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SAT0171

REVERSIBLE DECREASES IN ABSOLUTE NEUTROPHIL COUNT (ANC) IN RHEUMATOID ARTHRITIS (RA) PATIENTS (PTS) ON SARILUMAB: COMPARISON OF DOSE DELAY AND DOSE DECREASE VS CONTINUED TREATMENT

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Background: In randomized studies (RCTs: MOBILITY, TARGET and MONARCH), and open-label [OLE] EXTEND, for those patients who experienced decreases in ANC this typically occurred early after initiating sarilumab. For sarilumab patients with decreased ANC in the RCTs and the OLE, we assessed the outcomes associated with either continuing treatment, decreasing the sarilumab dose or delaying the dose.

Objectives: The effects of a dose decrease (200 to 150 mg), dose delay (>17 days), vs no change in treatment were evaluated in RA patients who experienced decreased ANC while on sarilumab 150 or 200 mg q2w. Outcomes data from patients in MONARCH, MOBILITY and TARGET, and MOBILITY and TARGET patients entering EXTEND were analyzed to compare the three strategies. In MONARCH, patients received sarilumab 200 mg q2w. In MOBILITY and TARGET, patients received sarilumab 150 or 200 mg q2w. In EXTEND, patients were switched to, or initiated on, 200 mg q2w.

Table 1 Outcomes following dose delay, dose decrease, or continued treatment with sarilumab among pts who experienced ANC <1000/mm³ at any time

	RCTs		OLE	
Total treated (N)	1346		1353	
ANC <1000/mm ³ at any time (n, %)	105 (8)		147 (11)	
Pts who did not continue* (n, %)	24 (23)		15 (10)	
Pts that continued, delayed, or decreased sarilumab dose (n, %)	81 (77)		132 (90)	
	Continued without change (n=38)	Dose delay (n=43)	Continued without change (n=31)	Dose delay (n=82)
Normalized on treatment after ≥1 episodes of ANC <1000/mm ³ (n, %)	25 (66)	27 (63)	29 (94)	66 (80)
Median time to normalization for patients with 1 episode (days)	9	15	27	17
Pts with ≥1 episode of ANC <1000/mm ³ who normalized on treatment** (n)	6	6	3	33
Normalized after treatment discontinuation (n, %)	2 (5)	9 (21)	1 (3)	7 (9)
Did not normalize after ≥1 episode of ANC <1000/mm ³ (n, %)	11* (29)	7* (16)	1 (3)	9 (11)
Discontinued treatment due to abnormal ANC after last episode (n)	1	1	1	9
ANC @ last episode (<2000/<1500/<1000/mm ³)	0/1/0	0/0/1	1/0/0	2/6/1
ANC @ last episode (<2000/<1500/<1000/mm ³)	1/4/1			

*10 and % pts enrolled into EXTEND

**ANC <500/mm³ confirmed or had evidence of an infection or had ANC 500 to 1000/mm³ and were discontinued at the investigators discretion.

**pts: ≥1 episode of ANC <1000/mm³ was defined as pts who, at least once, experienced ANC <1000/mm³, then displayed normalized ANC levels and were able to resume treatment, but later experienced ANC <1000/mm³ again.

Methods: In RCTs, patients were required to have baseline neutrophil levels ≥2000/mm³. In RCTs and EXTEND, patients who experienced ANC <500/mm³ (grade 4 [G4] neutropenia) or ≥500 to <1000/mm³ (grade 3 [G3] neutropenia) and signs of infection were required to permanently discontinue treatment. Patients with G3 neutropenia (no signs of infection) temporarily discontinued treatment (or permanently discontinued at the investigators discretion); patients were retested ≤48 hrs after identifying decreased ANC and before the next scheduled dose, and could resume if ANC ≥1000/mm³. In RCTs, patients restarted sarilumab at their randomized dose. In OLE, patients restarted sarilumab at 150 mg q2w, as per the protocol, or otherwise were able to restart at 200 mg q2w at the investigators discretion. In OLE, patients who required a dose decrease to 150 mg q2w sarilumab

received the reduced dose for the remainder of the treatment period. ANC normalization was defined as a return to the patient's baseline or within normal ranges.

Results: Of the 8–11% of patients who experienced ANC <1000/mm³ at any time, 81/105 (RCTs) and 132/147 (OLE) were able to continue or reinstitute sarilumab; the majority of patients who experienced ANC <1000/mm³ one or more times displayed normalized ANC levels and continued treatment when ANC ≥1000/mm³ (25/38 in RCTs; 29/31 in OLE). The majority of patients who dose delayed (27/43 in RCTs; 66/82 in OLE) or dose decreased (51/62, OLE) before ANC normalized resumed treatment.

Conclusions: More than three-quarters of patients who discontinued treatment until ANC normalized were able to reinstitute at their randomized dose (RCT), or at the open-label study dose (200 mg q2w; OLE) or were able to resume at the lower dose (150 mg q2w; OLE).

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SAT0172

LONG-TERM EFFICACY WITH 5-YEAR-RADIOGRAPHIC RESULTS AND SAFETY OF SARILUMAB IN COMBINATION WITH csDMARDs IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Long-term data are being collected on sarilumab in combination with csDMARDs in patients with RA originally enrolled in six trials (TARGET, NCT01709578; MOBILITY, NCT01061736; NCT01764997; NCT01768572; NCT02057250; NCT01217814) including those who continued into extension trials.

Objectives: To assess efficacy and safety of long-term treatment with sarilumab plus csDMARDs in patients with RA.

Methods: Long-term efficacy and safety data were available in patients enrolled in placebo-controlled trials of sarilumab 150 or 200 mg sc q2w who continued into the open-label EXTEND trial of sarilumab 200 or 150 mg sc q2w (NCT0146652). Safety data were evaluated in 2887 patients who received ≥1 dose of sarilumab sc in combination with csDMARDs.

Results: Clinical and radiographic efficacy of sarilumab plus csDMARDs was maintained over 5 years' follow-up (table 1; figure 1). Initial treatment with either dose of sarilumab was associated with significantly better radiographic outcome than placebo. Initial treatment with sarilumab 200 mg portended better radiographic outcome than sarilumab 150 mg or placebo. Mean duration of sarilumab treatment in the safety population was 2.6 years (max 6.8), representing 7412 cumulative patient-years of exposure. Incidence rate of adverse events of special interest (AESIs; table 2) was generally stable over >5 years' treatment, with no signal for increased rate of any AESI (including serious AEs and serious infection) over time. Incidences of injection site reaction, ANC <1 Giga/L, & elevated ALT declined over time.

Table 1 Clinical response, % (number of patients assessed)

	DAS28-CRP<2.6 (remission)			CDAI ≤2.8 (remission)		
Initial treatment	MOBILITY (52 weeks)→EXTEND					
Week	148	196	244	148	196	244
Placebo	58.6 (249)	59.3 (231)	63.8 (207)	28.1 (249)	32.9 (231)	36.4 (209)
Sarilumab 150 mg	61.9 (239)	63.0 (219)	63.1 (195)	30.5 (239)	32.6 (221)	34.2 (199)
Sarilumab 200 mg	67.5 (237)	65.3 (225)	70.7 (208)	36.6 (238)	36.7 (226)	39.8 (211)
	TARGET (24 weeks)→EXTEND					
Week	48	96	144	48	96	144
Placebo	38.1 (139)	39.3 (122)	41.0 (117)	15.9 (138)	19.5 (123)	17.2 (116)
Sarilumab 150 mg	44.9 (136)	49.1 (116)	53.8 (104)	18.1 (138)	22.4 (116)	23.4 (107)
Sarilumab 200 mg	41.4 (140)	49.2 (126)	53.5 (114)	15.7 (140)	23.0 (126)	24.3 (115)

Table 2 Treatment emergent adverse event rates per 100 patient-years

	Any AE/SAE	147/9.6
AEs of special interest	AE leading to death/discontinuation	0.4/9.1
	Infections (all/serious/opportunistic/TB)	54.7/3.7/0.9/0.1
	Injection site reactions	24.9
	Hypersensitivity reaction	5.6
	Malignancy (all/excluding NMSC)	0.7/0.5
	MACE (primary/narrow)	0.4/0.5
	Medically adjudicated GI perforation	0.1
	Lupus-like syndrome	0.1

Figure 1 Change in mTSS in patients who completed 52-week double-blind MOBILITY study and subsequently entered open-label EXTEND study. **Conclusions:** Clinical efficacy and inhibition of progression of structural damage with sarilumab plus csDMARDs was sustained up to 5 years of follow-up in patients with diverse prior pharmacologic therapies. The safety profile of sarilumab plus csDMARDs remained stable over >5 years' treatment.

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SAT0173 EFFECTS OF DENOSUMAB, A SUBCUTANEOUS RANKL INHIBITOR, ON THE PROGRESSION OF STRUCTURAL DAMAGE IN JAPANESE PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH CSDMARDs: RESULT FROM THE LONG-TERM TREATMENT OF PHASE 3, DESIRABLE STUDY

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Background: Denosumab is a fully human monoclonal antibody (IgG₂ subclass) that inhibits bone resorption by inhibiting RANKL, a key mediator of osteoclast formation, function, and survival. The effect of denosumab on the progression of joint damage in patients with RA on csDMARDs background treatment from the first 12 months (double-blind, placebo-controlled) of the Phase 3 DESIRABLE study has previously been reported.¹

Objectives: To evaluate the safety and efficacy of long-term treatment with denosumab 60 mg every 6 months (Q6M) or every 3 months (Q3M) with RA patients in long term treatment phase of the DESIRABLE study.

Methods: Upon completion of the 12-month, double-blind phase, all patients were to receive denosumab 60 mg/Q6M or 60 mg/Q3M and calcium and vitamin D daily during the 36-month, open-label extension phase. Patients were randomized in a 1:1:2:2 ratio to receive one of four treatments (figure 1). In this analysis, the continuous administration group received 36 months of denosumab treatment, and the cross-over group received 24 months of denosumab treatment (12 month of placebo in DB phase and 24 months of denosumab treatment phase). The radiographic evaluation was the change from baseline to 12, 24 and 36 months in the van der Heijde modified total Sharp score (mTSS). Radiographs of hands and feet at baseline, 12, 24 and 36 months were scored with blinded time order by 2 readers independently. Average score of the 2 readers is used for the analysis. Missing scores were imputed using linear extrapolation/interpolation.

Figure 1 Study design

Characteristic	Visit	Cross-over group		Continuous administration group	
		Placebo/denosumab 60mg Q6M N = 105	Placebo/denosumab 60mg Q3M N = 101	Denosumab 60mg Q6M N = 191	Denosumab 60mg Q3M N = 193
mTSS	12 months	1.29 ± 2.86	1.60 ± 3.62	1.25 ± 4.16	0.98 ± 3.01
	24 months	2.33 ± 4.73	2.05 ± 4.35	2.12 ± 6.10	1.42 ± 4.02
	36 months	2.93 ± 6.56	2.49 ± 4.70	2.26 ± 6.66	1.71 ± 4.59
ES	12 months	0.79 ± 1.76	0.97 ± 2.48	0.70 ± 2.39	0.27 ± 0.98
	24 months	1.23 ± 2.36	1.01 ± 2.48	1.09 ± 3.55	0.36 ± 1.35
	36 months	1.54 ± 3.39	1.18 ± 2.56	0.96 ± 3.36	0.40 ± 1.31
JSN score	12 months	0.51 ± 1.44	0.63 ± 1.75	0.56 ± 2.13	0.71 ± 2.42
	24 months	1.10 ± 2.87	1.04 ± 2.27	1.03 ± 3.13	1.07 ± 3.20
	36 months	1.39 ± 3.63	1.31 ± 2.57	1.30 ± 4.04	1.31 ± 3.67

Data presented are mean ± SD

Table 1 Change from baseline in mTSS, ES and JSN score in DB and long-term treatment phaseData presented are mean±SD

Results: 667 (placebo/Q6M (P/Q6M), n=113; placebo/Q3M (P/Q3M), n=110; Q6M, n=222; Q3M, n=222) received at least one dose of study drug, and 607 (P/Q6M, n=105; P/Q3M, n=103; Q6M, n=199; Q3M, n=200) completed the DB period and entered the long-term extension. In both continuous administration and