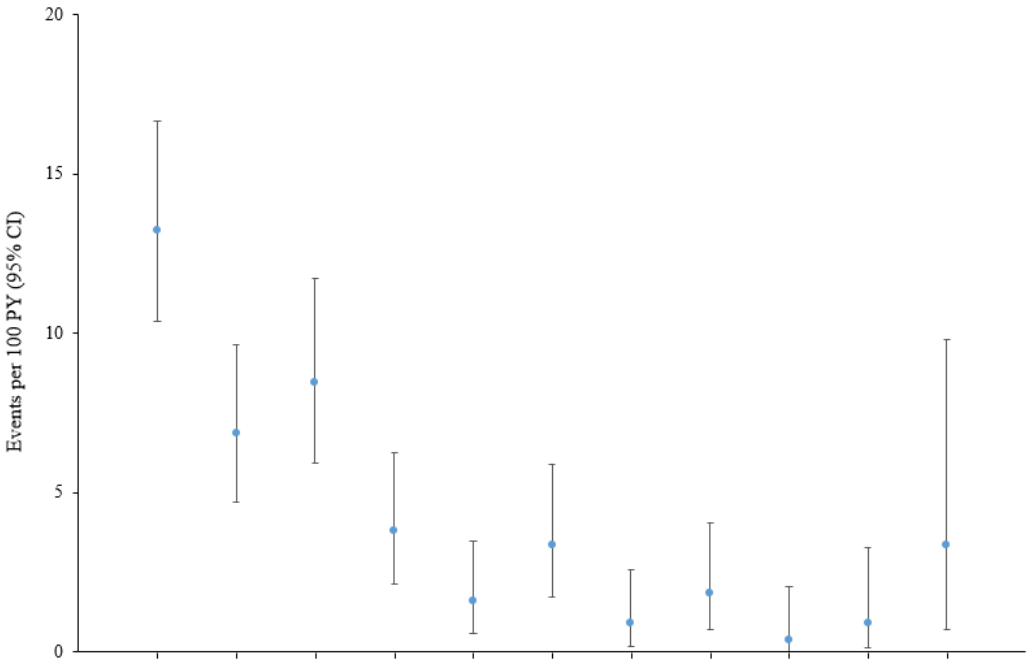
(F)



N	1135	1018	903	816	766	731	692	664	602	501	332
NE	67	42	28	24	15	12	11	10	7	6	2
PY	543.6	481.2	425.3	395.4	375.6	357.2	339.7	323.6	274.7	221.0	89.3

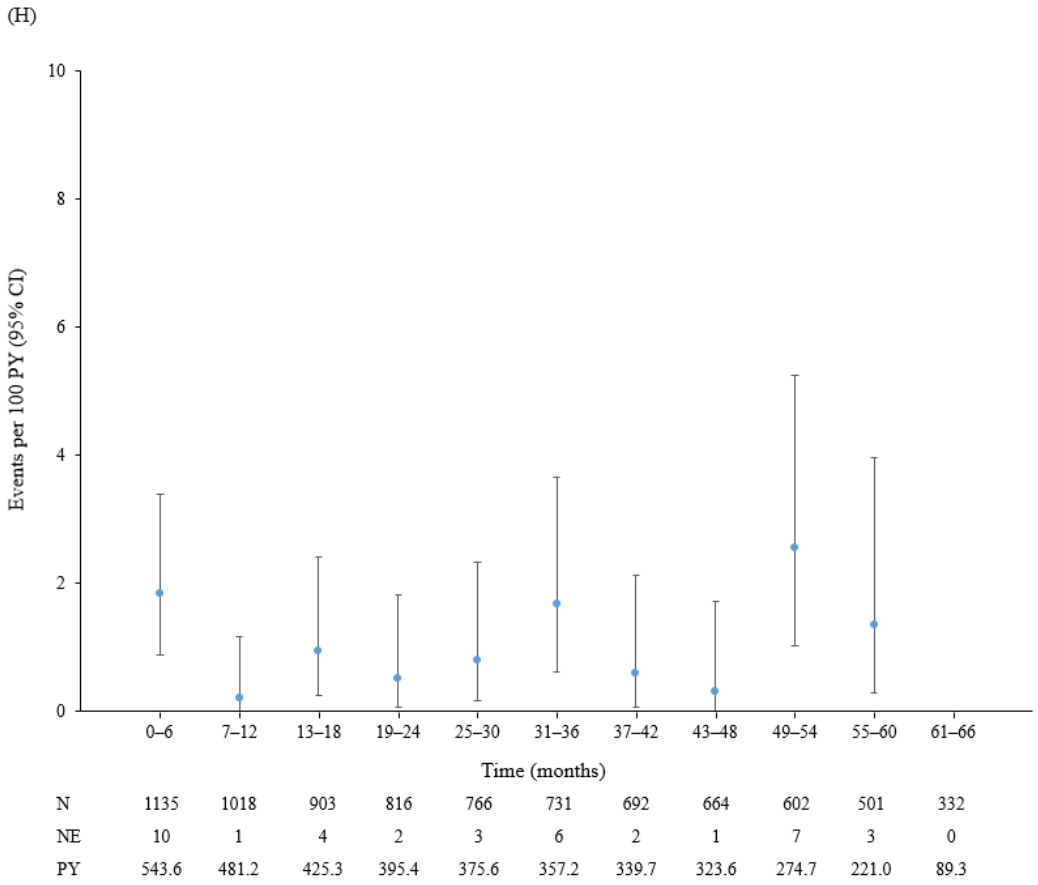
ALT >3× ULN

(G)



N	1135	1018	903	816	766	731	692	664	602	501	332
NE	72	33	36	15	6	12	3	6	1	2	3
PY	543.6	481.2	425.3	395.4	375.6	357.2	339.7	323.6	274.7	221.0	89.3

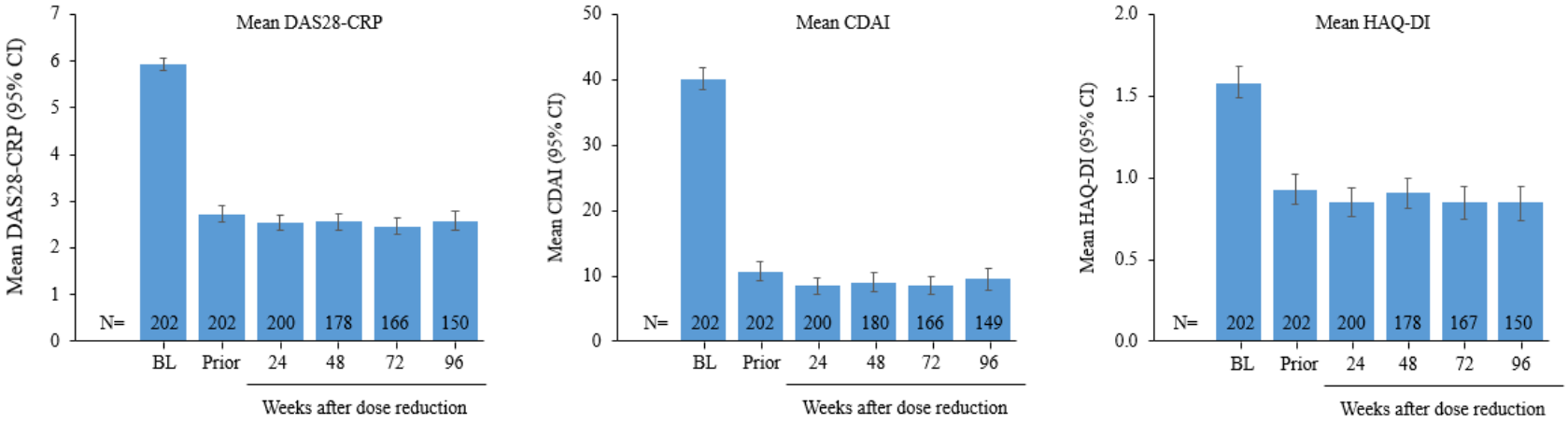
Platelet count <100 x 10^9 cells/L



	0–6	7–12	13–18	19–24	25–30	31–36	37–42	43–48	49–54	55–60	61–66
N	1135	1018	903	816	766	731	692	664	602	501	332
NE	10	1	4	2	3	6	2	1	7	3	0
PY	543.6	481.2	425.3	395.4	375.6	357.2	339.7	323.6	274.7	221.0	89.3

ALT, alanine aminotransferase; ANC, absolute neutrophil count; CI, confidence interval; MACE, major adverse cardiovascular events; NE, number of events; PY, patient-years; ULN, upper limit of normal.

Supplementary figure 3 Clinical efficacy following sarilumab dose reduction from 200 to 150 mg q2w.



BL, baseline of the double-blind study; CDAI, Clinical Disease Activity Index; CI, confidence interval; DAS28-CRP, Disease Activity Score (28 joints) using C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; Prior, most recent assessment before dose reduction in the open-label extension; N, number of patients with dose reduction and assessment at both baseline and the corresponding timepoint; q2w, every 2 weeks.